NOVARTIS

Clinical Development

BLZ945, PDR001

CBLZ945X2101 / NCT02829723

A phase I/II, open-label, multi-center study of the safety and efficacy of BLZ945 as single agent and in combination with PDR001 in adult patients with advanced solid tumors

Statistical Analysis Plan (SAP)

Author: [redacted], Trial Statistician

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13-May-2020	Prior to start of Phase II part	Document that patients who were not appropriately consented will be removed from all analysis activities.	Amendment 1.0	1. Section 2.1 Data analysis general information 2. Section 2.4 Protocol deviations
7-April-2021	Prior to IA of Phase II part	Update the analysis plan based on PA06	Amendment 2.0	1. Section 1.1, 1.2 2. Section 2.1, 2.2, 2.3, 2.5, 2.6, 2.7, 2.8, 2.10, 2.12 3. Section 3 4. Section 4
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17-Jan-2023	Prior to DBL	Update of LLOQ values	Amendment 4.0	1. Section 2.9
17-July-2023	Post-DBL	Inclusion of Japan vs non-Japan safety analysis along with requirements of clinicaltrials.gov and EudraCT.gov disclosure	Addendum	1. 2.5.1.2, 2.8.1, 2.6.1

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1 Introduction

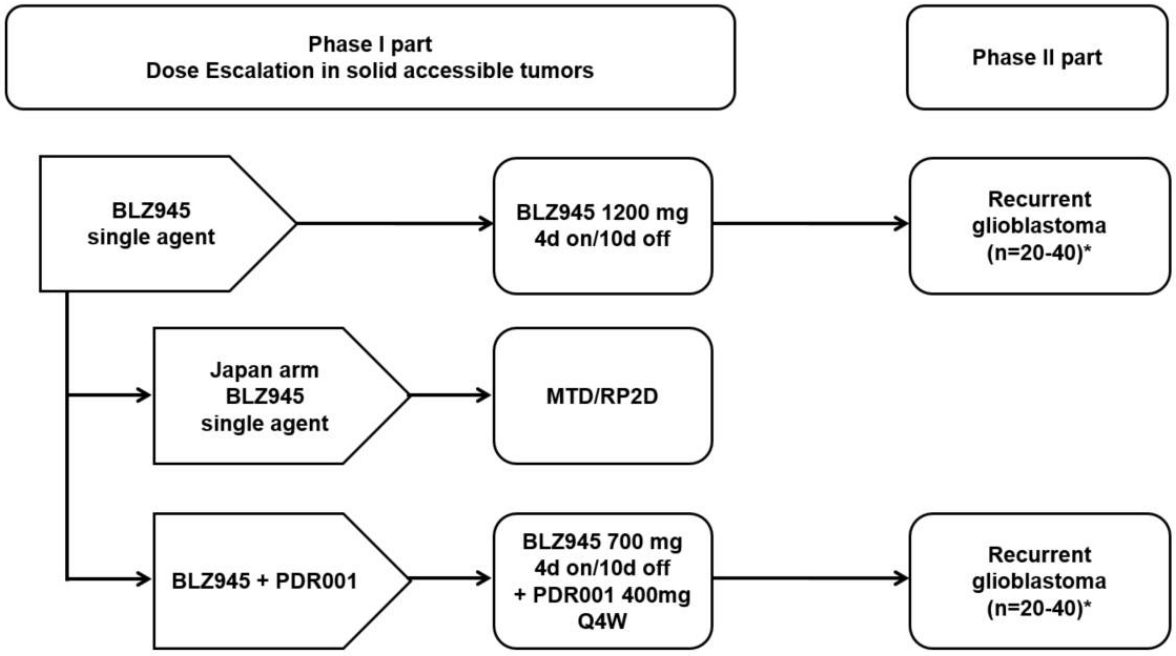
This Statistical Analysis Plan (SAP) provides detailed statistical methodology for the analysis of data from study BLZ945X2101 that will be presented in the Clinical Study Report (CSR) based on Protocol amendment 06 (PA06). The output shells (in-text and post-text) accompanying this document can be found in the TFL shells document. The specifications for derived variable and datasets can be found in the Programming Datasets Specifications (PDS) document.

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

The SAP, TFL shells and PDS documents may also serve as a reference for the creation of any outputs required outside of the CSR, e.g., MTD/RDE declaration, 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

Figure 1-1 Study design (effective after approval of PA06)



*: To be expanded to 40 patients if anti-tumor activity is observed in the first 20 patients

1.2 Study objectives and endpoints

Table 1-1 Objectives and related endpoints

Objective	Endpoint
Primary	
Phase I: To characterize the safety and tolerability and to estimate the MTDs and/or RP2Ds of BLZ945 as a single agent (in non-Japanese and Japanese patients, separately) and in combination with PDR001	Safety: Incidence and severity of Adverse Events (AEs) and serious Adverse Events (SAEs), including changes in laboratory parameters, vital signs and Electrocardiogram (ECGs) Tolerability: Dose interruptions, reductions and dose intensity The incidence of DLTs during the first cycle of treatment with single agent BLZ945 and with BLZ945 in combination with PDR001
Phase II: To assess the anti-tumor activity of BLZ945 in combination with PDR001 (and BLZ945 as single agent if appropriate)	PFS rate at 6 months (PFS6) per response assessment in Neuro-Oncology (RANO) Criteria for glioblastoma indication.
Secondary	
Phase I : To evaluate the preliminary anti-tumor activity of BLZ945 as single agent and in combination with PDR001	PFS, Best Overall Response (BOR), Overall Response Rate (ORR), Disease Control Rate (DCR) per RECIST v1.1 and immune-related response criteria (irRC), and RANO/iRANO Criteria for glioblastoma indication and the Guidelines for efficacy evaluation in lymphoma studies for lymphoma indication(s).
Phase II : To evaluate the preliminary anti-tumor activity of BLZ945 as single agent (if appropriate) and in combination with PDR001	PFS per immune response assessment in Neuro-Oncology (iRANO) for glioblastoma indication BOR, DOR and DCR per RANO and iRANO for glioblastoma
Phase II: To describe the survival distribution of patients treated with BLZ945 as single agent (if appropriate) and in combination with PDR001 Phase II: To further characterize the safety and tolerability of BLZ945 as a single agent and in combination with PDR001	Overall survival (OS) Safety: Incidence and severity of Adverse Events (AEs) and serious Adverse Events (SAEs), including changes in laboratory parameters, vital signs and Electrocardiogram (ECGs); Tolerability: Dose interruptions, reductions and dose intensity
Phase I/II parts: Characterize PK of BLZ945 as a single agent and in combination with PDR001	BLZ945 and PDR001 PK parameters [e.g. AUC, Cmax, Tmax]
Phase I/II parts: To assess emergence of anti-PDR001 antibodies following one or more i.v. infusions of PDR001 in combination with BLZ945	Presence and/or concentration of anti-PDR001 antibodies
Exploratory	
Phase I: To assess the pharmacodynamics effect of BLZ945 as single agent and in combination with PDR001 in tumor	Change from baseline in expression of immune-related genes. Change from baseline in expression of immune-oncology biomarkers including but not restricted to CD163; CD8 by immunohistochemistry.

2 Statistical Methods

2.1 Data analysis general information

The data will be analyzed by Novartis personnel and/or designated CRO(s) using SAS version 9.4 or higher, and for Bayesian modeling, R version 3.2.3 or higher and WinBUGS version 1.4.3 or higher. PK parameters will be calculated using non-compartmental methods available in Phoenix WinNonlin version 5.2.

The study data will be analyzed and reported (in a primary CSR if final DBL has not occurred) based on all patients' data of the dose escalation and phase II parts up to the time when all patients have potentially completed at least six cycles of treatment or discontinued the study and all patients from Phase II part have had at least one tumor assessment after six months of treatment or discontinued the study. The primary CSR will include all outputs planned within the TFL shells document. Additional data for patients continuing to receive study treatment past the data cutoff date of the primary CSR, as allowed by the protocol, will be reported once all patients have discontinued the study. However, only a selection of key outputs (indicated in the TFL shells document) for which additional data was collected will be provided for the final report.

Data from participating centers in this study protocol will be combined, so that an adequate number of patients will be available for analysis. No center effect will be assessed. The data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and all relevant pharmacokinetic (PK) using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) for quantitative data and contingency tables (frequencies and percentages) for qualitative data.

Both pre and post intra-patient dose escalation data will be listed and summarized together under the one dose level/treatment group.

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

- For the Phase I part, cohorts treated with the same dose or dose combination (dose levels and schedules) will be pooled into a single treatment group. All summaries, listings, figures and analyses will be performed by treatment group.
- For the Phase II part, all summaries, listings, figures for primary efficacy analysis and safety analyses will be presented by treatment group (S.A BLZ945 and BLZ945 in combination with PDR001). Patients from the Phase II part will be classified according to the treatment group to which they were assigned at baseline.

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

Patients who sign a non-Ethics Committee approved ICF prior to starting study procedures will not be included in any of the reporting activities.

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.
Treatment group is defined by the dose level and regimen of the study treatment (e.g. BLZ945 150 mg 7 days on/7 days off + PDR001 Q4W is one treatment group). A cohort is defined as a group of newly enrolled patients treated at a specific regimen and dose level (i.e. treatment group) at the same time. Therefore, a treatment group may consist of more than one cohort.

2.1.1 General defintions

Study drug and study treatment

For Single agent:

Study drug and study treatment both refer to BLZ945 and are used interchangeably.

For the combinations:

Study drug refers to the individual compound i.e. BLZ945, PDR001. Study treatment refers to combination of BLZ945 and PDR001.

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

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

Study day

The study day for all assessments/events will be calculated using the start date of study treatment as reference. For assessments/events occurring on or after the start date of study treatment, study day will be calculated as:

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

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

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

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

Study day will be displayed in the data listings.

Baseline

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

The last available assessment on or before the date of the start of study treatment will be taken as the "baseline" assessment. In case time of assessment and time of treatment start is captured, the last available assessment before the treatment start date/time is used for baseline.

On-treatment assessment/event

For both single agent and the combination the overall observation period will be divided into three mutually exclusive segments:

pre-treatment period:

from day of subject'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 non-zero actual administration of any study treatment (including start and stop date).

Post-treatment period:

starting at day 31 after last administration of study treatment.

Safety summaries (tables, figures) include only 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 on treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (***treatment-emergent*** AEs).

2.2 Analysis sets

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

Full Analysis Set

The Full Analysis Set (FAS) comprises all patients who received at least one dose of study treatment. Patients will be analyzed according to the planned treatment. 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.

Safety Set

The Safety Set includes all patients who received at least one dose of BLZ945 or PDR001. Patients will be analyzed according to the study treatment (regimen) they actually received, where treatment received is defined as:

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

Dose-determining Set

Single agent BLZ945 dose escalation cohort

The dose-determining analysis set (DDS) consists of all patients from the safety set in the dose escalation part who either meet the minimum exposure criterion and have sufficient safety evaluations, or have experienced a DLT during Cycle 1.

A patient is considered to have met the minimum exposure criterion if having received BLZ945 on at least 75% of the planned dosing days during Cycle 1 (as defined below). Patients who do not experience a DLT during the first cycle are considered to have sufficient safety evaluations if they have been observed for ≥ 28 days following the first dose and are considered by both the Sponsor and Investigators to have enough safety data to conclude that a DLT did not occur.

Combination of BLZ945 and PDR001 dose escalation cohort

The DDS consists of all patients from the safety set in the dose escalation part who either meet the minimum exposure criterion and have sufficient safety evaluations, or have experienced a DLT during the first cycle.

A patient is considered to have met the minimum exposure criterion if having received BLZ945 on at least 75% of the planned dosing days during Cycle 1 (as defined below) and at least one dose of PDR001 during Cycle 1. Patients who do not experience a DLT during the first cycle are considered to have sufficient safety evaluations if they have been observed for ≥ 28 days following the first dose, and are considered by both the Sponsor and Investigators to have enough safety data to conclude that a DLT did not occur.

For both once and twice a day dosing schedules, the 75% of the planned dosing days of BLZ945 is defined as:

- at least 11 days of taking planned doses in 7d on/7d off regimen
- at least 3 days of taking planned doses of BLZ945 in Q1W regimen
- at least 6 days of taking planned doses of BLZ945 in the 4d on/10d off regimen

Pharmacokinetic analysis Set

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

- Patient receives one of the planned treatments

- Patient provides at least one primary PK parameter
- Patient does not vomit within 4 hours after dosing of BLZ945

Immunogenicity (IG) analysis Set

The Immunogenicity Prevalence Set (IGPS) includes all patients in the FAS with a determinant baseline IG sample **or** at least one determinant post-baseline IG sample.

The Immunogenicity Incidence Set (IGIS) includes all patients in the IGPS with a determinant baseline IG sample **and** at least one determinant post-baseline IG sample.

See Section 2.10 for the definintion of determinant.

Withdrawal of informed consent

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

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

2.3 Patient disposition, demographics and other baseline characteristics

Summaries and listings described in this section will be based on the FAS.

2.3.1 Patient disposition

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

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

2.3.2 Basic demographic and background data

- Demographic data including age, sex, race, baseline weight, and ECOG performance status will be listed and summarized. In addition, age category (18 - <65 years, 65 - <85 years, >=85 years) will be summarized.

BMI is calculated using the following formula:

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

2.3.3 Medical History

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. Medical history and current (ongoing) medical conditions, including cancer-related conditions and symptoms will be listed.

2.3.4 Prior antineoplastic therapy

Prior anti-neoplastic therapy overall will be summarized. In addition these will be listed for medication, radiotherapy and surgery.

The summary of prior anti-neoplastic therapy overall will include the total number patients received medications, surgery and radiotherapy. IT will also include the total number of regimens (note: there can be more than one medication per regimen) Prior antineoplastic medications will also be summarized for Temozolomide, Lomustine and other medications for phase II part of study.

2.3.5 Diagnosis and extent of cancer

The summary and listing of diagnosis and extent of cancer (disease history) will include primary site of cancer, types of lesions at baseline and current extent of disease (metastatic sites).

2.4 Protocol deviations

The FAS will be used for the protocol deviation summary tables and listings. The number (%) of patients with any CSR-reportable protocol deviation will be tabulated by the deviation category (entry criteria not satisfied; wrong treatment or incorrect dose; developed withdrawal criteria, but not withdrawn; took an excluded concomitant medication; others). The full list of protocol deviations are documented in the Study Specification Document (SSD).

Patients who sign a non-Ethics Committee approved ICF prior to starting study procedures (PDID = OTH14) will be excluded from all analysis sets and not included in any of the reporting activities.

Major protocol deviations leading to exclusion from the PPS are given below:

Table 2-1 Major protocol deviations

PD Criterion	Protocol Deviation ID	Major PDs
The use of other investigational therapies while the patient is on the study	COMD01	Yes
Use of anticancer therapy (chemotherapy, biologic or radiation therapy, and surgery) other than the study treatment while the patient is on the study	COMD02	Yes

patient received pre-medication to prevent infusion reaction before first PDR001 infusion	COMD03	Yes
use of live vaccines while patient was on study treatment.	COMD04	Yes
consumption of Seville orange (and juice), grapefruit or grapefruit juice, grapefruit hybrids, pomelos and star citrus fruits at least 7 days prior to the first dose of study treatment and during the entire study treatment period	COMD05	Yes
Phase II only: patient without advanced/metastatic tumors in pancreatic cancer, triple breast negative breast cancer, recurrent glioblastoma and who did not fail to respond to standard treatment	INCL07	Yes
Systemic steroid therapy or any immunosuppressive therapy (≥10mg/day prednisone or equivalent).	EXCL19	Yes
Any vaccines against infectious diseases (e.g. varicella, pneumococcus) within 4 weeks of initiation of study treatment.	EXCL20	Yes
Systemic anti-cancer therapy within 2 weeks of the first dose of study treatment. For cytotoxic agents that have major delayed toxicity, e.g. mitomycin C and nitrosoureas, 4 weeks is indicated as washout period.	EXCL21	Yes
Major surgery within 2 weeks of the first dose of study treatment (mediastinoscopy, insertion of a central venous access device, and insertion of a feeding tube are not considered major surgery).	EXCL22	Yes
Pre-treatment with anti- cytotoxic T-Lymphocyte-associated protein 4 (CTLA4) antibodies in combination with any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathway. Patients pre-treated with anti-CTLA4 as single agent must have minimum 8 week washout period between the last dose of anti-CTLA4 and the first dose of PDR001	EXCL23	Yes
Participation in an interventional, investigational non-immunotherapy study within 2 weeks of the first dose of study treatment	EXCL24	Yes
Radiotherapy within 2 weeks of the first dose of study drug, except for palliative radiotherapy to a limited field, such as for the treatment of bone pain or a focally painful tumor mass. To allow evaluation for response to treatment, patients enrolled in the phase II part must have remaining measurable disease that has not been irradiated.	EXCL27	Yes
Phase II only: Patient treated with BLZ945 in combination with PDR001 who changes BLZ945 regimen	TRT07	Yes
Phase II: Patient did not receive planned treatment	TRT14	Yes
Patient was not fasted when BLZ945 was taken	TRT17	Yes
PDR001 infusion more than 2h	TRT01	Yes
PDR001 infusion less than 30 minutes	TRT02	Yes
PDR001 dose reduced	TRT04	Yes
PDR001 regimen changed	TRT05	Yes

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

Unless otherwise noted, the Safety set will be used for all medication data summaries and listings.

2.5.1 Study treatment

2.5.1.1 Last date of exposure to study treatment

The last date of exposure to study treatment is the latest of the last dates of exposure to investigational drug, and any combination partner.

- For single agent, last date of exposure to study treatment is the last date of administration of BLZ945 + X where X is the number of days from date of last administration until date of the next protocol planned dose administration.
- For the BLZ945 and PDR001 combination, last date of exposure to study treatment = max(last date of exposure to BLZ945, last date of exposure to PDR001).
  The last date of exposure to study drug corresponds to the last date of exposure to PDR001,
  or BLZ945, and is defined as the last date of administration of the study drug + X, where X is the number of days from date of last administration until date of the next protocol planned dose administration.

For PDR001 given Q4W, the last date of exposure is defined as the last day of administration + 27 days.
For BLZ945 given Q1W, the last date of exposure is defined as the last day of administration + 6 days.
For BLZ945 given 7 days on/7 days off, the last date of exposure is defined as the last day of administration + number of days within the "7 days on week" with missing treatment + 7 days.
For BlZ945 given 4 days on/10 days off, the last date of exposure is defined as the last day of administration + number of days within the "4 days on week" with missing treatment + 10 days.
If a patient dies or lost to follow-up within last date of treatment administration + X, then the last date of exposure is the death date or last contact date respectively. Similarly, if cut-off date falls within last date of treatment administration + X, then the last date of exposure is the cut-off date.

2.5.1.2 Other study treatment definitions

The below analyses will be summarized by on treatment period and overall.

Definitions of duration of exposure, cumulative dose, actual dose intensity (DI), planned dose intensity (PDI), relative dose intensity (RDI), percentage of days dosed, percentage of days the planned/intended dose was received, as well as intermediate calculations, are as follows:

- Duration of exposure (days)= last date of exposure to study treatment − first date of study treatment + 1 (periods of interruption are not excluded)
- Cumulative dose (mg): sum of all doses of study drug taken by a patient. The off-dosing days as per protocol will be considered as zero doses. For BID schedule, two doses will be considered for a day (if taken).
- Cumulative planned dose (*mg*): sum of all doses of study drug that was intended to have been taken during the treated period by a patient.
- Actual cumulative dose (*mg*): sum of all doses of study drug that was actually been taken during the treated period by a patient

- DI (mg/day): actual cumulative dose (mg) / number of dose days scheduled per protocol during treatment period
- PDI (mg/day): cumulative planned dose (mg) / number of dose days scheduled per protocol during treatment period
- RDI (%): 100 × DI (mg/day) / PDI (mg/day)

It is required to find the adjusted exposure duration to calculate the number of dose days scheduled per protocol during treatment period in the denominator of dose intensity (DI). Let D1 represent the duration of exposure, then the adjusted exposre duration (D) will be defined as:

- For 4 days on 10 days off regimen: D=4*[D1/14]+min(4, D1-14*[D1/14]) days, where [x] is integral part of x
- For 7 days on 7 days off regimen: D=7*[D1/14]+min(7, D1-14*[D1/14]) days, where [x] is integral part of x
- For Q1W regimen: D= [((last dosing date+X) – first dosing date)/7] , X=7. where [x] is integral part of x
- For Q4W regimen: D= [((last dosing date +X) – first dosing date)/28] , X=28. where [x] is integral part of x

The duration of exposure to study treatment (including categories: <4, 4-<8, 8-<24, 24-<52, ≥52 weeks) will be summarized. In addition, DI, and RDI will be summarized for each study drug using the duration of exposure to study drug. These will also be summarized for Japan vs non-Japan subgroup.

The number (%) of patients who have dose reductions and interruptions, and the corresponding reasons, will be provided for each study drug. The number of dose reductions and interruptions (and/or delays) per patient and the duration of dose reductions/interruptions/delays (days) will be summarized for each study drug.

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

Dose interruption: CRF field "dose interrupted" is selected as yes and dose administered equal to zero, between the first and last non-zero doses, following a non-zero dose administered. Reason "as per protocol" is not considered as interruption. A patient with multiple occurrences of a reason is only counted once in that category.
Dose reduction: CRF field "dose changed" is selected as yes and a non-zero actual dose (i.e. dose administered to the patient as defined above) that is less than the immediate previous non-zero actual dose (if not the first dose) and below the treatment received dose as per safety set definition.

2.5.2 Concomitant therapies

Concomitant therapies are defined as any medications (excluding study treatment, prior antineoplastic treatments) and significant non-drug therapies (including physical therapy and blood transfusions) administered in the study that are recorded in the Concomitant Medications/significant non-drug therapies eCRF. These therapies will be coded using the

WHO Drug Reference Listing (WHO DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (WHO ATC) classification system.

Any concomitant therapies starting prior to or after the start of study treatment will be listed.

The imputation of a concomitant medication start date will follow the same conventions as for an AE start date (see Section 2.8.1 Adverse events). No imputation will be performed for concomitant medication end dates.

2.5.3 Compliance

Compliance is presented as the percentage of patients who took a predefined percentage (RDI categories: <0.5, 0.5-<0.75, 0.75- <0.9, 0.9-<1.1, ≥1.1) of the number of prescribed doses of study treatment. Details are provided in Section 2.5.1.

2.6 Analysis of the primary variable(s)

2.6.1 Phase I part

The primary objective of the Phase I part is to to characterize the safety and tolerability and to estimate the MTD or RP2D of BLZ945 as a single agent and in combination with PDR001.

The primary variable is :

- ✓ Safety: Frequency and severity of AEs and SAEs, including changes in laboratory parameters, vital signs and ECGs
- ✓ Tolerability: dose interruptions, reductions and dose intensity.

See Section 2.8 for details of analysis for safety and tolerability.

- ✓ The DLT rate during the first cycle of treatment with single agent BLZ945 and with BLZ945 in combination with PDR001

DLTs will be listed and their incidence summarized by primary system organ class, worst grade based on the CTCAE version 4.03, type of adverse event, and by treatment. The dose determining set will be used for these summaries. DLTs will also be summarized for Japan vs non-Japan subgroup.

Estimation of the MTD(s)/RP2D(s) will be based upon the estimation by the BLRM of the probability of a DLT in the first cycle of treatment for patients in the DDS.
An adaptive BLRM guided by the escalation with overdose control (EWOC) principle will be used to make dose recommendations and estimate the MTD(s) for each regimen considered. The use of Bayesian response adaptive designs for Phase I studies has been advocated by the EMEA guideline on small populations (2006) and by Rogatko (2007), and and endorsed by numerous publications (Neuenschwander et al 2008, Neuenschwander et al 2010), and its development and appropriate use is one aspect of the FDA's Critical Path Initiative.
The BLRM will be fitted on the dose-limiting toxicity data (i.e. absence or presence of DLT) during the DLT window accumulated throughout the dose escalation to model the dose-toxicity relationship.

In the single-agent BLZ945 dose escalation part, the dose-toxicity (DLT) relationship is modeled by a 2-parameter BLRM.

In the dose escalation for the combinations, the dose-toxicity (DLT) relationship is modeled by a 5-parameter BLRM.

The Bayesian approach requires the specification of prior distributions for the model parameters. For BLZ945 component a weakly informative prior will be derived based on vague knowledge from pre-clinical studies. Available PDR001 single agent data will be used to derive Meta-Analytic-Predictive (MAP) priors for PDR001 component of the model based on available clinical data from [CPDR001X2101], the FIH PDR001 oncology study. At the time of each BLZ945 in combination with PDR001 dose escalation analysis, DLT data up to, and including, the last completed cohort from the single agent dose escalation will be included in the BLZ945 in combination with PDR001 BLRM. Single agent BLZ945 data will be incorporated directly into the BLRM since this data comes from the same study. For further details on the BLRM models including the prior specification for the model parameters, and examples of hypothetical decisions that may be followed during the dose escalation, refer to Appendix 5 in the protocol.

2.6.2 Phase II part

The primary analysis will be based on the estimation of the progression free survival rate at 6 months (PFS6).

The efficacy will be concluded if both of the following criteria are met for that specific group:

1. The posterior mean of PFS6 $\geq$ 40%
2. The posterior probability that PFS6 is $\geq$ 20% is at least 90%.

A Bayesian design will be used to estimate and provide inferential summaries of the PFS rate at 6 months. The PFS will be modeled using a Weibull distribution. A weakly informative prior distribution for the PFS at 6 months will be assumed. For further details, refer to Appendix 5 in the protocol. At the time of the primary analysis, the model will be updated with all available data of patients in the FAS for the relevant disease group, and the posterior distribution for the PFS at 6 months will be estimated. Inferential summaries based on the posterior distribution and posterior probabilities for activity interval below will be presented.

Categories for anti-tumor activity

The following classification of clinical relevance of the antitumor activity based on PFS rate at 6 months will be applied for all disease groups:

- [0, 20%) unacceptable anti-tumor activity
- [20%, 30%) limited anti-tumor activity
- [30%, 40%) moderate anti-tumor activity
- [40%, 100%] strong anti-tumor activity

If the estimated posterior mean of PFS rate at 6 months is at least 40% and the posterior risk of being in the unacceptable anti-tumor activity interval is less than 10%, then preliminary antitumor activity of the combination can be declared.

2.6.3 Handling of missing values/censoring/discontinuations

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

In the Phase II part, patients who discontinue the study and are lost to follow-up without a known date of progression or death due to any cause on or before the data cut-off date or when he/she receives any further anti-cancer therapy will be censored for PFS at the date of their last available tumor evaluation before the cut-off date or the anti-cancer therapy start date.

2.6.4 Supportive analyses

For the Phase II part, the proportion of patients with PFS rate at 6 months will be estimated using the Kaplan-Meier method along with the two-sided 90% confidence interval, using the FAS.

2.7 Analysis of the secondary efficacy variable(s)

Evaluation of anti-tumor activity will be based on investigator assessment according to RECIST v1.1 (solid tumor), irRC (solid tumor), RANO (glioblustoma), iRANO (glioblustoma) and guidelines for efficacy evaluation in lymphoma studies as appropriate. The variables used to evaluate anti-tumor activity are BOR, ORR, DOR, PFS and OS using the FAS (iBOR, iORR, iDOR in case of irRC). Unless otherwise specified, all the efficacy analyses will be performed by treatment group for both the Phase I part and Phase II part.

2.7.1 Best overall response (BOR)

The best overall response (BOR) is the best response recorded from the start of the treatment until disease progression/recurrence. However, any assessments taken more than 30 days after the last dose of study therapy will not be included in the best overall response derivation. Moreover, if any alternative cancer therapy is taken while on study, any subsequent assessments will be excluded from the best overall response determination.

As per RANO criteria, clear clinical deterioration not attributable to other causes apart from tumor also qualifies for the progressive disease (PD). Such PDs may be considered from disposition page. The best response for “PD from tumor assessment” and “PD as per clinical assessment” will be provided in table of best overall response. “PD from tumor assessment” will not form a part of “PD as per clinical assessment”.

2.7.2 Overall response rate (ORR), Disease control rate (DCR) and duration of response (DOR)

Overall response rate (ORR) is the proportion of patients with a best overall response of complete response (CR) or partial response (PR). CR and PRs must be confirmed by repeat assessments that should be performed not less than 4 weeks after the criteria for response are first met. Additionally, for iRano and irRC, progressive disease should be confirmed.

ORR and corresponding 90% confidence intervals (CIs) based on the exact binomial distribution will be presented.

Disease control rate (DCR) is the proportion of patients with a best overall response of CR or PR or SD. CR and PRs must be confirmed by repeat assessments that should be performed not less than 4 weeks after the criteria for response are first met. DCR and corresponding 90% confidence intervals (CIs) based on the exact binomial distribution will be presented.

DOR for patients who experience a CR or PR at any time on study will be listed by patient.

Details of responses par RECIST v1.1, irRC, RANO, iRANO and guidelines for efficacy evaluation in lymphoma studies can be found in the appendix 14.1, 14.2, 14.3, 14.4 and 14.10 respectively of study protocol.

For iRANO, the key difference from RANO in the assessment of progressive disease (PD) is the recommendation that progressive disease occurring within the first 24 weeks after the start of immunotherapy be confirmed by follow-up imaging 12 weeks after initial progression. When a such progressive disease is confirmed by a subsequent assessment, the date of the first of these assessments is then the date of progression. If initial PD is not confirmed by follow-up imaging post 12 weeks, then the initial PD will no longer be a PD as per iRANO and the previous best response will be considered to find the BOR, if available. In the absence of a response prior to initial PD, the BOR will be unknown in such cases. Few case are given below for better explanation:

- If there is only one assessment with overall response as PD then the the overall response will be unknown as per iRANO.
- If there are only two assessments with PD at both the assessments and that both the assessment are not 12 weeks apart then the overall response will be unknown as per iRANO.
- If there are only two assessments with SD at first assessment and PD at second assement. Then the overall response as per iRANO will be SD and SD respectively.
- Similarly, if there are only two assessments with PR at first assessment and PD at second assement. Then the overall response as per iRANO will be PR and PR respectively.

2.7.3 Progression free survival (PFS)

A Kaplan-Meier plot for PFS will be presented. Median PFS (in months) with corresponding 95% CI, 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997) and Kaplan-Meier estimated probabilities (PFS rate) with corresponding 95% CIs (Greenwood's formula, Kalbfleisch and Prentice 1980) at several time points (3, 6, 9 and 12 months) will be presented. The number (%) of progressions, deaths and patients censored will also be summarized.

PFS will be presented graphically using Kaplan Meier plots including all patients in Phase II by treatment group.

2.7.4 Overall survival (OS)

Overall survival (OS) is defined as the time from 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. OS will only be summarized by treatment groups for patients enrolled in phase II part. A

Kaplan-Meier plot for OS will be presented. Median OS (in months) with corresponding 95% CI, 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997) and Kaplan-Meier estimated probabilities (OS rate) with corresponding 95% CIs (Greenwood's formula, Kalbfleisch and Prentice 1980) at several time points (3, 6, 9 and 12 months) will be presented. The number (%) of deaths and patients censored will also be summarized.

Handling missign month/day in date of death

For rare cases when either day is missing or both month and day are missing for the date of death, the following imputation rule will be implemented:

- If only day is missing, then date of death is imputed as max[(1 mmm-yyyy), min(last contact date+1, cutoff date)].
- If both day and month are missing, then date of death is imputed as max[(1 Jan-yyyy), min(last contact date+1, cutoff date)].

2.8 Safety analysis

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

The Safety set will be used for summaries and listings of safety data with the exception of dose limiting toxicities (DLTs) for which the DDS will be used.

The safety summary tables will include on-treatment assessments collected no later than 30 days both BLZ945 as single agent and for the combination of BLZ945 in and PDR001after study treatment discontinuation.

2.8.1 Adverse events

AEs will be coded and graded using the latest version of MedDRA and CTCAE, respectively, available at the time of reporting. If CTCAE grading does not exist for an AE, grades 1, 2, 3, or 4 corresponding to the severity of mild, moderate, severe, and life-threatening, respectively, will be used. CTCAE grade 5 (death) will not be used in this study. Death information will be collected on the "End of Treatment" or "Survival Information" eCRF pages.

All AEs will be listed. All AE summaries will be summarized (frequency counts and percentages) by system organ class and/or preferred term, and maximum severity grades, unless noted otherwise.

The following AE summaries will be produced:

- AEs regardless of study drug relationship (including CTC grade 3/4)
- AEs suspected to be study drug related (including CTC grade 3/4)
- AEs regardless of study drug relationship leading to discontinuation of study drug
- AEs suspected to be study drug related leading to discontinuation of study drug
- AEs regardless of study drug relationship requiring dose adjustment or study drug interruption

- AEs which are not SAEs regardless of study drug relationship
- SAEs regardless of study drug relationship
- SAEs suspected to be study drug related
- On-treatment deaths with cause of death by preferred term
- All deaths with cause of death by primary system organ class and preferred term

The following AE summaries will be produced for Japan vs non-Japan subgroup:

- AEs regardless of study drug relationship (including CTC grade 3/4)
- AEs suspected to be study drug related (including CTC grade 3/4)
- AEs regardless of study drug relationship leading to discontinuation of study drug
- SAEs regardless of study drug relationship

A patient with multiple CTC grades for an AE will be summarized under the maximum CTC grade recorded for the event. A subject with multiple occurrences of an AE is counted only once in the AE category (e.g. system organ class, preferred term).

A missing AE start date will be imputed using the following logic matrix described in Table 2-2.

Table 2-2 Imputation rules for a partially missing AE start date

	AEM MISSING	**AEM < TRTM**	**AEM = TRTM**	**AEM > TRTM**
AEY MISSING	No imputation	No imputation	No imputation	No 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 2-3 is the legend to the logic matrix shown in Table 2-2 and details the relationship of AE start date to study treatment start date.

Table 2-3 Imputation legend and AE/treatment start date relationship

	AE start date relationship	**Imputation**
(A)	After treatment start or Uncertain	MAX(01MONYYYY, TRTSTD+1)
(B)	Uncertain	TRTSTD+1
(C)	Before treatment start	15MONYYYY
(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.

No imputation will be performed for AE end dates.

EudraCT and clinicaltrials.gov requirements for AEs and Deaths summaries

For the legal requirements of clinicaltrials.gov and EudraCT, two required tables on treatment-emergent adverse events which are not serious adverse events with an incidence greater than 5% and on treatment emergent SAEs and SAEs suspected to be related to study treatment will be provided by SOC and PT on the safety set population. These summaries will include any event starting or worsening in the on-treatment period. For combincation arm, the reporting period will be 150 days after last dose of study treatment.

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

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

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.8.2 Laboratory data

Laboratory data will be converted into SI units and classified (by Novartis statistical programming) into CTC grades according to CTCAE version 4.0.3. The calculation of laboratory CTC grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTC grades are given in Novartis internal criteria for CTC grading of laboratory parameters (Section 5.4).

For laboratory tests where grades are not defined by CTCAE version 4.0.3., 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 is not applicable. For laboratory tests that are graded for both low and high values, summaries will be done separately and labeled by direction.

The following summaries will be produced for hematology, biochemistry parameters and urinary laboratory tests:

- 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 listings will be produced:

- Listing of all CTC grade 3 or 4 laboratory toxicities

Table 2-4 and Table 2-5 list all laboratory parameters that will be summarized.

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

Hematology and coagulation		Biochemistry		Urinalysis	
White Blood Cells (WBC)	↑↓	Creatinine	↑	Protein	↓
Hemoglobin	↓	Sodium	↑↓		
Platelets counts	↓	Potassium	↑↓		
Absolute Neutrophils	↓	Calcium	↑↓		
Absolute Lymphocytes	↑↓	Magnesium	↑↓		
INR	↑	Albumin	↓		
		AST (SGOT)	↑		
		ALT (SGPT)	↑		
		Bicarbonate	↓		
		Total Bilirubin	↑		
		Glucose	↑↓		
		Amylase	↑		
		Lipase	↑		
		Alkaline Phosphatase	↑		
		Inorganic Phosphate	↓		
		Troponin	↑		

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

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

Hematology and coagulation	Biochemistry	Urinalysis
Prothrombin time (PT)	Blood urea nitrogen (BUN)	Specific gravity
Absolute Basophils	Urea	Glucose
Absolute Eosinophils	Direct bilirubin	Blood
Absolute Monocytes	Indirect bilirubin	pH
Hematocrit	Creatine phosphokinase	Protein
	TSH	Ketones
	Uric acid	WBC
	T4 Free	Bilirubin

Chloride

Liver function parameters

Liver function parameters of interest are total bilirubin (TBL), ALT and AST.

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

- 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 subjects 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 has to be conducted to assess potential confounding factor such as liver metastases, liver function at baseline, etc.

2.8.3 Vital signs, weight and physical examinations

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

Table 2-6 Criteria for notable vital sign values

Vital sign (unit)	Notable high value	Notable low value
Weight (kg)	increase >= 10% from baseline	decrease >= 10% from baseline
Systolic blood pressure (mmHg)	>=180 and increase from baseline of >=20	<=90 and decrease from baseline of >=20
Diastolic blood pressure (mmHg)	>=105 and increase from baseline of >=15	<=50 and decrease from baseline of >=15
Pulse rate (bpm)	>=100 and increase from baseline of >25%	<=50 and decrease from baseline of >25%
Body temperature (°C)	>= 39.1	--

Subjects with notable vital sign values (high/low) will be summarized and listed by treatment group.

2.8.4 Electrocardiograms

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

If a patient has more than one post-baseline measurement at a specific time point, the average of all available measurements associated with the nominal time point will be used for the analyses.

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

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

Table 2-7 Criteria for notable ECG values

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

A listing of notable ECG assessments will be produced by treatment group and notable values will be flagged. In the listing, the assessments collected during the post-treatment period will be flagged.

2.8.5 Doppler Echocardiography

For patients enrolled in the phase II part, Doppler echocardiography data will be reported. Any assessment conducted before or on the study day 1 will be considered as baseline.

The following summaries and listings will be provided:

- Parameters including left atrium volume, left atrium volume index, LV end-systolic dimension, LV end-diastolic dimension, posterior wall thickness and LVEF with the maximum change from baseline (both increase and/or decrease) will be summarized.
- Number (%) of patients having new apperance of abnormality by valve types and type of abnormality;
- The area of the valves with the maximum reduction due to stenosis will be summarized by valve types among patients who develop stenosis during the study;
- All Doppler Echocardiography assessments will be listed by treatment group

For patients enrolled in the phase I part, all Doppler Echocardiography assessments will be listed. Tolerability of study treatment will be assessed by summarizing the number of dose

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

2.9 Pharmacokinetic data

All PK analyses will be performed based on the PAS. Patient data may be removed on an individual basis.

Concentration values below the lower limit of quantitation (LLOQ) (<10 ng/mL for BLZ945 and <0.25 ug/mL for PDR001) will be displayed in listings as zero with a flag and handled as zero in the calculations for mean, CV for mean, standard deviation, minimum, median, maximum, but handled as missing for the calculation of the geometric means and their CV.

PK parameters will be calculated using non-compartmental methods and summarized as described in Table 2-8 by treatment group. All PK parameters will be listed.

Table 2-8 PK parameters – descriptive statistics

Parameters	Descriptive statistics
AUCinf, AUClast, Cmax, Tmax*, T1/2, RACC, AUC0-24hr/dose, Cmax/dose	Mean, standard deviation, CV% mean, geometric mean, CV% geometric mean, median, minimum and maximum
CV% = coefficient of variation (%) = sd/mean*100 CV% geometic mean = sqrt (exp (variance for log transformed data)-1)*100 * Only median and rangles will be presented for this parameter	

Anti-PDR001 antibody data will also be summarized. Descriptive graphical plots of mean concentration versus time profiles will be generated.

2.10 Immunogenicity

To assess the immunogenicity of PDR001, the incidence of Anti-Drug Antibodies (ADA) anti-PDR001 ADA will be summarized by treatment group.

2.10.1 Sample ADA status

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

Samples can test negative in either the screening or confirmatory assay but for statistical analysis purposes they are not differentiated. The following properties of each sample will be provided in the source data (i.e. the third party data output (e.g. WLIMS) processed by PreAdvance):

- 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 '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 the *Immunogenicity prevalence set*:

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

Listings will be provided of ADA sample status.

2.10.2 Subject ADA status

Subject ADA status is defined as follows:

- *Treatment-induced ADA-positive subject*: subject with ADA-negative sample at baseline and at least one treatment-induced ADA-positive sample
- *Treatment-boosted ADA-positive subject*: subject with ADA-positive sample at baseline and at least one treatment-boosted ADA-positive sample
- *Treatment-unaffected ADA-positive subject*: subject with ADA-positive sample at baseline, no treatment-boosted ADA-positive samples, and at least one treatment-unaffected ADA-positive sample

- *Treatment-reduced ADA-positive subject*: subject with ADA-positive sample at baseline and at least one non-missing post baseline sample, all of which are ADA-negative samples
- *ADA-negative subject*: subject with ADA-negative sample at baseline and at least one non-missing post baseline sample, all of which are ADA-negative samples
- *Inconclusive subject*: subject who does not qualify for any of the above definitions or a subject for which the baseline sample is missing

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

- Subjects with ADA-negative sample at baseline
- Subjects with ADA-positive sample at baseline
- ADA-negative subjects
- Treatment-induced ADA-positive subjects; for % the denominator is the number of subjects with ADA-negative sample at baseline.
- Treatment-boosted ADA-positive subjects; for % the denominator is the number of subjects with ADA-positive sample at baseline.
- ADA-positive subjects (i.e. ADA incidence): calculated as the number of treatment-boosted ADA-positive and treatment-induced ADA-positive subjects.

Listings of ADA subject status will be provided.

[redacted]

2.12 Interim analyses

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

Data from patients in the Phase II part will be reviewed on an ongoing basis to monitor the safety and tolerability of the RP2D in that part of the study. An interim analysis for futility will be conducted after 20 patients have been enrolled and completed the first post-treatment tumor assessment or have discontinued from the treatment as per protocol in each individual treatment arm. The interim analysis for futility will be based on DCR according to RANO criteria as determined by local assessment. The sample size of glioblastoma groups (both RP2D of BLZ945 as single agent and RP2D of BLZ945 in combination with PDR001) may be extended

to approximately 40 patients if the disease control rate is ≥ 60% (at least 60% of the first 20 patients have SD or better at their first tumor assessment). The Investigators and Novartis study personnel will make the decision based on a synthesis of all relevant data available including safety, PK and pharmacodynamics information.

3 Sample size calculation

Dose-escalation part

Cohorts of 3 to 6 evaluable patients will be enrolled in the dose-escalation part including at least six patients at the MTD/RP2D level, as described in Section 6.2.3 of the protocol. Multiple cohorts may be sequentially enrolled to the same dose level. At least 21 patients are expected to be treated in the in the single agent BLZ945 dose escalation part and at least 15 patients are required to be treated in each combo dose escalation, for the models to have reasonable operating characteristics relating to its MTD recommendation.

Phase II

Approximately 20 patients in GBM will be initially enrolled for each treatment group. . The sample size may be extended to approximately 40 patients per treatment group. In total, approximately 40-80 patients will be enrolled in the Phase II part. Based on the operating characteristics as described in Appendix 6 of the protocol, with a sample size of 40 patients when the true PFS6 is 60%, there is 97% chance to conclude clinically relevant efficacy, and when the true PFS6 is 20% there is less than 1% chance to wrongly conclude clinically relevant efficacy.

4 Change to protocol specified analyses

The analysis described in the supportive analysis section for phase I part will not be conducted.

5 Appendix

5.1 Baseline

Baseline is the last available and valid assessment performed or value measured within 28 days before the first administration of study treatment, unless otherwise stated under the related assessment section. Baseline can be the day before first treatment administration or the same day as first treatment administration if a pre-dose assessment/value is available (e.g., ECG, PK samples, samples for biomarkers).

If time is recorded for the first treatment dose and for a specific assessment performed the day of first dose, this assessment will be considered as baseline only if it is actually performed before the first dose, as checked using both times.

If time is not recorded, a specific assessment performed the day of first dose administration will be considered as baseline if, according to protocol, it should be performed before the first dose.

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

Computation of baseline for ECG, biomarker and other endpoints are described in each specific section.

5.2 Handling of missing and partial dates

For patients not known to have died prior to the cut-off date:

All events (e.g. AEs and concomitant medications) that started before or on the cut-off date, and with end date missing or after the cut-off date will be reported as continuing at the cut-off date. For these events, the end date will not be imputed.

For patients known to have died prior to or on the cut-off date:

All events (e.g. AEs and concomitant medications) that started before or on the cut-off date, and with end date missing or after the cut-off date will have the end date imputed to the date of death. For these events, the imputed end date will not appear in the listings.

If imputation of an end date is required for a specific analysis (e.g. a dose administration record with missing end date, or last date of study treatment is after the cut-off date), the end date will be imputed to the cut-off date in order to calculate e.g., the duration of exposure to study treatment. The imputed date will be displayed and flagged in the listings.

For rare cases, when either day is missing or both month and day are missing for the date of death, the following imputation rule will be implemented:

- If only day is missing, then date of death is imputed as max[(1 mmm-yyyy), min(last contact date+1, cutoff date)].
- If both day and month are missing, then date of death is imputed as max[(1 Jan-yyyy), min(last contact date+1, cutoff date)].

When either day is missing or both month and day are missing for the date of start of post antineoplastic therapy, the following imputation rule will be implemented:

- If day is missing, then impute to the max(reference start date, first date of the month)
- If day and month are missing then impute to the max(reference start date, Jan 1)
- Reference start date will be the last date of study treatment administration+1

End dates for post antineoplastic therapies will not be imputed.

In the listnigs of prior antineoplastic therapies, the partial dates will not be imputed.

5.3 Construction of waterfall graphs

Waterfall graphs will be used to depict anti-tumor activity. These plots will display the best percentage change from baseline in the sum of diameters of target lesions for each patient.

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

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

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

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

A special symbol (e.g. ∗) will be added below the bottom of respective bars for confirmed RECIST response (CR or PR), with corresponding specificatons in footnote. The total number of patients displayed in the graph (n) over the total number of patients in the FAS (N) will be shown. The best overall response (BOR) will be shown above each of the displayed bars in the graph. Symbols will be used to differentiate groups of interest, i.e. treatment group. A horizontal threshold line at -30% will be shown.

5.4 CTC grades for laboratory values in Novartis Oncology (based on CTCAE v4.03 – June 2010)

					CTC Grades[1]			
Lab test (toxicity)	**SI unit**	**Lab test (NCDS)**	**Normal ranges (Merck manual, July 2015) and *conversion factors***	**0**	**1**	**2**	**3**	**4**
Hematology								
WBC ↓	10^9/L	WBC	**3.9 – 10.7 x 10^9/L**	LLN	< LLN - 3.0 x 10^9 /L	< 3.0 – 2.0 x 10^9 /L	< 2.0 – 1.0 x 10^9 /L	< 1.0 x 10^9 /L
WBC (2) (Leukocytosis)	10^9/L	WBC			-	-	> 100 x 10^9 /L	-
Hemoglobin [2] (Anemia)	g/L	HGB	**120 - 160 g/L** or 7.4 - 9.9 mmol/L (F) **140 - 170 g/L** or 8.7 – 10.6 mmol/L (M)	LLN	< LLN - 100 g/L < LLN - 6.2 mmol/L	< 100 - 80 g/L < 6.2 - 4.9 mmol/L	< 80 g/L < 4.9 mmol/L	-
Hemoglobin ↑	g/L	HGB	*(16.113 x mmol/L = g/L)*		Increase >0-20 g/L above ULN	Increase >20-40 g/L above ULN	Increase >40 g/L above ULN	-
Platelets ↓	10^9/L	PLAT	**150 - 350 x 10^9/L**	LLN	< LLN - 75.0 x 10^9/L	< 75.0 - 50.0 x 10^9 L	< 50.0 - 25.0 x 10^9/L	< 25.0 x 10^9 /L
Neutrophils [3]↓	10^9/L	NEUT		2x1 0^9 /L	< 2.0 - 1.5 x 10^9 /L	< 1.5 - 1.0 x 10^9 /L	< 1.0 - 0.5 x 10^9 /L	< 0.5 x 10^9 /L
Lymphocytes [3]↓	10^9/L	LYM		1.5x 10^9 /L	< 1.5 - 0.8 x 10^9 /L	< 0.8 - 0.5 x 10^9 /L	< 0.5 - 0.2 x 10^9 /L	< 0.2 x 10^9 /L
Lymphocytes ↑	10^9/L	LYM			-	> 4 - 20 x 10^9 /L	> 20 x 10^9 /L	-
Biochemistry								
AST ↑	U/L	AST	**0 - 35 U/L** or 0 – 0.58 ukat/L *(60 x ukat/L = U/L)*	ULN	> ULN – 3.0 x ULN	> 3.0 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
ALT ↑	U/L	ALT	**0 - 35 U/L** or 0 – 0.58 ukat/L *(60 x ukat/L = U/L)*	ULN	> ULN – 3.0 x ULN	> 3.0 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN

Total bilirubin ↑	umol/L	BILI	**5.1 – 20.5 umol/L** or 0.3 – 1.2 mg/dL *(17.1 x mg/dL = umol/L)*	ULN	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 10.0 x ULN	> 10.0 x ULN
Alk. Phosphatase ↑	U/L	ALP	**36 - 92 U/L** or 0.5 - 1.5 ukat/L *(60 x ukat/L = U/L)*	ULN	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Creatinine [4]↑	umol/L	CREAT	**61.9 - 115 umol/L** or 0.7 – 1.3 mg/dL *(88.4 x mg/dL = umol/L)*	ULN	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 6.0 x ULN	> 6.0 x ULN
Creatinine kinase [4]↑	U/L	CK	**30 - 170 U/L** or 0.5 – 2.83 ukat/L *(60 x ukat/L = U/L)*	ULN	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 10.0 x ULN	> 10.0 x ULN
Albumin [2] (Hypoalbuminemia)	g/L	ALB	**35 - 55 g/L** or 3.5 to 5.5 g/dL	LLN	< LLN - 30 g/L	< 30 - 20 g/L	< 20 g/L	-
Total Cholesterol ↑	mmol/L	CHOL	**3.88 – 5.15 mmol**/L or 150 - 199 mg/dL *(38.67 x mg/dL = mmol/L)*	ULN	> ULN - 7.75 mmol/L > ULN - 300 mg/dL	> 7.75 -10.34 mmol/L > 300 – 400 mg/dL	>10.34-12.92 mmol/L > 400 – 500 mg/dL	>12.92 mmol/L > 500 mg/dL
Lipase ↑	U/L	LIPASE	**<95 U/L** or <1.58 ukat/L *(60 x ukat/L = U/L)*	ULN	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Amylase ↑	U/L	AMYLASE	**0 - 130 U/L** or 0 – 2.17 ukat/L *(60 x ukat/L = U/L)*	ULN	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Uric acid [2] (Hyperuricemia)	umol/L	URATE	**150 - 470 umol/L** or 2.5 – 8 mg/dL *(59.48 x mg/dL = umol/L)*	ULN	> ULN – 10 mg/dL > ULN – 595 umol/L	-	-	> 10 mg/dL > 595 umol/L
Phosphorus[2] (Hypophosphatemia)	mmol/L	PHOS	**0.97 – 1.45 mmol/L** or 3.0 - 4.5 mg/dL *(0.32 x mg/dL = mmol/L)*	LLN	< LLN - 2.5 mg/dL < LLN - 0.8 mmol/L	< 2.5 - 2.0 mg/dL < 0.8 - 0.6 mmol/L	< 2.0 - 1.0 mg/dL < 0.6 - 0.3 mmol/L	< 1.0 mg/dL < 0.3 mmol/L
Calcium (corrected) [2] (Hypercalcemia)	mmol/L	CACALC	**2.2 - 2.6 mmol/L** or 9 - 10.5 mg/dL *(0.2495 x mg/dL = mmol/L)*	ULN	> ULN - 11.5 mg/dL > ULN - 2.9 mmol/L	> 11.5 - 12.5 mg/dL > 2.9 - 3.1 mmol/L	> 12.5 - 13.5 mg/dL > 3.1 - 3.4 mmol/L	> 13.5 mg/dL > 3.4 mmol/L
Calcium (corrected) [2] (Hypocalcemia)	mmol/L	CACALC		LLN	< LLN - 8.0 mg/dL < LLN - 2.0 mmol/L	< 8.0 - 7.0 mg/dL < 2.0 - 1.75 mmol/L	< 7.0 - 6.0 mg/dL < 1.75 - 1.5 mmol/L	< 6.0 mg/dL < 1.5 mmol/L
Magnesium [2] (Hypermagnesemia)	mmol/L	MG	**0.62 – 0.99 mmol/L** or 1.5 – 2.4 mg/dL *(0.4114 x mg/dL = mmol/L)*	ULN	> ULN - 3.0 mg/dL > ULN - 1.23 mmol/L	-	> 3.0 – 8.0 mg/dL > 1.23 – 3.3 mmol/L	> 8.0 mg/dL > 3.3 mmol/L
Magnesium [2]	mmol/L	MG		LLN	< LLN - 1.2 mg/dL	< 1.2 - 0.9 mg/dL < 0.5 - 0.4 mmol/L	< 0.9 - 0.7 mg/dL	< 0.7 mg/dL

(Hypomagnesemia)					< LLN - 0.5 mmol/L		< 0.4 - 0.3 mmol/L	< 0.3 mmol/L
Glucose (non-fasting) (2) (Hyperglycemia)	mmol/L	GLUCSN	**<7.8 mmol/L** or <140 mg/dL *(0.05551 x mg/dL = mmol/L)*	ULN	-	> ULN - 250 mg/dL > ULN - 13.9 mmol/L	> 250 - 500 mg/dL > 13.9 - 27.8 mmol/L	> 500 mg/dL > 27.8 mmol/L
Glucose (fasting) (2) (Hyperglycemia)	mmol/L	GLUCSF	**3.9 – 5.8 mmol/L** or 70 - 105 mg/dL *(0.05551 x mg/dL = mmol/L)*	ULN	> ULN - 160 mg/dL > ULN - 8.9 mmol/L	> 160 - 250 mg/dL > 8.9 - 13.9 mmol/L	> 250 - 500 mg/dL > 13.9 - 27.8 mmol/L	> 500 mg/dL > 27.8 mmol/L
Glucose (2) (Hypoglycemia)	mmol/L	GLUCSN/ GLUCSF		LLN	< LLN - 55 mg/dL < LLN - 3.0 mmol/L	< 55 - 40 mg/dL < 3.0 - 2.2 mmol/L	< 40 - 30 mg/dL < 2.2 - 1.7 mmol/L	< 30 mg/dL < 1.7 mmol/L
Potassium (2) (Hyperkalemia)	mmol/L	K	**3.5 - 5.0 mmol/L** *(0.2558 x mg/dL = mEq/L = mmol/L)*	ULN	> ULN - 5.5 mmol/L	> 5.5 - 6.0 mmol/L	> 6.0 - 7.0 mmol/L	> 7.0 mmol/L
Potassium (2) (Hypokalemia)	mmol/L	K		LLN	< LLN - 3.0 mmol/L	-	< 3.0 - 2.5 mmol/L	< 2.5 mmol/L
Sodium (2) (Hypernatremia)	mmol/L	SODIUM	**136 - 145 mmol/L** *(0.435 x mg/dL = mEq/L = mmol/L)*	ULN	> ULN - 150 mmol/L	> 150 - 155 mmol/L	> 155 - 160 mmol/L	> 160 mmol/L
Sodium (2) (Hyponatremia)	mmol/L	SODIUM		LLN	< LLN - 130 mmol/L	-	< 130 - 120 mmol/L	< 120 mmol/L
Triglyceride (2) ↑	mmol/L	TRIG	**< 2.82 mmol/L** or < 250 mg/dL *(0.01129 x mg/dL = umol/L)*	< 150 < 1.71	150 - 300 mg/dL 1.71 – 3.42 mmol/L	> 300 - 500 mg/dL > 3.42 – 5.7 mmol/L	> 500 - 1000 mg/dL > 5.7 – 11.4 mmol/L	> 1000 mg/dL > 11.4 mmol/L
Coagulation								
INR (2)↑	1	INR	**0.8 – 1.2**	ULN	> ULN - 1.5 x ULN	> 1.5 - 2.5 x ULN	> 2.5 x ULN	-
Activated partial thromboplastin time(2)↑	sec	APTT	**25 - 35 sec**	ULN	> ULN - 1.5 x ULN	> 1.5 - 2.5 x ULN	> 2.5 x ULN	-
Fibrinogen (4)↓	g/L	FIBRINO	**1.5 – 3.5 g/L** or 150 – 350 mg/dL *(0.01 x mg/dL = g/L)*	LLN	< LLN - 0.75 x LLN	< 0.75 - 0.5 x LLN	< 0.5 - 0.25 x LLN	< 0.25 x LLN

ULN = Upper Limit of Normal range; LLN = Lower Limit of Normal range

(1) = **LAB CTC grades 1, 2, 3, 4 overrule the study specific (central or local) normal range criteria**, e.g. if ULN of Sodium is 151 mmol/L and the value is 151 mmol/L, CTC grade 2 is assigned although the value is ULN.

(2) = **Life-threatening consequences and/or hospitalization are <u>not</u> considered** for determination of LAB CTC grades 3 and 4. Concomitant usage of anticoagulation therapy (for INR and Fibrinogen) is not considered either.

(3) = Values and LNRs for blood differentials can be given as %, absolute values should then be calculated using WBC. Generally, **1.5 x 10^9 /L (lymphocytes) and 2 x 10^9 /L (neutrophils) are considered as LAB CTC grade 0**

(4) = For Creatinine and Fibrinogen, the **comparison with baseline is <u>not</u> considered** for derivation of LAB CTC grades

6 References

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