NOVARTIS

Clinical Development

BLZ945, PDR001

Protocol 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 adults patients with advanced solid tumors

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List of abbreviations

Abs	Antibodies
ADA	Anti-Drug Antibody
AE	Adverse Event
ALT	Alanine aminotransferase
ANC	Absolute Neutrophil Count
APTT	Activated Partial Thromboplastin Time
AST	Aspartate aminotransferase
AUC	Area Under the Curve
BLRM	Bayesian Logistic Regression Model
BHLRM	Bayesian Hierarchical Logistic Regression Model
BOR	Best Overall Response
BVN	Bivariate normal
CCL2	Chemokine (C-C motif) ligand 2
CNS	Central Nervous System
CLp	Plasma Clearance
CMO&PS	Chief Medical Office and Patient Safety
CR	Complete Response
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRS	Cytokine Release Syndrome
CSF-1	Colony-Stimulating Factor 1
CSF-1R	Colony-Stimulating Factor 1 Receptor
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-Lymphocyte-Associated Protein 4
CYP	Cytochrome P450
DCs	Dendritic Cells
DDI	Drug-Drug Interaction
DCR	Disease Control Rate
DLT	Dose Limiting Toxicity
DOR	Duration Of Response
DFS	Disease Free Survival
ECs	Ethic Committees
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
ELISA	Enzyme-Linked Immunosorbent Assay
EoT	End of Treatment
EWOC	Escalation With Overdose Control
FIH	First In Human
GBM	Glioblastoma Multiforme
GI	Gastrointestinal
GLP	Good Laboratory Practice
GM-CSF	Granulocyte Macrophage Colony-Stimulating Factor
HBV	Hepatitis B Virus
hCG	Human Chorionic Gonadotropin

[redacted]

HCV	Hepatitis C Virus
hERG	Human Ether-à-go-go-Related Gene
HIV	Human Immunodeficiency Virus
HNSTD	Highest Non-Severely Toxic Dose
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
[redacted]	[redacted]
IL	Interleukin
INR	International Normalized Ratio
irAE	immune Related Adverse Event
iRANO	immune Response Assessment in Neuro-Oncology Criteria
IRB	Institutional Review Board
irCR	immune-related Complete Response
irPD	immune-related Progressive Disease
irPR	immune-related Partial Response
irRC	immune-related Response Criteria
irSD	immune-related Stable Disease
i.v.	Intravenous(ly)
K_D	Dissociation constant
LLOQ	Lower Limit Of Quantification
M-CSF	Macrophage Colony-Stimulating Factor
MDSCs	Myeloid-Derived Suppressor Cells
MGMT	Methylguanine-DNA MethylTransferase
MHC	Major Histocompatibility Complex
MOA	Mechanism Of Action
MTD	Maximum Tolerated Dose
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
[redacted]	[redacted]
PD-1	Programmed Death-1
PDAC	Pancreatic Ductal Adenocarcinoma
PD-L1	Programmed Death-Ligand 1
PD-L2	Programmed Death-Ligand 2
PFS	Progression Free Survival
PFS6	Progression free survival rate at 6 months
PPS	Per protocol set
PFSR	Progression-Free Survival Rate
PGx	Pharmacogenetics
PK	Pharmacokinetics
p.o.	*per os*/by mouth/orally
PR	Partial Response
Q1W	Once a Week
Q4W	Every 4 Weeks
r/r	relapsed or refractory
RANO	Response Assessment in Neuro-Oncology Criteria
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria In Solid Tumors

[redacted]

RF	Rheumatoid Factor
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SEB	Staphylococcal Enterotoxin B
STAT3	Signal Transducer and Activator of Transcription 3
$T_{1/2}$	Half-life
TAMs	Tumor Associated Macrophages
TIL	Tumor Infiltrating Lymphocytes
TNBC	Triple Negative Breast Cancer
Tregs	Regulatory T cells
ULN	Upper Limit of Normal
Vss	Volume of distribution

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or study patient
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: q28 days)
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Subject Number (Subject No.)	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Randomization number	A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason
Supportive treatment	Refers to any treatment required by the exposure to a study treatment, e.g. premedication of vitamin supplementation and corticosteroid for pemetrexed disodium.
Treatment group	A treatment group defines the dose and regimen or the combination, and may consist of 1 or more cohorts. Cohorts are not expanded, new cohorts are enrolled.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints
Withdrawal of study consent	Withdrawal of consent from the study occurs only when a patient does not want to participate in the study any longer, and does not allow any further collection of personal data

[redacted]

Protocol summary:

Title	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 adults patients with advanced solid tumors
Brief title	Phase I/II study of BLZ945 single agent or BLZ945 in combination with PDR001 in advanced solid tumors
Sponsor and Clinical Phase	Novartis Phase I/II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this first-in-human (FIH) study of BLZ945 given as a single agent or in combination with PDR001 is to characterize the safety, tolerability, pharmacokinetics (PK), , and anti-tumor activity of BLZ945, administered orally, as a single agent or in combination with PDR001, administered intravenously (i.v.) in adult patients with advanced solid tumors.
Primary Objective(s)	Phase I: To characterize the safety and tolerability of BLZ945 as a single agent (in non-Japanese and Japanese patients) and in combination with PDR001 and to identify the Maximum Tolerated Dose (MTD) / Recommended Phase 2 Dose (RP2D). Phase II: To assess the anti-tumor activity of BLZ945 in combination with PDR001 (and as single agent if appropriate) in patients with advanced solid tumors.
Secondary Objectives	Phase I:. To characterize PK of BLZ945 as a single agent and in combination with PDR001. To assess the preliminary anti-tumor activity of BLZ945 as single agent and in combination with PDR001. Phase I and II: To assess emergence of anti-PDR001 antibodies when BLZ945 is administered in combination with PDR001.
Study design	This study is a FIH, open-label, multi-center, phase I/II, study which consists of a phase I dose escalation part of BLZ945 as single agent (including a separate Japanese BLZ945 single agent dose escalation arm) and in combination with PDR001. Alternative dosing regimens of BLZ945 may be evaluated. Once the MTD/RP2D for BLZ945 as a single agent is established, a phase II may commence, if signs of activity have been detected. Once the MTD/RP2D for BLZ945 in combination with PDR001 is established, a phase II part of the combination will commence. BLZ945 will be administered orally, and PDR001 will be administered i.v. every four weeks until patient experiences unacceptable toxicity, progressive disease and/or treatment is discontinued at the discretion of the Investigator or the patient.

[redacted]

Population	The phase I dose escalation of the study will be conducted in adult patients with advanced solid tumors. The phase II part of the study will be conducted in adult patients with glioblastoma.
Inclusion criteria **(Selected)**	Phase I: Patients with advanced/metastatic solid tumors (including lymphoma), with measurable or unmeasurable disease as determined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 or RANO (glioblastoma) who have progressed despite standard therapy or are intolerant of standard therapy, or for whom no standard therapy exists. Patients must have a site of disease amenable to biopsy, and be a candidate for tumor biopsy according to the treating institution's guidelines. Patient must be willing to undergo a new tumor biopsy at screening, and during treatment. Exceptions may be considered for glioblastoma patients after documented discussion with Novartis. Phase II: Patients with recurrent isocitrate dehydrogenase (IDH) wild-type glioblastoma (GBM), with at least one measurable lesion as determined by Response Assessment in Neuro-Oncology Criteria (RANO) patients with O6-methylguanine-DNA methyltransferase (MGMT) methylated recurrent glioblastoma that failed to respond to or progressed on radiotherapy and temozolomide patients with MGMT unmethylated recurrent gliobastoma that failed to respond to or progressed on radiotherapy (with or without temozolomide) patients who received no prior treatment with a VEGFR targeting agent (e.g. Avastin®).
Exclusion criteria **(Selected)**	History of severe hypersensitivity reactions to monoclonal antibodies. Impaired cardiac function or clinically significant cardiac disease, including any of the following: Clinically significant and/or uncontrolled heart disease such as congestive heart failure requiring treatment (NYHA grade ≥ 2), uncontrolled hypertension or clinically significant arrhythmia QTcF >470 msec on screening electrocardiogram (ECG) or congenital long QT syndrome Acute myocardial infarction or unstable angina pectoris < 3 months prior to study entry Active autoimmune disease or a documented history of autoimmune disease, including ulcerative colitis and Crohn's disease or any condition that requires systemic steroids, except vitiligo or resolved asthma/atopy that is treated with broncho-dilators (e.g. albuterol). Patients previously exposed to anti-PD-1/PD-L1 treatment who are adequately treated for skin rash or with replacement therapy for endocrinopathies should not be excluded. Systemic steroid therapy or any immunosuppressive therapy (≥10mg/day prednisone or equivalent). Topical, inhaled, nasal and ophthalmic steroids are not prohibited. For glioblastoma patients only: patients must not be receiving more than 2 mg dexamethasone per day (or an equivalent amount of an alternative corticosteroid) providing the dose is stable for at least 2 weeks prior to the baseline tumor assessments.

[redacted]

	Use of any vaccines against infectious diseases (e.g. varicella, pneumococcus) within 4 weeks of initiation of study treatment. Patient who received the following therapies: 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. Prior antibodies or other immunotherapies require 4 weeks washout period Pre-treatment with anti-CTLA-4 antibodies in combination with any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathway. Patients pre-treated with anti-CTLA-4 as single agent must have minimum 8 weeks washout period between the last dose of anti-CTLA-4 and the first dose of PDR001. Participation in an interventional, investigational non-immunotherapy study within 2 weeks of the first dose of study treatment 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). Use of hematopoietic colony-stimulating growth factors (e.g. G-CSF, GM-CSF, M-CSF) and thrombopoietin mimetics ≤2 weeks prior to start of study drug. An erythroid stimulating agent is allowed as long as it was initiated at least 2 weeks prior to the first dose of study treatment and the patient is on a stable dose. 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. For GBM patients in phase II part: last dose of radiotherapy within 3 months of the tumor assessment at screening. Patient receiving treatment with medications that are either strong inducers or inhibitors of CYP2C8 or CYP3A4/5, or patients receiving proton pump inhibitors, that cannot be discontinued at least 1 week prior to start of treatment and for the duration of the study Known human immunodeficiency virus (HIV), active hepatitis B virus (HBV) or active hepatitis C virus (HCV) infection. Patients whose HBV or HCV infection is controlled by antiviral therapy should not be excluded.
Investigational and reference therapy	BLZ945, PDR001
Efficacy assessments	Tumor assessment per RECIST v1.1, irRC, RANO, iRANO, lymphoma response criteria
Safety assessments	Incidence and severity of Adverse Events (AEs) and Serious Adverse Events (SAEs), including changes in laboratory values, vital signs and Electrocardiograms (ECGs).
Other assessments	PK parameters, immunogenicity [redacted]

[redacted]

Data analysis	The study data will be analyzed and reported based on all patients' data of the dose escalation and Phase II parts up to the time when all patients from dose escalation part 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.
Key words	Phase I/II, BLZ945, PDR001, PD-1, CSF-1R

[redacted]

Amendment 7 (05-May-2022)

Amendment rationale

The purpose of this amendment is as follows:

- This protocol amendment revises the end of study definition to include the option for patients still on study treatment and who, in the opinion of the investigator, are still deriving clinical benefit at the time of end of study, to transfer to another study or to use an alternative way to provide study treatment to these patients.
- The biomarker analysis is considered as exploratory and hypothesis generating (Section 10.5.7), hence the analysis of pharmacodynamics effect of BLZ945 as single agent and in combination with PDR001 are exploratory objectives. Therefore, all pharmacodynamic endpoints will be combined under these exploratory objectives.

Study update

The CBLZ945X2101 study started enrollment on 21-Oct-2016. As of 10-March-2022, 85 patients have been treated in the BLZ945 single agent dose escalation part and 70 patients have been treated in the BLZ945 and PDR001 combination dose escalation part. Two patients are on study treatment, all others discontinued before.

The RP2D of BLZ945 single agent and BLZ945 in combination with PDR001 were declared at 1200 mg at a 4 days on/10 days off schedule and at 700 mg at a 4 days on/10 days off schedule with 400 mg PDR001 Q4W, respectively. Forty-three (43) patients were treated in the phase II part of the study started in June 2020. Following a planned interim analysis in April/May 2021, it was decided, as per protocol, to not recruit any additional patients in each treatment arm, as the disease control rate (DCR) of 60% per RANO futility criteria pre-defined in the study protocol were met.

Based on the interim analysis (Section 10.7 for details), Novartis informed the Investigators on 18-Jun-2021 to halt patient recruitment to the dose escalation cohort in Japan.

Changes to the protocol

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

- [redacted]
- Section 3: Remove immunohistochemistry assessments from the secondary objectives, and specify, that these assessments are included in the ones assessing the pharmacodynamics effect of BLZ945 as single agent and in combination with PDR001 summarized under the exploratory endpoint section.
- Section 4.1: Sentence added regarding the enrollment completion of Phase II and the enrollment halt of the Japanese cohort.

[redacted]

- Section 4.3: Addition of language to account for patients who would transfer into another study or an alternative way to provide study treatment
- Section 7.1.3 and 7.1.5: Addition of language to specify that patients who transfer to another study or an alternative way to provide study treatment will not proceed to safety, disease progression and survival follow up.
- Table 7-17: Removal of "(secondary endpoint)".
- Section 10.5.7: Addition of language that this section is no longer applicable, as biomarker assessments are considered as exploratory and hypotheses generating.
- Section 10.6.1: Addition of language to clarify, that immunohistochemistry assessments are included in the exploratory objectives.

IRBs/IECs

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

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

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

[redacted]

Amendment 6 (20-Feb-2020)

Amendment rationale

The purpose of this amendment is as follows:

1. Update the patient population in the phase II part

- The phase II part of study (both BLZ945 single agent and in combination with PDR001) will focus on glioblastoma due to the encouraging results observed in the phase I part of the study. The phase II part in advanced pancreatic cancer and triple negative breast cancer will be removed from the study protocol due to business considerations.
- Clarification was included to refine the eligibility criteria of glioblastoma population in the phase II part of the study regarding the prior anti-neoplastic therapies and dosage of concomitantly used dexamethasone.
- Based on the emerging data from phase I part of the study, the number of glioblastoma patients to be enrolled in BLZ945 single agent phase II part is increased to better characterize the anti-tumor activity of BLZ945 as single agent.

2. Modify the study assessments to further characterize biological effects of BLZ945

- Elevation of liver enzymes are observed under treatment with BLZ945 both pre-clinically and clinically. To further characterize the biological mechanism behind these findings, optional research samples will be collected to look for novel biomarkers that are not yet clinically validated, but have received letters of support from FDA and EMEA for evaluation in clinical trials.
- To enable comprehensive assessment of tumor tissue from patients with glioblastoma enrolled in either phase I or phase II parts of the study, an archival tumor sample is requested for exploratory assessments, such as: [redacted] evaluation of predictive markers.
- Collection of biological samples is simplified in the phase II part of the study. Only plasma samples will be collected for pharmacodynamic assessments. PK serum samples will be collected during and at the end of cycle 1 and EoT only.
- Based on the preliminary results from a 13-week Good Laboratory Practice (GLP) study in Wistar rats (report in preparation), which showed reversible thickening of the heart valves in rats dosed at ≥30 mg/kg/day, Doppler echocardiography is added to monitor for any potential cardiac risk at baseline and day 1 of every cycle.

Other clarifications (such as: safety objectives in the phase I and phase II parts, formal interim analysis in the phase II part) and editorial changes have been made to this protocol for consistency and/or clarity.

[redacted]

Study update

The CBLZ945X2101 study started enrollment on 21-Oct-2016. As of 14-Aug-2019, 77 patients have been enrolled in the BLZ945 single agent dose escalation part and 69 patients have been enrolled in the BLZ945 and PDR001 combination dose escalation part.

The RP2D of BLZ945 single agent and BLZ945 in combination with PDR001 were declared at 1200 mg at a 4 days on/10 days off schedule and at 700 mg at a 4 days on/10 days off schedule with 400 mg PDR001 Q4W, respectively. The phase II part of the study will start upon the approval of protocol amendment 6.

The BLZ945 single agent dose escalation is ongoing for Japan arm and the MTD and/or RP2D in Japanese patients are not declared yet.

Changes to the protocol

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

- Protocol summary: Updated the targeted patient population in phase II and the selected inclusion and exclusion criteria.
- Section 1.1: Updated the treatment landscape of glioblastoma.
- Section 1.2.1.1.2: Updated the new findings from the 13-week GLP toxicology study in Wistar rats.
- Section 1.2.1.2: Updated the clinical experiences of BLZ945 and the declared RP2Ds
- Section 2.1 and Section 2.2: Updated the rationale of phase II indications for both BLZ945 single agent and in combination with PDR001.
- Section 2.2, Section 4.2 and Section 10.7: Updated the timing and design of interim analysis in phase II part of study.
- Table 3-1: Updated the endpoints of primary and secondary objectives based on the updated phase II indications. Clarified the safety objectives in the phase II part.
- Section 4.1: Updated the study design by increasing the number of patients in BLZ945 single agent Phase II part. Updated the corresponding descriptions based on the modified indications in Phase II part of BLZ945 in combination with PDR001.
- Section 4.2: Updated the timing of interim analyses and design adaptation based on the modified indications in Phase II part.
- Section 5.1, Section 5.2 and Section 5.3: Updated patient population and some inclusion or exclusion criteria regarding to patients diagnosed with recurrent GBM.
- Section 6.3.1 and Table 6-7: Added the table of dose reduction steps for BLZ945 based on the declared RP2D and/or MTD and the tested dose regimens in the Phase I part of the study.
- Table 6-5 and Table 6-6: Incorporated formatting changes slightly.
- Section 6.4.2: Clarified the steroids used for the treatment of glioblastoma are not prohibited.
- Section 7.1, Table 7-3 and Table 7-4: Updated Table 7-3 to include Doppler echocardiography. Added the Table 7-4 to outline the visit evaluation schedule in Phase II

[redacted]

of study. [redacted] In addition, the PK sample collection time points were adjusted as outlined in Table7-4.

- Table 7-2, Table 7-3, Section 7.1.1 and Section 7.2.4: Updated the screening assessments for submission of available archival tumor sample.
- Section 7.2.1.2: Added language for collection, storage and review MRI or CT scans obtained prior to baseline assessment, if applicable.
- Section 7.2.2.6.2: Added the Doppler echocardiography.
- Section 7.2.3: Added the PK blood collection logs for Phase II.
- [redacted]
- Section 10: Updated the statistical methods, safety objectives, data analysis and sample size calculation based on the modified phase II indications.

IRBs/IECs

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

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

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

[redacted]

Amendment 5 (16-Nov-2018)

Amendment rationale

The purpose of this amendment is as follows:

1. To clarify that patients with relapsed or refractory (r/r) lymphoma are eligible to enroll in the study and to implement the methodology for efficacy assessments that will follow the appropriate guidelines for these patient populations. The guidelines are to be used for all patients with r/r lymphoma, either previously treated or to be enrolled moving forward, as indicated in Appendix 9.
2. The option of twice per day dosing has been introduced to enable the exploration of higher doses while reducing the total number of BLZ945 capsules to be taken at each administration. This will also decrease steady state Cmax, potentially improving tolerability of study treatment. The dosing regimens defined in Section 6.1.1 remain the same while the total daily dose may be split into two doses per day.
3. To align with the recently published ImmunoOncology toxicity management guidelines (Brahmer 2018, Haanen 2017). The dose modification section of the protocol and corresponding tables were updated. The Appendix 9 ‘Recommended management algorithms for suspected toxicities’ were removed for the same purpose.
4. Removal of the baseline and on treatment blood sample collections for the assessment of serum cytokines used for retrospective analysis of a cytokine release syndrome adverse event. Blood samples for serum cytokines were included due to the unknown risk of Cytokine Release Syndrome (CRS) with ImmunoOncology agents alone and in combination, and to allow an assessment of any association between cytokines and clinical events. These samples have been drawn at baseline and at the time of a potential CRS event, stored, and analyzed retrospectively. Due to this, results are not intended to be used to support clinical decision-making for patients with possible CRS. There were no unexpected clinically assessed events of CRS observed across 19 studies including more than 2200 patients. The risk of CRS in the current study is deemed to be low, thus supporting the removal of this blood sample collection.

Other changes to the protocol include:

The ‘prohibited’ and ‘to be used with caution’ medications requirements have been updated with recent clinical data on drug interaction information for potential co-medications.

The time points of collection of PBMC and plasma biomarker samples have been updated to correlate with drug exposure.

The withdrawal of consent language has been revised to differentiate sample use after a patient withdraws consent based on the different regulations/laws around the world.

Other clarifications and editorial changes have been made to this amendment for consistency and/or clarity.

[redacted]

Study update

The CBLZ945X2101 study started enrollment on 21-Oct-2016. As of 27-Aug-2018, 52 patients have been enrolled in the BLZ945 single agent dose escalation part and 30 patients have been enrolled in the BLZ945 and PDR001 combination dose escalation part.

Changes to the protocol

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

Glossary of terms: updated the definition of Personal Data and Withdrawal of study consent

Section 2.2 and 2.3: added clarifications to study design of regimen and introduced twice per day administration for those dosing schedules

Table 3-1 and Section 10.5.2: updated the secondary objective of phase I part to include tumor assessment for lymphoma patients

Section 5.2: added the clarification for inclusion criteria of relapsed or refractory (r/r) lymphoma patients in the study

Section 6.1.1, 6.2.1.1 and Table 6-1: introduced the twice per day dosing frequency and the corresponding dose administration requirements

Section 6.1.3, 7.1.2, 7.1.3, 7.1.5: updated the duration of treatment period and the requirements of follow up period for lymphoma patients

Section 6.2.3.2.2 and 10.1.4: updated the minimum dose exposure for dose escalation decisions for twice per day dosing

Table 6-4: updated the Grade 3 electrolyte abnormalities that resolve to ≤ Grade 1 within 7 days after starting supplementation is not considered as dose-limiting toxicities

Table 6-5 and 6-6: updated the dose modifications and interruptions for selected toxicities to align with the recently published ImmunoOncology toxicity management guidelines

Section 6.4.2 and Appendix 7 and 8: added clarifications to the co-administration of moderate CYP3A4/5 and CYP2C8 inhibitors/inducers

Table 7-1, 7-2 and 7-3: updated the reference of tumor evaluations and corrected typos of BLZ945 administration frequency

Table 7-1, 7-2, 7-3, 7-6 and Section 7.2.2.5.6: removed the collection of blood samples for safety cytokines

Section 7.1.4: updated withdrawal of consent language and the use of samples after consent is withdrawn

Section 7.2.1.3 and Table 7-4: added the efficacy assessment requirements for lymphoma patients

Table 7-8 to 7-13: updated the PK sampling time points for twice per day dosing

[redacted]

[redacted]

Section 8.1.1 and 8.2.1: updated the definition of safety reporting for lymphoma patients

Section 8.3: updated to change the follow-up of a newborn child from 3 to 12 months

Section 10.1.3: updated the details of Per-Protocol Set for lymphoma patients

Appendix 5: updated the statistical methods applied to the twice per day dose administration

Appendix 7 and 8: updated the list of prohibited and 'to be used with caution' medications as per guidelines

Appendix 9: removed to align with the recently published ImmunoOncology toxicity management guidelines

Newly added Appendix 9: added "Guidelines for efficacy evaluation in Hodgkin and non-Hodgkin lymphoma studies" to standardize the response evaluations for lymphoma patients

IRBs/IECs

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

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

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

[redacted]

Amendment 4 (31-Jul-2018)

Amendment rationale

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

After the occurrence of a case of Steven Johnson Syndrome in a study with PDR001 in combination with another investigational agent, the dose modification guidelines for protocols using PDR001 were updated to mandate permanent discontinuation of study treatment for patients who experience SJS or Lyell syndrome/TEN. This change has already been implemented as part of an urgent safety measure released on 15 June 2018. This protocol amendment is now finalizing these changes in the dose modification section and corresponding tables describing the criteria for dose modification and interruption for selected toxicities.

Study update

The CBLZ945X2101 study started enrollment on 21-Oct-2016. As of 24-Jul-2018, 45 patients have been enrolled in the ongoing BLZ945 single agent dose escalation part and 26 patients have been enrolled in the BLZ945 and PDR001 combination dose escalation part.

Changes to the protocol

Tables 6-5 and 6-6 (Criteria for dose modifications and interruption for BLZ945 and PDR001 as combination treatment) have been updated to include permanent discontinuation of study treatment for SJS or Lyell syndrome/TEN.

IRBs/IECs

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

This amendment is required for formalization of the changes already implemented by the USM issued on 15 June 2018.

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

[redacted]

Amendment 3 (05-Feb-2018)

Amendment rationale

Analysis of pharmacodynamic changes is critical for the selection of the best dose and schedule for further evaluation of BLZ945. Therefore the main purpose of this amendment is to adjust biomarker and biochemistry sample collection time points based on information obtained during the study so far.

- To ensure a comprehensive assessment of pharmacodynamic changes in tumor tissue the on-treatment biopsy will be obtained at an earlier timepoint (at the beginning of cycle 2) and all patients must now have a site of disease amenable to biopsy. As a biopsy is typically not feasible in glioblastoma patients, such patients may enroll in the study without biopsy following documented agreement between Investigator and Novartis.
- To optimize the analysis of systemic humoral and cellular immune-modulation, the collection of plasma and PBMC biomarker samples will also be obtained earlier during the study.
- Elevation of liver enzymes are proposed to be a pharmacodynamic effect of BLZ945 due to decreased clearance by liver macrophages and were found to have an early onset (typically in cycle 1) in this study. To capture these pharmacodynamic modulations and to correlate with exposure to BLZ945, PK and biochemistry samples will be collected more frequently in cycles 1 and 2.

Other minor clarifications and editorial changes have been made and are included in the list of changes below.

Study update

The CBLZ945X2101 study started enrollment on 21-Oct-2016. As of 29-Nov-2017, 28 patients have been enrolled in the ongoing BLZ945 single agent dose escalation part. In addition, 5 patients have been enrolled in the BLZ945 and PDR001 combination dose escalation part.

Changes to the protocol

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

Section 5.2: updated inclusion criteria #4 removing the limitation that only patients in Phase 1 part were to have tumor biopsies, hence all patients must now provide tumor samples. Inclusion criteria #3 was clarified where appropriate that the tumor assessment of glioblastoma patients will use the RANO criteria.

Table 7-1, 7-2 and 7-3: updated the biomarker sample collection plan.

Table 7-1, 7-2 and 7-3: updated the PK sample collection.

Table 7-3: A typographical error regarding the on-treatment timepoint for Chest X-ray was corrected

Table 7-2: updated the schedule of clinical chemistry assessments by adding Cycle 1 Day 2, 9 and Cycle 2 Day 2.

[redacted]

Table 7-3: updated the schedule of clinical chemistry assessments by adding Cycle 1 Day 2, 19 and Cycle 2 Day 2.

Table 7-1, 7-2 and 7-3 and section 7.1.5: clarified the requirement regarding to safety follow-up to only include 30-day, 90-day and 150-day follow-up for patients treated with BLZ945 in combination with PDR001.

Section 7.2.2.6: clarified the instructions for ECG assessment

Section 7.2.2.6.1: clarified the sequence of blood sample and ECG collections

Table 7-8, 7-9, 7-10, 7-11, 7-12 and 7-13: updated the PK sample collection time points and the corresponding analytes.

Table 7-11, 7-12 and 7-13: clarified the reference treatments of specified PK sample collection time points.

Table 7-13: updated analytes to include PDR001 on Cycle 1 Day 5.

Table 7-14: updated biomarker sample collection plan for on-treatment tumor and blood samples [redacted]

Section 8.2.2: clarified the SAE collection period.

Appendix 9: updated Management Algorithms to include the neurological AEs.

IRBs/IECs

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

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

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

[redacted]

Amendment 2 (24-Oct-2017)

Amendment rationale

The purpose of this amendment is to revise definitions for dose limiting toxicities (DLTs) regarding Grade 3 febrile neutropenia, and update the definition of Grade 3 febrile neutropenia in line with CTCAE version 4.03, following Health Authority feedback.

Study update

The CBLZ945X2101 study started enrollment on 21-Oct-2016. As of 05-Oct-2017, 22 patients with advanced solid tumors have been enrolled in the ongoing BLZ945 single agent dose escalation part. The BLZ945 and PDR001 combination part opened for enrollment on 6-Oct-2017.

Changes to the protocol

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

- Section 6.2.4, Table 6-4: The grade 3 febrile neutropenia should be defined as DLTs without exception related to the duration of fever ≥38 °C.
- Section 6.3.2, Table 6-5 and Table 6-6: The grade 3 febrile neutropenia quoted for dose modifications and interruption is updated to be consistent with CTCAE version 4.03.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol require IRB/IEC approval prior to implementation.

[redacted]

Amendment 1 (04-Aug-2017)

Amendment rationale

The purpose of this amendment is to address the inclusion of Japanese patients in the study in a separate dose escalation arm, to permit the exploration of alternative BLZ945 dosing schedules, and to clarify eligibility criteria.

The single agent dose escalation part of this study is ongoing globally with the exception of Japan. At the time of this amendment patients are being treated with BLZ945 single agent at a dose higher than the starting dose of 150 mg QD 7d on/7d off. In order to ensure that the safety and pharmacokinetic profiles of single agent BLZ945 are adequately characterized in Japanese patients, a specific dose escalation of single-agent BLZ945 in a minimum of 12 Japanese patients has been included in the protocol. The Japanese dose escalation will run separately from the ongoing dose escalation. PDR001 has been administered as a single agent to Japanese patients in a separate study and no differences have been observed in either the safety profile or PK of PDR001 between Japanese patients and patients in the rest of the world. Therefore, if the recommended dose determined in the global dose escalation part of the BLZ945 phase I single agent is found to be the same in Japanese patients, then Japanese patients may also enter the combination part of study at whichever dose is being tested at that time.

To further characterize the safety and efficacy of BLZ945 an additional dosing schedule has been added to the protocol. PK/PD (preclinical and preliminary clinical PK) modeling results have suggested that an alternative schedule (4 daily doses of BLZ945 followed by 10 days off) may permit recovery of observed ALT elevations. This regimen repeats every 14 days.

As preliminary PK data has become available for this first in human study, the observed elimination half-life of BLZ945 was longer than predicted (24 versus 10 hours) and has been included in section 2.3. As a consequence of this, the exclusion criteria 20 and 21 have been updated to amend the follow-up requirements of contraception after the last dose of single agent BLZ945.

Following the request of a regulatory authority inclusion criteria 5 is modified. Previously it was stated that pancreatic cancer patients are eligible if they failed to respond or progressed on or after treatment with gemcitabine. However, in some regions the standard of care for pancreatic cancer may not only be gemcitabine. Therefore, gemcitabine is no longer specified, and has been replaced by standard of care.

The study prohibits systemic steroid therapy, however glioblastoma patients may be receiving dexamethasone for symptom relief. In order not to exclude such patients who may otherwise be eligible for study entry, these patients may be considered if they are receiving dexamathasone <1 mg/day.

Asymptomatic serum enzyme elevation, including grade 2 and 3 AST and ALT elevations, have been observed and reported as suspected to be related to BLZ945 treatment. The events resolved without interruption of study treatment except for one patient with liver metastases who had grade 2 AST/grade 1 ALT elevation at baseline. In order to ensure patient safety, an eligibility criterion has been revised to exclude patients with either AST or ALT laboratory values greater than grade 1 at screening (it had previously be stated AST and ALT >grade 1). This criterion now applies to all patients irrespective of liver tumor involvement.

[redacted]

To add clarity, Table 6-5 (Criteria for dose modifications and interruption for BLZ945 and PDR001) has been separated into two tables, one table for single agent BLZ945 and one table for BLZ945 and PDR001 in combination.

To add clarity, Table 7-1 (Visit Evaluation Schedule) has been separated into three tables, one table for each dosing schedule.

Other minor changes/corrections were made for consistency and/or clarification.

Study status

The current study began recruitment on 21-Oct-2016. As of 27-Jun-2017, 13 patients with advanced solid tumors have been enrolled and treated at dose levels of BLZ945 150 mg QD 7 d on/7d off (Cohort 1), BLZ945 300 mg QD 7d on/7d off (Cohort 2) or BLZ945 300 mg QD 7d on/7d off (Cohort 3).

Changes to the protocol

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

Section 1.2.1.2: updated BLZ945 clinical experience.

Section 2.2: updated rationale for the study design to include the Japanese dose escalation part and to allow exploration of an alternative BLZ945 dosing regimen.

Section 2.3: updated rationale for dose and regimen selection to include new BLZ945 regimen and clarify the RP2D/MTD in phase II. Updated median elimination half-life based on preliminary PK data.

Section 3, table 3-1: included the objective for the dose escalation in Japanese patients.

Section 4.1: updated study design to include the dose escalation in Japanese patients and the new BLZ945 regimen.

Section 5.2: updated inclusion criteria for **Japanese only**: written consent is necessary both from the patient and his/her legal representative if he/she is under the age of 20 years. Inclusion criteria 5 modified to clarify that patients with advanced pancreatic cancer who failed to respond or progressed on or after treatment with standard of care are eligible.

Section 5.3: updated criteria 3 to exclude patient with ALT or AST > 3 x ULN at screening. Clarified criteria 7 to exclude patients with ongoing symptomatic interstitial lung disease. Clarified criteria 9 to exclude GBM patients receiving greater than 1 mg dexamethasone per day (or an equivalent amount of an alternative corticosteroid). Clarified criteria 11 to include the washout period for prior immunotherapies. Updated criteria 20 and 21 to change the contraception follow-up from 3 to 14 days after last dose.

Section 6.1: updated dosing regimen instruction for the new BLZ945 regimen.

Section 6.2: updated starting dose rationale with the new BLZ945 regimen as a single agent and in combination with PDR001, and the dose rationale for the dose escalation in Japanese patients.

Section 6.3: clarified dose modifications to indicate in which circumstances immune-related etiology (irAE) AEs must lead to discontinuation of PDR001.

[redacted]

Section 6.3.2: Table 6-5 has been clarified by splitting it into two separate tables, one for single agent BLZ945 and one for the BLZ945 and PDR001 combination.

Section 6.4: clarified that not all concomitant medications which are known to increase the pH are prohibited.

Section 6.6.1: Clarified the formulation of PDR001

Section 7, table 7-1: updated section and table to include new assessments specific to Japanese patients, and table 7-1 split into three separate tables for each dosing schedule

Section 7.1.5: Clarified some follow up period procedures.

Section 8.1 and 8.2: clarified the AE/SAE reporting rule after initiation of new post-treatment antineoplastic therapy.

Section 10: Updated as per the new requirements for the Japanese dose escalation and the new dosing schedule.

Section 11.3: updated informed consent procedures for Japanese patients only: written consent is necessary both from the patient and his/her legal representative if he/she is under the age of 20 years.

Section 11.5: Novartis publication policy has been updated

Section 14.7: added statistical details of Phase I Bayesian logistic regression model in Japanese patients treated with BLZ945 single agent.

IRB/IEC/REB Approval

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, the changes herein affect the Informed Consent and sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

1 Background

One major challenge preventing successful tumor immunotherapy is the need to break immune tolerance and overcome local immunosuppression. In many cases, the tumor microenvironment is skewed toward an anti-inflammatory state, favoring immune-suppressive regulators, rather than immune effector cells (Mantovani et al 2008). Tumor cell-intrinsic mechanisms of immune evasion are reduced expression of major histocompatibility complex (MHC) molecules, increased expression of immunosuppressive molecules such as programmed death-ligand 1 (PD-L1) and cytokines such as interleukin (IL)-10 and TGF-β (Gajewski et al 2013).

Tumor-associated macrophages (TAMs), regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) greatly contribute to cancer-induced immune suppression (Bayne et al 2012). In contrast to anti-tumorigenic M1 subtype macrophages, M2 subtype macrophages have been shown to exert pro-tumorigenic functions (Mantovani et al 2002). These TAMs secrete proangiogenic and growth factors, as well as potently suppress T cell effector function by releasing immunosuppressive cytokines (Wynn et al 2013, Biswas and Mantovani 2010, Gordon and Martinez 2010). This will result in enhanced survival, proliferation, invasion and metastasis of tumor cells and also a supportive stroma by promoting tumor vascularization and suppression of the antitumor immunity (Qian and Pollard 2010). Additionally, increased macrophage infiltration has been identified as an independent poor prognostic factor in several cancer types, including breast, glioblastoma and pancreatic cancer, with infiltrating CD68+ or CD163+ TAMs shown to correlate with poor outcome (DeNardo et al 2011, Kurahara et al 2011, Shabo et al 2008).

Not surprisingly, a tumor microenvironment rich with TAMs can impede immunotherapy, and approaches to specifically reduce immune suppression within the tumor microenvironment are gaining momentum as a companion immune-base treatment. The major survival factor for these macrophages is macrophage colony-stimulating factor 1 (CSF-1). CSF-1 and its colony-stimulating factor 1 receptor (CSF-1R) regulate the migration, differentiation, and survival of tumor-associated macrophages and their precursors (Hume and MacDonald 2012, Chitu and Stanley 2006).

CSF-1R inhibition has been shown to deplete macrophages and reduces tumor volume in several xenograft models (Manthey et al 2009, Patel and Player 2009). BLZ945, a high affinity CSF-1R inhibitor, has been shown to significantly decrease TAMs survival *in vivo*, alter their accumulation and block tumor progression in a genetic mouse model of glioblastoma multiforme (GBM) (Pyonteck et al 2013). Further experiments combining BLZ945 with checkpoint inhibitors such as anti-programmed death-1 (PD-1) and PD-L1 have shown considerable additive or synergistic effects and may provide more efficient therapeutic options for patients with solid tumors.

[redacted]

1.1 Overview of disease pathogenesis, epidemiology and current treatment

TAMs and MDSCs are associated with high tumor grade and poor prognosis in many cancers, including gliomas, pancreatic cancer and triple negative breast cancer (Bingle et al 2002, Komohara et al 2008, Yuan et al 2014). A paracrine CSF-1/epidermal growth factor signaling loop has also been implicated in metastatic invasion (Coniglio 2012, Ruffell 2012).

Glioblastoma multiforme (GBM) is the most common and aggressive glioma, accounting for approximately 15% of all primary brain tumors in adults. There are numerous lines of evidence highlighting the importance of host immunity in GBM biology. GBM patients with effector T cell tumor infiltration on histopathology have improved prognosis (Lohr et al 2011). High expression levels of PD-L1 are associated with worse prognosis in patients with GBM. Of interest, high PD-L1 expression in the neurons adjacent to tumor cells is correlated with low PD-L1 expression in tumor cells and associated with improved survival (Liu et al 2013). TAMs in particular are associated with high tumor grade and poor prognosis including gliomas (Bingle et al 2002, Hussain et al 2006, Komohara et al 2008). TAMs are the predominant infiltrating immune cell in GBM and can account for up to 40% of the tumor cell mass (Kostianovsky et al 2008, Kennedy et al 2013) and have been shown to play a major role in the creation of a tumor microenvironment that promotes tumor progression. Shortcomings of attempts at anti-glioma immunotherapy may result from a failure to adequately address these effects. For patients with tumor progression after first-line treatment, management options include repeat surgical resection, stereotactic radiotherapy and systemic therapies such as bevacizumab, metronomic temozolomide, carmustine and lomustine (Weller et al 2013). However, these approaches lack significant efficacy and median overall survival (OS) is generally less than 1 year and a 5-year survival rate is only 3.3% (Weller et al 2013). Therefore, novel therapeutic strategies are clearly needed.

Recently, a Phase 3 trial evaluating the addition of nivolumab to the current standard of care (temozolomide and radiation therapy) versus the standard of care alone (CheckMate-548) did not meet the primary endpoint of progression-free survival (PFS), in patients with newly diagnosed glioblastoma multiforme (GBM) that is O6-methylguanine-DNA methyltransferase promoter (MGMT)-methylated (Bristol-Myers Squibb Company, press release, [https://bit.ly/2ktBxYb]). Nivolumab also failed to meet the primary endpoint of overall survival in combination with radiation therapy compared with temozolomide and radiation in the phase III CheckMate-498 trial, which looked at patients with newly diagnosed MGMT-unmethylated GBM (Bristol-Myers Squibb Company, press release, [https://bit.ly/2V9ceag]). A recent analysis from the Checkmate-143 study indicated that there are subgroups of patients who may derive benefit from anti-PD1 treatment, including patients requiring only low doses of corticosteroids (Weller et al 2019). Targeting the myeloid cells of the tumor microenvironment by inhibiting CSF-1R may add to the potential of immunotherapy in glioblastoma.

Breast cancer is one of the most frequent malignant neoplasms occurring in women in developed countries. Triple-negative breast cancer (TNBC) accounts for approximately 15% of newly diagnosed breast cancers, but due to its aggressive nature a disproportionate number (25%) of TNBC are reported in the metastatic setting (Carey et al 2006, Dahlberg et al 2009). TNBC is characterized by lack of expression of the estrogen and progesterone receptors and

[redacted]

lack of overexpression of the human epidermal growth factor receptor 2. The clinical course of TNBC is associated with a high probability of distant metastases, especially to the lung and brain (Dent et al 2007).

The tumor microenvironment plays an important role in breast cancer progression. Among the many cell types associated with the tumor microenvironment, TAMs are the most influential for breast cancer progression by promoting angiogenesis, tumor growth and dissemination (Leek et al 1996, Pollard 2004, Obeid et al 2013). Furthermore, TAMs have an immunosuppressive effect by inhibiting the CD8+ cytotoxic T-cells (Noy and Pollard 2014). High tumor infiltration of TAMs is associated with poor chemotherapy response and prognosis in breast cancer (DeNardo et al 2011, Yuan et al 2014). In human breast tumors expressing both CSF-1 and CSF-1R, invasion *in vivo* is dependent both on a paracrine interaction with TAMs and an autocrine regulation of CSF-1R in the tumor cells themselves (Patsialou et al 2009). Recently it has been shown that autocrine CSF-1R signaling mediates switching between invasion and proliferation downstream of TGFβ in claudin-low breast tumor cells (Patsialou et al 2015). Blockade of CSF-1 signaling to the macrophages has also been shown to reduce primary tumor growth due to decreased angiogenesis as well as to improve chemotherapeutic efficacy in tumor xenografts due to increased antitumor T-cell responses (Aharinejad et al 2004, Paulus et al 2006).

Currently, there are no targeted therapies for TNBC and the only treatment option is chemotherapy, though more recent clinical trials have shown some remarkable response to anti-PD-1/PD-L1 treatment (Emens et al 2015). Most patients receive anthracyclines and taxanes in the adjuvant setting and the standard of care for patients with metastatic TNBC also mainly includes cytotoxic chemotherapy (NCCN 2014, Cardoso et al 2018). For this reason, TNBC is considered a disease with high unmet medical need, as the median survival is approximately 1 year (Kassam et al 2009).

Pancreatic cancer is a very aggressive disease with dismal prognosis and expected to be the second deadliest malignancy in the USA by 2020. (Hidalgo 2010, Hidalgo et al 2015). The tumor microenvironment is characterized by a strong desmoplastic reaction, with a complex cross-talk between tumor cells and the stroma, which is a hallmark of disease. Kaplan–Meier survival analyses revealed that higher numbers of tumor-infiltrating CD163 M2 macrophages and MDSCs were significantly associated with shorter OS and disease free survival (DFS) in patients with pancreatic cancer.

Surgery remains the only curative treatment for pancreatic cancer, but therapeutic strategies based on initial resection have not substantially improved the survival of patients with resectable disease over the past 25 years; presently, more than 80% of patients suffer disease relapse after resection and the 5-year survival rate for these patients remains only 15–20% (Hidalgo et al 2015). In patients with advanced-stage disease, modest improvements in survival have recently been attained with FOLFIRINOX (folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin) or albumin-bound paclitaxel (nab-paclitaxel) plus gemcitabine (Conroy et al 2011, Von Hoff et al 2013). In the metastatic setting, single-agent gemcitabine therapy has been the standard of care for patients desiring active treatment. Checkpoint inhibitors, such as anti-PD‑1 or anti-CTLA‑4 have failed to show activity in pancreatic cancer as single agents (Royal et al 2010, Topalian et al 2012).

[redacted]

The common feature of these indications is the high unmet medical need and a tumor biology characterized by high levels of TAMs in the tumor microenvironment that may contribute to immune evasion and immune suppression. Novel therapeutic strategies are urgently needed. This study provides an opportunity to assess whether blockade of CSF-1R in conjunction with anti-PD-1 therapy may promote robust re-programming of TAMs and remove immune suppression of tumor infiltrating lymphocytes (TIL) potentially providing a new standard of care for these patients.

1.1.1 CSF-R1 Overview

Human macrophages are differentiated from monocytes *in vitro* in the presence of either CSF-1 or granulocyte macrophage colony-stimulating factor (GM-CSF). CSF-1-differentiated macrophages are pro-tumorigenic, are called M2 macrophages or TAMs when present in malignant tissues, and are characterized by the expression of CSF-1R and CD163, whereas differentiation with GM-CSF resulted in M1-macrophages with undetectable CD163 and CSF-1R, high expression of CD80+MHC-II and high antigen processing capacity (Geissmann et al 2010, Martinez et al 2008).

In cancer, CSF-1-differentiated macrophages reflect diminished tissue integrity and an adaptive process engaged by tumors to support growth (Noy and Pollard 2014). With the critical role for chemokine (C-C motif) ligand 2 (CCL2) and CSF-1 in recruiting macrophages to neoplastic tissue, there is growing interest in targeting these ligands and/or their respective receptors in an effort to ablate the pro-tumorigenic properties of macrophages.

For many solid tumor types, high densities of cells expressing macrophage-associated markers have generally been found to be associated with a poor clinical outcome (Komohara et al 2014, Zhang et al 2012). Expression of both CD163 and CD204 are associated with activation of macrophages toward a tumor-promoting and immunosuppressive phenotype, and significant correlations between CD163/CD204 and negative outcomes have been reported across multiple tumor types (Komohara et al 2014). To exert their pro-tumorigenic activity, M2 macrophages produce an array of cytokines, chemokines, growth factors, hormones, matrix-remodeling proteases, and metabolites such as CSF-1 and CCL2, prostaglandin E2, and damage-associated molecular patterns such as high-mobility group box 1 protein, extracellular adenosine triphosphate, and degraded extracellular matrix components (Ruffell et al 2012, Zelenay and Reis e Sousa 2013).

In vivo studies have revealed that M2-macrophages also mediate chemotherapy resistance by providing survival factors and/or activating anti-apoptotic programs in malignant cells. In murine pancreatic ductal adenocarcinoma (PDAC) cells, resistance to gemcitabine is dependent on the macrophage-mediated activation of signal transducer and activator of transcription 3 (STAT3) (Mitchem et al 2013). STAT3 activation promotes neoplastic cell proliferation and survival, and multiple tumor cell lines exhibit IL-6- or STAT3-dependent chemoresistance *in vitro* (Taniguchi and Karin 2014, Yu et al 2014). CSF-1 neutralization enhances the response to chemotherapy in mammary carcinomas (DeNardo et al 2011).

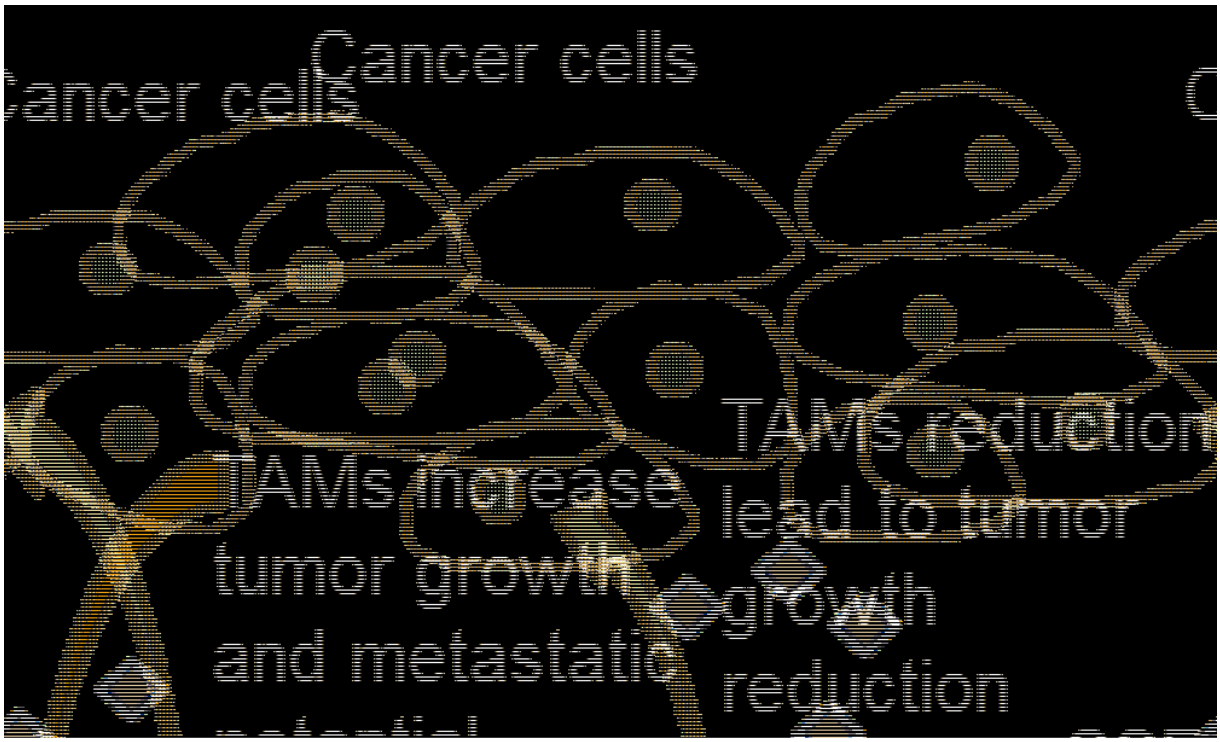
TAMs are also well described regulators of tumor angiogenesis, with supporting evidence derived from both clinical and experimental studies (Murdoch et al 2008, Ruffell et al 2012) in which much of their capability is associated with vascular endothelial growth factor signaling.

[redacted]

Furthermore, M2-macrophages can also directly suppress CD8+ T cell proliferation in murine tumor models (DeNardo et al 2011, Doedens et al 2010, Movahedi et al 2010, Ruffell et al 2014). In these models, T cell suppression by immature myeloid cells is typically linked to nutrient depletion via the metabolism of L-arginine or production of free radicals (Gabrilovich and Nagaraj 2009). Hypoxia also promotes macrophage-suppressive activity via expression of arginase-1 (Doedens et al 2010) and L-arginine depletion (Rodriguez et al 2003). In humans, however, there is no evidence for a role of nutrient depletion in mediating immune suppression by TAMs because macrophages conditioned by ovarian carcinoma ascites suppress T cell proliferation independent of arginase and NOS activity (Kryczek et al 2006). Instead, macrophages directly suppress T cell responses through PD-L1 expression in hepatocellular and ovarian carcinomas (Kuang et al 2009, Kryczek et al 2006).

It is therefore tempting to target CSF-1-derived macrophages to block tumor immunosuppression and thus enhance checkpoint blockade therapy. As monotherapy, CSF-1R inhibition alone impedes the growth of orthotopically implanted PDAC cell lines (Mitchem et al 2013) and induces regression of glioblastoma multiforme (GBM) (Pyonteck et al 2013). Interestingly, synergism in combination with immune checkpoint blockade has also been shown. CSF-1R inhibition provided additive efficacy to either PD-1 or CTLA-4 blockade in combination with gemcitabine in an orthotopic implant model of PDAC (Zhu et al 2014). Importantly, in this model CSF-1R inhibition also enhanced the response to combined PD-1/ CTLA-4 blockade in the absence of chemotherapy (Zhu et al 2014).

Figure 1-1 BLZ945 mechanism of action



[redacted]

1.1.2 PD-1 Overview

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

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

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

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

1.2.1 Overview of BLZ945

BLZ945 is a highly selective CSF-1R kinase inhibitor. BLZ945 potently inhibits CSF-1R [redacted] as determined in an *in vitro* kinase assay with recombinant CSF-1R kinase domain. The cellular activity of BLZ945 was shown by reducing the tyrosine-phosphorylated levels of CSF-1R in cells [redacted] and a significant anti-proliferative effect on the macrophage colony-stimulating factor (M-CSF) dependent cell line MNFS-60 [redacted]. Furthermore, biochemical and cellular kinase selectivity of BLZ945 has been shown with a kinase panel of more than 200 kinases and at the cellular level using auto-phosphorylation enzyme-linked immunosorbent assays (ELISA) and kinase transfected BaF3 proliferation assays. IC_{50}'s for a relevant subset of kinases, including related Class III RTKs [redacted] and [redacted] were at least [redacted] BLZ945 kinase selectivity has been confirmed at the cellular level as assessed by auto-phosphorylation assays (in-house ECL ELISA assays) and BaF3 proliferation assays. [redacted]

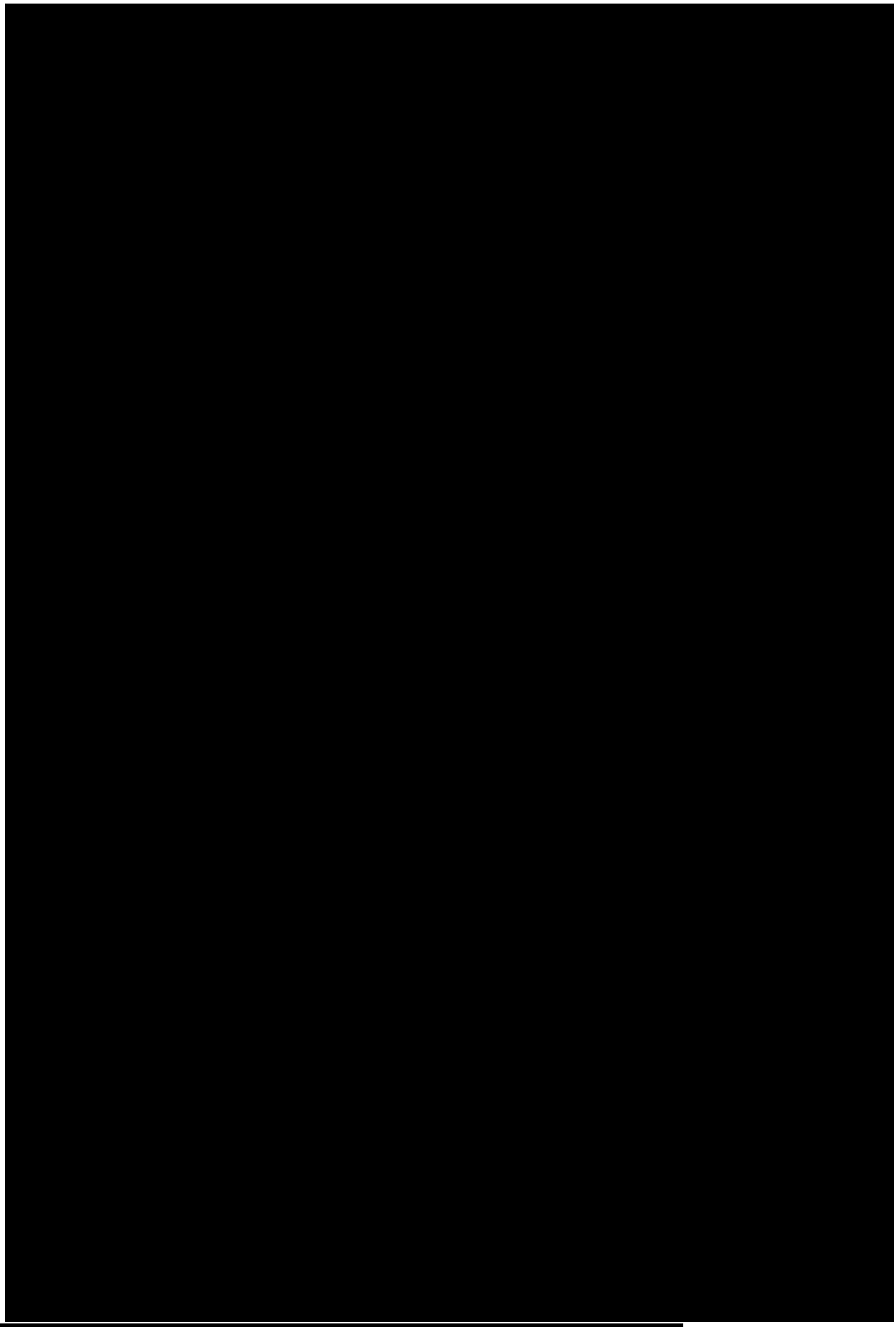
[redacted]

1.2.1.1 BLZ945 Non-clinical experience

The main biological effects of CSF-1R signaling are the differentiation, proliferation, migration and survival of the precursor macrophages and osteoclasts from the monocytic lineage. Activation of CSF-1R is mediated by its ligand, M-CSF and the recently identified tissue restricted IL-34 (Dai et al 2002, Lin et al 2008). While CSF1-R is an oncogene, the main mechanism by which BLZ945 mediates anti-tumor activity via CSF-1R signaling is when TAMs are reduced or reprogrammed to a classically activated phagocytic macrophage (Pyonteck et al 2013, Mao et al 2016). BLZ945 (200 mg/kg daily) has been shown to induce regression of established tumors and increase survival in a genetic mouse model of glioblastoma, and slow the growth of proneural glioblastoma-derived xenografts (Pyonteck et al 2013). In the genetic model (platelet derived growth factor B-driven, or PDG mice), efficacy of BLZ945 was not accompanied by a loss of TAMs, but rather by an apparent reprogramming from M2 to M1 phenotype. This was measured by BLZ945-induced changes in a 257-gene signature which was refined to five M2-related genes *Adm, Arg1, F13a1, Mrc1*, and *Serpinb2*. Both gene sets were used to analyze GBM patient data in the TCGA database and were shown to confer a survival advantage in subjects with proneural GBM. This finding is consistent with the results of another experimental study where the clinical potential of BLZ945 (200 mg/kg daily for 10 days) has been shown in an animal model of neuroblastoma (Mao et al 2016). This study showed that infiltrating CSF-1R+ myeloid cells are suppressive and predict poor clinical outcome in patients with neuroblastoma. Tumor derived supernatant from neuroblastoma cell lines inhibited the maturation of human CD34+ progenitor cells into DCs, monocytes and macrophages. Through systematic testing of cytokines it has been demonstrated that myelopoeisis of human CD34+ progenitor cells is modulated by tumor derived M-CSF. The addition of BLZ945 recovered the potential of myeloid cells to stimulate human T cell proliferation (Mao et al 2016). Similarly, human primary monocytes were co-cultured with neuroblastoma cell lines and then shown to acquire strong suppressive capacity against autologous T cells. Also in this case, the addition of BLZ945 was able to inhibit the suppressive function of the tumor-educated monocytes on CD8+ and CD4+ T cells (Mao et al 2016).

BLZ945 was also tested in combination with anti-PD-1 in the MC38 syngeneic colorectal cancer model, chosen based on the presence of TAMs and response to anti-PD-1 and shown to inhibit tumor growth and enhance survival as compared to anti-PD-1 alone (internal data) Figure 1-2. In this study, weekly administration of BLZ945 [redacted] in combination with anti-PD-1 was more efficacious [redacted]

[redacted]



Taken together, these pre-clinical data suggest that a weekly dose of BLZ945 in combination with anti-PD-1 performs at least as well as the daily dose. Alternative weekly or intermittent schedules of BLZ945 may provide a clinically significant reduction in Tregs and TAMs with reduced risks of toxicity.

The anti-tumor activity of BLZ945 has been demonstrated when TAMs are reduced in number and thereby the immunosuppressive function towards immune cells in the tumor is attenuated. CSF-1R signaling blockade using BLZ945 has also been shown to inhibit tumor growth (Strachan et al 2013) and enhance the activity of immune checkpoint inhibitors in multiple tumor models including a transgenic breast cancer model as well as a N-Myc transgenic neuroblastoma model (Strachan et al 2013, Mao et al 2016).

In summary BLZ945 has shown efficacy in syngeneic and transgenic mouse tumor models as a single agent and in combination with anti-PD-1. Changes in TAMs phenotype and number in the tumor upon BLZ945 treatment may explain the anti-tumor activity. The additional effects on MDSCs cells and T cells are likely also important contributors to the anti-tumor activity for BLZ945 as a single agent and in combination.

1.2.1.1.1 Non clinical pharmacokinetics and metabolism

The *in vivo* preclinical pharmacokinetics (PK) profile of BLZ945 has been investigated in mouse, rats, dog and monkeys. BLZ945 exhibited low to moderate clearance and volume of distribution [redacted] with an apparent terminal half-life between 1.7 and 7.5 hours. Bioavailability was high in all species [redacted] but low in dog [redacted]). Dose proportionality was observed in mice and rats up to [redacted]. Plasma protein binding was high, [redacted] in all species tested. The distribution of BLZ945 and related radioactive material to tissues was investigated in the rat using Quantitative Whole Body Autoradiography. The study demonstrated wide distribution of BLZ945-related components to organs and tissues including brain and pancreas (approximately [redacted]) which are relevant for the selected indications. The radiolabeled component(s) were generally eliminated from organs and tissues with apparent half-life ($T_{1/2}$) below 6.5 hours. However, elimination from liver and melanin containing tissues was slower with the slowest decline from the choroid structures of the eye (apparent [redacted]. Human pharmacokinetic parameters of BLZ945 were predicted based on Physiologically-Based Pharmacokinetic modeling and on allometric scaling using data from mouse, rat and monkey. BLZ945 is predicted in humans to have a low plasma clearance (CLp) [redacted]), a low volume of distribution (Vss) (mean Vss~ [redacted]), and almost complete oral absorption at starting dose of 150 mg in fasted state and a moderate half-life ($T_{1/2}$ ~ 10 hours). However, absorption may decrease with increasing doses [redacted].

The metabolite profile of BLZ945 was examined in hepatocytes across animal species and human and was qualitatively comparable.

Metabolic pathways included hydroxylation, glucuronidation, N-demethylation, and possible reduction of [redacted] metabolite to an [redacted] metabolite M9 (= LEL284, a diastereomer of BLZ945, which is also anticipated to be formed in human. In the 4-week Good Laboratory Practice (GLP) studies in monkeys the exposure to LEL284 represented between

[redacted]

[redacted] of BLZ945 exposure. LEL284 inhibits CSF-1R with [redacted] and is about [redacted]-fold less active than BLZ945 as determined in an in vitro kinase assay with the recombinant CSF-1R kinase domain.

Oxidative metabolites M1 and M2 as well as a very minor amount of M5 were observed only in human hepatocytes.

A radiolabeled study in rat at a single dose of [redacted] indicated that radiolabeled BLZ945 was predominantly excreted through biliary route and/or direct intestinal secretion with about [redacted] renal excretion.

To assess for potential drug-drug interactions (DDI), studies have been conducted with cytochrome P450 (CYP) enzymes and several transporters *in vitro*. Transporter phenotyping will be done, not yet available. Oxidative metabolism of BLZ945 occurs for a notable fraction of total metabolism with CYP3A4 (35%) and CYP2C8 (35%). In addition approximately 24% of the metabolism occurs via glucuronidation (Krauser et al 2015). Complete inhibition of the individual CYP2C8 or CYP3A4 could elevate the area under the curve (AUC) of BLZ945 by a factor 1.44 or 1.6-fold, respectively. Simultaneous and complete inhibition of both enzymes may cause a [redacted]-fold increase of BLZ945 AUC. Hence, concomitant use of potent CYP3A4 or CYP2C8 inhibitors or inducers might impact the exposure to BLZ945 in human. BLZ945 showed moderate to weak reversible inhibitory potency for CYP2C8, CYP2C9, and CYP2D6. BLZ945 is not a time dependent inhibitor of CYP1A2, CYP2C9 and CYP3A4/5. Based on the predicted free plasma concentration of [redacted], the inhibition of CYP isoforms are only clinically relevant if free plasma (unbound) is ≥ 10µM.

BLZ945 is a moderate reversible inhibitor towards MDR1 and mitoxantrone resistance/breast cancer resistance protein. Hence BLZ945 may alter the exposure of sensitive substrates of these enzymes and/or transporters.

In vitro solubility data indicated that the solubility of BLZ945 is strongly pH-dependent (solubility of BLZ945 dihydrochloride at ca 25°C is [redacted]) and decreased oral absorption is already expected at pH [redacted]. Refer to Section 6.4.2 for prohibited medications.

For details, please refer to [BLZ945 Investigator's Brochure].

1.2.1.1.2 Toxicology

The safety of BLZ945 has been investigated in safety pharmacology studies, genetic toxicity studies, and general toxicology studies in rats and monkeys for up to 4-weeks.

In safety pharmacology studies, in vitro human Ether-à-go-go-Related Gene (hERG) assay showed no significant inhibition of hERG current at concentrations up to [redacted] µM. Electrophysiology assessment with isolated rabbit heart showed a delay of repolarization at [redacted] µM (without pro-arrhythmic risk) which was reversed at [redacted] µM. The rat central nervous system (CNS)/respiratory function test showed no adverse effects on CNS or respiratory function at the tested dose of [redacted]. No adverse effects on cardiovascular function were detected in the telemetry study in monkeys at doses up to [redacted]. A slight and transient increase of QTc detected at the dose of [redacted] was considered non-adverse.

[redacted]

In genetic toxicology studies and based on weight of evidence approach, BLZ945 is considered non genotoxic.

For single dose toxicity studies, BLZ945 is well tolerated in rats at single dose up to [redacted] (and single doses up to [redacted] in a 2-week study), and in monkeys at single dose up to [redacted]

Repeated dose toxicity studies in rats and monkeys for up to 4-weeks duration showed that BLZ945 was well tolerated in-life at doses up to [redacted] in rats and up to [redacted] in monkeys, the highest dose tested in the 4-week studies. The following target organ effects were identified: clinical chemistry parameters (liver enzymes), bone, hypothalamic/pituitary/adrenal/gonadal axis, hematopoietic system, lymphoid organs/tissues, and gastrointestinal (GI) track. Additionally minor findings were observed in liver, lung, and kidney. Majority of the observed effects were considered to be a result of the pharmacological action of BLZ945. Reversibility or trend towards reversibility was observed for most effects. Follow up investigational studies demonstrated that the increase of liver enzymes are expected outcome of inhibition of macrophages (including Kupffer cells), and are not result of hepatocellular injury or muscle injury.

The 13-week toxicity studies in rats and monkeys are currently on-going. The preliminary results from the 13-week rat study identified new target organ effects, including vascular inflammation, heart valve thickening and increased incidence and severity of renal basophilic tubule/protein casts/inflammatory cell infiltrate. The finding of heart valve thickening is considered to be related to increased accumulation of extracellular matrix. This finding was reversible after the 8-weeks post-dosing interval.

Additionally, since BLZ945 is distributed in pigmented tissues, it was tested in a 3T3 cell neutron red uptake assay for potential phototoxicity. Under the conditions tested, BLZ945 showed no phototoxicity potential.

1.2.1.2 BLZ945 Clinical experience

As of 14-Aug-2019, 77 patients have been enrolled in the BLZ945 single agent dose escalation part and 69 patients have been enrolled in the BLZ945 and PDR001 combination dose escalation part.

The RP2D of BLZ945 single agent and BLZ945 in combination with PDR001 were declared at 1200 mg at a 4 days on/10 days off schedule and at 700 mg at a 4 days on/10 days off schedule with 400 mg PDR001 Q4W, respectively. For more information, refer to the [BLZ945 Investigator Brochure (IB)].

1.2.2 Overview of PDR001

PDR001 is a high-affinity, ligand-blocking, humanized anti-PD-1 IgG4 antibody (stabilized hinge, S228P) which blocks the binding of PD-1 to PD-L1 and PD-L2. PDR001 is cynomolgus monkey cross-reactive and shows functional activity *in vitro* and *in vivo*. For further details, please refer to the most recent edition of the [PDR001 Investigator's Brochure].

[redacted]

1.2.2.1 PDR001 Non-clinical experience

PDR001 binds specifically and with high affinity to human PD-1. In Biacore assays, the dissociation constant (K_D) of PDR001 on human PD-1 is [redacted] In *ex vivo* lymphocyte stimulation assays using human blood, PDR001 enhances IL-2 production by approximately 2-fold in response to super antigen stimulation with Staphylococcal enterotoxin B (SEB). PDR001 does not cross-react with rodent PD-1, and cannot be evaluated in murine tumor models. It does cross-react with cynomolgus monkey PD-1, and is functionally active, making cynomolgus monkey a relevant species for toxicology studies. A GLP tissue cross reactivity study using frozen human and cynomolgus monkey tissues was also done in support of the safety of PDR001. There was no unexpected binding observed.

The non-clinical toxicology of PDR001 was evaluated in a five week GLP toxicology study in cynomolgus monkeys with safety pharmacology endpoints and an eight week recovery. Repeat administration of PDR001 to monkeys was well tolerated at all doses tested in the GLP toxicology study. No test article-related in-life, mortality, organ weight changes, or macroscopic findings were noted. There were no PDR001-related effects seen in any of the safety pharmacology endpoints assessed (cardiovascular, neurobehavioral, and respiratory). Macrophage infiltrates into the splenic white pulp were observed in animals given 100 mg/kg/week and mononuclear cell infiltrates, often associated with fibrosis, around the injection site blood vessel (saphenous vein) in a few animals given 25 mg/kg/week. These PDR001-related microscopic changes were fully reversible after an eight week recovery.

The following changes were noted in main phase and recovery treated animals as well as control recovery animals. Mostly low grade changes were noted in several tissues in the form of mononuclear infiltrates in the vascular and perivascular space. In general, in most organs, vascular/perivascular changes were limited to one or a few blood vessels in each organ and sometimes involved a segment of a blood vessel with occasional vessel wall degeneration. No evidence of parenchymal damage was associated with the vascular/perivascular changes in any of the organs examined and the changes were not associated with any frank tissue injury. While these effects were not exclusive to treated animals, because of their nature and close association with the expected pharmacology of PD-1 blockade, a potential PDR001 related effect cannot be excluded and possibly explained by mild enhanced pharmacology of PDR001. There were no test article related effects seen in the cardiovascular assessments. All other microscopic findings were considered spontaneous or otherwise unrelated to PDR001 administration.

Dose-dependent exposure to PDR001 in each dose group was confirmed. A pharmacodynamics *ex vivo* superantigen stimulated whole blood assay measuring IL-2 release was performed. Blood from untreated control animals showed augmentation of IL-2 release when PDR001 was added *ex vivo*, whereas blood from treated animals at all doses did not show augmented IL-2 release, indicating target engagement and inability to further dis-inhibit the SEB induced response with the further addition of PDR001. The highest non-severely toxic dose (HNSTD) dose in this study was [redacted].

[redacted]

1.2.2.2 PDR001 Clinical experience

PDR001 is being tested in a first in human (FIH), multi-center, open-label study [CPDR001X2101] starting with a phase I dose escalation part, followed by a phase II part.

The objective of this study is to determine the safety and tolerability of PDR001, and define the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D), and PK of PDR001.

The CPDR001X2101 study started enrollment on 27 April 2015 and is ongoing. As of 17 December 2015, a total of 58 patients had been treated in the study at the dose levels of 1, 3 and 10 mg/kg every 2 weeks and 3 and 5 mg/kg every 4 weeks (Q4W). No patient experienced a dose limiting toxicity (DLT) and the toxicity profile appears to be similar to that of marketed inhibitors of PD-1. The PK data obtained from the dose escalation, and modeling of the exposure data, support the use of flat dosing for PDR001 of 400 mg given every 4 weeks. The expected PDR001 Ctrough concentrations are in line with observed steady state mean Ctrough concentrations for pembrolizumab, which is approved with substantial efficacy in several cancer types. The data also support the use of 300 mg every 3 weeks as an alternative dose regimen if it is more convenient for scheduling purposes, for example in combination treatment regimens.

Most frequent AEs observed were nausea (15 patients, 25.9%), anemia and fatigue (12 patients, 20.7%, respectively), diarrhea and vomiting (10 patients, 17.2%, respectively). The safety appeared to be similar across the different dose groups.

1.2.3 Overview of combination treatment

1.2.3.1 Non-clinical experience with combination of BLZ945 and PDR001

1.2.3.1.1 Non clinical pharmacokinetics and metabolism

Specific studies to investigate drug drug interactions (DDIs) have not been conducted with PDR001. As an antibody, PDR001 is eliminated through protein catabolism and target-mediated disposition. Therefore, PDR001 is not anticipated to be directly eliminated through hepatic/renal metabolism and excretion, to compete with the elimination of BLZ945, which is mainly eliminated through metabolism and renal excretion. However, immunomodulators which may regulate CYP enzymes may cause DDI with small molecule drugs because of the potential to alter CYP mediated metabolism (Lee et al 2010, Huang et al 2010, Girish et al 2011). Therefore, the risk of DDI between PDR001 and BLZ945 cannot be totally excluded, although anticipated to be low. For nivolumab, the Clinical Pharmacology and Biopharmaceutics Review (Nivolumab FDA application number: 125554Orig1s000) states that nivolumab showed a lack of CYP enzyme related cytokine modulation up to a dose of 10 mg/kg investigated in RCC patients. Nevertheless, PK of BLZ945 in the presence and absence of PDR001 will be characterized in this study to assess the DDI, if any, between PDR001and BLZ945 (Section 10.5.4).

1.2.3.1.2 Expected overlapping toxicities

For BLZ945, the target organ effects included: clinical chemistry parameters such as transaminases, bone, hypothalamic/pituitary/adrenal/gonadal axis, hematopoietic system,

[redacted]

lymphoid organs/tissues, and GI track. Additionally, minor findings were observed in liver, lung, and kidney.

Due to the lack of common target organ effects between BLZ945 and PDR001, the potential for synergistic toxicity in combination is not expected.

2 Rationale

2.1 Study rationale and purpose

Preclinical data indicate that TAMs represent an attractive therapeutic target as they represent key orchestrators of various tumor-promoting processes, such as escape of immune surveillance. Their differentiation, migration and survival are regulated by CSF-1R upon engagement with the soluble CSF. CSF-1R is a member of the receptor protein tyrosine kinase family of growth factor receptors, which includes several known proto-oncogenes (Ries et al 2014). By interfering with the CSF-1R pathway, BLZ945 induced reduction and re-programming of M2-type macrophages in animal models of glioma, providing significant antitumor efficacy by removing/reprogramming the immuno suppressive TAMs.

Checkpoint inhibitors have been successfully introduced to clinical practice with the recent approval of the antagonist antibodies to the CTLA-4 (ipilimumab) and PD-1 (e.g nivolumab and pembrolizumab) checkpoints. A large proportion of patients, however, do not respond to checkpoint inhibitors as monotherapy, and these patients therefore represent a population with high unmet medical needs that might benefit from alternative approaches. Results from use of checkpoint inhibitors in glioblastoma have not been encouraging so far, although subsets of patients may still benefit from the treatment, and the use of corticosteroids may affect the efficacy of these drugs (Weller et al 2019). The use of corticosteroids will be restricted at baseline and collected throughout the study for potential exploration as predictive factors.

Reasons for this limited success include immune regulation mediated by cancer cells and leukocyte populations through a variety of cell-expressed and secreted molecules. In many cases, immune regulation occurs locally within the tumor, leading to an ineffectual or suppressed antitumor response. Antitumor immunity within the tumor microenvironment can be suppressed by a variety of tumor infiltrating leukocytes, including Tregs, MDSCs and TAMs. TAMs and MDSCs can be found in large numbers in tumors and their immunomodulatory activity is often exerted locally within the tumor microenvironment. Mechanisms employed by these cell types to suppress effective immunity include secretion of cytokines such as IL-10 and TGF-β, and expression of inhibitory receptors such as CTLA-4 and PD-L1.

The removal of the TAMs and MDSCs which are so important in generative immunosuppression provide the basis for combination strategies with checkpoint inhibitors such as anti-PD-1 therapy in those malignancies in which TAMs contribute to tumor pathogenesis. For this reason, a CSF-1R inhibitor might enhance the clinical efficacy of a checkpoint inhibitor such as anti-PD-1, or induce clinical benefit in patients with tumors showing high expression of TAMs such as glioblastoma, TNBC and pancreatic cancer and in those who do not respond to anti-PD-1 as single agent.

[redacted]

By the end of phase I part of study (except for Japan), treatment with BLZ945 single agent and in combination with PDR001 showed preliminary anti-tumor activity and was well tolerated with manageable safety profiles. As of 14-Aug-2019, among 18 evaluable patients with relapsed/refractory glioblastoma (7 patients in BLZ945 arm and 11 patients in combination arm), 2 partial responses were reported per RANO (1 per arm). Among all 24 treated patients with GBM, 7 patients (29%) were on treatment for more than 16 weeks.

The phase II part of the study will investigate both BLZ945 single agent and BLZ945 in combination with PDR001 in glioblastoma due to the encouraging results observed during dose escalation. The TNBC and pancreatic cancer which were initially part of the phase II indications will no longer be pursued due to the business decision to focus on glioblastoma.

2.2 Rationale for the study design

This is an open-label, phase I/II study with BLZ945 as single agent or in combination with PDR001. The study consists of the following parts:

- A phase I dose escalation part with BLZ945 as single agent in advanced solid tumors, with a schedule of 7 days on/7 days off (7d on/7d off). Other dosing schedules such as once a week (Q1W) or 4 days on/10 days off (4d on/10d off) dosing may also be explored if deemed appropriate based on emerging PK and safety assessments. For each of these dosing schedules, once per day (QD) or twice per day (BID) dosing may be evaluated.
- A phase I dose escalation part with BLZ945 as single agent in advanced solid tumor Japanese patients, with the goal of informing subsequent clinical development in Japan. The purpose of the Japanese dose escalation is to ensure that the safety and pharmacokinetic profile of BLZ945 as single agent are adequately characterized in Japanese patients at more than one BLZ945 dose level. The Japanese dose escalation for BLZ945 single agent will run separately from the ongoing global dose escalation.
- A phase I dose escalation part with BLZ945 in combination with PDR001 in advanced solid tumors. The criteria for the starting dose are described in Section 6.2.1.2.
- A phase II part to evaluate clinical efficacy of BLZ945 in combination with PDR001 at the RP2D in glioblastoma, as shown in Figure 4-2.
- A phase II part to evaluate clinical efficacy of BLZ945 in glioblastoma as single agent at the RP2D based on the observed signs of anti-tumor activity and demonstrated proof of mechanism of action (MOA) for BLZ945.

The design of the phase I part was chosen to establish the regimen and the MTD/RP2D of BLZ945 as a single agent and in combination with PDR001 in patients with advanced solid tumors.

The dose escalation decision making will be guided by a Bayesian logistic regression model (BLRM) with Escalation With Overdose Control (EWOC) principle based on DLT data in the context of available safety, PK and PD information. For details of the dose escalation, please refer to Section 6.2.

This open-label dose escalation study design using a BLRM is a well-established method to estimate the MTD/RP2D in cancer patients. The adaptive BLRM will be guided by the EWOC principle to control the risk of DLT in future patients on study. The use of Bayesian response adaptive models for small datasets has been accepted by European Medicines Agency

(Guideline on clinical trials in small populations, 13-Feb-2007) and endorsed by numerous publications (Zacks and Hersh 1998, Neuenschwander et al 2008, Neuenschwander et al 2010), and its development and appropriate use is one aspect of the FDA's Critical Path Initiative.

In the phase II part, the anti-tumor effect of BLZ945 as single agent (if applicable) or in combination with PDR001 will be evaluated in terms of progression-free survival rate (PFSR) at 6 months. Progression status at 6 months is a strong predictor of survival, and PFSR at 6 months is a valid endpoint for the evaluation of treatment in very aggressive diseases such as recurrent malignant gliomas, pancreatic cancer and TNBC (Lamborn et al 2008, Teague et al 2015, Yadav et al 2014). A Bayesian design will be used to estimate and provide inferential summaries for the PFSR at 6 months. MGMT promoter methylation status and use of corticosteroids will be captured for potential exploration as predictive factors. The phase II part of the study will initially enroll 20 glioblastoma patients and may expand to 40 patients in total per treatment arm. An interim futility analysis will be conducted to inform a "go/no-go" decision (i.e. to continue enrolling up to the maximum sample size allowed) based on disease control rate at the first tumor assessment per RANO. This study design for phase II part is aiming to potentially reduces patient exposure to futile treatment. PDR001 has been administered as a single agent to Japanese patients in a separate study and no differences have been observed in either the safety profile or PK of PDR001 between Japanese patients and patients in the rest of the world. Therefore, if the recommended dose determined in the global dose escalation part of the BLZ945 phase I single agent is found to be the same in Japanese patients, then Japanese patients may also enter the combination part of study at whichever dose is being tested at that time.

2.3 Rationale for dose and regimen selection

The selection of the starting dose follows the International Conference Harmonization (ICH) S9 guidelines for choosing a starting a dose for a first-in-human trial conducted in patients with cancer, and is shown in Table 6-2.

Preclinical data suggest that comparable antitumor activity can be achieved with non continuous schedules. Experiments in rats and monkeys have shown significant transaminases elevation with continuous daily dosing. These transaminases elevations are however transitory and therefore the 7d on/7d off regimen has been selected to achieve a tolerable profile and TAMs depletion. The starting dose for BLZ945 (7d on/7d off) in combination with PDR001 will depend on the available data of single agent BLZ945. Preclinical data suggest that a Q1W of BLZ945 performs at least as well as the daily dose in terms of TAMs depletion and anti-tumor activity (refer to Section 1.2.1.1). The starting dose for BLZ945 (Q1W) in combination with PDR001 is described in Section.6.2.1.2.

Preclinical PK/PD modelling of BLZ945 plasma concentrations and ALT elevations suggest that a regimen of 4 daily doses of BLZ945 followed by 10 days off BLZ945 (4d on/10d off) could allow the recovery of elevated ALT values in most patients.

[redacted]

In any combination dose escalations, PDR001 will be administered at a fixed dose of 400 mg i.v. infusion every 4 weeks which has been shown to be well tolerated (refer to Section 1.2.2.2).

In the BLZ945 single agent dose escalation, up to three dosing schedules will be explored in parallel. When a dosing schedule reaches the MTD/RP2D in phase I and signs of anti-tumor activity are seen, a phase II part may commence with that regimen.

In the combination dose escalation, no more than two BLZ945 dosing schedules combined with PDR001 will be explored in parallel. When a combination dosing schedule reaches the MTD/RP2D in phase I, a phase II part may commence with that regimen.

In the dose escalation in Japanese patients, up to two dosing schedules of BLZ945 will be explored, for example Q1W and/or 4d on/10d off.

[redacted]

3 Objectives and endpoints

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

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4
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		Refer to Section 10.5
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	Overall survival (OS)	
Phase II: To further characterize the safety and tolerability of BLZ945 as a single agent 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	
Phase I/II parts:	BLZ945 and PDR001 PK parameters [e.g. AUC, Cmax, Tmax]	

[redacted]

Objective	Endpoint	Analysis
Characterize PK of BLZ945 as a single agent and in combination with PDR001		
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		Refer to Section 10.6
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.	

[redacted]

[redacted]

4 Study design

4.1 Description of study design

This study is a first in human, open-label, multi-center phase I/II study which consists of a phase I dose escalation part of BLZ945 as single agent, and of BLZ945 in combination with PDR001, where alternative dosing regimens of BLZ945 will be evaluated. Once the MTD/RP2D for BLZ945 as single agent is established, a phase II part may commence, should signs of anti-tumor activity been seen during the phase I. Once the MTD/RP2D for BLZ945 in combination with PDR001 is established, a phase II part will commence.

The single agent BLZ945 dose escalation may explore up to three dosing schedules in parallel, 7d on/7d off, Q1W or 4d on/10d off, if deemed appropriate based on emerging PK and safety assessments.

A separate Japanese single agent dose escalation will be performed in order to ensure that the safety and pharmacokinetic profiles of BLZ945 single agent are adequately characterized in Japanese patients. The Japanese dose escalation for BLZ945 single agent will run separately from the ongoing global dose escalation. Up to two dosing schedules may also be explored in parallel, for example Q1W and/or 4d on/10d off.

The BLZ945 and PDR001 combination dose escalation may explore up to two dosing schedules in parallel, for example Q1W and/or 4d on/10d off.

To minimize selection bias between dosing schedules, patients will be centrally assigned between the dosing schedules (Section 6.5.2).

Study treatment will be administered until a patient experiences unacceptable toxicity, progressive disease or treatment is discontinued at the discretion of the investigator or the patient.

Based on the outcome of the planned interim analysis (Section 10.7 for details), no further patients were enrolled in part II of phase 2 according to protocol. Therefore, the enrollment of the Japanese cohort was halted per Investigator letter, dated 18-Jun-2021.

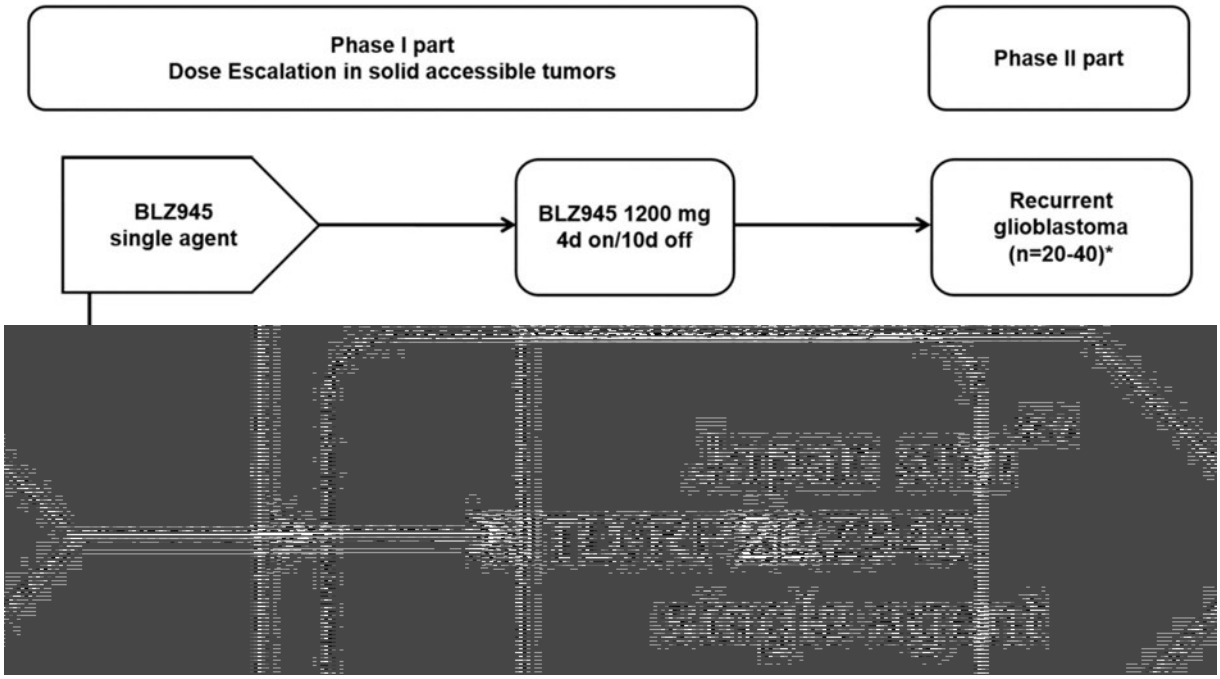
The study design is summarized in Figure 4-1.

[redacted]

Figure 4-1 Study design (effective prior to protocol amendment 6 approval)

1. Optional: To be opened if signs of anti-tumor activity is seen in the phase I with BLZ945 single agent and upon agreement between Investigators and Novartis
2. Best MTD/RP2D combination regimen to be selected by exploring the changes from baseline of CD163 and CD8/Foxp3 at Week 8
3. To be expanded to 40 patients if anti-tumor activity is observed in the first 20 patients
4. To be expanded to 20 patients if anti-tumor activity is observed in the first 10 patients

Figure 4-2 Study design (effective after approval of protocol amendment 06)



*: To be expanded to 40 patients if anti-tumor activity is observed in the first 20 patients
** Japan arm was halted as communicated on 18-Jun-2021 via Investigator letter

Phase I dose escalation BLZ945 as single agent

At least 21 patients are required during the dose escalation in BLZ945 single agent to define MTD; however, fewer than 21 patients may be treated if the RP2D is determined prior to reaching the MTD (for further details see Section 6.2.3).

Enrollment in the 7d on/7d off schedule may be stopped if early toxicity is observed, such as AST/ALT Grade 3 related to BLZ945 for more than 7 days in cycle 1, or AST/ALT Grade 2 with total bilirubin Grade 2, or any other event that would lead to a dosing delay of more than 7 days in cycle 1; then, the Q1W schedule or the 4d on/10d off schedule may be started as based on emerging PK and safety assessments..

In the Japanese dose escalation, at least 12 patients are required to be treated during dose escalation to define the MTD/RP2D. Dose escalation decisions will be guided by a separate BLRM to estimate the MTD /RP2D in Japanese patients (see Appendix 6).

Phase I dose escalation BLZ945 in combination with PDR001

The criteria for the starting dose for BLZ945 in combination with PDR001 is described in Section 6.2.1.2.

A minimum of 15 patients are required during dose escalation to define the MTD; however, fewer than 15 patients may be treated if the RP2D is determined prior to reaching the MTD (for further details see Section 6.2.3).

The escalation will also be guided by an adaptive BLRM following the EWOC principle. Pharmacodynamics tumor changes (CD163 and CD8/foxp3) at Week 8 will assist to make a decision of the RP2D**.**

BLZ945 single agent Phase II part

Should signs of anti-tumor activity (e.g. prolonged stable disease or PR) be seen in the phase I dose escalation with BLZ945 as single agent, and in agreement with the investigators, a phase II part will be opened in order to further explore BLZ945 single agent efficacy at a recommended dose and schedule. Patients with tumor types that have been shown to respond to single agent BLZ945 (maximum of two indications) will be enrolled.

Based on the signs of anti-tumor activity observed in the phase I dose escalation with BLZ945 as single agent in patients diagnosed with recurrent glioblastoma, this indication will be further explored in the phase II part (see Figure 4-2). This treatment group will initially enroll approximately 20 patients. If the disease control rate (DCR) is ≥ 60% (more than 12 SD or better at the first tumor assessment for each patient) per RANO, then the sample size may be expanded to approximately 40 patients.

[redacted]

Phase II part (BLZ945 in combination with PDR001)

Once the MTD and/or RP2D has been declared for BLZ945 in combination with PDR001, patients diagnosed with recurrent glioblastoma will be enrolled in the phase II part in order to assess the preliminary anti-tumor activity of the combination (see Figure 4-2).

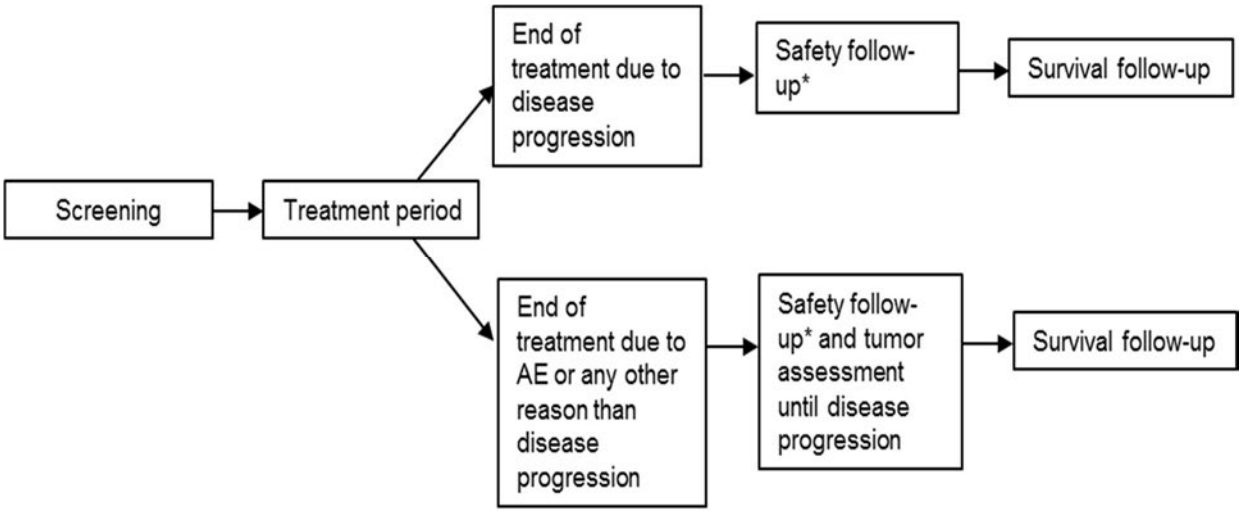
The combination treatment group in glioblastoma will initially enroll approximately 20 patients. If the disease control rate (DCR) is ≥ 60% (more than 12 SD or better at the first tumor assessment for each patient) per RANO, then the sample size may be expanded to approximately 40 patients. No enrollment halt is foreseen until analysis readout is available.

Details of the sample size calculations leading to the patient numbers are provided in Section 10.8. A Bayesian design will be used in order to estimate PFS rate at 6 months for patients with glioblastoma (see Section 10.8 for details of sample size).

Study flow

Patients will undergo safety and efficacy assessments during screening/baseline and periodically during treatment as outlined in Table 7-1, Table 7-2, Table 7-3 and Table 7-4. Additional information for study visit flow is provided on Section 7.1.

Figure 4-3 Study flow



*30-days follow-up for BLZ945 single agent and 150-days follow-up for BLZ945 in combination with PDR001.

4.2 Timing of interim analyses and design adaptation

No formal interim analysis is planned for the phase I part. However, the dose-escalation design foresees that decisions based on the current data will be taken before the end of the study. In the phase II part, an interim analysis for futility based on DCR will be conducted after approximately 20 patients have been enrolled and have had first protocol defined post-treatment evaluation (or discontinue from the treatment) in each treatment arm (i.e. BLZ945 single agent or BLZ945 in combination with PDR001). The purpose of the interim analysis will be to review the preliminary efficacy data to make decision on further expanding the enrollment. If DCR in

either or both of the treatment arms is ≥ 60%, the sample size may be expanded from 20 to approximately 40 patients for each individual treatment arm. Please refer to Section 10.7 for further details.

4.3 Definition of end of study

The end of the study will be when:

- at least 80% of the patients have completed the survival follow-up period (minimum 18 months after the first dose of treatment), or discontinued the study for any reason, and all patients have completed treatment as well as the 30-days (BLZ945 single agent) or 150-days (BLZ945 in combination with PDR001) safety follow-up period.

or

- Another clinical study becomes available that can continue to provide study treatment , all ongoing patients on treatment are transferred to that clinical study or an alternative way to provide study treatment, and all discontinued patients have completed the safety follow-up period. Follow-up for disease progression or survival will not be performed or pursued.

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

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

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible for End of Treatment (EoT) visit and the assessments for EoT should be performed as described in Section 7 for discontinued or withdrawn patients. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing Institutional Review Board (IRBs) and/or Ethic Committees (ECs) of the early termination of the trial.

5 Population

5.1 Patient population

In the phase I part of the study, both single and combination escalation will be conducted in all types of advanced solid tumors including r/r lymphoma.

In the phase II part (both single agent and combination groups), the study will be conducted in patients with glioblastoma.

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

[redacted]

5.2 Inclusion criteria

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

1. Written informed consent must be obtained prior to any screening procedures. **For Japanese patients only:** written consent is necessary both from the patient and his/her legal representative if he/she is under the age of 20 years.
2. Age ≥ 18 years
3. Phase I part: Patients with advanced/metastatic solid tumors, with measurable or unmeasurable disease as determined by RECIST v1.1 (refer to Appendix 1) or RANO (glioblastoma) (refer to Appendix 3), who have progressed despite standard therapy or are intolerant of standard therapy, or for whom no standard therapy exists, including patients with radiographically measurable r/r lymphoma according to the Guidelines for efficacy evaluation in Hodgkin and non-Hodgkin lymphoma studies (refer to Appendix 9) who have received at least two lines of available therapy and who have relapsed after transplant or who are not eligible for transplant.
4. Patients must have a site of disease amenable to biopsy, and be a candidate for tumor biopsy according to the treating institution's guidelines. Patients must be willing to undergo a new tumor biopsy at screening, and during treatment. Exceptions may be considered for glioblastoma patients after documented discussion with Novartis.
5. Phase II part (both single agent and combination groups): Patients with advanced/metastatic/recurrent isocitrate dehydrogenase (IDH) wild-type glioblastoma, with at least one measurable lesion as determined by RANO (refer to Appendix 3)
   - patients with O6-methylguanine-DNA methyltransferase (MGMT) methylated recurrent glioblastoma that failed to respond to or progressed on radiotherapy and temozolomide
   - patients with MGMT unmethylated recurrent glioblastoma that failed to respond to, or progressed on radiotherapy (with or without temozolomide)
   - patients who received no more than 2 prior lines of treatment (radiotherapy and temozolomide followed by temozolomide alone is considered one line of treatment)
   - patients who received no prior treatment with a VEGFR targeting agent (e.g. Avastin®).
6. Patient Eastern Cooperative Oncology Group (ECOG) performance status 0-1.
7. Life expectancy more than 12 weeks.
8. For glioblastoma patients enrolled in phase II of the study (both single agent and combination groups): if a newly obtained tumor sample cannot be safely collected at study entry, the patients must be willing to provide an archival tumor sample.

5.3 Exclusion criteria

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

1. Presence of symptomatic CNS metastases, or CNS metastases that require local CNS-directed therapy (such as radiotherapy or surgery), or increasing doses of corticosteroids within the prior 2 weeks before start of study treatment. Patients with treated brain metastases should be neurologically stable (for 4 weeks post-treatment and prior to

[redacted]

study enrollment) and off of steroids for at least 2 weeks before administration of any study drug (this exclusion criteria does not apply for GBM patients)

2. History of severe hypersensitivity reactions to study drugs(s) and other monoclonal antibodies and/or their excipients.
3. Having out of range laboratory values defined as:
   - Creatinine clearance (calculated using Cockcroft-Gault formula, or measured) < 40 mL/min or serum creatinine >1.5 x Upper Limit of Normal (ULN)
   - Total bilirubin > 1.5 x ULN, except for patients with Gilbert's syndrome who are excluded if total bilirubin > 3.0 x ULN or direct bilirubin > 1.5 x ULN
   - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 x ULN,
   - Absolute neutrophil count (ANC) < 1.0 x 10^9/L
   - Platelet count < 75 x 10^9/L
   - Hemoglobin < 9 g/dL
4. Impaired cardiac function or clinically significant cardiac disease, including any of the following:
   - Clinically significant and/or uncontrolled heart disease such as congestive heart failure requiring treatment (NYHA grade ≥ 2), uncontrolled hypertension or clinically significant arrhythmia
   - QTcF >470 msec on screening electrocardiogram (ECG) or congenital long QT syndrome
   - Acute myocardial infarction or unstable angina pectoris < 3 months prior to study entry
5. Known human immunodeficiency virus (HIV), active hepatitis B virus (HBV) or active hepatitis C virus (HCV) infection. No testing is required at screening. Patients whose HBV or HCV infection is controlled by antiviral therapy should not be excluded.
6. Malignant disease, other than that being treated in this study. Exceptions to this exclusion include the following: malignancies that were treated curatively and have not recurred within 2 years prior to study treatment; completely resected basal cell and squamous cell skin cancers; any malignancy considered to be indolent and that has never required therapy; and completely resected carcinoma *in situ* of any type.
7. Any medical condition that would, in the investigator's judgment, prevent the patient's participation in the clinical study due to safety concerns, compliance with clinical study procedures or interpretation of study results, including but not limited to:
   - ongoing symptomatic interstitial lung disease (ILD), noninfectious pneumonitis or history of drug induced interstitial lung disease
8. Active autoimmune disease or a documented history of autoimmune disease, including ulcerative colitis and Crohn's disease or any condition that requires systemic steroids, except vitiligo or resolved asthma/atopy that is treated with broncho-dilators (e.g. albuterol). Patients previously exposed to anti-PD-1/PD-L1 treatment who are adequately treated for skin rash or with replacement therapy for endocrinopathies should not be excluded.
9. Systemic steroid therapy or any immunosuppressive therapy (≥10mg/day prednisone or equivalent). Topical, inhaled, nasal and ophthalmic steroids are not prohibited. For GBM patients only: patients must not be receiving greater than 1 mg dexamethasone per day (or

[redacted]

an equivalent amount of an alternative corticosteroid) (Kostaras et al 2014). For the phase II part, patients must not be receiving more than 2 mg dexamethasone per day (or an equivalent amount of an alternative corticosteroid). The doses of corticosteroids must be stable within 2 weeks before baseline tumor assessments.

10. Use of any vaccines against infectious diseases (e.g. varicella, pneumococcus) within 4 weeks of initiation of study treatment.
11. 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. Prior antibodies or immunotherapies require a 4 weeks washout period.
12. Major surgery within 2 weeks of the first dose of study treatment (mediastinoscopy, insertion of a central venous access device, and insertion of a feeding tube are not considered major surgery).
13. Pre-treatment with anti-cytotoxic T-Lymphocyte-associated protein 4 (CTLA-4) antibodies in combination with any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathway. Patients pre-treated with anti-CTLA-4 as single agent must have minimum 8 week washout period between the last dose of anti-CTLA-4 and the first dose of PDR001.
14. Participation in an interventional, investigational non-immunotherapy study within 2 weeks of the first dose of study treatment.
15. Presence of ≥ common terminology criteria for adverse events (CTCAE) grade 2 toxicity (except alopecia, peripheral neuropathy and ototoxicity, which are excluded if ≥ CTCAE grade 3) due to prior cancer therapy.
16. Use of hematopoietic colony-stimulating growth factors (e.g. G-CSF, GM-CSF, M-CSF) and thrombopoietin mimetics ≤ 2 weeks prior to start of study drug. An erythroid stimulating agent is allowed as long as it was initiated at least 2 weeks prior to the first dose of study treatment and the patient is on a stable dose.
17. 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. For glioblastoma patients in phase II part only: last dose of radiotherapy within 3 months of the tumor assessment at screening.
18. Patient receiving treatment with medications that meet one of the following criteria and that cannot be discontinued at least 1 week prior to start of treatment and for the duration of the study (Appendix 6):
    - Strong inhibitors of CYP2C8 and of CYP3A4/5.
    - Strong inducers of CYP2C8 and of CYP3A4/5.
    - Proton pump inhibitors
    - Co-administration of moderate CYP2C8 and of CYP3A4/5 inhibitors
    - Co-administration of moderate CYP2C8 and of CYP3A4/5 inducers

[redacted]

19. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test.
20. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 14 days after last dose of BLZ945 as a single agent and for 150 days after the last dose of BLZ945 in combination with PDR001. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptom-thermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
    - Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient.
    - Use of oral (estrogen and progesterone), injected or implanted combined hormonal methods of contraception or placement of an intrauterine device or intrauterine system, or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

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

    Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (i.e. age appropriate [generally age from 40 to 59], history of vasomotor symptoms [e.g. hot flush] in the absence of other medical justification) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential
21. Sexually active males unless they use a condom during intercourse while taking the drug during treatment, for 14 days after stopping BLZ945 and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via semen.
22. Use of non-invasive antineoplastic therapy (e.g. Optune®) within 2 weeks of the tumor assessment at screening.

[redacted]

6 Treatment

6.1 Study treatment

For this study, the study drugs are BLZ945 and PDR001. The study treatment is defined as BLZ945 as a single agent or in combination with PDR001. Both study drugs will be provided by Novartis.

All dosages prescribed and dispensed to patients and all dose changes during the study must be recorded on the Dosage Administration Record electronic Case Report Form (eCRF).

6.1.1 Dosing regimen

BLZ945 dosing is being evaluated on the following schedules, 7 days on/7days off (i.e., administer BLZ945 for 7 days and suspend for 7 days), once weekly (Q1W), and 4 days on/10 days off (i.e., administer BLZ945 for 4 days and suspend for 10 days).

For each of these schedules, once per day (QD) or twice per day (BID) dosing may be evaluated. For once daily administration, patients should take their dose at approximately the same time in the morning. For the twice a day dosing, the first dose should be taken in the morning and the second dose should be taken approximately 10 to 12 hours after the morning dose.

On days that PK samples are obtained, the patient should take BLZ945 during the clinic visit after the pre-dose PK samples and prior to post-dose PK samples, when instructed by the study staff.

Patients should take BLZ945 on an empty stomach (i.e. fast from food and drink, except water) at least 1 hour before or 2 hours after a meal. Each dose should be taken with a glass of water.

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

If vomiting occurs during the course of treatment, patients should not take the study drug BLZ945 again before the next scheduled dose. For the BLZ945, a missed dose is defined as a case when the full dose is not taken up to one day after the approximate time of the usually daily dosing. That day's dose should be omitted and the patient should continue treatment with the next scheduled dose. If a patient forgets a prescribed once daily dose administration, and remembers in the morning within 4h of the scheduled dose time, BLZ945 can still be taken. Otherwise, dose must be skipped. For the twice a day dose administration, if a patient forgets to take the morning dose as scheduled but takes the morning dose within 4 hours of the scheduled dose time, the evening dose should be taken at least 8 hours apart from the morning dose. If the patient forgets to take the evening dose, it should be omitted except for the patient receiving BLZ945 once weekly as described below.

For the Q1W dosing, a missed once daily dose can still be taken the next morning. For the twice a day dose administration, a missed morning dose can still be taken the next morning 8h apart from the latest evening dose. A missed evening dose can still be taken the next morning at approximately the same time in the morning.

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
PDR001	Powder for solution for i.v. infusion	400 mg	every 4 weeks

[redacted]

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
BLZ945	Capsule, per os (p.o.)	150 mg (starting dose)	Once daily or twice a day either for 7days on/7days off Or Q1W Or 4days on/10days off

PDR001 will be administered via i.v. infusion over 30 minutes (up to 2 hours, if clinically indicated) once every 4 weeks. BLZ945 should be administered, whilst fasting, prior to PDR001. PDR001 infusion can start any time after BLZ945 intake.

Further instructions for the preparation and dispensation of PDR001 are described in the [BLZ945X2101 Pharmacy Manual].

The dose of PDR001 may be delayed by up to 7 days to recover from previous drug-related AEs. If the dose cannot be administered within the above mentioned 7-day window, then the dose should be skipped. Dosing will be resumed at the next scheduled dose. Dose modifications should be followed described in Section 6.3.1 and Section 6.3.2.

In case of study treatment interruption, visit schedule should still be followed and assessments performed as per Table 7-1.

6.1.2 Ancillary treatments

Patients should not receive pre-medication to prevent infusion reaction before the first infusion of PDR001, in order to determine if pre-medication is necessary. If a patient experiences an infusion reaction, he/she may receive pre-medication on subsequent dosing days. The pre-medication should be chosen per institutional standard of care, at the discretion of the treating physician.

Acute allergic reactions should be treated as needed per institutional standard of care. In the event of anaphylactic/anaphylactoid reactions, this includes any therapy necessary to restore normal cardiopulmonary status. If a patient experiences a Grade 3 anaphylactic/anaphylactoid reaction, the patient will be discontinued from the study.

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

Guidelines on management of PDR001 infusion reactions are provided in Table 6-6.

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

6.1.3 Treatment duration

All patients treated with either BLZ945 single agent or in combination with PDR001 will begin study treatment on Cycle 1 Day 1. Each cycle will consist of 28 days.

A patient may continue treatment with BLZ945 single agent until the patient experiences unacceptable toxicity, confirmed disease progression per irRC (or per iRANO for glioblastoma patients) or progressive (metabolic) disease per the Guidelines for efficacy evaluation in

[redacted]

Hodgkin and non-Hodgkin lymphoma studies for r/r lymphoma patients and/or treatment is discontinued at the discretion of the investigator or the patient.

A patient may continue treatment with BLZ945 in combination with PDR001 until the patient experiences unacceptable toxicity, confirmed disease progression per irRC (or per iRANO for glioblastoma patients) or progressive (metabolic) disease per the Guidelines for efficacy evaluation in Hodgkin and non-Hodgkin lymphoma studies for r/r lymphoma patients, and/or treatment is discontinued at the discretion of the investigator or the patient. In the first 24 weeks of treatment, patients will not be withdrawn from the study due to progressive disease per RECIST v1.1 (or per RANO for glioblastoma patients or per the Guidelines for efficacy evaluation in Hodgkin and non-Hodgkin lymphoma studies for r/r lymphoma patients). Refer to Section 7.1.2.

If treatment with BLZ945 has been interrupted for more than 4 consecutive weeks, then study treatment should be permanently discontinued. Refer to Table 6-5 and Table 6-6 for dose modification and interruption guidelines.

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

The above rules of discontinuation do not apply to GBM patients while evaluated with the iRANO criteria (Appendix 4).

Patients treated with BLZ945 in combination with PDR001 who meet criteria of discontinuation due to AE will not be allowed to continue on either drug as a single agent.

6.2 Dose escalation guidelines

6.2.1 Starting dose rationale

6.2.1.1 Starting dose of BLZ945 as a single agent

BLZ945 safety profile was investigated in 4-week GLP toxicology studies in rats (10, 50 and 150 mg/kg/day) and cynomolgus monkeys (10, 30 and 100 mg/kg/day). As shown below, the starting dose for BLZ945 of 150 mg as a single agent is estimated based on the STD10 in rat study, and the HNSTD from the monkey study following ICH S9 guidance:

- The STD10 for the GLP 4-week rat study is 150 mg/kg/day, with HED=24 mg/kg/day; 1/10 of STD10 HED=2.4 mg/kg/day
- The HNSTD for the 4-week GLP monkey study is 100 mg/kg/day, with HED=32 mg/kg/day; 1/6 of HNSTD HED=5.33 mg/kg/day.
- Rat is the sensitive species, thus the human starting dose will use HED calculated from 1/10 of STD10 in rat: 2.4 mg/kg*60kg = 144 mg/day

In order to evaluate the safety, PK and antitumor activity of BLZ945 across a range of doses, the recommended starting dose in this study will be 150 mg on a 7d on/7 off schedule.

[redacted]

Q1W or 4d on/10d off dosing may also be explored in parallel if deemed appropriate based on emerging PK and safety assessments. The starting dose of new schedule(s) will be equal or lower than the maximum dose that have been previously tested and met the EWOC criteria for the BLRM model on the 7d on/7d off schedule.

The Japanese dose escalation for BLZ945 single agent will run separately from the ongoing non-Japanese dose escalation with a starting dose deemed appropriate based on emerging PK and safety assessments and meeting the EWOC criteria of both the BLRM in the global dose escalation arm and that for the Japan specific escalation.

Twice daily dosing schedules may also be explored if deemed appropriate. The cumulative starting dose (i.e., morning dose plus evening dose) will not be higher than the dose of the once daily administration that has been tested and shown to satisfy the EWOC criteria using the Bayesian Hierarchical Logistic Regression Model (BHLRM) following a discussion with participating Investigators during a dose escalation teleconference.

6.2.1.2 Starting dose of BLZ945 and PDR001 combination

In order to administer a safe dose of BLZ945 in the combination with PDR001, the starting dose of BLZ945 will meet the following:

- Dose has already been tested in the single agent escalation arm
- At least one dose level below the highest investigated single agent dose for BLZ945 that satisfied the EWOC criterion under the appropriate single agent BLRM, is deemed appropriate based on emerging PK and safety assessments, and meets the EWOC criteria based on the BLRM of the combination model.
- Not less than the single agent starting dose (i.e. 150mg) unless DLT are observed at the starting dose.

In both combination dose escalations, PDR001 will be administered at a fixed dose of 400 mg i.v. every 4 weeks, which has been shown to be well tolerated.

6.2.2 Provisional dose levels

There will be three dose escalation arms in this study; Table 6-2 and Table 6-3 describe the starting doses and the provisional dose levels of the single-agent BLZ945 and the combinations of BLZ945 and PDR001 respectively that may be evaluated during this trial. With the exception of starting dose level 1, actual dose levels will be determined based on available toxicity, PK [redacted] data, guided by the BLRM, following a discussion with participating Investigators during dose escalation teleconference (Section 6.2.3). Dose escalation will continue until one or more MTDs/RP2Ds are determined.

[redacted]

Table 6-2 Provisional dose levels (BLZ945 single agent)

Dose level	Proposed dose of BLZ945*	Increment from previous dose
-1**	100 mg	-33%
1	150 mg	(starting dose)
2	300 mg	100%
3	600 mg	100%
4	900 mg	50%

*It is possible for additional and/or intermediate dose levels to be added during the course of the study Cohorts may be added at any dose level below the MTD in order to better understand safety, PK or PD.

**Dose level -1 represents treatment doses for patients requiring a dose reduction from the starting dose level. No dose reduction below dose level -1 is permitted for this study.

Table 6-3 Provisional dose levels (BLZ945 in combination with PDR001)

Dose level	Proposed dose of BLZ945*	Increment from previous dose	Proposed dose of PDR001
-1**	100 mg	-33%	400mg
1	150 mg	(starting dose)	400 mg
2	300 mg	100%	400 mg
3	600 mg	100%	400 mg
4	900 mg	50%	400 mg

*It is possible for additional and/or intermediate dose levels to be added during the course of the study Cohorts may be added at any dose level below the MTD in order to better understand safety, PK or PD.

**Dose level -1 represents treatment doses for patients requiring a dose reduction from the starting dose level. No dose reduction below dose level -1 is permitted for this study.

[redacted]

6.2.3 Guidelines for dose escalation and determination of MTD/RP2D

6.2.3.1 MTD definition

The maximum tolerated dose (MTD) is defined as:

- BLZ945 single agent and BLZ945 in combination with PDR001: the highest drug dosage that is unlikely (< 25% posterior probability) to cause DLT in 33% or more of the treated patients in the first cycle **(28 days)** of study treatment.

6.2.3.2 Dose cohort modification

6.2.3.2.1 Dose escalation cohorts

For the purposes of dose escalation decisions, each cohort will consist of 3 to 6 newly enrolled patients who will be treated at the specified dose level.

The dose escalation will proceed as follows:

BLZ945 single agent: The first cohort enrolled in the study will be treated with the starting dose as specified in Table 6-2. Once this cohort is complete and the dose escalation decision has been determined to escalate, the second cohort for the single agent will open.

BLZ945 in combination with PDR001: The combination dose escalation will proceed at least one dose level below the highest investigated single agent dose for BLZ945 shown to satisfy the EWOC criterion under the appropriate single agent BLRM, for more details refer to Section 6.2.1.2.

6.2.3.2.2 Dose escalation decisions

For the purpose of dose escalation decisions, patients can be considered evaluable after having met the following criteria:

BLZ945 single agent: Patients must complete a minimum of 1 cycle of BLZ945 treatment with the minimum safety evaluation and drug exposure (75% of the planned dosing days during cycle 1 as defined below) or have had a DLT within the first cycle of treatment to be considered evaluable for dose escalation decisions (Section 10.1.4).

BLZ945 in combination with PDR001:

Patients must complete a minimum of 1 cycle of treatment with the minimum safety evaluation and drug exposure (75% of the planned dosing days of BLZ945 as defined below and a dose of PDR001) or have had a DLT within the first cycle of treatment to be considered evaluable for dose escalation decisions (Section 10.1.4).

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

[redacted]

For other potential regimens, 75% of the planned dosing days of BLZ945 during cycle 1 will be determined using the same principle.

Dose escalation decisions will occur when the cohort of patients has met these criteria. If only 2 of the 3 patients in a cohort are evaluable and neither patient has experienced a treatment-related toxicity > CTCAE grade 2, dose escalation decisions may be considered.

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

The adaptive Bayesian methodology provides an estimate of all dose levels of BLZ945 as a single agent or in combination with PDR001 that do not exceed the MTD and incorporates all DLT information at all dose levels for this estimation. In general, the next dose will have the highest chance that the DLT rate will fall in the target interval [16-33%) and will always satisfy the EWOC principle. In all cases, the dose for the next cohort will not exceed a 100% increase from the previous dose. Smaller increases in dose may be recommended by the Investigators and Sponsor upon consideration of all of the available clinical data. Any dose escalation decisions made by investigators and Novartis personnel will not exceed the dose level identified by the BLRM as satisfying the EWOC principle.

If 2 patients in a previously untested dose level experience a DLT, enrollment to that cohort will stop, the BLRM will be updated and the next cohort will be opened at the next lower dose level or an intermediate dose level (see Table 6-2 and Table 6-3) that satisfies the EWOC criteria. However, if 2 patients in a new cohort at a previously tested dose level experience a DLT (e.g., a total of 8 patients are treated on this dose level with 2 DLT observed), further enrollment to that cohort will stop, the BLRM will be updated with this new information and re-evaluation of the available safety, PK, and PD data will occur. By incorporating information gained at the preceding dose cohorts, additional patients may be enrolled into the current dose cohort only if the combination still meets the EWOC criteria and as agreed by Investigators and Novartis personnel. Alternatively, if recruitment to the same cohort may not resume, a new cohort of patients may be recruited to a lower dose combination as agreed by Investigators and Novartis personnel and if the BLRM predicts that the risk for this lower dose combination to exceed the MTD remains below 25% (EWOC). Re-escalation may then occur if data in subsequent cohorts supports this (EWOC criteria are satisfied) and Investigators and Novartis personnel agree.

Dose escalation will continue until identification of the MTD or a suitable lower dose for expansion. This will occur when the following conditions are met:

1. at least 6 patients have been treated at this dose
2. this dose satisfies one of the following conditions:
    a. the posterior probability of targeted toxicity at this dose exceeds 50% and is the highest among potential doses, or

[redacted]

b. a minimum of 21 patients for single agent of global patients or 12 patients for the Japanese single agent dose escalation or 15 patients for combination have already been treated on the trial. Recommendation of RP2D may be made with fewer patients, prior to identification of MTD, or
c. significant activity is seen early in the phase I part, in which case a recommended dose for expansion may be identified and the phase II groups may be initiated without determination of the MTD.

3. it is the dose recommended for patients, either per the model or by review of all clinical data by Novartis and Investigators in a dose-escalation teleconference, see Section 6.2.3

To better understand the safety, tolerability and PK of single-agent BLZ945 or combinations of BLZ945 and PDR001 additional cohorts of patients may be enrolled at preceding dose levels, or to intermediate dose levels before or while proceeding with further dose escalation.

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

MTD of the combination would not exceed the MTD of the single agent as no DDI is expected.

6.2.3.3 Implementation of dose escalation decisions

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

6.2.3.4 Intra-Patient dose escalation

Intra-patient dose escalation is not permitted at any time within the first 4 cycles of treatment. After the 4th cycle is completed, individual patients may be considered for treatment at a dose of BLZ945 higher than the dose to which they were initially assigned. In order for a patient to be treated at a higher dose of BLZ945, he or she must have tolerated the lower dose for at least 2 cycles of therapy (i.e. he or she must not have experienced any BLZ945 or PDR001-related toxicity CTCAE grade ≥ 2 at the lower dose originally assigned). Moreover, the new, higher dose with which the patient is to be treated must be a dose that has completed evaluation and has been shown to satisfy the EWOC criterion. For any further increase after the initial intra-patient dose escalation, the following rules apply: the patient must have experienced no CTCAE grade ≥ 2, BLZ945 or PDR001-related toxicity over at least two cycles of therapy at the lower dose, and the higher dose being considered must have been fully evaluated and shown to satisfy the EWOC criterion. Consultation and agreement with Novartis must occur prior to any intra-patient dose escalation occurring. These changes must be recorded on the Dosage Administration Record eCRF. Data from the first cycle of treatment at the new dose level will

[redacted]

not be formally included into the statistical model describing the relationship between dose and occurrence of DLT. However, this data will be incorporated into the clinical assessment of safety within a dose escalation teleconference.

6.2.4 Definitions of dose limiting toxicities (DLTs)

A DLT is defined as an adverse event or abnormal laboratory value assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications that occurs within the first 28 days of treatment with BLZ945 as a single agent or in combination with PDR001 and meets any of the criteria included in Table 6-4. National Cancer Institute CTCAE version 4.03 will be used for all grading. For the purpose of dose-escalation decisions, DLTs will be considered and included in the BLRM.

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

The observation period for DLT in phase I part for Cycle 1 may be extended to 35 days for patients experiencing AE onset within the first 28 days of treatment and which requires to be followed up for up to 7 days to determine whether the AE is considered to be a DLT.

Table 6-4 Criteria for defining dose-limiting toxicities

For the purpose of dose escalation and cohort expansion, DLT will be adjudicated as follows: Any Grade 4 AEs will be considered DLTs with the exception of:	
	Neutropenia lasting <72 hours that is not associated with fever or other clinical symptoms.
	Lymphopenia.
	Electrolyte abnormalities that are not associated with clinical sequelae and are corrected with appropriate management or supplementation within 72 hours of the onset.
Any Grade 3 AEs will be adjudicated as DLTs with the exception of:	
	Infusion reaction that resolves to ≤ Grade 1 within 6 hours.
	Any hematologic toxicity lasting for < 7 consecutive days
	Lymphopenia
	Neutropenia lasting <7 days that is not associated with fever or other clinical symptoms.
	Nausea and vomiting persisting for < 2 days after optimal anti-emetic therapy.
	Thrombocytopenia without significant bleeding.
	Diarrhea persisting for < 2 days after optimal anti-diarrhea treatment.
	Hypertension persisting < 7 days after treatment.
	Infection or fever in the absence of neutropenia persisting < 5 days.
	Rash or photosensitivity persisting < 7 days after treatment.
	Fatigue lasting < 7 days.
	Immune-related adverse events persisting < 7 days after treatment with corticosteroids.
	AST or ALT for < 7 days
	Electrolyte abnormalities that resolve to ≤ Grade 1 < 7 days after starting supplementation.

[redacted]

For the purpose of dose escalation and cohort expansion, DLT will be adjudicated as follows: Any Grade 4 AEs will be considered DLTs with the exception of:	
The following Grade 2 AEs will be adjudicated as DLTs:	
	Total bilirubin ≥ CTCAE Grade 2 and AST or ALT Grade 2
	Pneumonitis persisting > 7 days despite treatment with corticosteroids.
	Eye pain or reduction of visual acuity that does not respond to topical therapy and does not improve to grade 1 severity within 2 weeks of the initiation of topical therapy OR requires systemic treatment.
	Other clinically significant toxicities, including a single event or multiple occurrences of the same event that lead to a dosing delay of > 7 days in cycle 1.

6.3 Dose modifications

6.3.1 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment (refer to Table 6-5 or Table 6-6 and Table 6-7). For the dose escalation part of the study, dose reductions during Cycle 1 are only allowed if a DLT is observed and recorded. Dose reductions are not permitted for PDR001.

The following guidelines may be applied:

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

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

If necessary, dose reduction will be conducted as indicated in Table 6-7. Any further dose reduction of BLZ945 may be performed only after documented discussion with the Novartis medical monitor.

[redacted]

Patients treated with BLZ945 in combination with PDR001 who meet criteria of discontinuation due to AE will not be allowed to continue on either drug as a single agent (refer to Section 6.1.3)

These changes must be recorded on the Dosage Administration Record Case Report Form (CRF).

6.3.2 Follow-up for toxicities

The emergence of immune-related AE (irAE) may be anticipated based on general experience in clinical studies with similar class of compounds that block the negative immune regulators or interfere with immune cell compartments.

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

Consensus management algorithms for irAEs have been developed and are available to assist investigators in assessing and managing irAEs (refer to Section 6.3.1).

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

In case of a suspected irAE, the relevant immunological assessments (e.g. rheumatoid factor (RF), anti-DNA antibody) should be performed. In case of a toxicity suspected to be a cytokine release syndrome, the assessments outlined in Section 7.2.2.5.6 must be performed. All patients must be followed up for irAEs, AEs and SAEs for 30 days following the last dose of BLZ945 single agent and for 150 days following the last dose of BLZ945 single agent in combination with PDR001.

Table 6-5 and Table 6-6 outlines the follow-up evaluation recommended for selected toxicities. For any irAEs/AEs Grade 1 and/or Grade 2, treatment with BLZ945 and/or PDR001 should be maintained at the determined dose and schedule, unless otherwise specified in Table 6-5.and Table 6-6

[redacted]

Table 6-5 Criteria for dose modifications and interruption of BLZ945 during treatment with BLZ945 as single agent

Recommended Dose Modification for BLZ945	
Worst toxicity CTCAE v4.03 Grade (unless otherwise specified)	**Recommended dose interruption, delay and discontinuation for study treatment during a cycle of treatment. These guidelines are recommendations only and should not obviate local Institutional Guidelines**
Hematology	
Neutropenia	
Grade 3 (ANC < 1000 - 500/mm^3)	Dose delay until resolved to ≤ Grade 1
Grade 4 (ANC < 500/mm^3)	Dose delay until resolved to ≤ Grade 1 if resolved in ≤ 7 days, then maintain dose level. If resolved in >7 days, ↓ 1 dose level.
Thrombocytopenia	
Grade 3 (PLT < 50,000 - 25,000/mm^3)	Dose delay until resolved to ≤ Grade 1 if resolved in ≤ 7 days, then maintain dose level. If resolved in >7 days, then ↓ 1 dose level. Discontinue for study treatment-related Grade 3 >21 days or associated with significant bleeding
Grade 4 (PLT < 25,000/mm^3)	Dose delay until resolved to ≤ Grade 1 if resolved to ≤ Grade 1 in ≤ 21 days, then ↓ 1 dose level. If resolved in >21days, then discontinue patient from study treatment.
Febrile neutropenia	
Grade 3 (ANC < 1.0 x 10^9/L, with a single temperature of > 38.3°C or a sustained temperature of ≥ 38°C for more than one hour)	Dose delay until resolved to ≤ Grade 1. if resolved in ≤ 21 days, then ↓ 1 dose level. If resolved in >21days, then discontinue patient from study treatment.
Grade 4 (ANC <500/mm^3)	Discontinue patient from study treatment

[redacted]

Recommended Dose Modification for BLZ945	
Worst toxicity CTCAE v4.03 Grade (unless otherwise specified)	**Recommended dose interruption, delay and discontinuation for study treatment during a cycle of treatment. These guidelines are recommendations only and should not obviate local Institutional Guidelines**
Lymphopenia	
Grade 3 (<0.5-0.2 x 10^9/L)	Maintain dose level for study treatment-related ≤ Grade 3.
Grade 4 (<0.2 x 10^9/L)	Dose delay until resolved to ≤ Grade 3. Grade 4 lymphopenia or leukopenia does not require discontinuation, delay treatment until resolved to ≤ Grade 3 in ≤ 28 days.
Renal	
Serum creatinine	
Grade 2 (> 1.5 - 3.0 x ULN)	Hold study treatment. Manage per institutional practice. Upon resolution to ≤ Grade 1, may resume study treatment without dose modification after discussion with the Novartis Medical Monitor.
Grade 3 (> 3.0 - 6.0 x ULN) or Grade 4 (> 6.0 x ULN)	Discontinue study treatment.
Hepatic	
Isolated total Bilirubin elevation	
Grade 2 (> 1.5 - 3.0 x ULN)	If baseline total bilirubin is within normal limits, dose delay until resolved to ≤ Grade 1. If baseline total bilirubin is Grade 1, patient may continue without dose delay.
Grade 3 (> 3.0 - 10.0 x ULN)	Dose delay until resolved to ≤ Grade 1, then may consider resuming study treatment after discussion with the Novartis Medical Monitor.
Grade 3 or Grade 4 (> 10.0 x ULN) due to the indirect (non-conjugated) component only	Firstly, rule out hemolysis as the etiology as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination). Then delay study treatment until resolved ≤ Grade 1, and resume study treatment at the discretion of the investigator.
Grade 4 (> 10.0 x ULN) due to other causes	Discontinue study treatment.

Recommended Dose Modification for BLZ945	
Worst toxicity CTCAE v4.03 Grade (unless otherwise specified)	**Recommended dose interruption, delay and discontinuation for study treatment during a cycle of treatment. These guidelines are recommendations only and should not obviate local Institutional Guidelines**
AST and/or ALT	
Grade 2 (> 3.0 - 5.0 x ULN)	Dose delay until resolved to ≤ Grade 1, then continue at same dose level. If baseline ALT/AST is Grade 1, patient may continue without dose delay if total bilirubin is less than Grade 2.
Grade 2 transaminase elevation with bilirubin >2 x ULN (unless Gilbert's syndrome)	If resolved in ≤7 days, then ↓ 1 dose level. If resolved in > 7 days: discontinue study treatment
Grade 3 (> 5.0 - 20.0 x ULN)	Dose delay until resolved to ≤ Grade 1. then: If resolved before the next scheduled administration of BLZ945 (7 days on/ 7 days off or once weekly: < 7 days; 4 days on / 10 days off: < 10 days), patient may continue at the same dose level. If resolved after the next scheduled administration of BLZ945: ↓ 1 dose level.
Grade 4 (> 20.0 x ULN)	Discontinue study treatment.
Asymptomatic amylase and/or lipase elevation**	
Grade 3 or Grade 4, not associated with symptoms or clinical manifestations of pancreatitis	Continue study treatment. If levels do not resolve to ≤ Grade 2 within ≤ 14 days after the initial report, hold study treatment. Upon resolution to ≤ Grade 2, may resume study treatment without dose modification, after discussion with the Novartis Medical Monitor.
Pancreatitis	
Grade 2/radiologic evidence	Hold study treatment. Manage per institutional practice. Upon resolution to ≤ Grade 1, may resume study treatment without dose modification, if no clinical evidence of pancreatitis and after discussion with the Novartis Medical Monitor.
Grade 3 or Grade 4	Discontinue study treatment.

[redacted]

Recommended Dose Modification for BLZ945	
Worst toxicity CTCAE v4.03 Grade (unless otherwise specified)	**Recommended dose interruption, delay and discontinuation for study treatment during a cycle of treatment. These guidelines are recommendations only and should not obviate local Institutional Guidelines**
Electrolyte abnormalities	
Grade 4	Isolated G4 electrolyte imbalances/abnormalities not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72hrs of their onset do not require discontinuation. Otherwise: If resolved to ≤ Grade 1 in ≤ 7 days, maintain dose level. If resolved to ≤ Grade 1 in > 7 days, then ↓ 1 dose level
Cardiovascular	
ECG QTc-Interval prolonged; hypertension	
Grade 3	Hold study treatment. Upon resolution to Grade ≤ 1 or baseline (hypertension, QTc) or < 30 msec difference from baseline (QTc) within ≤ 7 days, may resume study treatment without dose modification after discussion with the Novartis Medical Monitor. Baseline ECG refers to the ECG(s) collected at screening.
Grade 4	Discontinue study treatment.
Other cardiovascular disorders	
Grade 2 (except myocarditis)	Hold study treatment. Upon resolution to Grade ≤ 1 or baseline, may resume study treatment without dose modification after discussion with the Novartis Medical Monitor.
Grade 2 myocarditis, or Grade ≥ 3 other cardiac disorders related to study treatment	Discontinue study treatment.
Endocrine **Hypothyroidism or hyperthyroidism**	
Grade 2	May continue study treatment without dose modification. Management according to institutional practice.
Grade 3	Hold study treatment. Upon resolution to Grade ≤ 1 with appropriate management, may resume study treatment without dose modification.

[redacted]

Recommended Dose Modification for BLZ945	
Worst toxicity CTCAE v4.03 Grade (unless otherwise specified)	**Recommended dose interruption, delay and discontinuation for study treatment during a cycle of treatment. These guidelines are recommendations only and should not obviate local Institutional Guidelines**
Grade 4	May resume therapy following resolution or control with physiologic hormone replacement.
Other endocrine disorders	
Grade 2 and Grade 3	Hold study treatment. Upon resolution to Grade ≤ 1 with appropriate management, may resume study treatment without dose modification.
Grade 4	Hold study treatment. Grade 4 treatment-related endocrinopathies, such as adrenal insufficiency, adrenocorticotropic hormone (ACTH) deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Novartis Medical Monitor.
Dermatology (rash)	
Grade 1	Continue study treatment without dose modification. Topical steroids, antihistamines, topical emollients
Grade 2	Consider holding study treatment. Topical or oral steroids, antihistamines. If study treatment is held and resolution to ≤ Grade 1, resume study treatment without dose modification.
Grade 3 or Grade 4	Hold study treatment. Manage per institutional practice. After resolution to ≤ Grade 1, consider resuming study treatment after discussion with the Novartis Medical Monitor.
Bullous dermatitis	Hold study treatment. Grade 1-2 bullous dermatitis: discussion with the Novartis Medical Monitor is required before considering resuming study treatment. Grade 3 bullous dermatitis: consider resuming therapy after expert consultation and documented discussion with the Novartis medical monitor. Grade 4 bullous dermatitis: discontinue study treatment
Stevens-Johnson syndrome (SJS), or Lyell syndrome/toxic epidermal necrolysis (TEN)	
Any Grade	Permanently discontinue study treatment

[redacted]

Recommended Dose Modification for BLZ945	
Worst toxicity CTCAE v4.03 Grade (unless otherwise specified)	**Recommended dose interruption, delay and discontinuation for study treatment during a cycle of treatment. These guidelines are recommendations only and should not obviate local Institutional Guidelines**
Gastrointestinal	
Diarrhea/colitis ***	
Grade 1	May continue study treatment without dose modification. Manage per institutional standard guidelines which should include anti-diarrheal treatment, consideration of corticosteroid therapy, and hydration.
Grade 2	Hold study treatment. GI consultation. Upon resolution to ≤ Grade 1 and tapering of steroid requirement to ≤ 10 mg prednisone per day, resume treatment at same dose level after discussion with the Novartis Medical Monitor.
Grade 3	Hold study treatment. GI consultation. Upon resolution to ≤ Grade 1 and tapering of steroid requirement to ≤ 10 mg prednisone per day, consider resuming study treatment after discussion with the Novartis Medical Monitor.
Grade 4	Discontinue study treatment.
Fatigue/Asthenia	
Grade 3 or Grade 4	Dose delay until resolved to ≤ Grade 1 If resolved in ≤ 7 days, maintain dose level. If resolved in > 7 days, ↓ 1 dose level
Any neurological disorder	
Grade 2	Dose delay for study ≥ Grade 2 until resolved to ≤ Grade 1
Grade 3 or Grade 4	Discontinue for Grade 3 lasting > 7 days or Grade 4

[redacted]

Recommended Dose Modification for BLZ945	
Worst toxicity CTCAE v4.03 Grade (unless otherwise specified)	**Recommended dose interruption, delay and discontinuation for study treatment during a cycle of treatment. These guidelines are recommendations only and should not obviate local Institutional Guidelines**
Ocular (uveitis, eye pain, blurred vision)	
Grade 2	Dose delay for ≥ Grade 2 until resolved to ≤ Grade 1 If resolved in ≤ 21 days, then ↓ 1 dose level) Discontinue for any study treatment-related Grade 2 uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity in ≤ 21 days OR requires systemic treatment
Grade 3 or Grade 4	Discontinue for study treatment-related Grade 3 uveitis of any duration Discontinue for study treatment-related Grade 3 lasting > 7 days or Grade 4
Pulmonary (pneumonitis)	
Grade 1	Consider study treatment hold. Manage per institutional practice. Consider resuming study treatment upon radiographic evidence of improvement.
Grade 2	Hold study treatment. Pulmonary and infection workup. Upon resolution to ≤ Grade 1, may resume study treatment without dose modification.
Grade 3 or Grade 4	Discontinue study treatment.
Other non-laboratory toxicities	
Grade 3	Dose delay until resolved to ≤ Grade 1 If resolved in ≤ 21 days, ↓ 1 dose level. If resolved in >21 days, discontinue patient from study treatment.
Grade 4	Discontinue patient from study treatment.

[redacted]

Recommended Dose Modification for BLZ945	
Worst toxicity CTCAE v4.03 Grade (unless otherwise specified)	**Recommended dose interruption, delay and discontinuation for study treatment during a cycle of treatment. These guidelines are recommendations only and should not obviate local Institutional Guidelines**
Any other laboratory toxicities	
Grade 3 or Grade 4	Dose delay until resolved to ≤ Grade 1
****Note**: A CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within 1 week of the first occurrence of any ≥ Grade 3 of amylase and/or lipase. *****Note**: antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea.	

Table 6-6 Criteria for dose modifications and interruption for BLZ945 and PDR001 as combination treatmen

Recommended Dose Modification for BLZ945 and PDR001 For BLZ945 in combination with PDR001 treatment: Dose level maintenance, dose omission, and treatment discontinuation refer to both BLZ945 and PDR001. Reduction of one level refers to BLZ945 only, while PDR001 dose level should be maintained, unless otherwise specified.	
Worst toxicity CTCAE v4.03 Grade (unless otherwise specified)	**Recommended dose interruption, delay and discontinuation for study treatment during a cycle of treatment. These guidelines are recommendations only and should not obviate local Institutional Guidelines**
Infusion/Hypersensitivity reactions (for PDR001 only)	
Grade 1	Decrease PDR001 infusion rate until recovery of the symptoms
Grade 2	Stop PDR001 infusions immediately, and keep line open. Follow institutional guidelines for the management and follow-up of infusion reaction. Restart PDR001 infusion at 50% of previous rate under continuous observation. Ensure that there is a minimum observation period of 1 hour prior to restarting the infusion(s) If the AE recurs at the reinitiated slow rate of infusion, and despite oral pre-medication, then discontinue patient from study treatment
Grade 3 or Grade 4	Discontinue PDR001 infusion immediately, and discontinue patient from study Provide supplemental oxygen, fluids, and other resuscitative measures and/or measures for symptomatic relief (see under Grade 2, above) as needed. Monitor vital signs (e.g. blood pressure, pulse, respiration, and temperature) every 15 ± 5 minutes until resolution

[redacted]

Recommended Dose Modification for BLZ945 and PDR001 For BLZ945 in combination with PDR001 treatment: Dose level maintenance, dose omission, and treatment discontinuation refer to both BLZ945 and PDR001. Reduction of one level refers to BLZ945 only, while PDR001 dose level should be maintained, unless otherwise specified.	
Worst toxicity CTCAE v4.03 Grade (unless otherwise specified)	**Recommended dose interruption, delay and discontinuation for study treatment during a cycle of treatment. These guidelines are recommendations only and should not obviate local Institutional Guidelines**
Hematology	
Neutropenia	
Grade 3 (ANC < 1000 - 500/mm^3)	Dose delay until resolved to ≤ Grade 1
Grade 4 (ANC < 500/mm^3)	Dose delay until resolved to ≤ Grade 1 If duration > 7 days, discontinue patient for BLZ945 and PDR001
Thrombocytopenia	
Grade 3 (PLT < 50,000 - 25,000/mm^3)	Dose delay until resolved to ≤ Grade 1 in ≤ 21 days. If resolved in ≤ 7 days, then maintain dose level. If resolved in >7 days, then ↓ 1 dose level for BLZ945 and maintain PDR001 dose level. Discontinue patient from study treatment for Grade 3 >21 days or associated with significant bleeding
Grade 4 (PLT < 25,000/mm^3)	Discontinue study treatment
Febrile neutropenia	
Grade 3 (ANC < 1.0 x 10^9/L, with a single temperature of > 38.3°C or a sustained temperature of ≥ 38°C for more than one hour)	Dose delay for until resolved to ≤ Grade 1. If resolved in ≤ 21 days, then ↓ 1 dose level for BLZ945 and maintain PDR001 dose level. If resolved in >21days, then discontinue patient from study treatment.
Grade 4 (ANC <500/mm^3)	Discontinue patient from study treatment

[redacted]

Recommended Dose Modification for BLZ945 and PDR001 For BLZ945 in combination with PDR001 treatment: Dose level maintenance, dose omission, and treatment discontinuation refer to both BLZ945 and PDR001. Reduction of one level refers to BLZ945 only, while PDR001 dose level should be maintained, unless otherwise specified.	
Worst toxicity CTCAE v4.03 Grade (unless otherwise specified)	**Recommended dose interruption, delay and discontinuation for study treatment during a cycle of treatment. These guidelines are recommendations only and should not obviate local Institutional Guidelines**
Lymphopenia	
Grade 3 (<0.5-0.2 x 10^9/L)	Maintain dose level for study treatment-related ≤ Grade 3
Grade 4 (<0.2 x 10^9/L)	Dose delay until resolved to ≤ Grade 3 Study treatment-related Grade 4 lymphopenia or leukopenia does not require discontinuation, delay treatment until resolved to ≤ Grade 3 in ≤ 28 days.
Renal	
Serum creatinine	
Grade 2 (> 1.5 - 3.0 x ULN)	Hold study treatment. Manage per institutional practice. Upon resolution to ≤ Grade 1, may resume study treatment without dose modification after discussion with the Novartis Medical Monitor.
Grade 3 (> 3.0 - 6.0 x ULN) or Grade 4 (> 6.0 x ULN)	Discontinue study treatment.
Hepatic	
Isolated total Bilirubin elevation	
Grade 2 (> 1.5 - 3.0 x ULN)	If baseline total bilirubin is within normal limits, dose delay until resolved to ≤ Grade 1 If baseline total bilirubin is Grade 1, patient may continue without dose delay.
Grade 3 (> 3.0 - 10.0 x ULN)	Dose delay until resolved to ≤ Grade 1, then may consider resuming study treatment after discussion with the Novartis Medical Monitor.
Grade 3 or Grade 4 (> 10.0 x ULN) due to the indirect (non-conjugated) component only	Firstly, rule out hemolysis as the etiology as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination). Then delay study treatment until resolved ≤ Grade 1, and resume study treatment at the discretion of the investigator.
Grade 4 (> 10.0 x ULN) due to other causes	Discontinue study treatment.

[redacted]

Recommended Dose Modification for BLZ945 and PDR001 For BLZ945 in combination with PDR001 treatment: Dose level maintenance, dose omission, and treatment discontinuation refer to both BLZ945 and PDR001. Reduction of one level refers to BLZ945 only, while PDR001 dose level should be maintained, unless otherwise specified.	
Worst toxicity CTCAE v4.03 Grade (unless otherwise specified)	**Recommended dose interruption, delay and discontinuation for study treatment during a cycle of treatment. These guidelines are recommendations only and should not obviate local Institutional Guidelines**
AST and/or ALT	
Grade 2 (> 3.0 - 5.0 x ULN)	Dose delay until resolved to ≤ Grade 1, then continue at same dose level. If baseline ALT or AST is Grade 1, patient may continue without dose delay if total bilirubin is less than Grade 2.
Grade 2 transaminase elevation with bilirubin >2 x ULN (unless Gilbert's syndrome)	If resolved in ≤ 7 days, then ↓ 1 dose level for BLZ945, if resolved in > 7 days, then discontinue study treatments
Grade 3 (> 5.0 - 20.0 x ULN)	Dose delay until resolved to ≤ Grade 1. then: If resolved before the next scheduled administration of BLZ845 (7 days on/ 7 days off or once weekly: < 7 days; 4 days on / 10 days off: < 10 days), patient may continue at the same dose level. If resolved after the next scheduled administration of BLZ845 ↓ 1 dose level for BLZ945 and maintain PDR001 dose level.
Grade 4 (> 20.0 x ULN)	Discontinue study treatments.
Asymptomatic amylase and/or lipase elevation**	
Grade 3 or Grade 4, not associated with symptoms or clinical manifestations of pancreatitis	Continue study treatments. If levels do not resolve to ≤ Grade 2 within ≤ 14 days after the initial report, hold study treatments. Upon resolution to ≤ Grade 2, may resume study treatments without dose modification, after discussion with the Novartis Medical Monitor.
Pancreatitis	
Grade 2/radiologic evidence	Hold study treatments. Manage per institutional practice. Upon resolution to ≤ Grade 1, may resume study treatments without dose modification, if no clinical evidence of pancreatitis and after discussion with the Novartis Medical Monitor.
Grade 3 or Grade 4	Discontinue study treatments.

[redacted]

Recommended Dose Modification for BLZ945 and PDR001 For BLZ945 in combination with PDR001 treatment: Dose level maintenance, dose omission, and treatment discontinuation refer to both BLZ945 and PDR001. Reduction of one level refers to BLZ945 only, while PDR001 dose level should be maintained, unless otherwise specified.	
Worst toxicity CTCAE v4.03 Grade (unless otherwise specified)	**Recommended dose interruption, delay and discontinuation for study treatment during a cycle of treatment. These guidelines are recommendations only and should not obviate local Institutional Guidelines**
Electrolyte abnormalities	
Grade 4	Isolated G4 electrolyte imbalances/abnormalities not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72hrs of their onset do not require discontinuation. Otherwise: If resolved to ≤ Grade 1 in ≤ 7 days, maintain dose level. If resolved to ≤ Grade 1 in > 7 days, then ↓ 1 dose level for BLZ945 and maintain PDR001 dose level.
Cardiovascular	
ECG QTc-Interval prolonged; hypertension	
Grade 3	Hold study treatments. Upon resolution to Grade ≤ 1 or baseline (hypertension, QTc) or < 30 msec difference from baseline (QTc) within ≤ 7 days, may resume study treatments without dose modification after discussion with the Novartis Medical Monitor. Baseline ECG refers to the ECG(s) collected at screening.
Grade 4	Discontinue study treatments.
Other cardiovascular disorders	
Grade 2 (except myocarditis)	Hold study treatments. Upon resolution to Grade ≤ 1 or baseline, may resume study treatments without dose modification after discussion with the Novartis Medical Monitor.
Grade 2 myocarditis, or Grade ≥ 3 other cardiac disorders related to study treatment	Discontinue study treatments.

[redacted]

Recommended Dose Modification for BLZ945 and PDR001 For BLZ945 in combination with PDR001 treatment: Dose level maintenance, dose omission, and treatment discontinuation refer to both BLZ945 and PDR001. Reduction of one level refers to BLZ945 only, while PDR001 dose level should be maintained, unless otherwise specified.	
Worst toxicity CTCAE v4.03 Grade (unless otherwise specified)	**Recommended dose interruption, delay and discontinuation for study treatment during a cycle of treatment. These guidelines are recommendations only and should not obviate local Institutional Guidelines**
Endocrinopathy **Hypothyroidism or hyperthyroidism**	
Grade 2	May continue study treatment without dose modification. Management according to institutional practice.
Grade 3	Hold study treatment. Upon resolution to Grade ≤ 1 with appropriate management, may resume study treatment without dose modification.
Grade 4	May resume therapy following resolution or control with physiologic hormone replacement.
Other endocrine disorders	
Grade 2 and Grade 3	Hold study treatment. Upon resolution to Grade ≤ 1 with appropriate management, may resume study treatment without dose modification.

[redacted]

Recommended Dose Modification for BLZ945 and PDR001 For BLZ945 in combination with PDR001 treatment: Dose level maintenance, dose omission, and treatment discontinuation refer to both BLZ945 and PDR001. Reduction of one level refers to BLZ945 only, while PDR001 dose level should be maintained, unless otherwise specified.	
Worst toxicity CTCAE v4.03 Grade (unless otherwise specified)	**Recommended dose interruption, delay and discontinuation for study treatment during a cycle of treatment. These guidelines are recommendations only and should not obviate local Institutional Guidelines**
Dermatology (rash)	
Grade 1	Continue study treatment without dose modification. Topical steroids, antihistamines, topical emollients
Grade 2	Consider holding study treatment. Topical or oral steroids, antihistamines. If study treatment is held and resolution to ≤ Grade 1, resume study treatment without dose modification.
Grade 3 or Grade 4	Hold study treatment. Manage per institutional practice. After resolution to ≤ Grade 1, consider resuming study treatment after discussion with the Novartis Medical Monitor.
Bullous dermatitis	Hold study treatment. Grade 1-2 bullous dermatitis: discussion with the Novartis Medical Monitor is required before considering resuming study treatment. Grade 3 bullous dermatitis: consider resuming therapy after expert consultation and documented discussion with the Novartis medical monitor. Grade 4 bullous dermatitis: discontinue study treatment
Stevens-Johnson syndrome (SJS), or Lyell syndrome/toxic epidermal necrolysis (TEN)	
Any Grade	Permanently discontinue study treatment

[redacted]

Recommended Dose Modification for BLZ945 and PDR001 For BLZ945 in combination with PDR001 treatment: Dose level maintenance, dose omission, and treatment discontinuation refer to both BLZ945 and PDR001. Reduction of one level refers to BLZ945 only, while PDR001 dose level should be maintained, unless otherwise specified.	
Worst toxicity CTCAE v4.03 Grade (unless otherwise specified)	**Recommended dose interruption, delay and discontinuation for study treatment during a cycle of treatment. These guidelines are recommendations only and should not obviate local Institutional Guidelines**
Gastrointestinal	
Diarrhea/colitis ***	
Grade 1	May continue study treatment without dose modification. Manage per institutional standard guidelines which should include anti-diarrheal treatment, consideration of corticosteroid therapy, and hydration.
Grade 2	Hold study treatment. GI consultation. Upon resolution to ≤ Grade 1 and tapering of steroid requirement to ≤ 10 mg prednisone per day, resume treatment at same dose level after discussion with the Novartis Medical Monitor.
Grade 3	Hold study treatment. GI consultation. Upon resolution to ≤ Grade 1 and tapering of steroid requirement to ≤ 10 mg prednisone per day, consider resuming study treatment after discussion with the Novartis Medical Monitor.
Grade 4	Discontinue study treatment.
Fatigue/Asthenia	
Grade 3 or Grade 4	Dose delay for study treatment-related Grade 3 until resolved to ≤ Grade 1 Discontinue for study treatment-related Grade 3 lasting > 7 days or Grade 4.
Any neurological disorder	
Grade 2	Dose delay for ≥ Grade 2 until resolved to ≤ Grade 1
Grade 3 or Grade 4	Discontinue for Grade 3 lasting > 7 days or Grade 4

[redacted]

Recommended Dose Modification for BLZ945 and PDR001 For BLZ945 in combination with PDR001 treatment: Dose level maintenance, dose omission, and treatment discontinuation refer to both BLZ945 and PDR001. Reduction of one level refers to BLZ945 only, while PDR001 dose level should be maintained, unless otherwise specified.	
Worst toxicity CTCAE v4.03 Grade (unless otherwise specified)	**Recommended dose interruption, delay and discontinuation for study treatment during a cycle of treatment. These guidelines are recommendations only and should not obviate local Institutional Guidelines**
Ocular (uveitis, eye pain, blurred vision)	
Grade 2	Dose delay for ≥ Grade 2 until resolved to ≤ Grade 1 (If resolved in ≤ 21 days, then ↓ 1 dose level for BLZ945 and maintain PDR001 dose level) Discontinue for any study treatment-related Grade 2 uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity in ≤ 21 days OR requires systemic treatment
Grade 3 or Grade 4	Discontinue for study treatment-related Grade 3 uveitis of any duration Discontinue for study treatment-related Grade 3 lasting > 7 days or Grade 4
Pulmonary (pneumonitis)	
Grade 1	Consider study treatment hold. Manage per institutional practice. Consider resuming study treatment upon radiographic evidence of improvement.
Grade 2	Hold study treatment. Pulmonary and infection workup. Upon resolution to ≤ Grade 1, may resume study treatment without dose modification.
Grade 3 or Grade 4	Discontinue study treatment.
Cytokine release syndrome (CRS)	
Grade 2	Stop infusion immediately, and keep line open. Follow institutional guidelines for the management and follow-up of infusion reaction. Restart infusion at 50% of previous rate under continuous observation. Ensure that there is a minimum observation period of 1 hour prior to restarting the infusion. If the AE recurs at the reinitiated slow rate of infusion, and despite oral pre-medication, then permanently discontinue study treatment.
Grade 3 or Grade 4	Discontinue study treatment.
Follow-up CRS as per institutional guidelines.	

[redacted]

Recommended Dose Modification for BLZ945 and PDR001 For BLZ945 in combination with PDR001 treatment: Dose level maintenance, dose omission, and treatment discontinuation refer to both BLZ945 and PDR001. Reduction of one level refers to BLZ945 only, while PDR001 dose level should be maintained, unless otherwise specified.	
Worst toxicity CTCAE v4.03 Grade (unless otherwise specified)	**Recommended dose interruption, delay and discontinuation for study treatment during a cycle of treatment. These guidelines are recommendations only and should not obviate local Institutional Guidelines**
Other non-laboratory adverse events	
Grade 3	Dose delay until resolved to ≤ Grade 1 Discontinue from study treatment if lasting > 7 days. If resolved in ≤ 7 days, ↓ 1 dose level for BLZ945 and maintain PDR001 dose level.
Grade 4	Discontinue patient from study treatment.
Any other laboratory toxicities	
Grade 3 or Grade 4	Dose delay until resolved to ≤ Grade 1
Note: Dose reductions for PDR001 are not permitted ****Note**: A CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within 1 week of the first occurrence of any ≥ Grade 3 of amylase and/or lipase. *****Note**: antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea.	

[redacted]

Table 6-7 Dose reduction steps for BLZ945 (Phase II only)

Dose reduction (BLZ945 administered as single agent)			
	Starting dose level and schedule	Dose reduction level – 1 and schedule	Dose reduction level – 2 and schedule#
BLZ945	1200 mg, 4 days on/10 days off	800 mg, 4 days on/10 days off	600 mg, 4 days on/10 days off
Dose reduction (BLZ945 in combination with PDR001)*			
BLZ945	700 mg, 4 days on/10 days off	450 mg, 4 days on/10 days off	300 mg, 4 days on/10 days off
*: PDR001 dose remains fixed at 400 mg, every 4 weeks #: Any further dose reduction beyond the Dose level -2 of BLZ945 may be performed only after documented discussion with the Novartis medical monitor.			

6.3.3 Anticipated risks and safety concerns of the study drugs

Appropriate eligibility criteria and specific DLT definitions, as well as specific dose modification and stopping rules are included in this protocol. Recommended guidelines for prophylactic or supportive management of study-drug induced AEs are provided in Table 6-5 and Table 6-6. The risk to subjects in this trial may be minimized by compliance with the eligibility criteria and study procedures as well as close clinical monitoring. There may be unforeseen risks with BLZ945 and PDR001 treatment which could be serious. Refer to the [BLZ945 Investigator's Brochure] and [PDR001 Investigator's Brochure] respectively.

6.4 Concomitant medications

6.4.1 Permitted concomitant therapy

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

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

6.4.2 Prohibited concomitant therapy

Preclinical data suggest that BLZ945 is metabolized in human via CYP3A4/5 and CYP2C8.

The following medications are prohibited in this study:

- Strong inhibitors or inducers of CYP3A4/5 or CYP2C8 are prohibited (refer to Appendix 7).
- Co-administration of moderate CYP3A4/5 and CYP2C8 inhibitors
- Co-administration of moderate CYP3A4/5 and CYP2C8 inducers

[redacted]

- Furthermore, concomitant medications with known QT risk or possible risk to prolong the QT interval are also prohibited.
- The use of proton pump inhibitors is not allowed since they alter the pH of the upper GI tract with a long duration of action of 48 to 72 hours.

BLZ945 shows pH dependent solubility (refer to Section 1.2.1.1.1). Concomitant medications which are known to increase the pH in the GI tract will have an impact on the solubility of BLZ945. Concomitant use of long-acting proton pump inhibitors is prohibited. Examples of this class of drugs include: omeprazole, pantoprazole, and lansoprazole. If patients are using proton pump inhibitors at the time of screening, these drugs must be discontinued at least 7 days prior to the first dose of study treatment.

Treatment with hematopoietic colony-stimulating growth factors (e.g. G-CSF, GM-CSF, M-CSF) and thrombopoietin mimetics should not be taken during the study.

During the course of the study, patients must not receive other additional study drugs, devices, chemotherapy, or any other therapies that may be active against cancer or modulate the immune responses. Additionally, no other therapeutic monoclonal antibodies and no immunosuppressive medication should be administered while on this study.

The use of systemic steroid therapy and other immunosuppressive drugs is not allowed, with the only exclusion of steroids for the treatment of an infusion reaction, irAEs, replacement-dose steroids in the setting of adrenal insufficiency (providing this is ≤ 10mg/day prednisone or equivalent) or treatment of glioblastoma. Systemic corticosteroids required for the control of infusion reactions or irAEs must be tapered and be at non-immunosuppressive doses (≤ 10 mg/day of prednisone or equivalent) before the next study drug administration. If more than 10 mg/day prednisone is used, study treatment should be suspended (Topical, inhaled, nasal and ophthalmic steroids for any purpose or steroids for the treatment of glioblastoma are not prohibited).

The use of live vaccines is not allowed through the whole duration of the study. Other vaccines are excluded, except inactivated seasonal influenza vaccines.

Refer to Appendix 7 for a list of prohibited medications. If a patient must use a drug in Appendix 7, the patient must be discontinued from the study.

6.4.3 Permitted concomitant therapy requiring caution and/or action

The following medications are to be used with caution in this study:

Concomitant medications which are known to be moderate inhibitors or inducers of CYP3A4/5 or CYP2C8 are permitted to be used with caution but not in combination.

Refer to Appendix 8 for permitted medications that require caution when concomitantly used with study treatment.

Drugs that alter the pH of the upper GI tract (e.g., H2-receptor antagonists, antacids) may alter the solubility of BLZ945 and reduce its bioavailability. Short acting gastric acid modulators containing aluminum hydroxide and magnesium hydroxide, (e.g., Maalox®) or calcium carbonate (e.g., TUMS®) can be taken. However, it is recommended to take these drugs at least 1 hour before or 2 hours after administration of BLZ945. H2 receptor antagonists should be

[redacted]

avoided. If patients are using H2 receptor antagonists (e.g. ranitidine) during the course of this study, patients should take BLZ945 at least 3 hours before H2 receptor antagonists. In addition, next dose schedule of BLZ945 administration should be at least 6 hours after taking H2 receptor antagonists.

If a patient is using erythropoiesis stimulating agents prior to enrollment (at least 2 weeks before start of study treatment), he/she may continue at the same dose.

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

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

A brief (< 24 hours) course of steroids for prophylaxis against contrast dye allergy is permitted for patients undergoing tumor assessments with exposure to the allergen.

6.4.4 Prohibited food

Patients must avoid 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 due to potential CYP3A interaction.

6.5 Patient numbering, treatment assignment or randomization

6.5.1 Patient numbering

Each patient is identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each patient is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Subject No. available to the investigator through the Oracle Clinical RDC interface. Once assigned, the Patient No. must not be reused for any other patient and the Patient No. for that individual must not be changed, even if the patient is re-screened. If the patient fails to start treatment for any reason, the reason will be entered into the Screening Disposition eCRF page.

6.5.2 Treatment assignment or randomization

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

6.6 Study drug preparation and dispensation

The Investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Study drug(s) will be dispensed to the patient by authorized site

[redacted]

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

BLZ945

BLZ945 capsules including instructions for administration are dispensed by study personnel on an outpatient basis. Patients will be provided with adequate supply of study treatment for self-administration at home until at least their next scheduled visit.

PDR001

PDR001 will be administered intravenously as an infusion (Section 6.1.1). Further instructions for the preparation and dispensation of PDR001 are described in the [BLZ945X2101 Pharmacy Manual].

6.6.1 Study treatment packaging and labeling

Study treatment will be provided as global clinical open supply and will be packed and labeled under the responsibility of Novartis, Drug Supply Management.

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

BLZ945 (50 mg and 200 mg strengths capsules) will be prepared by Novartis and supplied to investigator in blister packs or high density polyethylene bottles.

Study treatment labels will be in the local language and comply with the legal requirements of each country and will include storage conditions for the drug and a unique medication number. If the label has 2-parts (base plus tear-off label), immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the package and affix it to the patient‘s source document.

6.6.2 Drug supply and storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, BLZ945 and/or PDR001 should be stored according to the instructions specified on the drug labels and in the [Investigator’s Brochure].

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug compliance

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

6.6.3.2 Study drug accountability

The Investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field

[redacted]

monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

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

6.6.4 Disposal and destruction

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

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1, Table 7-2, Table 7-3 and Table 7-4 list all of the assessments and indicates with an "X", the visits when they are performed. **For Japan only**: patients are required to be hospitalized in Cycle 1 of the dose escalation part. All data obtained from these assessments must be supported in the patient's source documentation.

No CRF will be used as a source document.

Screening evaluations must be performed ≤ 28 days of Cycle 1 Day 1 (except for the pregnancy test which has to be performed within 72 hours before first dose). Assessments performed as part of the screening evaluations and within 3 days prior to the first dose of study treatment, are not required to be repeated on Cycle 1 Day 1. Laboratory and radiological assessments performed as part of standard of care prior to signing informed consent may be used if performed ≤ 28 days of Cycle 1 Day 1.

During the course of the study visits, test and/or procedures should occur on schedule whenever possible. A visit window of ± 3 days is allowed. On PK collection days the windows are provided in Section 7.2.3.

Radiological assessments must be performed ±7 days of the scheduled date of the assessment.

[redacted]

Table 7-1 Visit evaluation schedule for BLZ945 7d on / 7d off

Visit Name	Category	Protocol Section	Screening	Cycle 1						Cycle 2			Cycle 3			Subsequent cycles	EoT	30 days or 150 days Safety*	Disease progression	Survival
Day of cycle			**-28 to -1**	**1**	**2**	**7**	**8**	**11**	**15**	**1**	**2**	**15**	**1**	**8**	**15**	**1**				
Obtain Informed Consent	D	7.1.1	X																	
Demography	D	7.1.1.2	X																	
Inclusion/ exclusion criteria	D	5.2 5.3	X																	
Medical History	D	7.1.1.2	X																	
Diagnosis and extent of cancer	D	7.1.1.2	X																	
Prior antineoplastic therapies	D	7.1.1.2	X																	
Prior/concomitant medications, surgery and medical procedures	D	7.1.1.2	X	Continuous																
Physical examination	S	7.2.2.1	X	X			X		X	X		X	X			X	X			
Chest X-ray+	D	7.2.2.7	X							X										
Vital signs	D	7.2.2.2	X	X			X		X	X		X	X			X	X			
Height	D	7.2.2.3	X																	
Weight	D	7.2.2.3	X	X						X			X			X	X			
ECOG status	D	7.2.2.4	X	X						X			X			X	X			
Hematology	D	7.2.2.5	X	X			X		X	X		X	X			X	X			
Chemistry	D	7.2.2.5	X	X	X		X		X	X	X	X	X			X	X			
Coagulation	D	7.2.2.5	X	X						X			X			X	X			
Urinalysis	D	7.2.2.5	X	If clinically indicated													X			

[redacted]

Visit Name	Category	Protocol Section	Screening	Cycle 1						Cycle 2			Cycle 3			Subsequent cycles	EoT	30 days or 150 days Safety*	Disease progression	Survival
Day of cycle			**-28 to -1**	**1**	**2**	**7**	**8**	**11**	**15**	**1**	**2**	**15**	**1**	**8**	**15**	**1**				
Thyroid function	D	7.2.2.5	X	X						X			X			X	X			
Serology exam	D	7.2.2.5	X	X						X			X			X	X			
Serum Pregnancy test	D	7.2.2.5	X							X			X			X	X			
Urine pregnancy test	S	7.2.2.5																X		
Antineoplastic therapies since discontinuation of study treatment	D	7.1.5																X	X	X
Tumor evaluation	D	7.2.1	X	**During treatment**: starting on Cycle 3 Day 1, every 2 cycles until Cycle 11 Day 1, and then every 3 cycles until progression of disease or patient withdrawal. **Follow-up for progression:** every 8 weeks until week 40, then every 12 weeks until progression of disease or lost to follow-up. **EOT:** if a scan was not conducted within 30 days prior to end of study treatment. Additional assessments may be performed to confirm progressive disease as described in Section 7.2.1																
12-Lead ECG	D	7.2.2.6	X	X		X							X			X (Cycle 6 only)	X			
Adverse events	D	8	Continuous																	
Collection of new tumor sample	D	7.2.4	X								X (day 2-3)									
Blood collection for biomarker analyses (plasma & PBMC)	D	7.2.4		X	X (day 2-3)						X (day 2-3)		X			X (Cycle 5 only)	X			
PDR001 infusion (only in combination)	D	6.1.1		i.v. every 4 weeks																
BLZ945 administration	D	6.1.1		7d on /7d off																

[redacted]

Visit Name	Category	Protocol Section	Screening	Cycle 1						Cycle 2			Cycle 3			Subsequent cycles	EoT	30 days or 150 days Safety*	Disease progression	Survival
Day of cycle			**-28 to -1**	**1**	**2**	**7**	**8**	**11**	**15**	**1**	**2**	**15**	**1**	**8**	**15**	**1**				
Blood sample for PK analysis (for BLZ945 single agent)	D	7.2.3		X	X	X	X	X+		X			X				X			
Blood sample for PK analysis (for BLZ945 + PDR001)	D	7.2.3		X	X	X	X	X+	X	X			X	X	X	X (up to Cycle 6)	X	X		
Blood sample for ADA analysis(for BLZ945 + PDR001)	D	7.2.3		X						X			X			X (up to Cycle 6)	X	X		
[redacted]																				
Survival contact (every 3 months)	D	7.1.5																		X

* 30-day safety follow-up for patients treated with BLZ945 single agent. 150 days safety follow-up for patients treated with BLZ945 in combination with PDR001 with safety evaluations (i.e. 30-day, 90-day and 150-day follow-up)

+ Only for patients in Japan during dose escalation

Patients in Japan enrolled in dose escalation are required to be hospitalized during cycle 1

[redacted]

Table 7-2 Visit evaluation schedule for BLZ945 Q1W

Visit Name	Category	Protocol Section	Screening	Cycle 1						Cycle 2			Cycle 3					Subsequent cycles	EoT	30 days or 150 days	Disease progression	Survival
Day of cycle			**-28 to -1**	**1**	**2**	**8**	**9**	**11**	**15**	**1**	**2**	**15**	**1**	**2**	**8**	**11**	**15**	**1**				
Obtain Informed Consent	D	7.1.1	X																			
Demography	D	7.1.1.2	X																			
Inclusion/ exclusion criteria	D	5.2 5.3	X																			
Medical History	D	7.1.1.2	X																			
Diagnosis and extent of cancer	D	7.1.1.2	X																			
Prior antineoplastic therapies	D	7.1.1.2	X																			
Prior/concomitant medications, surgery and medical procedures	D	7.1.1.2	X	Continuous																		
Physical examination	S	7.2.2.1	X	X		X			X	X		X	X					X	X			
Chest X-ray+	D	7.2.2.7	X							X												
Vital signs	D	7.2.2.2	X	X		X			X	X		X	X					X	X			
Height	D	7.2.2.3	X																			
Weight	D	7.2.2.3	X	X						X			X					X	X			
ECOG status	D	7.2.2.4	X	X						X			X					X	X			
Hematology	D	7.2.2.5	X	X		X			X	X		X	X					X	X			
Chemistry	D	7.2.2.5	X	X	X	X	X		X	X	X	X	X					X	X			
Coagulation	D	7.2.2.5	X	X						X			X					X	X			

[redacted]

Visit Name	Category	Protocol Section	Screening	Cycle 1						Cycle 2			Cycle 3					Subsequent cycles	EoT	30 days or 150 days	Disease progression	Survival
Day of cycle			**-28 to -1**	**1**	**2**	**8**	**9**	**11**	**15**	**1**	**2**	**15**	**1**	**2**	**8**	**11**	**15**	**1**				
Urinalysis	D	7.2.2.5	X	If clinically indicated															X			
Thyroid function	D	7.2.2.5	X	X						X			X					X	X			
Serology exam	D	7.2.2.5	X	X						X			X					X	X			
Serum Pregnancy test	D	7.2.2.5	X							X			X					X	X			
Urine pregnancy test	S	7.2.2.5																		X		
Antineoplastic therapies since discontinuation of study treatment	D	7.1.5																		X	X	X
Tumor evaluation	D	7.2.1	X	**During treatment**: starting on Cycle 3 Day 1, every 2 cycles until Cycle 11 Day 1, and then every 3 cycles until progression of disease or patient withdrawal. **Follow-up for progression:** every 8 weeks until week 40, then every 12 weeks until progression of disease or lost to follow-up. **EOT:** if a scan was not conducted within 30 days prior to end of study treatment. Additional assessments may be performed to confirm progressive disease as described in Section 7.2.1																	
12-Lead ECG	D	7.2.2.6	X	X		X							X					X (Cycle 6 only)	X			
Adverse events	D	8	Continuous																			
Collection of new tumor sample	D	7.2.4	X								X (day 2-3)											

[redacted]

Visit Name	Category	Protocol Section	Screening	Cycle 1						Cycle 2			Cycle 3					Subsequent cycles	EoT	30 days or 150 days	Disease progression	Survival
Day of cycle			**-28 to -1**	**1**	**2**	**8**	**9**	**11**	**15**	**1**	**2**	**15**	**1**	**2**	**8**	**11**	**15**	**1**				
Collection of archival tumor sample & associated de-identified pathology report	D	7.2.4	X[#]																			
Blood collection for biomarker analyses (plasma & PBMC)	D	7.2.4		X	X (day 2-3)						X (day 2-3)			X (day 2-4)				X (Cycle 5 only)	X			
PDR001 infusion (only in combination)	D	6.1.1		i.v. every 4 weeks																		
BLZ945 administration	D	6.1.1		Q1W																		
Blood sample for PK analysis (for BLZ945 single agent)	D	7.2.3		X	X	X	X	X[+]		X	X		X	X					X			
Blood sample for PK analysis (for BLZ945 + PDR001)	D	7.2.3		X	X	X	X	X[+]	X	X	X	X	X	X	X		X	X (up to Cycle 6)	X	X		
Blood sample for ADA analysis(for BLZ945 + PDR001)	D	7.2.3		X						X			X					X (up to Cycle 6)	X	X		

[redacted]

Visit Name	Category	Protocol Section	Screening	Cycle 1						Cycle 2			Cycle 3					Subsequent cycles	EoT	30 days or 150 days	Disease progression	Survival
Day of cycle			**-28 to -1**	**1**	**2**	**8**	**9**	**11**	**15**	**1**	**2**	**15**	**1**	**2**	**8**	**11**	**15**	**1**				
[redacted]																						
Survival contact (every 3 months)	D	7.1.5																				X

* 30-day safety follow-up for patients treated with BLZ945 single agent. 150 days safety follow-up for patients treated with BLZ945 in combination with PDR001 with safety evaluations (i.e. 30-day, 90-day and 150-day follow-up)

For glioblastoma patients for whom the newly obtained tumor samples were not collected at study entry only. For any glioblastoma patients who completed the screening phase and are ongoing at the time of protocol amendment 6 approval, if a newly obtained tumor sample was not collected at study entry, retrospective submission of an archival tumor sample is required. The associated de-identified pathology report is also requested.

+ Only for patients in Japan during dose escalation

Patients in Japan enrolled in dose escalation are required to be hospitalized during cycle 1

[redacted]

Table 7-3 Visit evaluation schedule for BLZ945 4d on / 10d off (phase I)

Visit Name	Category	Protocol Section	Screening	Cycle 1								Cycle 2			Cycle 3				Subsequent cycles	EoT	30 days or 150 days	Disease progression	Survival
Day of cycle			**-28 to -1**	**1**	**2**	**4**	**5**	**8**	**11**	**15**	**19**	**1**	**2**	**15**	**1**	**2**	**8**	**15**	**1**				
Obtain Informed Consent	D	7.1.1	X																				
Demography	D	7.1.1.2	X																				
Inclusion/ exclusion criteria	D	5.2 5.3	X																				
Medical History	D	7.1.1.2	X																				
Diagnosis and extent of cancer	D	7.1.1.2	X																				
Prior antineoplastic therapies	D	7.1.1.2	X																				
Prior/concomitant medications, surgery and medical procedures	D	7.1.1.2	X	Continuous																			
Physical examination	S	7.2.2.1	X	X			X			X		X		X	X				X	X			
Chest X-ray+	D	7.2.2.7	X									X											
Vital signs	D	7.2.2.2	X	X			X			X		X		X	X				X	X			
Height	D	7.2.2.3	X																				
Weight	D	7.2.2.3	X	X								X			X				X	X			
ECOG status	D	7.2.2.4	X	X								X			X				X	X			
Hematology	D	7.2.2.5	X	X			X			X		X		X	X				X	X			
Chemistry	D	7.2.2.5	X	X	X		X			X	X	X	X	X	X				X	X			
Coagulation	D	7.2.2.5	X	X								X			X				X	X			

[redacted]

Visit Name	Category	Protocol Section	Screening	Cycle 1								Cycle 2			Cycle 3				Subsequent cycles	EoT	30 days or 150 days	Disease progression	Survival
Day of cycle			**-28 to -1**	**1**	**2**	**4**	**5**	**8**	**11**	**15**	**19**	**1**	**2**	**15**	**1**	**2**	**8**	**15**	**1**				
Urinalysis	D	7.2.2.5	X	If clinically indicated																X			
Thyroid function	D	7.2.2.5	X	X								X			X				X	X			
Doppler echocardiography	D	7.2.2.6	X									X			X				X	X			
Serology exam	D	7.2.2.5	X	X								X			X				X	X			
Serum Pregnancy test	D	7.2.2.5	X									X			X				X	X			
Urine pregnancy test	S	7.2.2.5																			X		
Antineoplastic therapies since discontinuation of study treatment	D	7.1.5																			X	X	X
Tumor evaluation	D	7.2.1	X	**During treatment**: starting on Cycle 3 Day 1, every 2 cycles until Cycle 11 Day 1, and then every 3 cycles until progression of disease or patient withdrawal. **Follow-up for progression:** every 8 weeks until week 40, then every 12 weeks until progression of disease or lost to follow-up. **EOT:** if a scan was not conducted within 30 days prior to end of study treatment. Additional assessments may be performed to confirm progressive disease as described in Section 7.2.1																		
12-Lead ECG	D	7.2.2.6	X	X		X									X				X (Cycle 6 only)	X			
Adverse events	D	8	Continuous																				

[redacted]

Visit Name	Category	Protocol Section	Screening	Cycle 1								Cycle 2			Cycle 3				Subsequent cycles	EoT	30 days or 150 days	Disease progression	Survival
Day of cycle			**-28 to -1**	**1**	**2**	**4**	**5**	**8**	**11**	**15**	**19**	**1**	**2**	**15**	**1**	**2**	**8**	**15**	**1**				
Collection of new tumor sample	D	7.2.4	X										X (day 2-3)										
Collection of archival tumor sample & associated de-identified pathology report	D	7.2.4	X#																				
Blood collection for biomarker analyses (plasma & PBMC)	D	7.2.4		X	X (day 2-3)								X (day 2-3			X (day 2-4)			X (Cycle 5 only)	X			
PDR001 infusion (only in combination)	D	6.1.1		i.v. every 4 weeks																			
BLZ945 administration	D	6.1.1		4d on/10d off																			
Blood sample for PK analysis (for BLZ945 single agent)	D	7.2.3		X	X	X	X		X+		X	X	X		X	X				X			
Blood sample for PK analysis (for BLZ945 + PDR001)	D	7.2.3		X	X	X	X	X	X+	X	X	X	X	X	X	X	X	X	X (up to Cycle 6)	X	X		

[redacted]

Visit Name	Category	Protocol Section	Screening	Cycle 1								Cycle 2			Cycle 3				Subsequent cycles	EoT	30 days or 150 days	Disease progression	Survival
Day of cycle			**-28 to -1**	**1**	**2**	**4**	**5**	**8**	**11**	**15**	**19**	**1**	**2**	**15**	**1**	**2**	**8**	**15**	**1**				
Blood sample for ADA analysis(for BLZ945 + PDR001)	D	7.2.3		X								X			X				X (up to Cycle 6)	X	X		
[redacted]																							
Survival contact (every 3 months)	D	7.1.5																					X

* 30-day safety follow-up for patients treated with BLZ945 single agent. 150 days safety follow-up for patients treated with BLZ945 in combination with PDR001 with safety evaluations (i.e. 30-day, 90-day and 150-day follow-up)

For glioblastoma patients for whom the newly obtained tumor samples were not collected at study entry only. For any glioblastoma patients who completed the screening phase and are ongoing at the time of protocol amendment 6 approval, if a newly obtained tumor sample was not collected at study entry, retrospective submission of an archival tumor sample is required. The associated de-identified pathology report is also requested.

+ Only for patients in Japan during dose escalation

Patients in Japan enrolled in dose escalation are required to be hospitalized during cycle 1

Table 7-4 Visit evaluation schedule for phase II (BLZ945 4d on / 10d off)

Visit Name	Category	Protocol Section	Screening	Cycle 1							Cycle 2			Cycle 3		Subsequent cycles	EoT	30 days or 150 days Safety*	Disease progression	Survival
Day of cycle			**-28 to -1**	**1**	**2**	**4**	**5**	**8**	**15**	**19**	**1**	**2**	**15**	**1**	**2**	**1**				
Obtain Informed Consent	D	7.1.1	X																	
Demography	D	7.1.1.2	X																	
Inclusion/ exclusion criteria	D	5.2	X																	

[redacted]

Visit Name	Category	Protocol Section	Screening	Cycle 1							Cycle 2			Cycle 3		Subsequent cycles	EoT	30 days or 150 days Safety*	Disease progression	Survival
Day of cycle			**-28 to -1**	**1**	**2**	**4**	**5**	**8**	**15**	**19**	**1**	**2**	**15**	**1**	**2**	**1**				
		5.3																		
Medical History (including MGMT and IDH status for GBM patients)	D	7.1.1.2	X																	
Diagnosis and extent of cancer	D	7.1.1.2	X																	
Prior antineoplastic therapies	D	7.1.1.2	X																	
Prior/concomitant medications, surgery and medical procedures	D	7.1.1.2	X	Continuous																
Physical examination	S	7.2.2.1	X	X			X		X		X		X	X		X	X			
Vital signs	D	7.2.2.2	X	X			X		X		X		X	X		X	X			
Height	D	7.2.2.3	X																	
Weight	D	7.2.2.3	X	X							X			X		X	X			
ECOG status	D	7.2.2.4	X	X							X			X		X	X			
Hematology	D	7.2.2.5	X	X			X		X		X		X	X		X	X			
Chemistry	D	7.2.2.5	X	X			X		X	X	X		X	X		X	X			
Coagulation	D	7.2.2.5	X	X							X			X		X	X			
Urinalysis	D	7.2.2.5	X	If clinically indicated													X			
Thyroid function	D	7.2.2.5	X	X							X			X		X	X			
Serology exam	D	7.2.2.5	X	X							X			X		X	X			
Doppler echocardiography	D	7.2.2.6	X								X			X		X	X			
Serum Pregnancy test	D	7.2.2.5	X								X			X		X	X			
Urine pregnancy test	S	7.2.2.5																X		

[redacted]

Visit Name	Category	Protocol Section	Screening	Cycle 1							Cycle 2			Cycle 3		Subsequent cycles	EoT	30 days or 150 days Safety*	Disease progression	Survival
Day of cycle			**-28 to -1**	**1**	**2**	**4**	**5**	**8**	**15**	**19**	**1**	**2**	**15**	**1**	**2**	**1**				
Antineoplastic therapies since discontinuation of study treatment	D	7.1.5																X	X	X
Tumor evaluation**	D	7.2.1	X	**During treatment**: starting on Cycle 3 Day 1, every 2 cycles until Cycle 11 Day 1, and then every 3 cycles until progression of disease or patient withdrawal. **Follow-up for progression:** every 8 weeks until week 40, then every 12 weeks until progression of disease or lost to follow-up. **EOT:** if a scan was not conducted within 30 days prior to end of study treatment. Additional assessments may be performed to confirm progressive disease as described in Section 7.2.1															
12-Lead ECG	D	7.2.2.6	X	X		X								X		X (Cycle 6 only)	X			
Adverse events	D	8	Continuous																	
Collection of new tumor sample	D	7.2.4	X									X (day 2-3)								
Collection of archival tumor sample & associated de-identified pathology report			X#																	
Blood collection for biomarker analyses (plasma)	D	7.2.4		X	X			X				X			X	X (Cycle 5 only)	X			
[redacted]																				
PDR001 infusion (only in combination)	D	6.1.1		i.v. every 4 weeks																

[redacted]

Visit Name	Category	Protocol Section	Screening	Cycle 1							Cycle 2			Cycle 3		Subsequent cycles	EoT	30 days or 150 days Safety*	Disease progression	Survival
Day of cycle			**-28 to -1**	**1**	**2**	**4**	**5**	**8**	**15**	**19**	**1**	**2**	**15**	**1**	**2**	**1**				
BLZ945 administration	D	6.1.1		4d on/10d off																
Blood sample for PK analysis (for BLZ945 single agent)	D	7.2.3		X	X	X	X										X			
Blood sample for PK analysis (for BLZ945 + PDR001)	D	7.2.3		X	X	X	X	X	X		X						X	X		
Blood sample for ADA analysis(for BLZ945 + PDR001)	D	7.2.3		X							X						X	X		
[redacted]																				
Survival contact (every 3 months)	D	7.1.5																		X

* 30-day safety follow-up for patients treated with BLZ945 single agent. 150 days safety follow-up for patients treated with BLZ945 in combination with PDR001 with safety evaluations (i.e. 30-day, 90-day and 150-day follow-up)

** MRI or CT scans obtained prior to study baseline evaluation and used for determination of disease progression from prior line of anti-neoplastic treatments might be requested for central review of response assessment and/or baseline characterization.

For glioblastoma patients enrolled in the phase II part of study, if a newly obtained tumor sample cannot be safely collected at study entry, submission of an archival tumor sample is required. The associated de-identified pathology report is also requested.

[redacted]

7.1.1 Screening

The study IRB/ Independent Ethics Committee (IEC) informed consent form must be signed and dated before any screening procedures are performed, except for evaluations performed as part of standard of care.

Patients will be evaluated against study inclusion and exclusion criteria and safety assessments. For details of assessments, refer to Table 7-1, Table 7-2, Table 7-3 and Table 7-4. Screening assessments must be repeated if performed outside of the specified screening window.

Submission of a newly (up to 3 months prior to study treatment and after completion of the last therapy) obtained tumor sample (formalin fixed, or in ethanol, please refer to [CBLZ945X2101 Laboratory Manual] for details) at screening is requested from all patients. For details refer to Section 7.2.4

For the glioblastoma patients for whom a newly obtained tumor was not collected at screening, submission of an available archival tumor sample is required (refer to Section 7.2.4 for details).

7.1.1.1 Information to be collected on screening failures

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failure. The reason for not being started on treatment will be entered on the Screening Phase Disposition Page. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for Screen Failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a Serious Adverse Event during the Screening Phase (see Section 8 for SAE reporting details) or died (Death eCRF should be completed) or withdrew consent (Withdrawal of consent eCRF should be completed).

7.1.1.2 Patient demographics and other baseline characteristics

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

7.1.2 Treatment period

For the purpose of scheduling and evaluations, a treatment cycle will consist of 28 days for patients treated with BLZ945 as a single agent or in combination with PDR001.

For Japan only, patients enrolled in dose escalation are required to be hospitalized during the DLT evaluation period (Cycle 1).

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

- Patients with SD, PR, CR, and unconfirmed progressive disease (PD) who do not show signs of clinical deterioration or toxicity (according to RECIST v1.1, irRC and iRANO).

Patients who meet the following criteria **may continue treatment** in additional cycles (after discussion Novartis):

[redacted]

- Patients with confirmed PD (according to RECIST v1.1, irRC and iRANO) or progressive (metabolic) disease (according to the Guidelines for efficacy evaluation in Hodgkin and non-Hodgkin lymphoma studies), if the Investigator considers it to be in the patient's best interest to remain on the study, and after discussion with Novartis.

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

- Patients who experience unacceptable toxicity
- Patients with confirmed PD (according to RECIST v1.1, irRC and iRANO). These patients will then enter the Safety follow-up period.
- Patients with progressive (metabolic) disease (according to the Guidelines for efficacy evaluation in Hodgkin and non-Hodgkin lymphoma studies). These patients will then enter the Safety follow-up period.
- Patients with an unconfirmed PD (according to RECIST v1.1, irRC and iRANO) who show signs of clinical deterioration or toxicity will enter the Safety follow-up period (see Section 7.1.5), and will be continued to be followed up until confirmed PD or initiation of a new treatment. Patients will then enter the Survival Follow-up period.

Patients with confirmed progressive disease/ immune-related Progressive Disease (irPD) in stable or improved clinical status can remain under treatment until there is a further progression or clinical deterioration under the following circumstances:

- Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression;
- No decline in ECOG performance status;
- Absence of rapid progression of disease;
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

Accumulating evidence indicates that objective responses to immunotherapy follows delayed kinetics of weeks or months, and can be preceded by initial apparent radiological progression or appearance of new lesions or some enlarging lesions while other target lesions are regressing ("mixed response") (Wolchok et al 2009). It is therefore reasonable to allow for these possibilities and continue to treat the patient until progression is confirmed and found to be advancing at the next imaging assessment as per irRC and iRANO. An outline of the irRC and iRANO are provided in Appendix 2 and Appendix 4 respectively.

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

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

The decision to continue or stop treatment should be discussed with the Novartis Medical Responsible and will be documented in the study files.

Please refer to Table 7-1, Table 7-2, Table 7-3 and Table 7-4 for details of the timing of required assessments and Section 7.1 for visit windows.

[redacted]

7.1.3 Discontinuation of study treatment

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

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

Study treatment may be discontinued under the following circumstances:

- Adverse event
- Lost to follow-up
- Physician's decision
- Progressive disease as per confirmed irRC (**not** as per RECIST v1.1)
- For glioblastoma patients, progressive disease as per confirmed iRANO (**not** as per RANO)
- For lymphoma patients, progressive (metabolic) disease as per the Guidelines for efficacy evaluation in Hodgkin and non-Hodgkin lymphoma studies
- Confirmed Complete response (CR) (as per RECIST v1.1)
- Patient/guardian decision
- Protocol deviation

Patients must be discontinued if any of the following occur:

- Death
- Pregnancy

Patients who discontinue study treatment should not be considered discontinued from the study. They should return for the EoT assessments as soon as possible and within 14 days of the last dose of study treatment or within 14 days of the decision to discontinue study treatment, and then enter the follow-up period as indicated in Section 7.1.5. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone calls, e-mail, letter) should be made to contact them as specified in Section 7.1.6. If a patient discontinues study treatment, but continues study assessments, the patient remains on study until such time as he/she completes protocol criteria for ending study assessments.

Patients who transfer into another study or an alternative way to provide study treatment will perform the end of treatment procedures only. The follow-up for safety, disease progression and survival visits will not be performed.

If the decision to discontinue the patient occurs at a regular scheduled visit, that visit may become the EoT visit rather than having the patient return for an additional visit. An End of Treatment Phase Disposition eCRF should be completed, giving the reason for stopping the study treatment. End of treatment/Premature withdrawal visit is not considered as the end of the study.

[redacted]

7.1.3.1 Replacement policy

Escalation part:

Patients will not be replaced on study. However, if a patient is considered as non-evaluable for the dose determining set (DDS), enrollment of a new patient to the current cohort will be considered if there is less than the required number of evaluable patients. Enrollment of new patients may be considered until at least the minimum number (3) or at most the maximum number (6) of evaluable patients is achieved within the cohort. A minimum of 2 patients is acceptable as long as neither patient has experienced a treatment-related toxicity > CTCAE grade 2. Minimum and maximum numbers of evaluable patient per cohort are defined in Section 6.2.3.

Phase II part:

During the phase II part no replacements will be considered.

7.1.4 Withdrawal of consent

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

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

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

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

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

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

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

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

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

[redacted]

7.1.5 Follow up period

Patients treated with BLZ945 single agent must have a safety evaluation 30 days after last dose and patients treated with BLZ945 in combination with PDR001 must have safety evaluations for 150 days after the last study treatment dose. The evaluations can be done either by telephone call or visit for the 30-, 90- and 150- days safety follow up visits.

Data collected should be added to the Adverse Events CRF and the Concomitant Medications CRF until the safety follow-up has been completed or the start of a new antineoplastic therapy. Only study treatment related AEs should be reported after initiation of new antineoplastic therapy.

Antineoplastic therapies since discontinuation of study drug will be collected during this follow-up period in the appropriate eCRF page.A PK and immunogenicity sample should be collected at 150 days as described in Section 7.2.3 (Pharmacokinetics and Immunogenicity assessments). If the 150-day safety evaluation is conducted by phone, samples do not need to be collected.

Patients who discontinue study treatment for any reason other than death, disease progression per confirmed irRC (per iRANO for glioblastoma patients; per Guidelines for efficacy evaluation in Hodgkin and non-Hodgkin lymphoma studies for lymphoma patients), clinical deterioration, lost to follow-up, consent withdrawal or study termination, also should return for tumor evaluation assessments and should not be considered withdrawn from the study until at least 80% of the patients enrolled had completed the survival follow-up period (minimum 18 months after the first dose of treatment) or discontinued the study for any reason.

If patients refuse to return for these visits or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine if the patient had disease progression.

Upon completion of the 30- day or 150-day safety follow up or disease progression follow up, patients will be followed for survival every 3 months (can be done by telephone call) until death or until the end of the study is reached, unless they withdraw consent or are lost to follow-up.

For patients who transfer to another clinical study or an alternative way to provide study treatment as described in Section 4.3, the safety follow up, disease progression or survival follow up visits will not be performed.

7.1.6 Lost to follow-up

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

[redacted]

7.2 Assessment types

7.2.1 Efficacy assessments

7.2.1.1 Solid tumors (except glioblastoma)

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

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

The local investigator's assessment will be used for the analysis of response according to both RECIST v1.1 and irRC, and for treatment decision making (study discontinuation due to PD as per irRC). During the course of the study, Novartis may decide to have a central review of the radiological assessments performed. In such case, the investigator's staff will be instructed on how to send data from these radiological assessments to a Contract Research Organization (CRO) for central review when needed.

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

Tumor assessments will be performed at the time points as described in Table 7-5. PR or CR, per both RECIST v1.1 and irRC, will be confirmed by a new assessment after at least 4 weeks. Also PD, as per irRC, will be confirmed after at least 4 weeks. Disease progression follow-up should be performed as described in Section 7.1.5.

7.2.1.2 Glioblastoma

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

- RANO (Appendix 3)
- iRANO (Appendix 4)

Tumor response and progression will be assessed using the Response Assessment in Neuro-Oncology (RANO) Working Group updated response assessment criteria for high-grade gliomas (Wen et al 2010b) as detailed in Appendix 3. Since Standard RANO criteria may not be adequate in case of immunotherapy treatment, a new assessment criteria (iRANO) will be used to deal with pseudoprogression in the first 24 weeks of treatment (Okada et al 2015).

Novartis may decide to collect and store MRI or CT scans for central review of response assessment and/or baseline characterization. Novartis may decide to collect, store and review MRI or CT scans obtained prior to study baseline evaluation and used for determination of disease progression from prior lines of anti-neoplastic treatments.

[redacted]

Throughout the study, RANO (Appendix 3) or iRANO criteria (Appendix 4) must be applied when assessing any responses to the study treatment. All CRs and PRs must be confirmed by a second assessment at least 4 weeks later.

To distinguish pseudoprogression from progressive disease and minimize premature discontinuation of study treatment, patients meeting RANO criteria for disease progression may continue receiving study medication until confirmation of progression with an MRI performed approximately 12 weeks later, unless they experience significant clinical decline. Whenever possible, patients discontinuing from the study for progressive disease must have their disease progression documented by radiological and clinical evaluations following RANO criteria.

Tumor assessments will be performed at the time points as described in Table 7-5.

Note: in case a patient cannot tolerate MRI, the patient may still participate in the study following discussion between Novartis and the investigator. In this case, all efficacy assessments will be made by CT scans for that patient. Efficacy assessments should be performed by using the same technique throughout the study for each patient.

7.2.1.3 Relapsed or refractory lymphoma

For all patients with r/r lymphoma, the tumor response will be determined locally according to the Guidelines for efficacy evaluation in Hodgkin and non-Hodgkin lymphoma studies (Appendix 9). The local investigator's assessment will be used for treatment decision making as well as analyses of primary and secondary endpoints.

In order to understand the disease stage, documentation of status of bone marrow involvement by lymphoma based on prior bone marrow biopsy/aspirate is required. If no such documentation is available then a bone marrow biopsy/aspirate is required at screening.

At screening, all patients will undergo FDG PET-CT scan. For patients with FDG avid tumors, all subsequent disease assessments will be performed with FDG-PET CT, using the 5-point scale (Barrington et al 2014). The avidity of up to six representative index lesions must be documented and the rest as non-index lesions. For patients with non-avid or variably FDG-avid tumors, CT scan with IV contrast of chest/abdomen/pelvis/additional known lesions will be performed. If at screening, a patient has a medical contraindication to CT IV contrast or develops a contraindication during the trial, a non-contrast chest CT and a contrast abdomen/pelvis Magnetic Resonance Imaging (MRI) will be performed.

Tumor assessments will be performed at the time points as described in Table 7-5. Depending on regulatory requirements it is allowed to have the EOT PET-CT scan performed within an extended time frame but no later than 8 weeks from the last PET-CT scan. Imaging evaluations subsequent to an off-schedule confirmatory scan should be performed according to the original assessment schedule. The same method of assessment and the same technique should be used to characterize each individual and reported lesion at screening and during follow-up.

Bone marrow biopsy should be performed to confirm complete responses in patients with bone marrow involvement prior to study treatment.

Skin lesions present at screening should be documented using color photography, including a ruler, so that the size of the lesion(s) can be determined from the photograph. Skin photographs

[redacted]

should be continued at subsequent tumor assessments for any lesions that were photographed at screening.

All patients discontinuing from the study for progressive disease must have their disease progression documented by radiologic evaluation. In cases of clinically-evident disease progression, all efforts should be made to perform a radiologic evaluation.Tumor assessments will be performed at the time points as described in Table 7-5.

Table 7-5 Disease assessment collection plan

Procedure	Screening	During Treatment/Follow-up
Solid tumors		
CT or MRI **with contrast enhancement** (Chest, Abdomen, Pelvis)	Mandated	**During treatment**: starting on Cycle 3 Day 1, every 2 cycles until Cycle 11 Day 1, and then every 3 cycles until progression of disease as per irRC or patient withdrawal. **Follow-up for progression**: every 8 weeks until week 40, then every 12 weeks until progression of disease per irRC or lost to follow-up. If progressive disease is detected: confirmatory CT or MRI at least 4 weeks after first progressive disease assessment. **EOT**: if a scan was not conducted within 30 days prior to end of study treatment.
Brain CT or MRI **with contrast**	Mandated	If disease was detected at baseline, or if clinically indicated
Glioblastoma		
Brain CT or MRI **with contrast**	Mandated	**During treatment**: starting on Cycle 3 Day 1, every 2 cycles until Cycle 11 Day 1, and then every 3 cycles until progression of disease as per iRANO for glioblastoma or patient withdrawal. **Follow-up for progression**: every 8 weeks until week 40, then every 12 weeks until progression of disease per iRANO for glioblastoma or lost to follow-up. If progressive disease is detected: confirmatory CT or MRI 12 weeks after first progressive disease assessment **EoT**: if a scan was not conducted within 30 days prior to end of study treatment.
CT or MRI **with contrast enhancement** (Chest, Abdomen, Pelvis)	Mandated	If disease was detected at baseline, or if clinically indicated
Lymphoma		

[redacted]

Procedure	Screening	During Treatment/Follow-up
Solid tumors		
PET-CT or CT chest/abdomen/pelvis/ additional known lesions	PET-CT is mandated at screening	**During treatment**: starting on Cycle 3 Day 1, every 2 cycles until Cycle 11 Day 1, and then every 3 cycles until progression of disease as per the Guidelines for efficacy evaluation in Hodgkin and non-Hodgkin lymphoma studies or patient withdrawal. If FDG avid: use PET-CT, and if non-avid/mixed avidity: CT **Follow-up for progression**: every 8 weeks until week 40, then every 12 weeks until progression of disease as per the Guidelines for efficacy evaluation in lymphoma studies or lost to follow-up. **EOT**: if a scan was not conducted within 30 days prior to end of study treatment.
Bone marrow biopsy	Mandated except for Hodgkin lymphoma patients	To confirm complete responses in patients with bone marrow tumor involvement prior to study treatment
Skin color photography with ruler (skin lesions only)	Mandated if skin lesions at screening	If skin lesions at screening, Cycle 3 **During treatment**: starting on Cycle 3 Day 1, every 2 cycles until Cycle 11 Day 1, and then every 3 cycles until progression of disease as per the Guidelines for efficacy evaluation in Hodgkin and non-Hodgkin lymphoma studies or patient withdrawal. **Follow-up for progression**: every 8 weeks until week 40, then every 12 weeks until progression of disease as per the Guidelines for efficacy evaluation in Hodgkin and non-Hodgkin lymphoma studies or lost to follow-up. **EOT**: if a scan was not conducted within 30 days prior to end of study treatment.

7.2.2 Safety and tolerability assessments

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

7.2.2.1 Physical examination

At screening and Cycle 1 Day 1 prior to treatment administration, a complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

[redacted]

From Cycle 1 Day 8 onwards (or from Cycle 1 Day 5 for patients treated with the 4d on/10d off schedule), a short physical exam will include the examination of general appearance and vital signs (blood pressure and pulse) (refer to Table 7-1, Table 7-2, Table 7-3 and Table 7-4).

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

For Japanese patients in phase I only: oxygen saturation (SpO2) will be measured by pulse oximetry for Japanese patients every time physical examination is performed as indicated in Table 7-1, Table 7-2 and Table 7-3.

7.2.2.2 Vital signs

Vital signs (body temperature, pulse rate, blood pressure in supine position when ECG is collected) must be performed prior to treatment administration and as indicated in Table 7-1, Table 7-2, Table 7-3 and Table 7-4 as per institutional standards. Vital signs should be assessed in the same position through the study.

More frequent examinations may be performed at the discretion of the Investigator if medically indicated, and will be recorded as unscheduled assessment.

7.2.2.3 Height and weight

Height and body weight will be measured as indicated in Table 7-1, Table 7-2, Table 7-3 and Table 7-4 as per institutional standards.

7.2.2.4 Performance status

ECOG performance status will be assessed according to Table 7-6 and as indicated in Table 7-1, Table 7-2, Table 7-3 and Table 7-4.

Table 7-6 ECOG performance status

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

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

[redacted]

7.2.2.5 Laboratory evaluations

All laboratory parameters assessed for safety purposes will be evaluated locally (except serology examinations that will be evaluated centrally). Refer to Table 7-7 for a summary of the parameters to be evaluated.

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

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

Table 7-7 Local/Central Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, White blood cells with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)
Chemistry	Amylase, Lipase, Albumin, Alkaline phosphatase, ALT, AST, Bicarbonate, Calcium, Chloride, Sodium, Potassium, Creatinine, Glucose, Magnesium, Inorganic Phosphate, Total Bilirubin (also measure direct and indirect bilirubin if total bilirubin is > grade 1), Blood Urea Nitrogen or Urea, creatine phosphokinase, troponin and, uric acid
Coagulation	Prothrombin time or INR, Activated partial thromboplastin time (APTT)
Urinalysis	Bilirubin, Blood, Glucose, Ketones, pH, Protein, Specific Gravity, White Blood Cells
Thyroid	Free T4,Thyroid Stimulation Hormone
Serology exam*	Anti-DNA antibodies (Abs), Anti-nuclear Abs, Anti-mitochondrial Abs, c-Reactive protein, RF
Pregnancy	Serum or urine samples only for women of childbearing potential
* To be performed by a Central laboratory. Details will be provided in the [CBLZ945X2101 Laboratory Manual]	

7.2.2.5.1 Hematology

Hematology panel outlined in Table 7-7 will be performed as per the assessment schedule in Table 7-1, Table 7-2, Table 7-3 and Table 7-4.

7.2.2.5.2 Clinical chemistry

Clinical chemistry panel outlined in Table 7-7 will be performed as per the assessment schedule in Table 7-1, Table 7-2, Table 7-3 and Table 7-4.

It should be noted in the patient's eCRF if the patient was fasting at the time of blood sampling.

7.2.2.5.3 Coagulation

Coagulation panel outlined in Table 7-7 will be performed as per the assessment schedule in Table 7-1, Table 7-2, Table 7-3 and Table 7-4.

7.2.2.5.4 Urinalysis

Dipstick measurements for specific gravity, protein, glucose and blood will be performed. Any significant findings on dipstick will be followed up with a microscopic evaluation where WBC and RBC sediments will also be measured.

[redacted]

Urinalysis panel outlined in Table 7-7 will be performed as per the assessment schedule in Table 7-1, Table 7-2, Table 7-3 and Table 7-4.

7.2.2.5.5 Thyroid function and Serology exam

Thyroid and Serology panels outlined in Table 7-7 will be performed as per the assessment schedule in Table 7-1, Table 7-2, Table 7-3 and Table 7-4.

7.2.2.5.6 Pregnancy and assessments of fertility

All females of childbearing potential will have a serum pregnancy test at screening within ≤ 72 hours before first dose of study treatment. During the study, a serum pregnancy test should be done at day 1 of each cycle from cycle 2 onwards, and at EOT visit.

A urine pregnancy test should be performed every month during and at the end of the safety follow-up period (i.e. 150 days after the last dose of PDR001). If the patient is not coming to the clinic during the safety follow-up, it can be performed at home or at a local doctor's office, and the results will be communicated to the site staff. These follow-up pregnancy tests will be recorded only in the source documentation, not in the CRF.

A positive pregnancy test requires immediate discontinuation of study treatment and discontinuation from study. See Section 8.3 for pregnancy reporting.

7.2.2.6 Cardiac assessments

7.2.2.6.1 Electrocardiogram (ECG)

A standard 12-lead ECG will be performed as per the assessment schedule in Table 7-1, Table 7-2, Table 7-3, Table 7-4 and Table 7-8. For patients receiving BLZ945 twice per day, the ECG will be collected following the morning dose of BLZ945, and 1-2 hours after the evening dose, if feasible. Blood samples scheduled at the same clock time point should be taken **after** the ECGs are completed. The ECGs must be performed in triplicate in supine position during study treatment as indicated in Table 7-1, Table 7-2, Table 7-3 and Table 7-4.

The post-infusion ECGs in the combination part will be collected after the completion of the infusion. The next meal can be taken after the 4 hours ECG assessments.

Table 7-8 Central ECG collection plan

Cycle	Day	Time	ECG type
Screening	-28 to -1	Anytime	Single
1	1	Pre-dose (fasting, baseline ECG)	Triplicate
1	1	0.5 h post-dose (± 10 min)	Triplicate
1	1	1 h post-dose (± 10 min)	Triplicate
1	1	2 h post-dose (± 10 min)	Triplicate
1	1	4 h post-dose (± 15 min)	Triplicate
1	1	6 h post-dose (± 1 h)	Triplicate
1	1	8 h post-dose (± 1 h)	Triplicate
1	1	1-2 h post-evening dose#	Triplicate
1	4*	Pre-dose (fasting)	Triplicate
1	4*	0.5 h post-dose (± 10 min)	Triplicate

Cycle	Day	Time	ECG type
1	4*	1 h post-dose (± 10 min)	Triplicate
1	4*	2 h post-dose (± 10 min)	Triplicate
1	4*	4 h post-dose (± 15 min)	Triplicate
1	4*	1-2 h post-evening dose#	Triplicate
1	7†	Pre-dose (fasting)	Triplicate
1	7†	0.5 h post-dose (± 10 min)	Triplicate
1	7†	1 h post-dose (± 10 min)	Triplicate
1	7†	2 h post-dose (± 10 min)	Triplicate
1	7†	4 h post-dose (± 15 min)	Triplicate
1	7†	1-2 h post-evening dose#	Triplicate
1	8‡	Pre-dose (fasting)	Triplicate
1	8‡	0.5 h post-dose (± 10 min)	Triplicate
1	8‡	1 h post-dose (± 10 min)	Triplicate
1	8‡	2 h post-dose (± 10 min)	Triplicate
1	8‡	4 h post-dose (± 15 min)	Triplicate
1	8‡	1-2 h post-evening dose#	Triplicate
3	1	Pre-dose	Triplicate
3	1	1h (±10 min) hour post dose	Triplicate
6	1	Pre-dose	Triplicate
6	1	1h (±10 min) hour post dose	Triplicate
EoT	-	Anytime	Single
Unscheduled*	-	Anytime	Single

*A PK sample should be collected just after an ECG performed due to an unexpected cardiac signal.
* When BLZ945 4d on/10d off regimen
† When BLZ945 7d on/7d off regimen
‡ When BLZ945 Q1W regimen
# Only for twice a day dosing and if deemed logistically feasible

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

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

7.2.2.6.2 Doppler echocardiography

Doppler echocardiography will be performed as outlined in Table 7-3 and Table 7-4. Additional assessments may be performed if clinically indicated. When possible, the same cardiologist should read and report the outcome to minimize the variability in results.

[redacted]

7.2.2.7 Radiological examinations (Japanese patients only)

7.2.2.7.1 Chest X-ray

A 2-view chest X-ray will be performed at the following time points during dose escalation:

- screening
- cycle 2 day 1

7.2.3 Pharmacokinetic and immunogenicity assessments

To assess PK of BLZ945 when administered as single agent or in combination with PDR001 and determine concentrations and immunogenicity of PDR001, blood samples will be collected. **Blood samples should be collected from the arm opposite from the study drug infusion, or from another site.** Approximately of 5 mL of blood may be collected at each time point. For time points when BLZ945, LEL284 (BLZ945's metabolite) or PDR001 PK and anti-drug antibody (ADA) are to be measured, a single blood sample will be collected. Complete instructions for sample processing, handling and shipment will be provided in the [CBLZ9452101 Laboratory Manual].

The exact date and clock times of study drug administration and blood sample collection will be recorded on the appropriate eCRF. Any sampling issues should be noted on the eCRF and on appropriate source documentation.

[redacted]

While the goal of the pharmacokinetic and immunogenicity assessments is to address the secondary objectives, there may be circumstances when a decision is made to stop the collection of the samples in the phase II part of study due to either practical or strategic reasons.

Table 7-9 Pharmacokinetic blood collection log for BLZ945 7d on/7d off regimen (single agent)

Cycle	Day	Scheduled Time Point (h)	Analytes
1	1	Pre-dose of Cycle 1	BLZ945, LEL284
1	1	0.5 h post-dose (± 10 min)	BLZ945, LEL284
1	1	1 h post-dose (± 10 min)	BLZ945, LEL284
1	1	2 h post-dose (± 10 min)	BLZ945, LEL284
1	1	4 h post-dose (± 15 min)	BLZ945, LEL284
1	1	6 h post-dose (± 1 h)	BLZ945, LEL284
1	1	8 h post-dose (± 1 h)	BLZ945, LEL284
1	1	10-12 h post-C1D1 morning dose and pre-C1D1 evening dose[#]	BLZ945, LEL284
1	1	1-2 h post-C1D1 evening dose[†]	BLZ945, LEL284
1	2	24 h post-C1D1 dose / 12 h post-C1D1 evening dose[#] and pre-dose C1D2	BLZ945, LEL284
1	7	Pre-dose	BLZ945, LEL284
1	7	0.5 h post-dose (± 10 min)	BLZ945, LEL284

[redacted]

Cycle	Day	Scheduled Time Point (h)	Analytes
1	7	1 h post-dose (± 10 min)	BLZ945, LEL284
1	7	2 h post-dose (± 10 min)	BLZ945, LEL284
1	7	4 h post-dose (± 15 min)	BLZ945, LEL284
1	7	6 h post-dose (± 1 h)	BLZ945, LEL284
1	7	8 h post-dose (± 1 h)	BLZ945, LEL284
1	7	10-12 h post-C1D7 morning dose and pre-C1D7 evening dose[#]	BLZ945, LEL284
1	7	1-2 h post-C1D7 evening dose[†]	BLZ945, LEL284
1	8	24 h post-C1D7 dose / 12 h post-C1D7 evening dose[#]	BLZ945, LEL284
1	11[+]	96 h post-dose	BLZ945, LEL284
2	1	Pre-dose of Cycle 2	BLZ945, LEL284
3	1	Pre-dose of Cycle 3	BLZ945, LEL284
EoT		Anytime	BLZ945, LEL284
Unscheduled		Anytime	BLZ945, LEL284

[+]Only for Japanese patients
[#]Only for twice a day dosing
[†]Only for twice a day dosing and if deemed logistically feasible

Table 7-10 Pharmacokinetic blood collection log for BLZ945 once weekly (Q1W) regimen (single agent)

Cycle	Day	Scheduled Time Point (h)	Analytes
1	1	Pre-dose of Cycle 1	BLZ945, LEL284
1	1	0.5 h post-dose (± 10 min)	BLZ945, LEL284
1	1	1 h post-dose (± 10 min)	BLZ945, LEL284
1	1	2 h post-dose (± 10 min)	BLZ945, LEL284
1	1	4 h post-dose (± 15 min)	BLZ945, LEL284
1	1	6 h post-dose (± 1 h)	BLZ945, LEL284
1	1	8 h post-dose (± 1 h)	BLZ945, LEL284
1	1	10-12 h post-C1D1 morning dose and pre-C1D1 evening dose[#]	BLZ945, LEL284
1	1	1-2 h post-C1D1 evening dose[†]	BLZ945, LEL284
1	2	24 h post-C1D1 dose / 12 h post-C1D1 evening dose[#]	BLZ945, LEL284
1	8	Pre-dose C1D8	BLZ945, LEL284
1	8	0.5 h post-dose (± 10 min)	BLZ945, LEL284
1	8	1 h post-dose (± 10 min)	BLZ945, LEL284
1	8	2 h post-dose (± 10 min)	BLZ945, LEL284
1	8	4 h post-dose (± 15 min)	BLZ945, LEL284
1	8	6 h post-dose (± 1 h)	BLZ945, LEL284
1	8	8 h post-dose (± 1 h)	BLZ945, LEL284
1	8	10-12 h post-C1D8 morning dose and pre-C1D8 evening dose[#]	BLZ945, LEL284
1	8	1-2 h post-C1D8 evening dose[†]	BLZ945, LEL284
1	9	24 h post-C1D8 dose / 12 h post-C1D8 evening dose[#]	BLZ945, LEL284
1	11[+]	72 h post-dose	BLZ945, LEL286
2	1	Pre-dose of Cycle 2	BLZ945, LEL284
2	2	24 h post-C2D1 dose	BLZ945, LEL284
3	1	Pre-dose of Cycle 3	BLZ945, LEL284

[redacted]

Cycle	Day	Scheduled Time Point (h)	Analytes
3	2	24 h post-C3D1 dose	BLZ945, LEL284
EoT		Anytime	BLZ945, LEL284
Unscheduled		Anytime	BLZ945, LEL284

[+]Only for Japanese patients
[#]Only for twice a day dosing
[†]Only for twice a day dosing and if deemed logistically feasible

Table 7-11 Pharmacokinetic blood collection log for BLZ945 4d on/10d off regimen (single agent) in phase I

Cycle	Day	Scheduled Time Point (h)	Analytes
1	1	Pre-dose of Cycle 1	BLZ945, LEL284
1	1	0.5 h post-dose (± 10 min)	BLZ945, LEL284
1	1	1 h post-dose (± 10 min)	BLZ945, LEL284
1	1	2 h post-dose (± 10 min)	BLZ945, LEL284
1	1	4 h post-dose (± 15 min)	BLZ945, LEL284
1	1	6 h post-dose (± 1 h)	BLZ945, LEL284
1	1	8 h post-dose (± 1 h)	BLZ945, LEL284
1	1	10-12 h post-C1D1 morning dose and pre-C1D1 evening dose[#]	BLZ945, LEL284
1	1	1-2 h post-C1D1 evening dose[†]	BLZ945, LEL284
1	2	24 h post-dose / 12 h post-C1D1 evening dose[#] and pre-dose C1D2	BLZ945, LEL284
1	4	Pre-dose	BLZ945, LEL284
1	4	0.5 h post-dose (± 10 min)	BLZ945, LEL284
1	4	1 h post-dose (± 10 min)	BLZ945, LEL284
1	4	2 h post-dose (± 10 min)	BLZ945, LEL284
1	4	4 h post-dose (± 15 min)	BLZ945, LEL284
1	4	6 h post-dose (± 1 h)	BLZ945, LEL284
1	4	8 h post-dose (± 1 h)	BLZ945, LEL284
1	4	10-12 h post-C1D4 morning dose and pre-C1D4 evening dose[#]	BLZ945, LEL284
1	4	1-2 h post-C1D4 evening dose[†]	BLZ945, LEL284
1	5	24 h post-dose / 12 h post-C1D4 evening dose[#]	BLZ945, LEL284
1	11[+]	168 h post-dose	BLZ945, LEL284
1	19	24 h post-C1D18 dose	BLZ945, LEL284
2	1	Pre-dose of Cycle 2	BLZ945, LEL284
2	2	24 h post-C2D1 dose	BLZ945, LEL284
3	1	Pre-dose of Cycle 3	BLZ945, LEL284
3	2	24 h post-C3D1 dose	BLZ945, LEL284
EoT		Anytime	BLZ945, LEL284
Unscheduled		Anytime	BLZ945, LEL284

[+]Only for Japanese patients
[#]Only for twice a day dosing frequency
[†]Only for twice a day dosing and if deemed logistically feasible

[redacted]

Table 7-12 Pharmacokinetic blood collection log for BLZ945 4d on/10d off regimen (single agent) in phase II

Cycle	Day	Scheduled Time Point (h)	Analytes
1	1	Pre-dose of Cycle 1	BLZ945, LEL284
1	1	0.5 h post-dose (± 10 min)	BLZ945, LEL284
1	1	1 h post-dose (± 10 min)	BLZ945, LEL284
1	1	2 h post-dose (± 10 min)	BLZ945, LEL284
1	1	4 h post-dose (± 15 min)	BLZ945, LEL284
1	1	6 h post-dose (± 1 h)	BLZ945, LEL284
1	1	8 h post-dose (± 1 h)	BLZ945, LEL284
1	2	24 h post-dose (± 2 h) and pre-C1D2 dose	BLZ945, LEL284
1	4	Pre-dose	BLZ945, LEL284
1	4	0.5 h post-dose (± 10 min)	BLZ945, LEL284
1	4	1 h post-dose (± 10 min)	BLZ945, LEL284
1	4	2 h post-dose (± 10 min)	BLZ945, LEL284
1	4	4 h post-dose (± 15 min)	BLZ945, LEL284
1	4	6 h post-dose (± 1 h)	BLZ945, LEL284
1	4	8 h post-dose (± 1 h)	BLZ945, LEL284
1	5	24 h post-dose (± 2 h)	BLZ945, LEL284
EoT		Anytime	BLZ945, LEL284
Unscheduled		Anytime	BLZ945, LEL284

Table 7-13 Pharmacokinetic blood collection log for BLZ945 and PDR001 and ADA (BLZ945 and PDR001 combination) 7d on/7d off regimen

Cycle	Day	Scheduled Time Point (h)	Analytes	ADA analysis [a]
1	1	Pre-dose of Cycle 1	BLZ945, LEL284, PDR001	ADA
1	1	0.5 h post-dose (± 10 min)	BLZ945, LEL284	
1	1	1 h (± 10 min) post-PDR001 dose	BLZ945, LEL284, PDR001	
1	1	2 h post-dose (± 10 min)	BLZ945, LEL284	
1	1	4 h post-dose (± 15 min)	BLZ945, LEL284	
1	1	6 h post-dose (± 1 h)	BLZ945, LEL284	
1	1	8 h post-dose (± 1 h)	BLZ945, LEL284	
1	1	10-12 h post-C1D1 morning dose and pre-C1D1 evening dose[#]	BLZ945, LEL284	
1	1	1-2 h post-C1D1 evening dose[†]	BLZ945, LEL284	
1	2	24 h (± 2h) post-BLZ945 C1D1 dose / 12 h post-C1D1 evening dose[#] and pre-dose C1D2	BLZ945, LEL284, PDR001	
1	7	Pre-dose	BLZ945, LEL284,	
1	7	0.5 h post-dose (± 10 min)	BLZ945, LEL284	
1	7	1 h post-dose (± 10 min)	BLZ945, LEL284	
1	7	2 h post-dose (± 10 min)	BLZ945, LEL284	
1	7	4 h post-dose (± 15 min)	BLZ945, LEL284	
1	7	6 h post-dose (± 1 h)	BLZ945, LEL284	
1	7	8 h post-dose (± 1 h)	BLZ945, LEL284	
1	7	10-12 h post-C1D7 morning dose and pre-C1D7 evening dose[#]	BLZ945, LEL284	
1	7	1-2 h post-C1D7 evening dose[†]	BLZ945, LEL284	

Cycle	Day	Scheduled Time Point (h)	Analytes	ADA analysis [a]
1	8	24 h (± 2h) post-BLZ945 C1D7 dose / 12 h post-C1D7 evening dose[#] and 168h (± 8h) post-PDR001 C1D1 dose	BLZ945, LEL284, PDR001	
1	11[+]	96 h post-dose	BLZ945, LEL284	
1	15	Pre-dose / 336h post dose	BLZ945, LEL284, PDR001	
2	1	Pre-dose of cycle 2	BLZ945, LEL284, PDR001	ADA
2	1	1 h (± 10 min) post-PDR001 C2D1 dose	PDR001	
3	1	Pre-dose of Cycle 3	BLZ945, LEL284, PDR001	ADA
3	1	1 h (± 10 min) post-PDR001 C3D1 dose	PDR001	
3	8	24 h (± 2h) post-BLZ945 C3D7 dose/ 168 h (± 8h) post-PDR001 C3D1 dose	BLZ945, LEL284, PDR001	
3	15	336h (±24h) post-PDR001 C3D1 dose	PDR001	
4	1	Pre-dose of cycle 4	BLZ945, LEL284, PDR001	ADA
4	1	1 h (± 10 min) post-PDR001 C4D1 dose	PDR001	
5	1	Pre-dose of Cycle 5	BLZ945, LEL284 PDR001	ADA
5	1	1h (± 10 min) post-PDR001 C5D1 dose	PDR001	
6	1	Pre-dose of Cycle 6	BLZ945, LEL284, PDR001	ADA
6	1	1h (± 10 min) post-PDR001 C6D1 dose	PDR001	
EoT		Anytime	BLZ945, LEL284, PDR001	ADA
150 day safety FU[c]		Anytime	PDR001	ADA
Unscheduled		Anytime	BLZ945, LEL284, PDR001	ADA

a ADA samples associated with PDR001 are to be collected together with PK samples.
c Only for patients who come to the site for the 150-day safety FU
PK samples will be collected from the arm opposite of infusion site.
[+]Only for Japanese patients
[#]Only for twice a day dosing frequency
[†]Only for twice a day dosing and if deemed logistically feasible

Table 7-14 Pharmacokinetic blood collection log for BLZ945 and PDR001 and ADA (BLZ945 and PDR001 combination) once weekly (Q1W) regimen

Cycle	Day	Scheduled Time Point (h)	Analytes	ADA analysis [a]
1	1	Pre-dose of Cycle 1	BLZ945, LEL284, PDR001	ADA
1	1	0.5 h post-dose (± 10 min)	BLZ945, LEL284	
1	1	1 h (± 10 min) post-PDR001 dose	BLZ945, LEL284, PDR001	
1	1	2 h post-dose (± 10 min)	BLZ945, LEL284	
1	1	4 h post-dose (± 15 min)	BLZ945, LEL284	
1	1	6 h post-dose (± 1 h)	BLZ945, LEL284	
1	1	8 h post-dose (± 1 h)	BLZ945, LEL284	
1	1	10-12 h post-C1D1 morning dose and pre-C1D1 evening dose[#]	BLZ945, LEL284	

[redacted]

Cycle	Day	Scheduled Time Point (h)	Analytes	ADA analysis [a]
1	1	1-2 h post-C1D1 evening dose†	BLZ945, LEL284	
1	2	24 h (± 2h) post-BLZ945 C1D1 dose / 12 h post-C1D1 evening dose#	BLZ945, LEL284, PDR001	
1	8	Pre-dose C1D8 / 168h post dose	BLZ945, LEL284, PDR001	
1	8	0.5 h post-dose (± 10 min)	BLZ945, LEL284	
1	8	1 h post-dose (± 10 min)	BLZ945, LEL284	
1	8	2 h post-dose (± 10 min)	BLZ945, LEL284	
1	8	4 h post-dose (± 15 min)	BLZ945, LEL284	
1	8	6 h post-dose (± 1 h)	BLZ945, LEL284	
1	8	8 h post-dose (± 1 h)	BLZ945, LEL284	
1	8	10-12 h post-C1D8 morning dose and pre-C1D8 evening dose#	BLZ945, LEL284	
1	8	1-2 h post-C1D8 evening dose†	BLZ945, LEL284	
1	9	24 h post-dose / 12 h post-C1D8 evening dose#	BLZ945, LEL284	
1	11+	72 h post-dose	BLZ945, LEL284	
1	15	Pre-dose / 336h post dose	BLZ945, LEL284, PDR001	
2	1	Pre-dose of cycle 2	BLZ945, LEL284, PDR001	ADA
2	1	1 h (± 10 min) post-PDR001 C2D1 dose	PDR001	
2	2	24 h (± 2h) post-BLZ945 C2D1 dose/ PDR001 C2D1 dose	BLZ945, LEL284, PDR001	
2	15	336 h post-dose (± 24h) of PDR001 C2D1 dose	PDR001	
3	1	Pre-dose of Cycle 3	BLZ945, LEL284, PDR001	ADA
3	1	1 h (± 10 min) post-PDR001 dose	PDR001	
3	2	24 h (± 2h) post-BLZ945 C3D1 dose/ PDR001 C3D1 dose	BLZ945, LEL284, PDR001	
3	8	168 h (± 8h) post-PDR001 C3D1 dose	PDR001	
3	15	336h (±24h) post-PDR001 C3D1 dose	PDR001	
4	1	Pre-dose of cycle 4	BLZ945, LEL284, PDR001	ADA
4	1	1 h (± 10 min) post-PDR001 dose	PDR001	
5	1	Pre-dose of Cycle 5	BLZ945, LEL284, PDR001	ADA
5	1	1h (± 10 min) post-PDR001 dose	PDR001	
6	1	Pre-dose of Cycle 6	BLZ945, LEL284, PDR001	ADA
6	1	1h (± 10 min) post-PDR001 dose	PDR001	
EoT		Anytime	BLZ945, LEL284, PDR001	ADA
150 day safety FU[c]		Anytime	PDR001	ADA
Unscheduled		Anytime	BLZ945, LEL284, PDR001	ADA

a ADA samples associated with PDR001 are to be collected together with PK samples.
c Only for patients who come to the site for the 150-day safety FU
+Only for patients in Japan
#Only for twice a day dosing frequency
†Only for twice a day dosing and if deemed logistically feasible
PK samples will be collected from the arm opposite of infusion site.

[redacted]

Table 7-15 Pharmacokinetic blood collection log for BLZ945 and PDR001 and ADA (BLZ945 and PDR001 combination) 4d on/10d off regimen in phase I

Cycle	Day	Scheduled Time Point (h)	Analytes	ADA analysis [a]
1	1	Pre-dose of Cycle 1	BLZ945, LEL284, PDR001	ADA
1	1	0.5 h post-dose (± 10 min)	BLZ945, LEL284	
1	1	1 h post-PDR001 dose (± 10 min)	BLZ945, LEL284, PDR001	
1	1	2 h post-dose (± 10 min)	BLZ945, LEL284	
1	1	4 h post-dose (± 15 min)	BLZ945, LEL284	
1	1	6 h post-dose (± 1 h)	BLZ945, LEL284	
1	1	8 h post-dose (± 1 h)	BLZ945, LEL284	
1	1	10-12 h post-C1D1 morning dose and pre-C1D1 evening dose[#]	BLZ945, LEL284	
1	1	1-2 h post-C1D1 evening dose[†]	BLZ945, LEL284	
1	2	24 h (± 2h) post-BLZ945 C1D1 dose / 12 h post-C1D1 evening dose[#] and pre-dose C1D2	BLZ945, LEL284, PDR001	
1	4	Pre-dose	BLZ945, LEL284,	
1	4	0.5 h post-dose (± 10 min)	BLZ945, LEL284	
1	4	1 h post-dose (± 10 min)	BLZ945, LEL284	
1	4	2 h post-dose (± 10 min)	BLZ945, LEL284	
1	4	4 h post-dose (± 15 min)	BLZ945, LEL284	
1	4	6 h post-dose (± 1 h)	BLZ945, LEL284	
1	4	8 h post-dose (± 1 h)	BLZ945, LEL284	
1	4	10-12 h post-C1D4 morning dose and pre-C1D4 evening dose[#]	BLZ945, LEL284	
1	4	1-2 h post-C1D4 evening dose[†]	BLZ945, LEL284	
1	5	24 h post-dose / 12 h post-C1D4 evening dose[#]	BLZ945, LEL284, PDR001	
1	8	168 h post-PDR001 C1D1 dose	PDR001	
1	11[+]	168 h post-dose	BLZ945, LEL284	
1	15	336h post-dose	PDR001	
1	19	24 h post-C1D18 dose	BLZ945, LEL284	
2	1	Pre-dose of cycle 2	BLZ945, LEL284, PDR001	ADA
2	1	1 h post-PDR001 dose (± 10 min)	PDR001	
2	2	24 h (± 2h) post-PDR001 C2D1 dose	BLZ945, LEL284, PDR001	
2	15	336 h (± 24h) post-PDR001 C2D1 dose	PDR001	
3	1	Pre-dose of Cycle 3	BLZ945, LEL284, PDR001	ADA
3	1	1 h (± 10 min) post-PDR001 C3D1 dose (± 10 min)	PDR001	
3	2	24 h (± 2h) post-PDR001 C3D1 dose	BLZ945, LEL284, PDR001	
3	8	168 h (± 8h) post-PDR001 C3D1 dose	PDR001	
3	15	336h (±24h) post-PDR001 C3D1 dose	PDR001	
4	1	Pre-dose of cycle 4	BLZ945, LEL284, PDR001	ADA

Cycle	Day	Scheduled Time Point (h)	Analytes	ADA analysis [a]
4	1	1 h (± 10 min) post- PDR001 C4D1 dose	PDR001	
5	1	Pre-dose of Cycle 5	BLZ945, LEL284, PDR001	ADA
5	1	1h (± 10 min) post-PDR001 dose	PDR001	
6	1	Pre-dose of Cycle 6	BLZ945, LEL284, PDR001	ADA
6	1	1h (± 10 min) post-PDR001 dose	PDR001	
EoT		Anytime	BLZ945, LEL284, PDR001	ADA
150 day safety FU[c]		Anytime	PDR001	ADA
Unscheduled		Anytime	BLZ945, LEL284, PDR001	ADA

a ADA samples associated with PDR001 are to be collected together with PK samples.
c Only for patients who come to the site for the 150-day safety FU
[+]Only for Japanese patients
[#]Only for twice a day dosing frequency
[†]Only for twice a day dosing and if deemed logistically feasible
PK samples will be collected from the arm opposite of infusion site.

Table 7-16 Pharmacokinetic blood collection log for BLZ945 and PDR001 and ADA (BLZ945 and PDR001 combination) 4d on/10d off regimen in phase II

Cycle	Day	Scheduled Time Point (h)	Analytes	ADA analysis [a]
1	1	Pre-dose of Cycle 1	BLZ945, LEL284, PDR001	ADA
1	1	0.5 h post-dose (± 10 min)	BLZ945, LEL284	
1	1	1 h post-PDR001 dose (± 10 min)	BLZ945, LEL284, PDR001	
1	1	2 h post-dose (± 10 min)	BLZ945, LEL284	
1	1	4 h post-dose (± 15 min)	BLZ945, LEL284	
1	1	6 h post-dose (± 1 h)	BLZ945, LEL284	
1	1	8 h post-dose (± 1 h)	BLZ945, LEL284	
1	2	24 h (± 2h) post-BLZ945 C1D1 dose and pre-C1D2 dose	BLZ945, LEL284, PDR001	
1	4	Pre-dose	BLZ945, LEL284,	
1	4	0.5 h post-dose (± 10 min)	BLZ945, LEL284	
1	4	1 h post-dose (± 10 min)	BLZ945, LEL284	
1	4	2 h post-dose (± 10 min)	BLZ945, LEL284	
1	4	4 h post-dose (± 15 min)	BLZ945, LEL284	
1	4	6 h post-dose (± 1 h)	BLZ945, LEL284	
1	4	8 h post-dose (± 1 h)	BLZ945, LEL284	
1	5	24 h (± 2 h) post-dose	BLZ945, LEL284, PDR001	
1	8	168 h post-PDR001 C1D1 dose	PDR001	
1	15	336h post-PDR001 C1D1 dose	PDR001	
2	1	Pre-dose of cycle 2	PDR001	ADA
EoT		Anytime	BLZ945, LEL284, PDR001	ADA
150 day safety FU[c]		Anytime	PDR001	ADA
Unscheduled		Anytime	BLZ945, LEL284, PDR001	ADA

a ADA samples associated with PDR001 are to be collected together with PK samples.
c Only for patients who come to the site for the 150-day safety FU

[redacted]

Cycle	Day	Scheduled Time Point (h)	Analytes	ADA analysis [a]
PK samples will be collected from the arm opposite of infusion site.				

The actual collection date and time of each sample will be entered on the Pharmacokinetics and immunogenicity Blood Collection eCRF pages.

7.2.3.1 Bioanalytical methods

Bioanalysis for pharmacokinetic studies will employ three validated assays:

- BLZ945/LEL284

  Serum concentrations of BLZ945 and its pharmacologically active metabolite LEL284 will be measured in serum using a validated liquid chromatography-tandem mass spectrometry assay by Novartis Bioanalytics. Concentrations below the lower limit of quantification (LLOQ) will be reported as 0.00 ng/mL and missing samples will be labeled accordingly. The details of the assay will be documented in the [CBLZ945X2101 Laboratory Manual].
- PDR001

  The assay to quantify PDR001 will be a validated Liquid Chromatography Mass Spectrometry (LC-MS). The details of the assay will be documented in the [CBLZ945X2101 Laboratory Manual].
- Anti PDR-antibody

  The assay to quantify and assess the ADA against PDR001 will be using a validated homogeneous ELISA. The details of the assay will be documented in the [CBLZ945X2101 Laboratory Manual].

7.2.4 Biomarkers

In this study biomarker analyses will be used to investigate the effect of the BLZ945 single agent or in combination with PDR001 at the molecular and cellular level as well as to determine how changes in the markers may relate to exposure and clinical outcomes. [redacted]

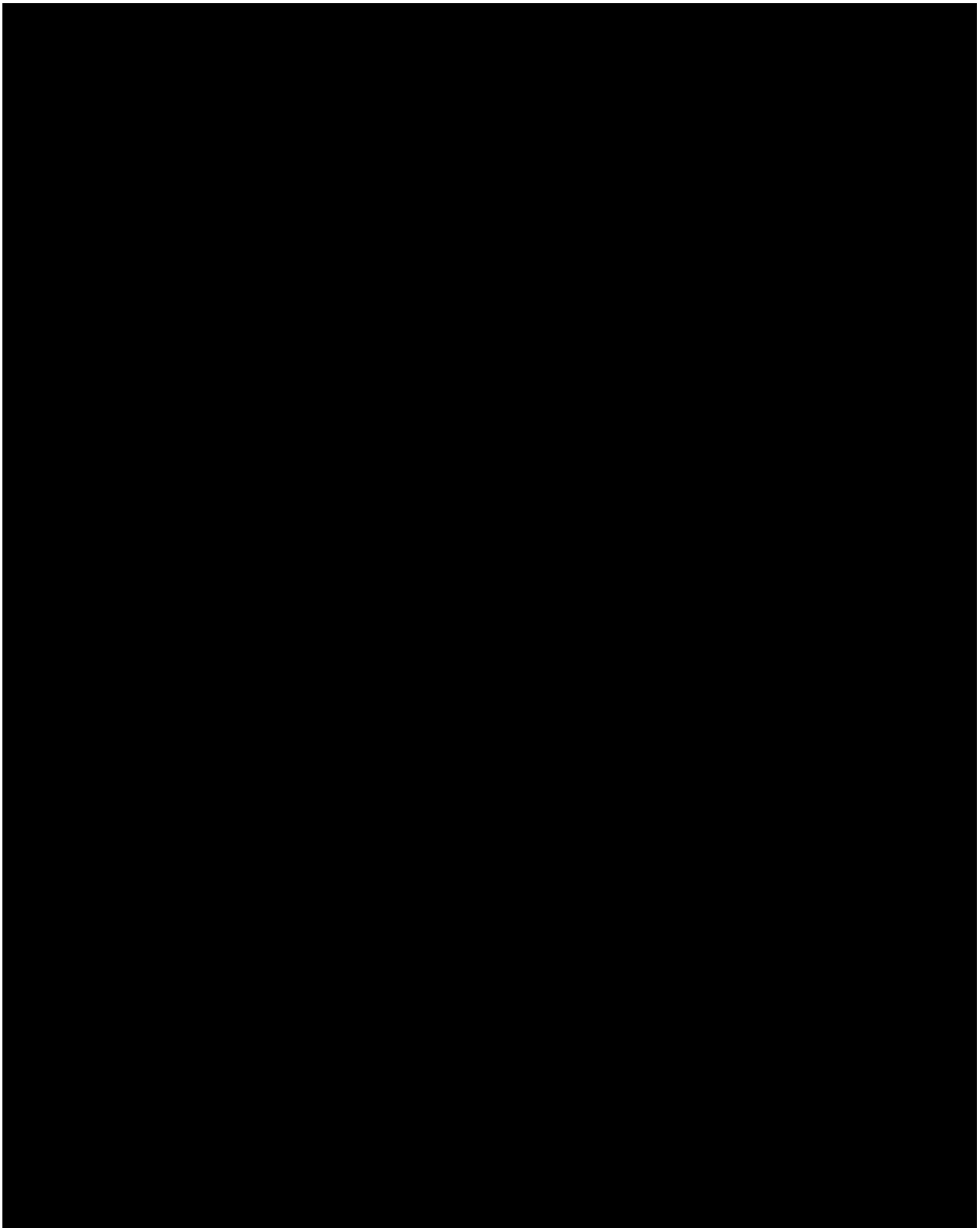
While the goal of the biomarker assessments is to provide supportive data for the MOA, there may be circumstances when a decision is made to stop a collection, or not perform or discontinue an analysis due to either practical or strategic reasons (e.g., inadequate sample number, issues related to the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

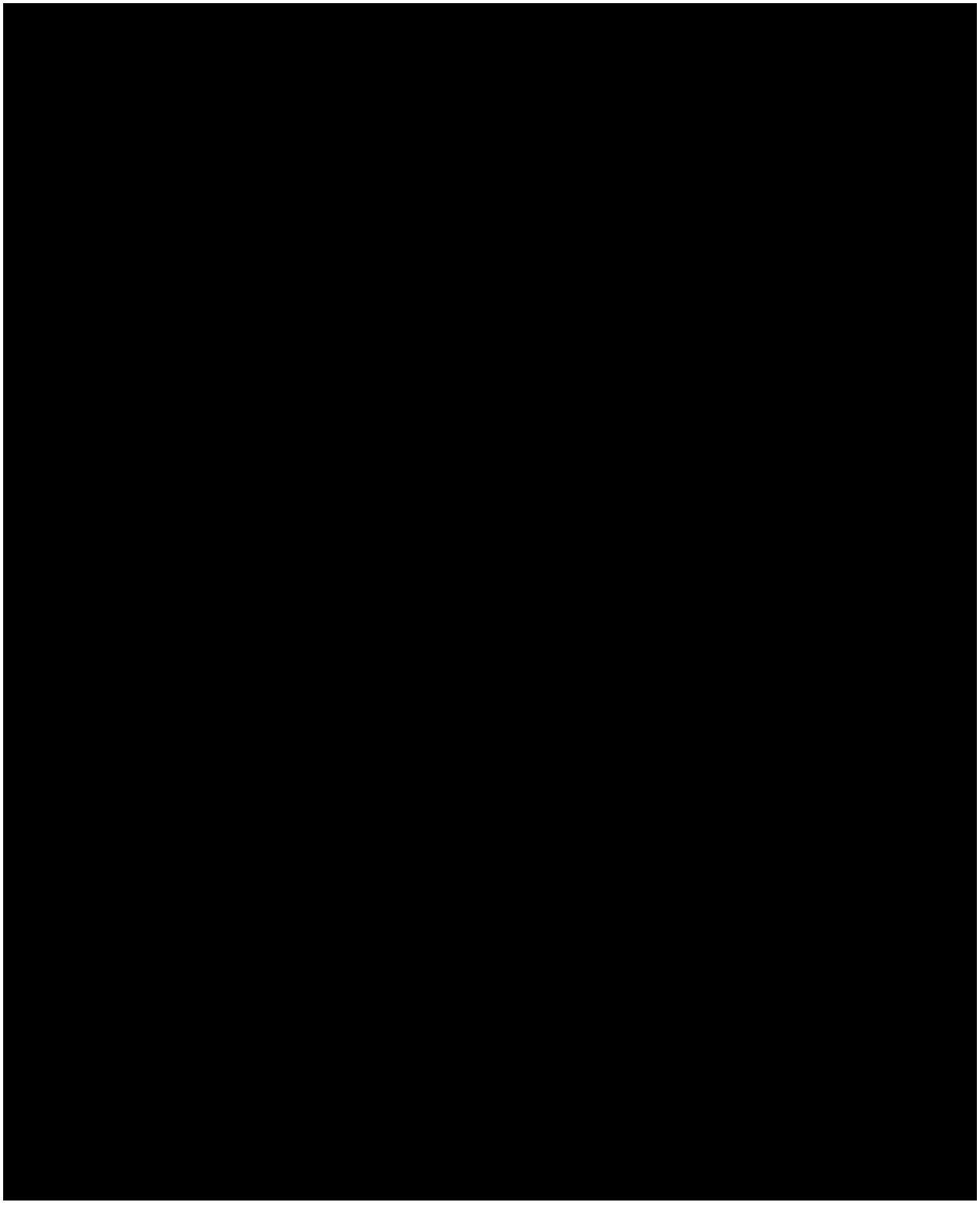
The sample collection information must be entered on the appropriate sample collection log eCRF and requisition form(s). Tumor and blood samples should be sent to a Novartis designated central laboratory. Detailed instructions for the collection, handling, and shipment of tumor and blood samples are outlined in the [CBLZ945X2101 Laboratory Manual].

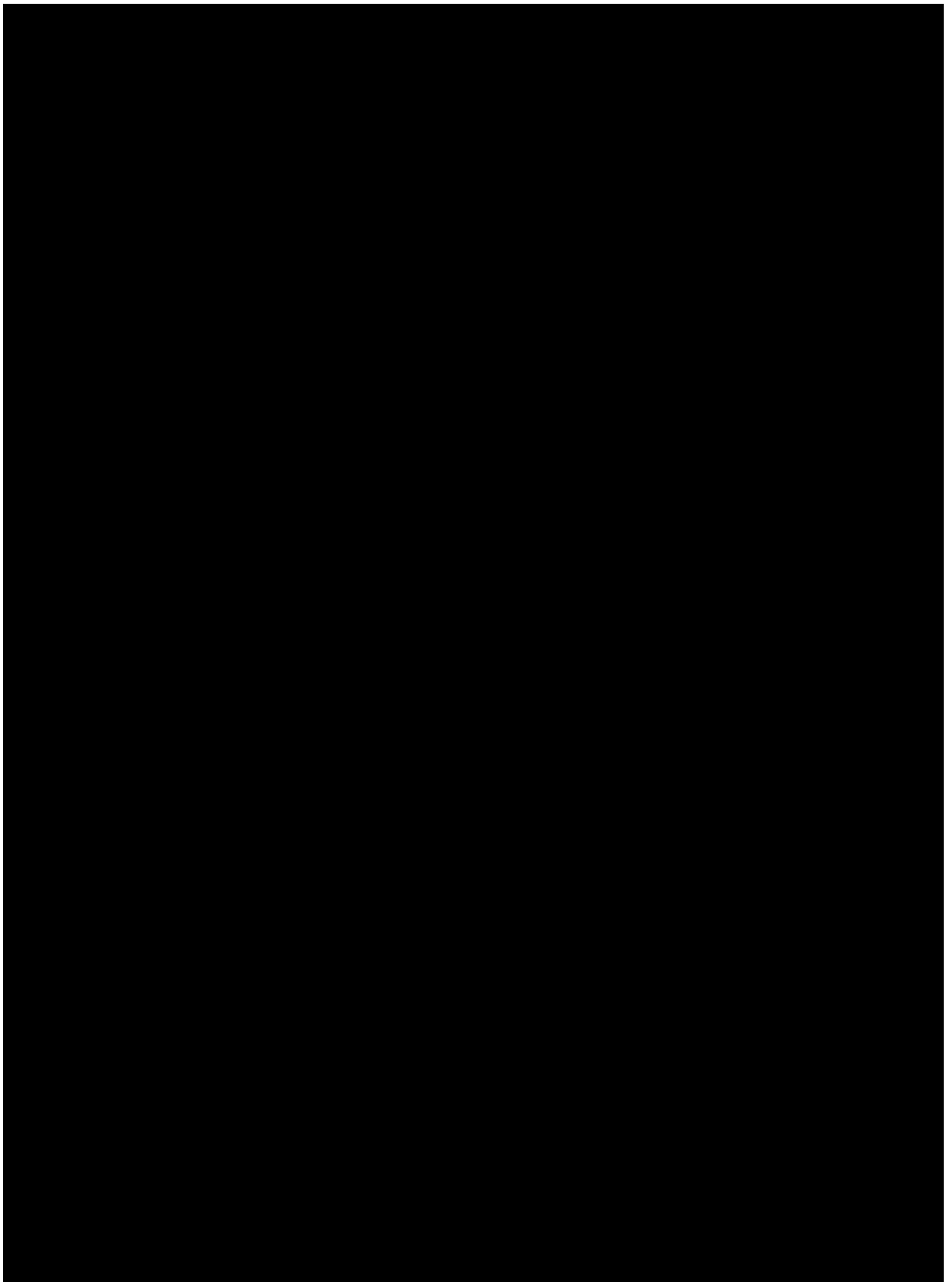
[redacted]

Table 7-17 Biomarker sample collection plan (tumor/blood samples)

Sample Type	Visit/ Time point	Material	Marker*	Purpose
Tumor Newly obtained tumor sample#	Screening Cycle 2 Day 2-3	**Newly obtained tumor#:** formalin fixed tumor sample in ethanol (3-6 passes) or minimum 18 freshly cut slides **Archival tumor & associated de-identified pathology report#** (Only applicable for glioblastoma patients): Block (preferred) or minimum 18 freshly cut slides	immunohistochemistry (IHC) expression of markers such as (but not limited to) CD163, CD8, FOXP3, PD-L1 [redacted]	[redacted] Identification of potential predictive markers
[redacted]				







8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained. For additional details about irAE, please refer to Section 6.3.2.

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

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events eCRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's eCRF. Adverse event monitoring should be continued for at least 30 days for BLZ945 single agent and 150 days for BLZ945 in combination with PDR001 following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed according to the CTCAE version 4.03.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study but is collected as a seriousness criteria; rather, information about deaths will be collected though a Death form.

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

- The severity grade (CTCAE Grade 1-4)
- The duration (Start and end dates)
- The relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
- The action taken with respect to study treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
- Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
- Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)
- Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1, and which seriousness criteria have been met.

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

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

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per irRC, RECIST v1.1, RANO or iRANO, the Guidelines for efficacy evaluation in Hodgkin and non-Hodgkin lymphoma studies) should not be reported as a serious adverse event.

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

After initiation of new post-treatment antineoplastic therapy, only AEs suspected to be related to study treatment will be collected in the Adverse Events CRF.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

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

[redacted]

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

8.2 Serious adverse events

8.2.1 Definitions

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

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

Progression of underlying malignancy is not reported as an adverse event if it is clearly consistent with the suspected progression of the underlying cancer as defined by irRC, RECIST v1.1, RANO or iRANO, the Guidelines for efficacy evaluation in Hodgkin and non-Hodgkin lymphoma studies. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as a serious adverse event.

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

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

[redacted]

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

8.2.2 Reporting

SAE collection will start upon signing the informed consent whether the patient is a screen failure or not. SAEs will be followed until resolution or until clinically relevant improvement or stabilization.

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided main informed consent and until at least 30 days after the patient has stopped BLZ945 single agent and 150 days after the patient has stopped BLZ945 in combination with PDR001 must be reported to Novartis within 24 hours of learning of its occurrence. If a patient starts a post treatment antineoplastic therapy, then only SAEs suspected to be related to study treatment will be reported.

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

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

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

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

If the SAE is not previously documented in the BLZ945 or PDR001 Investigator's Brochures or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Chief Medical Office and Patient Safety (CMO&PS) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

[redacted]

8.3 Pregnancies

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

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

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

8.4 Warnings and precautions

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

8.5 Data Monitoring Committee

A data monitoring board will not be used for this study. This is an open-label, Phase I-II study in which all patients receive either BLZ945 or the combination of BLZ945 with PDR001. Novartis will have access to the Safety Data on a regular basis. Novartis will host investigator teleconferences on a regular basis during the study. Further, during the phase I part of the study Novartis and the investigators will meet at the end of each treatment cohort to discuss and evaluate all of the gathered safety data. At the dose escalation teleconference the clinical course (safety information including both DLTs and all CTCAE Grade 2 or higher toxicity data during the first cycle of treatment, and PK data) for each patient in the current dose cohort will be described in detail. Updated safety data on other ongoing patients, including data in later cycles, will be discussed as well.

Dose escalation decisions will be based on a clinical synthesis of all relevant available data and not solely on DLT information. Selection of the actual dose for the next cohort of patients will be guided by the BLRM with EWOC, and a medical review of relevant clinical, PK and laboratory data. Novartis and the investigator parties must reach a consensus on whether to declare MTD, escalate the dose any further, or whether to de-escalate and/or recruit an additional cohort of patients at the current dose level Section 10.4.4, and Section 10.7.

During the phase II part of the study, individual patient data will be reviewed on an ongoing basis. Aggregate safety data will be monitored quarterly by the study team across the duration

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

8.6 Steering Committee

A Steering Committee constituted of members of the Translational Clinical Oncology Leadership Team will be formed for this study. If the monitoring of the study data requires a decision to be taken on the continuation of the study, then the relevant data (e.g., safety data or primary analysis and predictive probability of success) will be communicated to the Steering Committee for decision making purposes.

9 Data collection and management

9.1 Data confidentiality

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

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

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

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

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

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the

protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on CRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

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

9.3 Data collection

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

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

PK and biomarker (blood, serum, plasma and/or tissue) samples obtained during the course of the study will be collected from the Investigator sites and analyzed by a Novartis designated laboratory, contracted central laboratories, or local laboratories.

ECG data collected during the study will be reviewed and processed centrally by a specialist CRO.

During the course of the study, Novartis may decide to have a central review of the radiological assessments performed. In such case, the investigator’s staff will be instructed on how to send data from these radiological assessments to a CRO for central review when needed.

Designated investigational site staff will enter the information required by the protocol into the appropriate eCRF and/or designated laboratory requisition forms. Field monitors will review the eCRFs and laboratory paper requisition forms for accuracy and completeness and instruct site personnel to make any required corrections or additions. One copy of the requisition form will be forwarded to each analytical laboratory with the respective sample(s) by the field monitor or by the designated investigational site staff; and one copy will be retained at the investigational site.

9.4 Database management and quality control

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

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

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

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

10 Statistical methods and data analysis

It is planned that the data from participating centers in this protocol will be combined, so that an adequate number of patients will be available for analysis. Data will be summarized using descriptive statistics (continuous data) and/or contingency table (categorical data) for demographic and screening characteristics, efficacy measurements, safety measurements and all relevant PK and PD measurements. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

The study data will be analyzed and reported based on all patients' data of the dose escalation and Phase II parts up to the time when all patients from dose escalation part 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. Any additional data for patients continuing to receive study treatment past the data cutoff date for the primary Clinical Study Report (CSR), as allowed by the protocol, will be reported at completion of the study as defined in Section 4.3.

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

- 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 for glioblastoma patients will be presented by treatment arms (i.e., BLZ945 as single agent at the RP2D, and BLZ945 at the RP2D in combination with PDR001).

Note: patients from the phase I dose escalation part and the phase II part will not be pooled in any analyses unless otherwise specified.

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

[redacted]

10.1 Analysis sets

10.1.1 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.

10.1.2 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.

10.1.3 Per-Protocol set

The Per-Protocol Set (PPS) consists of a subset of the patients in the FAS in the phase II part who meet the following criteria:

- Presence of at least one measurable lesion according to RANO as per Appendix 3;
- Evaluable per RANO, or have discontinued due to clinical progression
- Have received the planned treatment

All major protocol deviations leading to exclusion from the PPS will be detailed in the statistical analysis plan (SAP). Patients will be classified according to planned treatment.

The PPS will be used in the phase II part of the study only and will define the patients used in the sensitivity analysis of the primary endpoint (Section 10.4). If the PPS and the FAS are identical, then analyses described by the PPS below will not be performed.

10.1.4 Dose-determining analysis 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.

[redacted]

Combination of BLZ945 and PDR001 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 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 $\geq$ 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

For other schedules, 75% of the planned dosing days of BLZ945 during cycle 1 will be determined following the same principle.

10.1.5 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

10.1.6 Other analysis sets

Not applicable

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data (including disease characteristics) will be summarized descriptively by treatment group for both phase I and phase II with the FAS.

[redacted]

10.3 Treatments (study treatment, concomitant therapies, compliance)

For each of BLZ945 and PDR001, the actual dose and duration in days of treatment as well as the dose intensity (actual dose received/actual duration) and relative dose intensity (the ratio of dose intensity to planned dose/planned duration) will be listed and summarized by means of descriptive statistics by treatment group. Categories for relative dose intensity of BLZ945 or PDR001 will be specified as < 0.5, ≥ 0.5 - < 0.75, ≥ 0.75 - < 0.9, ≥ 0.9 - < 1.1 and ≥ 1.1. The number and proportion of patients within each category will be presented by treatment group in phase I and phase II.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed by patient and summarized by anatomical therapeutic chemical (ATC) term and treatment group in phase I and phase II.

The reason for discontinuation from treatment will be summarized and listed, along with dates of first and last dose of BLZ945 and PDR001 (if applicable), duration of exposure to BLZ945 and PDR001 (if applicable) and date of discontinuation for each patient.

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

10.4 Primary objective

Phase I part

To characterize the safety and tolerability and to estimate the MTD or RP2D of BLZ945 as a single agent and in combination with PDR001.

To characterize the safety and tolerability and to estimate the MTD or RP2D of BLZ945 as a single agent for Japanese patients

Phase II part

To assess the anti-tumor activity of BLZ945 as single agent and in combination with PDR001 among patients with GBM.

10.4.1 Variable

Phase I part

- 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 10.5.3 for details of analysis.

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

[redacted]

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.

Phase II part

The primary variable is the PFS rate at 6 months, defined as the time from the date of start of treatment to the date of the first documented progression or death due to any cause. Disease progression is defined as per RANO for glioblastoma.

10.4.2 Safety objectives

10.4.2.1 Analysis set and grouping for the analyses

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

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

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

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

10.4.2.2 Adverse events (AEs)

Summary tables for adverse events (AEs) have to include only AEs that started or worsened during the on-treatment period, the ***treatment-emergent*** AEs. However, all safety data (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period are to be flagged.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment by treatment group in phase I.

Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event and by treatment group in phase I.

Specific safety event categories (SEC) will be considered. Such categories consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with the study treatment(s).

For each specified SEC, number and percentage of patients with at least one event part of the SEC will be reported.

[redacted]

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

10.4.2.3 Laboratory abnormalities

For laboratory tests covered by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, the study's biostatistical and reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

The following by-treatment summaries will be generated separately for hematology, biochemistry and urinary laboratory tests:

- frequency table for newly occurring on-treatment grades 3 or 4
- shift tables using CTCAE grades to compare baseline to the worst on-treatment value
- for laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value
- listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.

[redacted]

10.4.2.4 Other safety data

ECG

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

Vital signs

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

- shift table of baseline to worst on-treatment result
- table with descriptive statistics at baseline, one or several post-baseline time points and change from baseline to this/these post-baseline time points.

10.4.3 Tolerability

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

[redacted]

10.4.4 Statistical hypothesis, model, and method of analysis

Phase I

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 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.

For Japanese patients, separate single-agent BLRM model will be applied to guide single agent dose escalation decisions. Currently available information about the dose-DLT relationships of single agent from global patients will be used to derive informative priors for the BLRM parameters describing the dose-DLT relationships of this agent taking into consideration the heterogeneity between the global population and Japanese patients. For further details on the statistical model including the prior specification for the model parameters refer to in Appendix 6.

After each cohort of patients, the posterior distributions for the probabilities of DLT rates at different dose levels (or combinations) will be obtained. Dose recommendation will be based on posterior summaries including the mean, median, standard deviation, 95%-credible interval, and the probability that the true DLT rate for each dose lies in one of the following categories:

- [0,16%) under-dosing
- [16%,33%) targeted toxicity
- [33%,100%] excessive toxicity

Dose recommendation will also be guided by the EWOC principle, which mandates the dose for the next cohort to have less than 25% chance of excessive toxicity. The final estimate of the MTD(s)/ RP2D(s) will also satisfy this condition.

[redacted]

Phase II

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

The efficacy in glioblastoma for both treatment arms of BLZ945 as single agent and in combination with PDR001 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. At the time of the primary analysis, the model will be updated with all available data of patients in the FAS by treatment arm (i.e. RP2D of BLZ945 as single agent and RP2D of BLZ945 in combination with PDR001, both in glioblastoma patients), 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 both treatment 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 can be declared.

10.4.5 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, when a patient discontinued treatment for ‘disease progression’, but without documentation of radiological evidence of progression, it will not be counted as a PFS event. 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.

10.4.6 Supportive analyses

For the phase I part, a method that takes into account both toxicity and PD markers response in order to further guide the estimation of the recommended phase II dose(s) by finding an optimal dose or range of doses that maximizes the PD response while safety is controlled may be used.

[redacted]

First of all, two independent models to assess dose-toxicity and dose-PD response relationships will be presented. The toxicity model is a BLRM model and the PD response model is a polynomial logistic regression model describing the PD markers response and dose levels relationships. This model generalizes the monotonic relationships and allow for different dose-response shapes. In addition, a bivariate modelling of both PD parameters and safety may be explored if appropriate. Details of the analyses will be described in the SAP. 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. In addition, the primary analysis on PFS may be repeated using PPS. Additional supportive analyses will be conducted if appropriate and will be defined in the SAP.

10.5 Secondary objectives

10.5.1 Key secondary objective(s)

Not applicable

10.5.2 Other secondary efficacy objectives

For all efficacy parameters, data will be listed, summarized, and/or analyzed by treatment group for the phase I and phase II.

Tumor response will be determined per local investigators' assessment, according to RECIST v1.1, RANO, irRC and iRANO and the Guidelines for efficacy evaluation in Hodgkin and non-Hodgkin lymphoma studies as appropriate. Response related efficacy assessments will be defined and analyzed based on RECIST v1.1, RANO, irRC, iRANO or the Guidelines for efficacy evaluation in Hodgkin and non-Hodgkin lymphoma studies as appropriate.

ORR, DCR and PFS will be listed and summarized with accompanying 90% confidence interval.

DOR for patients who experience a CR or PR at any time on study will be listed by patient. PFS will be presented graphically using Kaplan Meier plots including all patients in phase II by treatment group. Median PFS time and the proportion of patients who are progression-free at 3, 6, 9, and 12 months will be estimated for each group. If there are a large number of patients achieving response, the Kaplan-Meier plots for DOR will also be produced and the median DOR will be estimated.

Individual lesion measurements and overall response assessments will be listed by patient and assessment date. Best overall response per RECIST v1.1, RANO, irRC, iRANO or the Guidelines for efficacy evaluation in Hodgkin and non-Hodgkin lymphoma studies will be listed and tabulated.

OS will be presented graphically using Kaplan Meier plots including all patients in phase II by treatment group. Median OS time and the proportion of patients who are alive at 3, 6, 9, and 12 months will be estimated for each group.

10.5.3 Safety objectives

Phase II part of the study will further characterize the safety and tolerability of BLZ945 as a single agent and in combination with PDR001 in glioblastoma patients. For all safety analyses,

[redacted]

the safety set will be used. All listings and tables will be presented by treatment arm in phase II. The analysis plan follows the same as indicated in Section 10.4.2.

10.5.4 Tolerability

Phase II part of the study will continue evaluating tolerability of study treatment in glioblastoma patients (refer to Section 10.4.3 and Section 10.3).

10.5.5 Supportive analyses for secondary objectives

Not applicable.

10.5.5.1 Tolerability

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

[redacted]

10.5.6 Pharmacokinetics

All subjects who have evaluable PK data will be included in the PK data analysis. The pharmacokinetic parameters listed in Table 10-1 will be estimated when feasible. The parameters that require terminal phase determination ($T_{1/2}$ and AUC_{inf}) may not be adequately calculated by non-compartmental methods.

Table 10-1 Non-compartmental pharmacokinetic parameters

AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume-1)
AUCinf	The AUC from time zero to infinity (mass x time x volume-1)
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass x volume-1)
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)
$T_{1/2}$	The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve (time). Use qualifier for other half-lives
CLp/F	The total body clearance of drug from the plasma (volume x time-1)
Vz/F	The apparent volume of distribution during terminal phase (associated with λz) (volume)
AR	Accumulation Ratio = AUC (multiple Dose)/AUC (single dose)

PAS will be used in all pharmacokinetic data analysis and PK summary statistics. PK data from Japanese patients treated on the single agent Japanese dose escalation will be analyzed separately.

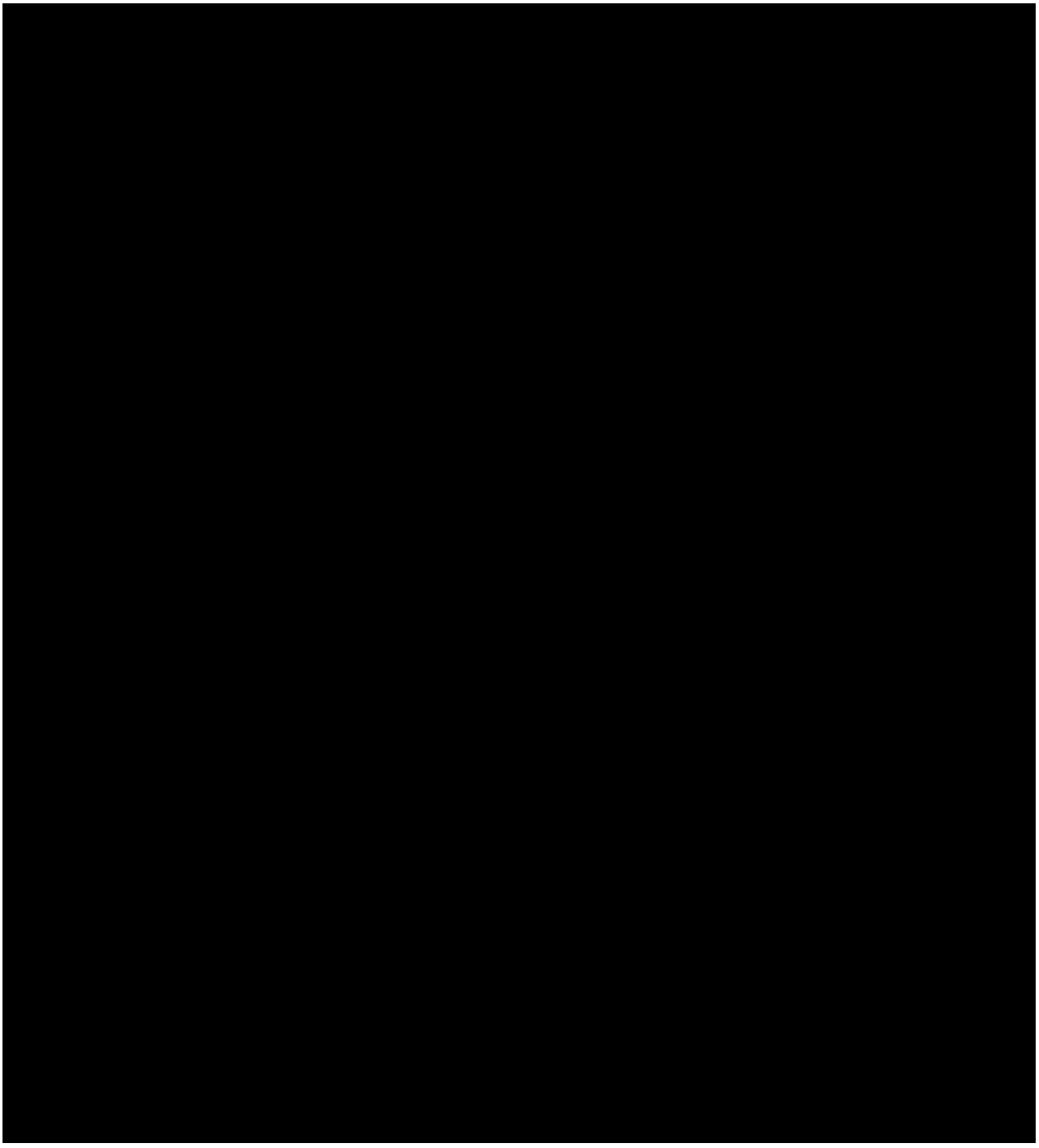
10.5.6.1 Data handling principles

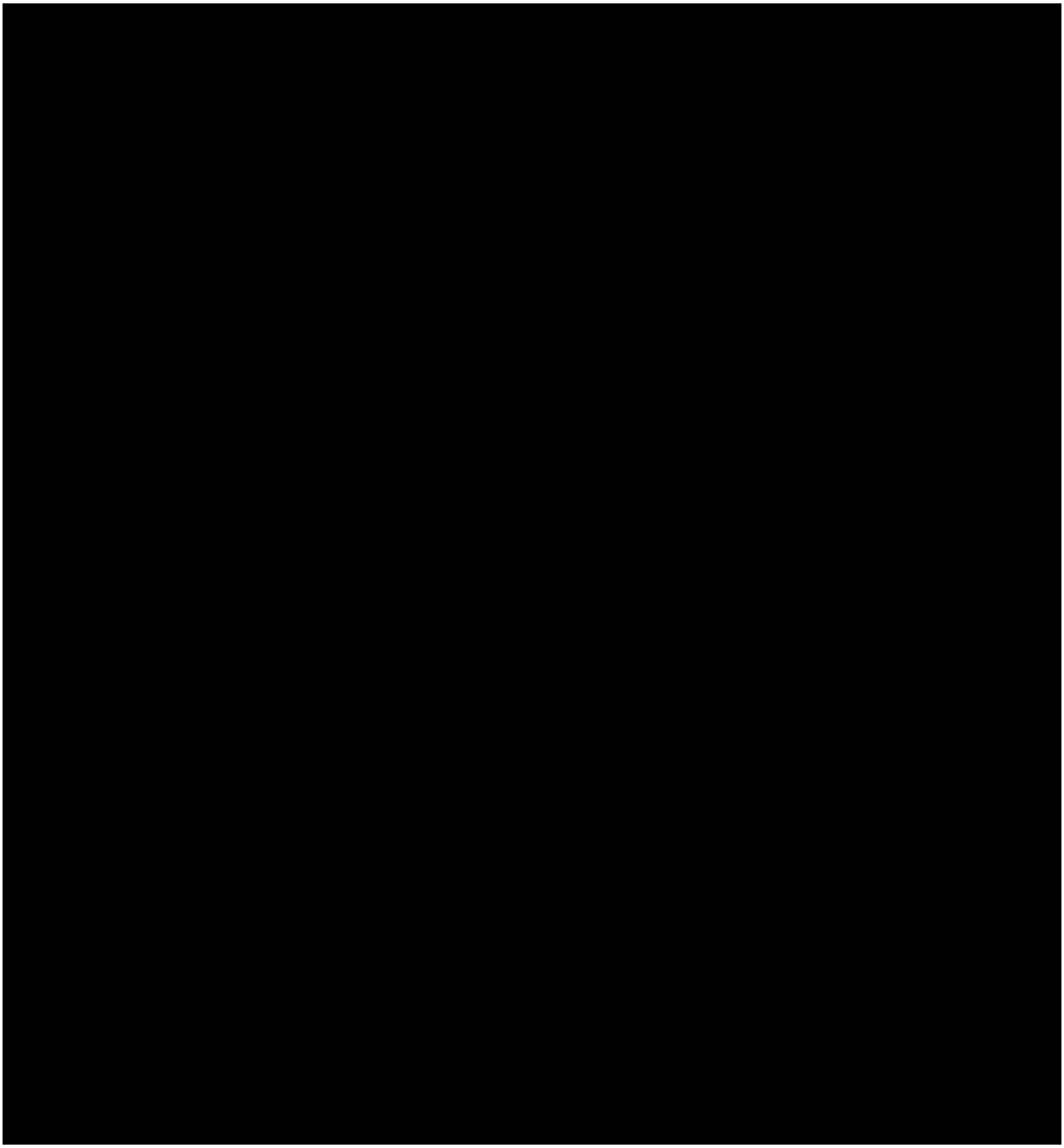
Only PK blood samples with the date and time and for which the last prior dose dates and times are adequately recorded will be included in the PK analyses. Missing concentration values will be reported as is in data listings. Concentration values below LLOQ will be handled as zero in summary statistics,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

10.5.6.2 Basic Tables, Figures and Listings

Descriptive statistics (mean, standard deviation, CV% or median (range)) will be presented for all pharmacokinetic parameters. When a geometric mean is presented, it will be stated as such. Zero concentrations will not be included in the geometric mean calculation. Since Tmax is generally evaluated by a nonparametric method, median values and ranges will be presented for this parameter. Summary statistics will be presented for BLZ945, LEL284 and PDR001 serum concentrations at each scheduled time point. Anti-PDR001 antibody data will also be summarized. Descriptive graphical plots of individual serum concentration versus time profiles and mean concentration versus time profiles will be generated. [redacted]

[redacted]





10.5.8 Resource utilization

Not applicable

10.5.9 Patient-reported outcomes

Not applicable

10.6 Exploratory objectives

10.6.1 Biomarkers

[redacted] Assessments at screening and on-treatment and change from baseline may be listed by patient and summarized (when sample size is sufficient) using descriptive statistics including but not restricted to CD163 and CD8 by immunohistochemistry. [redacted]

[redacted]

10.7 Interim analysis

Phase I

No formal interim analyses are planned for the phase I part of the study.

However, 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] and 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.

Phase II

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 DCR is $\geq$ 60% (at least 60% of the first 20 patients have SD or better at their first tumor assessment). This threshold is selected based on evaluation of operating characteristics of the corresponding design via simulations as detailed in Section 14.6. It has desired operating characteristics that if the true PFSR6 is 20%, the probability of stopping at interim is high (71%) while the probability of stopping at interim is low (21%) if the true PFSR6 is 40% (Table 10-2).

[redacted]

Table 10-2 Operating characteristics

True PFSR6	Complete success rate	Complete failure rate	Probability of stop at interim
20	0.004	0.996	0.71
30	0.09	0.91	0.43
40	0.57	0.43	0.21
50	0.90	0.10	0.08
60	0.97	0.03	0.03

The Investigators and Novartis study personnel will make the decision based on a synthesis of all relevant data available including safety, PK [redacted] information.

10.8 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. 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, at least 12 patients are required to be treated in the Japanese single agent dose escalation 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 glioblastoma patients will be initially enrolled at the RP2D of BLZ945 as single agent and at the RP2D of BLZ945 in combination with PDR001, with the possibility of expanding to 40 patients for each treatment arm. Based on the operating characteristics as described in Appendix 5, 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.

10.9 Power for analysis of key secondary variables

Not applicable.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

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

[redacted]

11.2 Responsibilities of the investigator and IRB/IEC/REB

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

11.3 Informed consent procedures

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

For Japan only: written consent is necessary both from the patient and his/her legal representative if he/she is under the age of 20 years.

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

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

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

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11.4 Discontinuation of the study

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

11.5 Publication of study protocol and results

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

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

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

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

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

11.6 Study documentation, record keeping and retention of documents

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

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

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at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

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

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

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

11.7 Confidentiality of study documents and patient records

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

11.8 Audits and inspections

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

11.9 Financial disclosures

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

12 Protocol adherence

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

12.1 Amendments to the protocol

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

[redacted]

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[redacted]

14 Appendices

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

Harmonization of Efficacy Analysis of Solid Tumor Studies

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Glossary

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

14.1.1 Introduction

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

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

14.1.2 Efficacy assessments

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

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14.1.2.1 Definitions

14.1.2.1.1 Disease measurability

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

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

For patients without measurable disease see Section 14.1.3.2.8

Measurable lesions (both nodal and non-nodal)

- Measurable non-nodal - As a rule of thumb, the minimum size of a measurable non-nodal target lesion at baseline should be no less than double the slice thickness or 10mm whichever is greater - e.g. the minimum non-nodal lesion size for CT/MRI with 5mm cuts will be 10 mm, for 8 mm contiguous cuts the minimum size will be 16 mm.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components, that can be evaluated by CT/MRI, can be considered as measurable lesions, if the soft tissue component meets the definition of measurability.
- Measurable nodal lesions (i.e. lymph nodes) - Lymph nodes ≥15 mm in short axis can be considered for selection as target lesions. Lymph nodes measuring ≥10 mm and <15 mm are considered non-measurable. Lymph nodes smaller than 10 mm in short axis at baseline, regardless of the slice thickness, are normal and not considered indicative of disease.
- Cystic lesions:
  - Lesions that meet the criteria for radiographically defined simple cysts (i.e., spherical structure with a thin, non-irregular, non-nodular and non-enhancing wall, no septations, and low CT density [water-like] content) should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
  - 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.
- Non-measurable lesions - all other lesions are considered non-measurable, including small lesions (e.g. longest diameter <10 mm with CT/MRI or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions e.g., blastic bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

14.1.2.1.2 Eligibility based on measurable disease

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

14.1.2.2 Methods of tumor measurement - general guidelines

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

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

- All measurements should be taken and recorded in metric notation (mm), using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.
- For optimal evaluation of patients, the same methods of assessment and technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a 5 mm slice thickness with a contiguous reconstruction algorithm. CT/MRI scan slice thickness should not exceed 8 mm cuts using a contiguous reconstruction algorithm. If, at baseline, a patient is known to have a medical contraindication to CT contrast or develops a contraindication during the trial, the following change in imaging modality will be accepted for follow up: a non-contrast CT of chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.
- A change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change in methodology will result by default in a UNK overall lesion response assessment. However, another response assessment than the Novartis calculated UNK response may be accepted from the investigator or the central blinded reviewer if a definitive response assessment can be justified, based on the available information.
- FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  - No FDG-PET at baseline with a positive FDG-PET at follow-up:
- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

[redacted]

- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT are needed to determine if there is truly progression occurring at that Site (if so, the date of PD will be the date of the initial abnormal CT scan).
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- Ultrasound: When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- Endoscopy and laparoscopy: The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when tumor samples are obtained.
- Tumor markers: Tumor markers alone cannot be used to assess response. However, some disease specific and more validated tumor markers (e.g. CA-125 for ovarian cancer, PSA for prostate cancer, alpha-FP, LDH and Beta-hCG for testicular cancer) can be integrated as non-target disease. If markers are initially above the upper normal limit they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- **Cytology and histology**: Cytology and histology can be used to differentiate between PR and CR in rare cases (i.e., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors). Cytologic confirmation of neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met the criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response and stable disease (an effusion may be a side effect of the treatment) or progressive disease (if the neoplastic origin of the fluid is confirmed).
- **Clinical examination**: Clinical lesions will only be considered measurable when they are superficial (i.e., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

[redacted]

14.1.2.3 Baseline documentation of target and non-target lesions

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

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

Minimum target lesion size at baseline

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

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

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

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

To assess tumor response, the sum of diameters for all target lesions will be calculated (at baseline and throughout the study). At each assessment response is evaluated first separately for the target (Table 14-1) and non-target lesions (Table 14-2) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 14-3) as well as the presence or absence of new lesions.

14.1.2.4.1 Follow-up and recording of lesions

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

[redacted]

Non-nodal lesions

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

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

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

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

Nodal lesions

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

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

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

[redacted]

14.1.2.4.2 Determination of target lesion response

Table 14-1 Response criteria for target lesions

Response Criteria	Evaluation of target lesions
Complete Response (CR):	Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm [1]
Partial Response (PR):	At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm^2.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for PD.
Unknown (UNK)	Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a different method than baseline.[3]
SOD for CR may not be zero when nodal lesions are part of target lesions	
Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10 mm in size. In this case, the target lesion response is CR	
Methodology change See Section 14.1.2.2.	

Notes on target lesion response

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

- The lesion is a new lesion, in which case the overall tumor assessment will be considered as progressive disease
- The lesion is clearly a reappearance of a previously disappeared lesion, in which case the size of the lesion has to be entered in the eCRF and the tumor assessment will remain based on the sum of tumor measurements as presented in Table 14-1 above (i.e., a PD will be determined if there is at least 20% increase in the sum of diameters of **all** measured target lesions, taking as reference the smallest sum of diameters of all target lesions recorded at or after baseline with at least 5 mm increase in the absolute sum of the diameters). Proper documentation should be available to support this decision. This applies to patients who have not achieved target response of CR. For patients who have achieved CR, please refer to last bullet in this section.
- For those patients who have only one target lesion at baseline, the reappearance of the target lesion which disappeared previously, even if still small, is considered a PD.

[redacted]

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

[redacted]

14.1.2.4.3 Determination of non-target lesion response

Table 14-2 Response criteria for non-target lesions

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

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

Notes on non-target lesion response

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

[redacted]

14.1.2.4.4 New lesions

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

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

14.1.2.5 Evaluation of overall lesion response

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

Table 14-3 Overall lesion response at each assessment

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

[1] This overall lesion response also applies when there are no non-target lesions identified at baseline.

[2] Once confirmed PR was achieved, all these assessments are considered PR.

[3] As defined in Section 14.1.2.4.

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

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

[redacted]

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

14.1.3 Efficacy definitions

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

14.1.3.1 Best overall response

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

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

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

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

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

[redacted]

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

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

Overall lesion responses of CR must stay the same until progression sets in, with the exception of a UNK status. A patient who had a CR cannot subsequently have a lower status other than a PD, e.g. PR or SD, as this would imply a progression based on one or more lesions reappearing, in which case the status would become a PD.

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

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

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

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

[redacted]

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

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

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

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

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

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

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

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

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

14.1.3.2 Time to event variables

14.1.3.2.1 Progression-free survival

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

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

[redacted]

14.1.3.2.2 Overall survival

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

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

14.1.3.2.3 Time to progression

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

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

14.1.3.2.4 Time to treatment failure

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

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

14.1.3.2.5 Duration of response

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

[redacted]

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

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

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

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

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

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

14.1.3.2.6 Time to response

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

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

- at maximum follow-up (i.e. FPFV to LPLV used for the analysis) for patients who had a PFS event (i.e. progressed or died due to any cause). In this case the PFS event is the worst possible outcome as it means the patient cannot subsequently respond. Since the statistical analysis usually makes use of the ranking of times to response it is sufficient to

[redacted]

assign the worst possible censoring time which could be observed in the study which is equal to the maximum follow-up time (i.e. time from FPFV to LPLV)

- at last adequate tumor assessment date otherwise. In this case patients have not yet progressed so they theoretically still have a chance of responding

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

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

Assessment date

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

Start dates

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

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

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

End dates

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

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

[redacted]

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

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

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

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

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

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

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

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

[1] As defined in Section 14.1.2.4.

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

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

[redacted]

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

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

14.1.3.2.9 Sensitivity analyses

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

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

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

Situation		Options for end-date (progression or censoring)[1] (1) = default unless specified differently in the protocol or RAP	Outcome
A	No baseline assessment	(1) Date of randomization/start of treatment[3]	Censored
B	Progression at or before next scheduled assessment	(1) Date of progression (2) Date of next scheduled assessment[2]	Progressed Progressed
C1	Progression or death after exactly one missing assessment	(1) Date of progression (or death) (2) Date of next scheduled assessment[2]	Progressed Progressed
C2	Progression or death after two or more missing assessments	(1) Date of last adequate assessment[2] (2) Date of next scheduled assessment[2] (3) Date of progression (or death)	Censored Progressed Progressed
D	No progression	(1) Date of last adequate assessment	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	(1) N/A (2) Date of discontinuation (visit date at which clinical progression was determined)	Ignored Progressed

[redacted]

Situation		Options for end-date (progression or censoring)[1] (1) = default unless specified differently in the protocol or RAP	Outcome
F	New anticancer therapy given	(1) Date of last adequate assessment (2) Date of secondary anti-cancer therapy (3) Date of secondary anti-cancer therapy (4) N/A	Censored Censored Event Ignored
G	Deaths due to reason other than deterioration of 'Study indication'	(1) Date of last adequate assessment	Censored (only TTP and duration of response)
= Definitions can be found in Section 14.1.3.2.7			
=After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 14.1.3.2.7			
=The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.			

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

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

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

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

Situation E: Treatment discontinuation due to 'Disease progression' without documented progression: By default, option (1) is used for situation E as patients without documented PD should be followed for progression after discontinuation of treatment. However, option (2) may be used as sensitivity analysis. If progression is claimed based on clinical deterioration instead of tumor assessment by e.g. CT-scan, option (2) may be used for indications with high early progression rate or difficulties to assess the tumor due to clinical deterioration.

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

Additional suggestions for sensitivity analyses

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

[redacted]

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

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

14.1.4 Data handling and programming rules

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

14.1.4.1 Study/project specific decisions

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

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

14.1.4.2 End of treatment phase completion

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

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

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

- Adverse event(s)
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Patient/guardian decision
- Death
- Progressive disease per irRC (not per RECIST)
- Study terminated by Novartis

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

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

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

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

14.1.4.4 Medical validation of programmed overall lesion response

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

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

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

[redacted]

14.1.4.5 Programming rules

The following should be used for programming of efficacy results:

14.1.4.5.1 Calculation of 'time to event' variables

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

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

14.1.4.5.2 Incomplete assessment dates

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

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

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

14.1.4.5.3 Incomplete dates for last known date patient alive or death

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

14.1.4.5.4 Non-target lesion response

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

14.1.4.5.5 Study/project specific programming

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

14.1.4.5.6 Censoring reason

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

For survival the following censoring reasons are possible:

- Alive
- Lost to follow-up

[redacted]

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

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

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

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

14.1.5 References (available upon request)

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

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

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

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

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

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

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

[redacted]

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

14.2.1 Introduction

The currently used immune-related response criteria (irRC) uses unidimensional measurements to assess tumor response and it is an adaptation of the original irRC published by Wolchok (Wolchok et al. 2009, Nishino 2013).

The purpose of this document is to summarize the irRC guidelines in details focusing on differences in tumor response assessments between irRC and RECIST v1.1.

The primary difference between irRC and RECIST 1.1 is the definition of progressive disease. The definitions of baseline target/non target lesions, number of lesions selected at baseline, the criteria for lesion measurement method of evaluation of response and definition of response are the same for irRC and RECIST 1.1 and are available in the RECIST 1.1 guidelines (Appendix 1).

14.2.2 New lesions and non-target lesions

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

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

New measureable lesions are defined using the same criteria as for baseline target lesions in RECIST v1.1. New measurable lesions shall be prioritized according to size, and the largest lesions shall be selected as new measured lesions. Up to five new measurable lesions (and a maximum of two per organ) are allowed in total and will be included in the overall tumor assessment.

Non-target lesions (baseline and new non-measurable lesions) are used primarily for determination of Complete Response (CR). The RECIST v1.1 definitions for the assessment of non-target lesions apply. A CR requires that all non-target lesions disappear (both those present at baseline and any new non-measurable lesions that have appeared during the study). If after worsening a non-target lesion becomes measurable, it should still be followed as a non-target lesion. Worsening of non-target lesions and new non-measurable lesions only indicate disease progression if there is unequivocal evidence of disease progression (Table 14-6).

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

To assess tumor response, the sum of longest diameters for all target lesions is calculated (at baseline and throughout the study). The longest diameters of any new measurable lesions are included in the sum of longest diameters at each assessment to provide the total tumor burden. At each assessment, percent change in the sum of longest diameters is calculated and compared to baseline or to nadir in order to evaluate the target lesion response (including new measurable lesions) (Section 14.2.4). This evaluation combined with the status of non-target lesions (baseline and new non-measurable lesions) is then used to determinate the overall lesion response (Table 14-6). The thresholds for immune-related partial response (irPR) and irPD assessment are the same as for RECIST v1.1.

[redacted]

14.2.4 Definitions of response categories and evaluation of overall lesion response

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

Like in RECIST v1.1, irCR and irPR must be confirmed at a new assessment after at least 4 weeks. Unlike RECIST v1.1, irPD also requires confirmation at a new assessment after at least 4 weeks.

The response categories are defined as follows:

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

[redacted]

Table 14-6 Overall response at each assessment

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

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

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

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

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

14.2.5 Only non-measurable disease at baseline

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

14.2.6 References (available upon request)

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

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

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14.3 Appendix 3: Response assessment in neuro-oncology (RANO) criteria for high-grade gliomas

Antitumor response will be primarily evaluated by the Response Assessment in Neuro-Oncology (RANO) working group (Wen et al 2010) criteria in this study. The RANO Criteria updates its established predecessor, the modified Macdonald Criteria (Macdonald et al 1990), by adding assessment of non-enhancing lesions.

Patients will undergo MRI assessments for response evaluation on an every 8 weeks interval from the start of the study until disease progression, as outlined in the Visit schedule Table 7-1, Table 7-2 and Table 7-3.

The following components will be taken into account when assessing a patient's overall response at an individual evaluation.

- Tumor evaluation eCRF for measureable enhancing lesions (T1-Gd+)
- Tumor evaluation eCRF for non-enhancing lesions (T2/FLAIR)
- Tumor evaluation eCRF for new lesion
- Concomitant medication eCRF for steroid usage
- Clinical status eCRF for ECOG and other clinical evaluation finding
- Overall response eCRF for response category (CR/PR/PD/SD/NA)

14.3.1 Antitumor effect – definitions

Evaluable for toxicity

All participants who receive at least one dose of study treatment will be evaluable for toxicity from the time of their first treatment.

Evaluable for objective response

Only those participants who have measurable disease present at screening (Day -28 to -1 scan) and have received at least one dose of therapy will be considered evaluable for response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression or die prior to the end of Cycle 1 will also be considered evaluable.)

Measurable disease

Bi-dimensionally, contrast-enhancing, measurable lesions with clearly defined margins by CT or MRI scan, with a minimal diameter of 1 cm, and visible on 2 axial slices which are at least 5 mm apart with 0 mm skip. Measurement of tumor around a cyst or surgical cavity, if necessary, requires a minimum thickness of 3 mm. If there are too many measurable lesions to measure at each evaluation, the investigator must choose the largest two to be followed before a participant is entered on study. The remaining lesions will be considered non-measureable for the purpose of objective response determination. Unless progression is observed, objective response can only be determined when all measurable and non-measurable lesions are assessed.

[redacted]

Non-measurable evaluable disease

Uni-dimensionally measurable lesions, masses with margins not clearly defined, lesions with maximal diameter < 1 cm.

14.3.2 Response/progression categories

Complete response (CR)

All of the following criteria must be met:

a. Complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks. In the absence of a confirming scan 4 weeks later, this scan will be considered only stable disease.
b. No new lesions.
c. All measurable and non-measurable lesions must be assessed using the same techniques as baseline.
d. Participants must be on no steroids or on physiologic replacement doses only.
e. Stable or improved non-enhancing (T2/FLAIR) lesions.
f. Stable or improved clinically, for clinical signs and symptoms present at baseline and recorded to be disease related.

Participants with non-measurable disease cannot have a complete response. The best response possible is stable disease.

Partial response (PR)

All of the following criteria must be met:

a. Greater than or equal to 50% decrease compared to baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks. In the absence of a confirming scan 4 weeks later, this scan will be considered only stable disease.
b. No progression of non-measurable disease.
c. No new lesions.
d. All measurable and non-measurable lesions must be assessed using the same techniques as baseline.
e. The steroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan.
f. Stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan.
g. Stable or improved, for clinical signs and symptoms present at baseline and recorded to be disease related clinically.

Participants with non-measurable disease cannot have a partial response. The best response possible is stable disease.

[redacted]

Progressive disease (PD)

The following criterion must be met:

a. 25% increase in sum of the products of perpendicular diameters of enhancing lesions (over best response or baseline if no decrease) on stable or increasing doses of corticosteroids

and/or one or more of the following:

b. Significant increase in T2/FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids steroids compared to baseline scan or best response following initiation of therapy, not due to co-morbid events (radiation therapy, demyelination, ischemic injury, infection, seizures, post-operative changes, or other treatment effects).
c. Any new lesion
d. Clear clinical deterioration not attributable to other causes apart from the tumor (e.g. seizures, medication side effects, complications of therapy, cerebrovascular events, infection, etc.). The definition of clinical deterioration is left to the discretion of the investigator but it is recommended that a decline in the Easter cooperative Oncology Group (ECOG) performance scores from 0 or 1 to 2 or 2 to 3 would be considered neurologic deterioration, unless attributable to co-morbid events or changes in corticosteroid dose.
e. Failure to return for evaluation due to death or deteriorating condition

Stable disease (SD)

All of the following criteria must be met:

a. Does not qualify for CR, PR, or progression.
b. All measurable and non-measurable sites must be assessed using the same techniques as baseline.
c. Stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan. In the event that the corticosteroid dose has been increased, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.
d. Stable clinically.

[redacted]

Unknown response status

Progressive disease has not been documented and one or more measurable or non-measurable lesions have not been assessed.

These RANO Response Criteria are also summarized in Table 14-7.

Table 14-7 Summary of the RANO response criteria

	CR	PR	SD	PD
T1-Gd +	None	≥50% decrease	<50% decrease but <25% increase	≥25% increase*
T2/FLAIR	Stable or decrease	Stable or decrease	Stable or decrease	Increase*
New Lesion	None	None	None	Present*
Corticosteroids	None	Stable or decrease	Stable or decrease	NA**
Clinical Status	Stable or improve	Stable or improve	Stable or improve	Deterioration*
Requirement for Response	All	All	All	Any*
CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease *: Progression when this criterion is met **: Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration				

14.3.3 Methods for evaluation of measurable disease

All measurements should be taken and recorded in metric notation, using a ruler, calipers, or digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 14 days before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

14.3.4 Evaluation of best response

The best overall response is the best response recorded from the start of the treatment until disease progression (taking as reference for progressive disease the smallest measurements recorded since the treatment started). If a response recorded at one scheduled MRI does not persist at the next regular scheduled MRI, the response will still be recorded based on the prior scan, but will be designated as a non-sustained response. If the response is sustained, i.e. still present on the subsequent MRI, it will be recorded as a sustained response, lasting until the time of tumor progression. Participants without measurable disease may only achieve SD or PD as their best "response."

[redacted]

14.3.5 Other effect measures

14.3.5.1 Neurological exam

Although not used for determining response, it is useful to evaluate changes in the neurological exam compared to the previous exam. The following scale may be used:

+2	Definitely better
+1	Possibly better
0	Unchanged
-1	Possibly worse
-2	Definitely worse

14.3.5.2 Performance status

Participants will be graded according to ECOG score.

14.3.5.3 Overall survival time

From date of first dose (date of first post-surgery treatment for participants in Dose Level 1) to date of death due to any cause.

14.3.5.4 Progression-free survival time

From date of first dose (date of first post-surgery treatment for participants in Dose Level 1) to date of progression or death. Participants who stop treatment for causes other than progression may be censored if other therapy is initiated or if regular assessments for assessing progression are no longer available.

14.3.6 References

Macdonald DR, Cascino TL, Schold SC Jr, et al (1990) Response criteria for phase II studies of supratentorial malignant glioma. J Clin Oncol; 8: 1277-80. In appendix 3

Wen PY, Prados M, Schiff D, et al (2010a) Phase II study of XL184 (BMS 907351), an inhibitor of MET, VEGFR2, and RET, in patients (pts) with progressive glioblastoma (GB). J.Clin Oncol; 28:15s (suppl, abstr 2006)

Wen PY, Macdonald DR, Reardon DA, et al (2010b) Updated Response Assessment Criteria for High-Grade Gliomas: Response Assessment in Neuro-Oncology Working Group. J Clin Oncol; 28:1963-1972

[redacted]

14.4 Appendix 4: Immunotherapy Response Assessment in Neuro-Oncology (iRANO) criteria for high-grade gliomas

The iRANO criteria, provide special considerations for the development of pseudoprogression, given that the treatment is designed to evoke an immune/inflammatory response. This appendix is based on the report of the RANO working group (Okada et al 2015).

14.4.1 Immunotherapy Continuation Beyond Initial Progressive Disease

Correct interpretation of progressive imaging findings after administration of immunotherapy is essential because early progressive radiographic changes (i.e. pseudoprogression) not always preclude subsequent therapeutic benefit.

Pseudoprogression occurring within the first 24 weeks after the start of immunotherapy may be difficult to differentiate from true tumor progression and may have important implications for patient management.

In order to distinguish between pseudoprogression and true tumor progression, and therefore minimize premature discontinuation of study treatment, the iRANO working committee recommends that for patients with early progressive imaging findings, including patients who develop new lesions but who do not have significant neurological decline, confirmation of radiographic progression by follow-up imaging should be sought 12 weeks after initial radiographic evidence of progressive disease to decrease the likelihood of prematurely declaring progressive disease in patients with pseudoprogression or delayed response.

In such patients, those with confirmation of further radiographic progression based on a comparison with the scan that first showed evidence of disease progression, or who develop significant clinical decline at any time, should be classified as having progressive disease with the date of disease progression back-dated to the first date that the patient met criteria for radiographic progression. For these patients, immunotherapy should be discontinued and patients will enter the survival follow up phase. In the event that follow-up imaging does not confirm further disease progression compared with the scan of the tumor that first showed initial progressive changes, but instead there is stabilization or reduction in tumor burden, treatment should be continued or resumed in the absence of increased corticosteroid dosing (i.e. > 4mg of dexamethasone or equivalent per day). A treatment algorithm to summarize guidance for follow-up imaging after initial progressive changes is provided in Table 14-8.

In those cases in which radiologic progression cannot be differentiated from pseudoprogression and which acquisition of tumor histopathology by biopsy or resection is thought to be feasible, pathological assessment might be considered to clarify the cause of progressive imaging findings. If pathology confirms a predominance of recurrent tumor, the cause should be considered to be true progression. For cases where there is no evidence of a viable tumor, or where a prominence of gliosis or inflammation with restricted viable tumor is reported, the cause should be deemed consistent with treatment effect, and such patients should be classified as stable and allowed to continue therapy.

14.4.2 Response Assessment

Standard RANO criteria may not provide an accurate response assessment of immunotherapeutic agents. Therefore, the following adaptations of the RANO criteria will be used to assess response for patients treated with immunotherapeutics (Table 14-8):

Table 14-8 Imaging and Treatment after 1st Radiologic Evidence of PD

First radiologic evidence of PD within 24 weeks and			
patient does not have new or significant neurological decline		patient has new or significant neurological decline	
perform scan at week 12 Continue study treatment		perform scan at week 12 whenever possible Interrupt study treatment	
The scan performed at week 12 confirms PD			
Yes	No	Yes	NO
No additional imaging assessments Discontinue Study treatment	Continue imaging assessments as per protocol Continue study treatment at the clinician's discretion	No additional imaging assessments Discontinue study treatment	Continue imaging assessments as per protocol Resume study treatment

14.4.3 References

Okada H, Weller M, Huang R,et al. (2015) Immunotherapy response assessment in neuro-oncology: a report of the RANO working group. Lancet Oncol. 16(15): 534-542.

[redacted]

14.5 Appendix 5: Statistical methods

14.5.1 Statistical details of Bayesian regression models, priors, design operating characteristics and hypothetical dose escalation scenarios

An adaptive Bayesian design using escalations with overdose control (EWOC) will guide the dose escalation of single agent and combination treatment to its MTD(s)/RP2D(s). The use of Bayesian response adaptive designs for Phase I studies has been advocated by the EMEA guideline on small populations (2007) and by Rogatko (2007), and is one of the key elements of the FDA's Critical Path Initiative.

The BLRMs will study the dose-toxicity relationship of BLZ945 when given alone and in combination with PDR001. This Bayesian analysis will be based on the dose limiting toxicity data (absence or presence of DLT) of the first 28 days of the single agent as well as the combination treatment, accumulated throughout the dose escalation. This appendix provides details of the statistical models and the derivation of prior distributions for the model parameters.

To check the performance of the model, some hypothetical dose escalation scenarios and operation characteristics for the single agent and the combination models are presented.

14.5.2 Single agent BLZ945

14.5.2.1 Statistical model

In the single-agent BLZ945 dose escalation part, the dose-toxicity (DLT) relationship will be described by a 2-parameter BLRM formulated in the following way:

$$\text{logit}(\pi(d)) = \log(\alpha) + \beta \log(d/d^*)$$

Where, $\pi(d)$ is the probability that a patient has a DLT during the first 28 days when BLZ945 is given as single agent at the 7 days on/7 days off dose d, where d is the planned total dose (mg) in cycle 1, and d*=900x14mg is the reference dose.

$\alpha, \beta > 0$ are the parameters of the model.

14.5.2.2 Prior specification

Pre-clinical toxicology data showed no definitive BLZ945 related toxicity, thereby making it impossible to predict the MTD in human. For this reason the priors of model parameter distributions are defined based on a weakly informative prior. A vague bivariate normal prior distribution for the model parameters, (log(α), log(β)), was elicited based on a plausible mean values but allowing for considerable uncertainty, essentially making sure that the a-priori range for the parameters cover a wide range of plausible values.

Assuming a median prior probability of DLT equal to 0.15 at the dose reference results in a mean of log(α) equal to logit(0.15) = -1.735.

Assuming the odds is doubled when doubling the dose results in a mean of log(β) equal to 0.

The standard deviations of log(α) and log(β) are set respectively to 2 and 1, and the correlation is assumed to be 0.

[redacted]

The prior distribution parameters of the BLRM for single agent are provided in Table 14-9 and summary of prior distribution of DLT rates in Table 14-10.

Table 14-9 Prior distribution parameters-BLZ945 SA (7d on/ 7d off schedule)

(log(α) , log(β))		
Means	**SDs**	**Correlation**
(-1.735 , 0)	(2 , 1)	0

Table 14-10 Summary of prior distribution of DLT rates- BLZ945 SA (7d on/ 7d off schedule)

Dose level (mg)	Prior probabilities that P(DLT) is in interval:					Quantiles		
	0-0.16	0.16-0.33	0.33-1	Mean	SD	0.025	Median	0.975
100	0.843	0.077	0.080	0.083	0.164	0.000	0.012	0.644
150*	0.816	0.088	0.096	0.097	0.176	0.000	0.018	0.686
300	0.748	0.115	0.137	0.132	0.202	0.000	0.038	0.764
600	0.630	0.155	0.215	0.193	0.236	0.001	0.087	0.846
900	0.515	0.182	**0.302**	0.255	0.263	0.003	0.149	0.898

* Starting dose

14.5.2.3 Hypothetical dose escalation scenarios

In order to show how the proposed approach works, hypothetical dose escalation scenarios are investigated. The model will be used to assess risk to future patients during the clinical trial based on the observed DLTs. This assessment of risk is then used to guide future dosing decisions. In choosing a dose to explore, the clinical team will also consider all available clinical, safety, PK and PD, but will not consider a dose for use unless it satisfies the EWOC criterion.

Table 14-11 illustrates a selection of possible dose escalation scenarios.

Table 14-11 Hypothetical scenarios

Scenario	Cohort	Dose level (mg)	Ntox / Npat	Next dose level (NDL) (mg)	P(target) at NDL	P(over) at NDL	Median at NDL
1	1	150	0/3	300	0.084	0.032	0.021
2	1	150	1/3	150	0.297	0.240	0.177
3	1	150	2/3	STOP			
4	1	150	0/3				
4	2	300	2/3	150	0.356	0.183	0.174
5	1	150	1/5				
5	2	300	2/6	150	0.445	0.107	0.174
6	1	150	1/5				
6	2	300	1/4	300	0.432	0.208	0.206
7	1	150	0/3				
7	2	300	0/3	600	0.116	0.054	0.040
8	1	150	0/3				
8	2	300	0/3				
8	3	600	1/3	600	0.306	0.124	0.134

[redacted]

Scenario	Cohort	Dose level (mg)	Ntox / Npat	Next dose level (NDL) (mg)	P(target) at NDL	P(over) at NDL	Median at NDL
9	1	150	0/3				
9	2	300	0/3				
9	3	600	2/4	300	0.249	0.046	0.101
10	1	150	0/3				
10	2	300	0/3				
10	3	600	0/4				
10	4	900	2/3	600	0.285	0.054	0.113

14.5.2.4 Operating characteristics

In order to show how the proposed design performs under different true dose- DLT profiles, various hypothetical scenarios were investigated.

14.5.2.5 Simulation setup

Table 14-12 shows 5 dose-DLT scenarios, taking scenario 1 (true DLT rates equal to median prior DLT rates) as the basis. Scenario 2 has decreased DLT rates compared to scenario 1. Scenarios 3, 4 and 5 have increased DLT rates compared to scenario 1:

The following table presents the true underlying probabilities of DLT for each scenario

Table 14-12 dose-DLT scenarios

Test scenarios	Assigning DLT probabilities to each dose level					Note
	100 mg	150 mg	300 mg	600 mg	900 mg	
1	0.012	0.018	0.038	0.087	0.149	Scenario1: Median DLT probabilities
2	0.006	0.009	0.019	0.045	0.08	Scenario2: the odds of DLTs are 50% smaller than the ones of scenario 1
3	0.024	0.035	0.073	0.16	0.259	Scenario3: 2-fold odds inflation from scenario 1
4	0.057	0.084	0.165	0.323	0.467	Scenario4: 5-fold odds inflation from scenario 1
5	0.108	0.155	0.283	0.488	0.636	Scenario5: 10-fold odds inflation from scenario 1

For each scenario, data for 1000 trials were generated, with randomly chosen cohorts of size 3 to 6. The starting dose is 150 mg for BLZ945.

The following metrics were assessed in the simulations:

- percentage of patients receiving a dose that is in the target toxicity (TT) interval (metric I)
- percentage of patients receiving an overdose (OD) (metric II)
- percentage of patients receiving an underdose (UD) (metric III)
- probability that recommended MTD at the end of the trial is in the target toxicity interval (metric IV)
- probability that recommended MTD is an overdose (metric V)

[redacted]

- probability that recommended MTD is an underdose (metric VI)
- percentage of trials stopped without MTD declaration (metric VII)
- average sample size
- average number of DLT

The maximum number of patients per trial was set to 60. The trial was stopped using the rules defined in the protocol in Section 6.2.3.2.

Table 14-13 Operating characteristics

Metric	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
I	0.0	0.0	54.1	58.5	40.4
II	0.0	0.0	0.0	14.1	13.4
III	100	100	45.9	27.4	46.2
IV	0.0	0.0	85.0	76.7	48.1
V	0.0	0.0	0.0	7.0	4.2
VI	99.4	99.7	11.6	6.5	30.9
VII	0.6	0.3	3.4	9.8	16.8
Average sample size	24	23	24	23	20
Average number of DLT	2.2	1.2	3.5	4.9	5.1

The simulated operating characteristics presented show that the BLRM performs well under the hypothetical profiles investigated. Indeed, the simulations performed illustrate that the model has reasonable operating characteristics and the number of patients with DLT was limited through a trial.

In scenario 1, the probability of DLT by dose is aligned with the prior with all the doses lie within the underdose interval. The simulations show that there is 99.4% of chance for identifying the MTD at underdose interval. The chance to stop the trial at overly toxic dose is very low (0.6%).

While in scenario 4, with 5-fold odds inflation from test scenario 1 where the underlying P (DLT) is above 33% for only 900 mg, there is about 77% of chance for selecting MTD within the target toxicity interval. Finally, in scenario 5, with 10-fold odds inflation from test scenario 1, the simulations show that there is about 4.2% of chance for identifying the MTD within the over dose toxicity interval. The chance to stop the trial due to high toxicity of all dose levels is high (16.8%).

In conclusion, the simulations performed illustrate that the model has good operating characteristics under the 5 hypothetical profiles investigated.

14.5.3 Combination of BLZ945 (7days on/7days off) and PDR001

14.5.3.1 Statistical model

In the combination BLZ945 and PDR001 dose escalation part, the dose-toxicity (DLT) relationship will be described by a 5-parameter BLRM formulated in the following way:

The respective single agent dose-DLT relationships are defined as:

$$\text{BLZ945:} \quad \text{logit}(\pi_1(d_1)) = \log(\alpha_1) + \beta_1 \log(d_1/d_1^*)$$

$$\text{PDR001:} \quad \text{logit}(\pi_2(d_2)) = \log(\alpha_2) + \beta_2 \log(d_2/d_2^*)$$

Where, $\pi_1(d_1)$ and $\pi_2(d_2)$ are respectively the probability that a patient has a DLT when BLZ945 and PDR001 are given as single agent at the dose d_1 and d_2, and d_1^*=900x14mg and d_2^*=400mg at Q4W are respectively the BLZ945 and PDR001 reference doses. $\alpha_\cdot, \beta_\cdot > 0$ are the parameters of the model.

Then, the dose-DLT relationship of the dual combinations of BLZ945 with PDR001 is defined as:

$$\text{Odds}\left(\pi_{12}(d_1, d_2)\right) = \frac{\pi_{12}(d_1,d_2)}{1-\pi_{12}(d_1,d_2)} = \exp(\eta \frac{d_1}{d_1^*} \frac{d_2}{d_2^*}) \left[\frac{\pi_1(d_1)+\pi_2(d_2)-\pi_1(d_1)\pi_2(d_2)}{(1-\pi_1(d_1))(1-\pi_2(d_2))}\right],$$

Where η is the interaction term.

14.5.3.2 Prior specification

The Bayesian approach requires the specification of prior distributions for all model parameters, which include the single-agent parameters for BLZ945 and PDR001, and the interaction parameter: $(\log(\alpha 1),\log(\beta 1))$, $(\log(\alpha 2),\log(\beta 2))$ and η respectively. A meta-analytic-predictive (MAP) approach was used to derive the prior distribution for the single-agent model parameters. The derivation of the prior distributions is provided in the following subsections.

14.5.3.2.1 Prior distribution for the logistic parameters

The mixture prior distributions for the single-agent PDR001 model parameters and BLZ945 model parameters will be derived separately as follows.

It consists of a mixture of:

- a meta-analytic-predictive (MAP) prior derived using the available historical dose-DLT data (which is approximated by a mixture of bivariate normal (BVN) distributions)
- and a weakly informative prior corresponding to high toxicity to make the prior more robust.

To obtain the mixture prior, 50% weight was assigned to the MAP prior, and 50% weight was assigned to the weakly informative prior of BLZ945 whereas 80% weight was assigned to the MAP prior, and 20% weight was assigned to the weakly informative prior of PDR001.

14.5.3.2.2 Description of the MAP approach

The aim of the MAP approach is to derive a prior distribution for the logistic parameters $\left(\log(\alpha^*),\ \log(\beta^*)\right)$ of the new trial using DLT data from historical studies.

[redacted]

Let r_{ds} and n_{ds} be the number of patients with a DLT, and the total number of patients at dose d in historical trial s ($s = 1, \ldots, S$). The corresponding probability of a DLT is π_{ds}. The model specifications for the derivation of the MAP prior are as follows:

$$r_{ds} \mid \pi_{ds} \sim \mathrm{Bin}(\pi_{ds}, n_{ds})$$

$$\mathrm{logit}(\pi_{ds}) = \log(\alpha_s) + \beta_s \log(d/d^*)$$

$$\left(\log(\alpha_s), \log(\beta_s)\right) \mid \mu, \psi \sim \mathrm{BVN}(\mu, \psi), \qquad s = 1, \ldots, S$$

$$\left(\log(\alpha^*), \log(\beta^*)\right) \mid \mu, \psi \sim \mathrm{BVN}(\mu, \psi)$$

The parameters $\mu = (\mu_1, \mu_2)$ and ψ are the mean and between-trial covariance matrix for the logistic parameters, the latter with standard deviations t_1, t_2, and correlation r. The parameters t_1 and t_2 quantify the degree of between trial heterogeneity. The following priors will be used for these parameters:

- normal priors for μ_1 and μ_2,
- log-normal priors for t_1 and t_2, and
- a uniform prior for r.

The MAP prior for single-agent model parameters in the new trial, $\left(\log(\alpha^*), \log(\beta^*)\right)$, is the predictive distribution

$$\left(\log(\alpha^*), \log(\beta^*)\right) \mid (r_{ds}, n_{ds} : s = 1, \ldots, S)$$

Since the predictive distribution is not available analytically, MCMC is used to simulate values from this distribution. This is implemented using JAGS version 3.4.0. The sample from this distribution is then approximated by a mixture of bivariate normal (BVN) distributions. BVN mixtures with increasing numbers of mixture components are fitted to the sample using the expectation-maximization (EM) algorithm (Dempster 1977). The optimal number of components of the mixture is then identified using the Akaike information criterion (AIC) (Akaike 1974).

14.5.3.2.3 Implementation of the MAP approach for BLZ945

For the MAP model, data from the available data from the SA arms in the current study (as per protocol, the combination part will only start after at least two cohorts of BLZ945 as single agent have been completed, and safety data suggests acceptable toxicity for patients to begin treatment in combination). The details of the derivation of the priors using available data from single agent BLZ945 arm will be given in the SAP. For illustrative purpose, it is assumed that there are 3 evaluable patients in each of the first two cohorts (doses 150mg and 300mg at 7days on/7 days off regimen) and 0 DLTs are observed as described in Table 14-14.

Table 14-14 Hypothetical data from single agent part

BLZ945 dose level (mg 7days on/7days off)	N DLTs / N patients in first 28 days
150	0/3
300	0/3

Note: These data are hypothetical and the real current available data from single agent part will be incorporated directly in the combination part during the DETCs

Weakly informative priors are assumed for $\mu_1$and μ_2, with means corresponding to a risk of DLT at the reference dose of 9%, and a doubling in dose leading to a doubling in the odds of the risk of a DLT, respectively. Priors for t_1 and t_2 are assigned such that (1) their medians correspond to moderate between trial heterogeneity, and (2) their uncertainty (95% prior interval) cover plausible between-trial standard deviations (Neuenschwander 2014). The prior distributions for the model used for deriving the MAP priors are specified in Table 14-15.

Table 14-15 Prior distributions for the parameters of the MAP model used to derive the prior

Parameter	Prior distribution
μ_1	N(mean = logit(0.09), sd = 2)
μ_2	N(mean = 0, sd=1)
t_1	log-normal(mean = 0.25, sd = log(2)/1.96)
t_2	log-normal(mean = 0.125, sd = log(2)/1.96)
r	uniform(-1,1)

14.5.3.2.4 Derivation of the weakly informative prior

A weakly informative BVN prior to allow higher toxicity than MAP prior is derived by assuming median probability of DLT at 900x14 mg to be 24%, as well as a log-linear relationship between dose and the odds of DLT as defined in Section 14.5.2. This results in setting the mean of log(α) equal to -1.153. The mean of log(β) is set to 0. Furthermore, setting standard deviation of log(α) = 2 and log(β) = 1, and setting the correlation between log(α) and log(β) = 0 to complete the determination of this prior. See Table 14-18.

14.5.3.2.5 Weight in the mixture prior

To obtain the mixture prior, 50% weight is assigned to the MAP prior, and 50% weight is assigned to the weakly informative prior

14.5.3.2.6 Implementation of the MAP approach for PDR001

For PDR001, currently available historical data of PDR001 from study [CPDR001X2101] has been used in order to derive the prior distribution for the BLRM parameters (log(α2),log(β2)) using MAP approach.

Table 14-16 Data from PDR001X2101 study

PDR001 dose level (mg/kg)	PDR001 dose in first 28 days (mg)	N DLTs / N patients in first 28 days
3 q4w	240	0/6
5 q4w	400	0/10

*A weight of 80kg is considered to convert weight adjusted dose to a flat dose
Note: Data cut-off date: 17 December 2015.

Weakly informative priors are assumed for μ_1 and $\mu_2$with means corresponding to a risk of DLT at the reference dose of 10%, and a doubling in dose leading to a doubling in the odds of the risk of a DLT, respectively. Priors for t_1 and t_2 are assigned such that (1) their medians correspond to substantial between trial heterogeneity, and (2) their uncertainty (95% prior interval) cover plausible between-trial standard deviations (Neuenschwander 2014).

[redacted]

The prior distributions for the model used for deriving the MAP priors are specified in Table 14-17.

Table 14-17 Prior distributions for the parameters of the MAP model used to derive the prior for the single-agent PDR001 model parameters

Parameter	Prior distribution
μ_1	N(mean = logit(0.10), sd = 2)
μ_2	N(mean = 0, sd=1)
t_1	log-normal(mean = 0.5, sd = log(2)/1.96)
t_2	log-normal(mean = 0.25, sd = log(2)/1.96)
r	uniform(-1,1)

14.5.3.2.7 Derivation of the weakly informative prior

A weakly informative BVN prior to allow higher toxicity than MAP prior is derived by assuming median probability of DLT at 400 mg to be 25%, as well as a log-linear relationship between dose and the odds of DLT as defined in Section 14.5.2. This results in setting the mean of $\log(\alpha)$ equal to -1.099. The mean of $\log(\beta)$ is set to 0. Furthermore, setting standard deviation of $\log(\alpha)$ = 2 and $\log(\beta)$ = 1, and setting the correlation between $\log(\alpha)$ and $\log(\beta)$ = 0 to complete the determination of this prior. See Table 14-18.

14.5.3.2.8 Weight in the mixture prior

To obtain the mixture prior, 80% weight is assigned to the MAP prior, and 20% weight is assigned to the weakly informative prior

14.5.3.2.9 Prior for the interaction parameter

Although no interaction is expected, considerable uncertainty remains. A normal prior distribution for the interaction parameter η is to be derived to reflect the current uncertainty about the toxicity profile of the combination of PDR001 and BLZ945. The risk of significant positive interaction between PDR001 and BLZ945 cannot be totally excluded. The interaction parameter η was chosen accordingly but with a degree of uncertainty in order to allow for the possibility that the interaction may be positive or negative. Therefore the following assumption is made for the interaction parameter:

η is normally distributed, with mean 0 and standard deviation 3.363

At the starting dose of 150 mg BLZ945 and 400 mg PDR001 of the corresponding distribution for the odds ratio has mean 1 and a 97.5th percentile of 3, i.e. 3-fold increase in odds of DLT due to interaction compared to no interaction.

14.5.3.3 Summary of prior distributions

The prior distributions of the model parameters are summarized in Table 14-18.

Prior summaries for DLT rates are summarized at each provisional dose level in Table 14-19.

[redacted]

Table 14-18 Prior distribution of model parameters

Parameter	Mean	Standard deviations	Correlation	Weight
PDR001 MAP prior, BVN mixture $(log(\alpha_2), log(\beta_2))$*, weight = 80%*				
BVN mixture 1	(-4.545, 0.014)	(1.528 , 1.039)	-0.013	0.445
BVN mixture 2	(-3.235 , 0.103)	(1.074 , 1.046)	0.094	0.355
Weakly informative prior $(log(\alpha_2), log(\beta_2))$***, weight = 20%***				
Weakly informative	(-1.099, 0)	(2, 1)	0	0.200
BLZ945 MAP prior, BVN mixture $(log(\alpha_1), log(\beta_1))$***, weight = 50%***				
BVN mixture 1	(-2.632, -0.020)	(1.181, 1.060)	0.156	0.206
BVN mixture 2	(-4.096 , 0.216)	(1.586 , 0.989)	0.129	0.203
BVN mixture 3	(-1.066,0.580)	(1.305, 0.759)	0.437	0.091
Weakly informative prior $(log(\alpha_1), log(\beta_1))$***, weight = 50%***				
Weakly informative	(-1.153, 0)	(2, 1)	0	0.500
Interaction BLZ945-PDR001	0	3.363		

[redacted]

Table 14-19 Summary of prior distribution of DLT rates- BLZ945 (7d on/ 7d off)+ PDR001

BLZ945 + PDR001(400 mg)	Prior probabilities that P(DLT) is in interval:					Quantiles		
	0-0.16	0.16-0.33	0.33-1	Mean	SD	0.025	Median	0.975
100	0.698	0.130	0.172	0.169	0.230	0.002	0.066	0.864
150*	0.671	0.139	0.190	0.183	0.239	0.003	0.073	0.885
300	0.600	0.147	0.254	0.226	0.270	0.002	0.100	0.934
600	0.498	0.131	0.371	0.316	0.336	0.001	0.162	0.987
900	0.449	0.101	0.450	0.390	0.384	0.000	0.233	0.998

*Starting dose

14.5.3.4 Hypothetical dose escalation scenarios

Table 14-20 shows on-study dosing recommendations for some hypothetical data scenarios. Note that the next dose is selected in concordance with the provisional dose levels specified in Section 6.2.2 of the protocol wherever it is allowed, to mimic possible on study escalation steps.

Table 14-20 Hypothetical dose escalation scenarios for on-study decisions – Combination of BLZ945 (7 days on/7days off) and PDR001

Scenario	Cohort	Dose level (mg) BLZ945/PDR001	Ntox / Npat	Next dose level (NDL) (mg)	P(target) at NDL	P(over) at NDL	Median at NDL
1	1	150/400	0/4	300/400	0.122	0.055	0.045
2	1	150/400	1/4	150/400	0.286	0.168	0.143
3	1	150/400	2/3	STOP			
4	1	150/400	0/4				
4	2	300/400	0/3	600/400	0.113	0.119	0.036
5	1	150/400	1/4				
5	2	150/400	0/5	300/400	0.237	0.105	0.103
6	1	150/400	0/3				
6	2	300/400	2/3	150/400	0.378	0.193	0.184
7	1	150/400	1/3				
7	2	150/400	0/3	300/400	0.266	0.190	0.143
8	1	150/400	1/6				
8	2	300/400	0/4	600/400	0.165	0.190	0.085
9	1	150/400	1/6				
9	2	300/400	2/5	150/400	0.450	0.123	0.179
10	1	150/400	1/6				
10	2	300/400	1/4	300/400	0.389	0.182	0.183
11	1	150/400	0/4				
11	2	300/400	0/3				
11	2	600/400	0/6	900/400	0.069	0.051	0.012
12	1	150/400	0/4				
12	2	300/400	0/3				
12	3	600/400	1/5	600/400	0.273	0.107	0.119
13	1	150/400	0/3				

[redacted]

Scenario	Cohort	Dose level (mg) BLZ945/PDR001	Ntox / Npat	Next dose level (NDL) (mg)	P(target) at NDL	P(over) at NDL	Median at NDL
13	2	300/400	0/4				
13	3	600/400	2/3	300/400	0.315	0.053	0.126

Within Table 14-20, it can be seen that the model generally leads to decisions that are in agreement with clinical sense: progressive increase of the provisional doses if no DLT is observed, enrolling of a new cohort at the same provisional dose level when 1 DLT is reported, and de-escalate when more than 1 DLT is reported in a cohort.

14.5.3.5 Operating characteristics

In order to show how the proposed design performs under different true dose- DLT profiles, various hypothetical scenarios were investigated.

Simulation Setup

Table 14-21 shows 3 dose-DLT scenarios, taking scenario 1 (true DLT rates equal to median prior DTL rates) as the basis. Scenarios 2 and 3 have increased DLT rates compared to scenario 1:

- Scenario 2: the odds of DLTs are 50% larger than the ones of scenario 1
- Scenario 3: the odds of DLTs are 100% larger than the ones of scenario 1

The following table presents the true underlying probabilities of DLT for each scenario

Table 14-21 Dose-DLT scenarios

BLZ945/PDR001 (mg)	Scenario 1	Scenario 2	Scenario 3
100/400	0.066	0.096	0.124
150/400	0.073	0.106	0.136
300/400	0.100	0.143	0.182
600/400	0.162	0.225	0.279
900/400	0.233	0.313	0.378

For each scenario data for 1000 trials were generated, with randomly chosen cohorts of size 3 to 6. The starting dose is 400 mg for PDR001 and 150 mg for BLZ945.

[redacted]

The following metrics were assessed in the simulations:

- percentage of patients receiving a dose combination that is in the target toxicity (TT) interval (metric I)
- percentage of patients receiving an overdose (OD) (metric II)
- percentage of patients receiving an underdose (UD) (metric III)
- probability that recommended MTD at the end of the trial is in the target toxicity interval (metric IV)
- probability that recommended MTD is an overdose (metric V)
- probability that recommended MTD is an underdose (metric VI)
- percentage of trials stopped without MTD declaration (metric VII)
- average sample size
- average number of DLT

The maximum number of patients per trial was set to 60. The trial was stopped using the rules defined in the protocol in Section 6.2.3.2.

14.5.3.5.1 Simulation Results

Operating characteristics are presented in Table 14-22.

Table 14-22 Operating characteristics

	Scenario 1	Scenario 2	Scenario 3
Average proportion of patients in target dose (metric I)	38.2	28.1	56.8
Average proportion of patients in over dose(metric II)	0.0	0.0	4.3
Average proportion of patients in under dose(metric II)	61.8	71.9	39.0
Proportion of trials with MTD within target dose region(metric IV)	54.6	34.3	68.7
Proportion of trials with MTD within over dose region(metric V)	0.0	0.0	2.5
Proportion of trials with MTD within under doses region(metric VI)	42.3	59.1	15.7
Proportion of trials stopped before declaring MTD, when all dose combinations were considered too toxic(metric VII)	3.1	6.6	13.1
Average sample size	22	20	19
Average number of DLT	2.8	3.1	3.5

In scenario 1, since there is no dose combination which has median DLT rate fall into the over toxicity interval, it is expected that there is no patient receive over-toxic dose combination (metric II) on study, and no trial was recommended with over-toxic dose as MTD (metric V). Under this scenario, the proportion of trials with MTD within target dose region is about 55%

In scenario 2, the proportion of patients receiving target dose is low (28.1%) and so does the proportion of trial with target dose as recommended dose (34.3%). This is due to the fact that only the 600/400 mg dose level is in the target interval and the 900/400 mg dose level lies in the boundary of the over toxicity interval.

[redacted]

In scenario 3, the proportion of patients receiving target dose is 56.8% and proportion of trial with target dose as recommended dose is 68.7%. The proportion of patients receiving a dose combination with true P(DLT) ≥ 33% or trials that were recommended a dose combinations with true P(DLT) ≥ 33% as the MTD (patient risk) is very low (metric II: 4.3% and metric V: 2.5%).

In all scenarios, the average sample sizes are between 19 and 22, and the percentages of trials that were stopped when all dose combinations were considered too toxic are low (3.1%) in scenario 1 but relatively high in scenario 3 (13.1%). However, in this scenario, the average number of DLTs is comparable to the other scenarios.

In conclusion, the simulations performed illustrate that the model has good operating characteristics.

14.5.4 Combination BLZ945 (Q1W) and PDR001

14.5.4.1 Statistical model and prior specification

In the combination BLZ945 and PDR001 dose escalation part, the dose-toxicity (DLT) relationship will be described by a 5-parameter BLRM formulated in the following way:

The respective single agent dose-DLT relationships are defined as:

$$\text{BLZ945:} \quad \text{logit}(\pi_1(d_1)) = \log(\alpha_1) + \beta_1 \log(d_1/d_1^*)$$

$$\text{PDR001:} \quad \text{logit}(\pi_2(d_2)) = \log(\alpha_2) + \beta_2 \log(d_2/d_2^*)$$

Where, $\pi_1(d_1)$ and $\pi_2(d_2)$ are respectively the probability that a patient has a DLT when BLZ945 and PDR001 are given as single agent at the dose d_1 and d_2, and d_1^*=3600mg and d_2^*=400mg are respectively the BLZ945 and PDR001 reference doses. $\alpha_.$, $\beta_. > 0$ are the parameters of the model.

Then, the dose-DLT relationship of the dual combinations of BLZ945 with PDR001 is defined as:

$$\text{Odds}(\pi_{12}(d_1, d_2)) = \frac{\pi_{12}(d_1,d_2)}{1-\pi_{12}(d_1,d_2)} = \exp(\eta \frac{d_1}{d_1^*} \frac{d_2}{d_2^*}) \left[\frac{\pi_1(d_1)+\pi_2(d_2)-\pi_1(d_1)\pi_2(d_2)}{(1-\pi_1(d_1))(1-\pi_2(d_2))}\right],$$

Where η is the interaction term.

The methodology to derive prior for this combination is similar to the combination with 7d on/ 7d off. As per protocol, the combination part will only start after at least two cohorts of BLZ945 as single agent have been completed, and safety data suggests acceptable toxicity for patients to begin treatment in combination. The derivation of the priors will be based on several assumptions (either safe data from with 7days on/7days off or from Q1W data if early toxicity was observed with the former schedule), and therefore the details of the derivation of the prior will not be given in this appendix, but will be detailed in the SAP before the first dose escalation of this schedule.

14.5.5 Split dosing regimen (two doses per day)

In case of exploring split dosing regimen (two doses per day) during dose escalation, separate adaptive Bayesian hierarchical logistic regression models (BHLRM) for all single agent dosing schedules (i.e. 7dOn/7dOff, Q1W and 4dOn/10dOff) and appropriate BLRM for the combination dosing regimens will be used to guide the dose escalation by the EWOC principle.

For each single agent regimen, the BHLRM estimates the relationship between dose and the probability of a patient experiencing a DLT in the same original one-dose (per day) regimen (stratum 1), and the split dosing regimen (two doses per day, stratum 2). The BHLRM will allow for both full exchangeability between the strata parameters and non-exchangeability between strata parameters, which introduces more flexibility and potentially improve the estimation of dose-toxicity relationship.

When in combination with PDR001, the dose escalation of the split dosing regimen will be guided by a meta-analytic-combined (MAC) model based on the first Cycle DLT data of the study treatment. The model will integrate both single agent and combination toxicity parts with either the same original one-dose per day dosing or split dosing regimen. Both historical data and concurrent data are incorporated into the model. For different dosing regimens, once or twice per day, a plausible between-cohorts heterogeneity will be assumed, allowing for non-exchangeability across trial parameters.

A full description including parameter specification, operating characteristics and hypothetical dose scenarios of each model will be given in a standalone document, prior to the first patient treated on the respective schedule.

14.6 Sample size determination for Phase II

As described in Section 10.8, a Bayesian approach will be used to analyze glioblastoma patients treated with BLZ945 single agent or in combination with PDR001 separately. The number of patients expected to be treated in each treatment arm are estimated such that the model would have reasonable characteristics.

14.6.1 Prior specifications

The PFS time will be modeled using a Weibull distribution, which is a flexible distribution allowing for time varying hazard rate. The Weibull probability density function is given by

$$f(x) = \gamma\lambda x^{\gamma-1} exp(-l\, x^{\gamma}), \qquad x \geq 0$$

where γ is a shape parameter and λ a scale parameter. The corresponding survival function is

$$S(x) = exp[-\, l\, x^{\gamma}]$$

and the median PFS can be calculated as

$$x_{median} = \left(\frac{\log(2)}{l}\right)^{1/\gamma}$$

[redacted]

and the PFS rate at 6 month, which will be denoted PFSR6, can be calculated as

$$x_6 = PFSR6 = exp(-l\ 6^{\gamma})$$

For the shape parameter, an exponential prior distribution will be used

$$\gamma \sim \exp(r)$$

and for the log-scale parameter, a normal prior distribution will be used

$$\log(l) \sim N(m, s^2)$$

A weakly-informative prior distribution for γ and log(λ) will be assumed, such that the mean PFS rate at 6 months (PFSR6) is approximately equal to the indifference point (i.e., close to 40%).

The prior distributions are then derived as follows:

The rate r of the exponential prior distribution for γ is set to 0.2, which allows a wide range of values for γ.

The mean m of the normal distribution for log(λ) is set to 0.

The standard deviation s of the normal distribution for log(λ) is chosen such that E(S(6)) ≈ 0.40 This results in the prior distributions shown in Table 14-23.

Table 14-23 Specifications for Prior distribution

Prior parameter		Prior distribution of PFS rate at 6 months		
Rate for γ	log(λ) (mean, SD)	Mean	Probability of unacceptable activity	Probability of clinical relevant activity
0.2	(0, 9)	0.40	0.556 in [0%, 20%)	0.418 in [40%, 100%]

14.6.2 Operating characteristics

The posterior distribution of PFS is not available in closed form. Therefore, the operating characteristics for the Bayesian analysis described above are evaluated by performing simulations. The operating characteristics for this Bayesian design are obtained by performing extensive simulations using R software (JAGS is used for the posterior computations involving MCMC).

Different scenarios assuming different possible values for the true PFS rate at 6 months varying from 0.20 to 0.60 have been evaluated. For each scenario, 1000 simulations were run. In each of these simulation run, a sample of size 40 is generated with the PFSR6 corresponding to the true PFSR6 for that scenario assuming PFS times follow an exponential distribution. Accrual time of the patients is assumed to follow an exponential distribution with rate of 3 patients per month. In addition, censoring occurs following an exponential distribution with rate of 0.03 corresponding to a median censoring of about 23 months. Taking the priors as mentioned above, the interim analysis is performed based on 20 first patients. The trial will expand to 40 patients if the DCR ≥60% after performing the first tumor assessment for the first 20 patients (at month 2). The complete success rate (i.e. the probability of concluding clinically relevant efficacy)

[redacted]

under different scenarios is calculated using simulated data. It is obtained according to the following Bayesian rules:

a) At interim analysis, the disease control rate is ≥ 60%
b) At final analysis, the estimated posterior mean of PFSR6 ≥ 0.4
c) At final analysis, the posterior probability that PFSR6 is ≥ 0.2 is at least 90%).

Table 14-24 and Table 14-25 show the operating characteristics under different scenarios.

14.6.2.1 Simulation of datasets

This section defines the variables used for the simulations of datasets:

- Accrual waiting time: It is expected that 3 patients will be enrolled in each month; hence, the average accrual rate is about 0.3 month per patient. The accrual waiting time is in unit of months and set to 0 for the first patient.
- Accrual calendar time: This is the cumulative sum of the accrual waiting times. The origin is set to 0 at Cycle 1 Day 1 of the first patient. The interval from the origin to Cycle 1 Day 1 of the last patient is the accrual duration.
- PFS time: It is assumed that PFS time follows an exponential distribution to get the desired PFSR at 6 months.
- PFS calendar time: This is the sum of the accrual calendar time and PFS time.
- Censoring time: It is assumed that the censoring time follows an exponential distribution with a rate of 0.03.
- Censoring calendar time: This is the sum of the accrual calendar time and censoring time
- Cut-off date: is defined as the sum of accrual calendar time and 6 months.
- Event indicator: For non-censored patients, if PFS calendar time is smaller than cut-off date, then the PFS event is observed; otherwise PFS is censored.
- Interim event indicator: DCR≥60%. This rate is assessed at the first scan for all patients in the interim population.

Several possible values for true PFSR6 are specified. For each scenario with one of the specified values for true PFSR6, the hypothetical PFS dataset is generated by the following steps:

- Set accrual waiting time to zero for the first patient. Generate a random sample of accrual waiting times for the remaining patients from an exponential distribution with the accrual waiting time rate defined above.
- Generate a random sample of 40 PFS times from an exponential distribution corresponding to the true PFSR6.
- Generate censoring time from an exponential distribution

14.6.2.2 Posterior analysis

- Perform an interim analysis for the first 20 patients.
  - If the DCR ≥ 60% then expand to 40 patients, otherwise stop the trial.

Perform final analysis using the 40 patients and provide posterior final analysis

These steps are repeated to simulate 1000 datasets for each scenario. For each of the 1000 simulated datasets, the posterior distribution of PFSR6 is obtained by performing MCMC

[redacted]

simulations. Complete success rate, complete failure rate and the probability to stop at interim (proportion of trials stopped at interim) are given below for each disease group:

Table 14-24 Operating Characteristics

True PFSR6	Complete success rate	Complete failure rate	Probability of stop at interim
20	0.004	0.996	0.71
30	0.09	0.91	0.43
40	0.57	0.43	0.21
50	0.90	0.10	0.08
60	0.97	0.03	0.03

Table 14-25 Operating Characteristics for TNBC group (no longer effective after approval of protocol amendment 06)

True PFSR6	Complete success rate	Complete failure rate	Probability of stop at interim
20	0.03	0.97	0.55
30	0.20	0.80	0.35
40	0.58	0.42	0.22
50	0.84	0.16	0.12
60	0.94	0.06	0.05

Table 14-24 show that the Bayesian design has good operating characteristics. The probability of wrongly declaring the study as a success is very low when true PFSR6 is 20% (probability of success is less than 0.01). The probability of declaring success when the true PFSR6 is 40% months is close to 50% as desired. Finally, when the true efficacy is highly significant there is a very high probability for the study to be declared a success (when true PFSR6 is 60%, the probability of declaring success is larger than 0.94).

14.6.3 References

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[redacted]

14.7 Appendix 6: Statistical details of Phase I Bayesian logistic regression model (BLRM) in Japanese patients treated with single agent of BLZ945

This appendix provides details of the statistical model, the derivation of prior distributions from historical data of BLZ945 from global patients, and the results of the Bayesian analyses and respective dosing decisions for some hypothetical data scenarios.

14.7.1 Statistical model

An adaptive Bayesian logistic regression model (BLRM) guided by the escalation with overdose control (EWOC) principle will be used to make dose recommendations and estimate the maximum tolerated dose (MTD) and/or identify the recommended dose for phase II(RP2D) during the dose escalation part of the study. The use of Bayesian response adaptive models for Phase I studies has been advocated by the EMEA guideline on small populations (2007) and by Rogatko (2007) and is one of the key elements of the FDA's Critical Path Initiative.

Single agent BLZ945 for Japanese patients: In the single-agent BLZ945 dose escalation part, the dose-toxicity (DLT) relationship is described by the following 2-parameter BLRM:

$$\text{logit}(\pi(d)) = \log(\alpha) + \beta \log(d/d^*),\ \alpha>0,\ \beta>0$$

Where [redacted], and $\pi(d)$ is the probability of a DLT at dose d.

Doses are rescaled as d/d* with reference dose d*=900x14mg of BLZ945. As a consequence α is equal to the odds of DLT rate at d*, and β (>0) is the increase in the log-odds of a DLT by a unit increase in log-dose. Note that for a dose equal to zero, the probability of toxicity is zero.

The Bayesian approach requires the specification of prior distributions for all model parameters. This section provides details of the statistical model, the derivation of prior distributions for the model parameters, and the properties of the adaptive design (dosing recommendations for hypothetical data scenarios and operating characteristics).

14.7.2 Prior specifications

The Bayesian approach requires the specification of prior distributions for all model parameters. A meta-analytic-predictive (MAP) approach was used to derive the prior distribution for the model parameters.

14.7.2.1 Prior distribution for the logistic parameters

A mixture prior distribution for the single-agent BLZ945 model parameters was derived. It consists of a mixture of a meta-analytic-predictive (MAP) prior and a weakly informative prior corresponding to high toxicity to make the prior more robust. To obtain the mixture prior, 50% weight was assigned to the MAP prior, and 50% weight was assigned to the weakly informative prior.

[redacted]

14.7.2.1.1 Description of the MAP approach

The aim of the MAP approach is to derive a prior distribution for the logistic parameters ($\log(\alpha^*)$, $\log(\beta^*)$) of the new trial (eg., Japanese sub-population in the BLZ945x2101 study) using DLT data from the ongoing dose-escalation in global patients (BLZ945x2101 study).

Let r_{ds} and n_{ds} be the number of patients with a DLT, and the total number of patients at dose d in historical trial s ($s = 1, \ldots, S$). The corresponding probability of a DLT is π_{ds}. The model specifications for the derivation of the MAP prior are as follows:

$$r_{ds} \mid \pi_{ds} \sim \text{Bin}(\pi_{ds}, n_{ds})$$

$$\text{logit}(\pi_{ds}) = \log(\alpha_s) + \beta_s \log(d/d^*)$$

$$(log(\alpha_s), log(\beta_s)) \mid \mu, \psi \sim \text{BVN}(\mu, \psi), \qquad s = 1, \ldots, S$$

$$(log(\alpha^*), log(\beta^*)) \mid \mu, \psi \sim \text{BVN}(\mu, \psi)$$

Where $d^* = 900*14$mg and $S = 1$ in this study and refers to the global patients. The parameters $\mu = (\mu_1, \mu_2)$ and ψ are the mean and between-trial covariance matrix for the logistic parameters, the latter with standard deviations τ_1, τ_2, and correlation p. The parameters τ_1 and τ_2 quantify the degree of between trial heterogeneity. The main objective is to estimate the predictive distribution

$$(log(\alpha^*), log(\beta^*)) \mid (r_{ds}, n_{ds} : s = 1, \ldots, S)$$

based on DLT data from arm A. To do that, it is assumed:

- normal priors for μ_1 and μ_2,
- log-normal priors for τ_1 and τ_2, and
- a uniform prior for p.

Since the predictive distribution is not available analytically, the Markov Chain Monte Carlo (MCMC) method is used to simulate values from this distribution. This is implemented using WinBUGS 14.1.3. The sample from this distribution is approximated by a mixture of bivariate normal (BVN) distributions. BVN mixtures with increasing numbers of mixture components are fitted to the sample using the expectation-maximization (EM) algorithm (Dempster 1977). The optimal number of components of the mixture is then identified using the Akaike information criterion (AIC) (Akaike 1974).

14.7.2.1.2 Implementation of the MAP approach

For the MAP model, data from global patients treated the global study [CBLZ945X2101] was used (Table 14-26). The details of the derivation of the priors using available data from single agent global patients will be finalized and documented prior to the first patient being treated in Japanese dose escalation. For illustrative purpose, assuming the following hypothetical global patients' data was observed.

[redacted]

Table 14-26 Hypothetical data from global patients in study CBLZ945X2101

Dose of BLZ945	No of DLTs/No of evaluable patients
150mg 7d on/7d off	0/5
300mg 7d on/7d off	1/10
600mg 7d on/7d off	2/6

Note: These data are hypothetical and the real current available data from single agent global patients will be incorporated directly in the Japanese patient dose escalation during the DETCs.

Weakly informative priors are assumed for μ_1 and μ_2, with means corresponding to a risk of DLT at the reference dose of 9%, and a doubling in dose leading to a doubling in the odds of the risk of a DLT, respectively. Priors for τ_1 and τ_2 are assigned such that (1) their medians correspond to moderate between trial heterogeneity, and (2) their uncertainty (95% prior interval) cover plausible between-trial standard deviations (Neuenschwander 2014). The prior distributions for the model used for deriving the MAP priors are specified in Table 14-27.

Table 14-27 Prior distributions for the parameters of the MAP model used to derive the prior

Parameter	Prior distribution
μ_1	N(mean = logit(0.09), sd = 2)
μ_2	N(mean = 0, sd=1)
τ_1	log-normal(mean = 0.25, sd = log(2)/1.96)
τ_2	log-normal(mean = 0.125, sd = log(2)/1.96)
p	uniform(-1,1)

14.7.2.1.3 Derivation of the weakly informative prior

A weakly informative BVN prior to allow higher toxicity than MAP prior is derived by assuming median probability of DLT at 900x14 mg to be 24%, as well as a log-linear relationship between dose and the odds of DLT as defined in Section 14.5.2. This results in setting the mean of log(α) equal to -1.153. The mean of log(β) is set to 0. Furthermore, setting standard deviation of log(α) = 2 and log(β) = 1, and setting the correlation between log(α) and log(β) = 0 to complete the determination of this prior. See Table 14-24.

14.7.2.1.4 Summary of prior distributions

The prior distributions of the model parameters are summarized in Table 14-28.

Prior summaries for DLT rates are summarized at each provisional dose level in Table 14-29.

Table 14-28 Prior distribution of model parameters

Parameter	Mean	Standard deviations	Correlation	Weight
BLZ945 MAP prior, BVN mixture (*log*(α), *log*(β)), weight = 50%				
BVN mixture 1	(-0.625, 0.528)	(1.052 , 0.490)	0.618	0.213
BVN mixture 2	(-0.868 , -0.195)	(0.780 , 0.555)	0.534	0.172
BVN mixture 2	(-1.700, -0.844)	(0.746, 0.780)	0.074	0.115
Weakly informative prior (*log*(α), *log*(β)), weight = 50%				
Weakly informative	(-1.153, 0)	(2, 1)	0	0.5

[redacted]

Table 14-29 Summary of prior distribution of DLT rates

BLZ945 dose(mg), 7d on/7d off	Prior probabilities that P(DLT) is in interval:					Quantiles		
	[0, 0.16)	[0.16, 0.33)	[0.33, 1]	Mean	SD	2.5%	50.0%	97.5%
100	0.864	0.073	0.063	0.083	0.150	0.000	0.028	0.605
150	0.830	0.094	0.076	0.100	0.160	0.000	0.042	0.657
300	0.716	0.170	0.115	0.146	0.182	0.000	0.085	0.744
600	0.464	0.294	0.242	0.236	0.212	0.000	0.175	0.837
900	0.321	0.277	**0.402**	0.320	0.244	0.004	0.261	0.896

SD = standard deviation.
Bold values indicate dose(s) not meeting the EWOC principle with the prior information only.

14.7.3 BLRM design properties for hypothetical data scenarios

Table 14-30 shows on-study dosing recommendations for some hypothetical data scenarios. Note that the next dose is selected in concordance with the provisional dose levels specified in Section 6.2.2 of the protocol wherever it is allowed, to mimic possible on study escalation steps.

Table 14-30 Hypothetical dose escalation scenarios for on-study decisions – phase I single agent BLZ945

Scenario	Cohort	Dose level (mg)	Ntox / Npat	Next dose level (NDL) (mg)	P(target) at NDL	P(over) at NDL	Median at NDL
1	1	150	0/3	300	0.138	0.032	0.062
2	1	150	1/3	150	0.256	0.140	0.127
3	1	150	2/3	STOP			
4	1	150	0/3				
4	2	300	2/3	150	0.286	0.113	0.130
5	1	150	1/5				
5	2	300	2/6	150	0.350	0.063	0.143
6	1	150	1/5				
6	2	300	1/4	300	0.456	0.122	0.179
7	1	150	0/3				
7	2	300	0/3	600	0.264	0.096	0.111
8	1	150	0/3				
8	2	300	0/3				
8	3	600	1/3	600	0.441	0.146	0.184
9	1	150	0/3				
9	2	300	0/3				
9	3	600	2/4	300	0.226	0.026	0.103
10	1	150	0/3				
10	2	300	0/3				
10	3	600	0/4				
10	4	900	2/3	600	0.431	0.085	0.165

Within Table 14-30, it can be seen that the model generally leads to decisions that are in agreement with clinical sense: progressive increase of the doses if no DLT is observed, enrolling of a new cohort at the same dose level when 1 DLT is reported, and de-escalation when more

[redacted]

than 1 DLT is reported in a cohort. It is expected that the dose-DLT relationship in Japanese patients will be very similar to that observed outside Japan.

14.7.3.1 Operating characteristics

In order to show how the proposed design performs under different true dose- DLT profiles, various hypothetical scenarios were investigated.

Table 14-31 shows 5 dose-DLT scenarios, taking scenario 1 (true DLT rates equal to median prior DLT rates) as the basis. Scenario 2 has decreased DLT rates compared to scenario 1. Scenarios 3, and 4 have increased DLT rates compared to scenario 1, scenario 5 have toxicity >33% at all dose levels.

The following table presents the true underlying probabilities of DLT for each scenario

Table 14-31 dose-DLT scenarios

Test scenarios	Assigning DLT probabilities to each dose level					Note
	100 mg	150 mg	300 mg	600 mg	900 mg	
1	0.028	0.042	0.085	0.175	0.261	Scenario1: Median DLT probabilities
2	0.014	0.021	0.044	0.096	0.15	Scenario2: the odds of DLTs are 50% smaller than the ones of scenario 1
3	0.054	0.081	0.157	0.298	0.414	Scenario3: 2-fold odds inflation from scenario 1
4	0.126	0.180	0.317	0.515	0.638	Scenario4: 5-fold odds inflation from scenario 1
5	0.419	0.523	0.699	0.841	0.898	Scenario5: toxicity>33% at all dose levels

For each scenario, data for 1000 trials were generated, with randomly chosen cohorts of size 3 to 6. The starting dose is 150 mg for BLZ945.

[redacted]

The following metrics were assessed in the simulations:

- percentage of patients receiving a dose that is in the target toxicity (TT) interval (metric I)
- percentage of patients receiving an overdose (OD) (metric II)
- percentage of patients receiving an underdose (UD) (metric III)
- probability that recommended MTD at the end of the trial is in the target toxicity interval (metric IV)
- probability that recommended MTD is an overdose (metric V)
- probability that recommended MTD is an underdose (metric VI)
- percentage of trials stopped without MTD declaration (metric VII)
- percentage of trials stopped due to toxicity (metric VIII)
- average sample size
- average number of DLT

The maximum number of patients per trial was set to 60. The trial was stopped using the rules defined in the protocol in Section 6.2.3.2.

Table 14-32 Operating characteristics

Metric	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
I	52.7	0.0	26.5	85.5	0
II	0.0	0.0	9.3	11.3	100
III	47.3	100.0	64.2	3.2	0.0
IV	81.7	0.0	37.1	78.4	0
V	0.0	0.0	7.3	3.9	6
VI	14.7	97.9	50.9	0.8	0
VII	3.3	2.0	2.7	1.7	0
VIII	0.3	0.1	2.0	15.2	94.0
Average sample size	23.5	23.7	21.7	18.0	7.7
Average number of DLT	3.3	2.1	4.3	4.9	4.0

14.7.3.2 Results

The simulated operating characteristics presented show that the BLRM performs well under the hypothetical profiles investigated. Indeed, the simulations performed illustrate that the model has reasonable operating characteristics and the number of patients with DLT was limited through a trial.

In scenario 1, the probabilities of DLT are aligned with the median prior information. In this scenario, the simulations show that there is 14.7% of chance for identifying the MTD at underdose interval, and 81.7% of chance identifying the MTD at target toxicity interval.

In scenario 2, the probabilities for all doses lie within the underdose interval. The simulations show that there is 97.9% of chance for identifying the MTD at underdose interval. The chance to stop the trial without identifying a recommended dose because all doses are estimated to be too toxic is very low (0.1%).

[redacted]

In scenario 4, with 5-fold odds inflation from test scenario 1, the simulations show that there is 78.4% of chance to select the MTD at target toxicity interval.

Although the dose 300 mg has acceptable toxicity, it towards the upper bound of the target interval, this leads to the high chance to stop the trial due to high toxicity of all dose levels (15.2%)

Finally in scenario 5, with the probabilities of DLT are all within the excessive toxicity interval. The simulations show that the chance to stop the trial without identifying an MTD due to doses being estimated as too toxic is very high (94%).

In conclusion, the simulations performed illustrate that the model has good operating characteristics under the 5 hypothetical profiles investigated.

14.7.4 Alternative dosing schedule

If the alternative Q1W or other dosing schedule have been explored when the enrollment of Japanese patients starts, the dose escalation for Japanese patients will start with the same dosing schedule at a dose deemed same at global dose escalation. The BLRM model will be updated for that dosing schedule, and the prior construction will follow the similar way introduced previously, using a mixture of a MAP prior and weekly informative prior corresponding to high toxicity to make the prior more robust.

For the MAP model, data from global patient on the same dosing schedule will be used.

14.7.5 References (available upon request)

EMEA (2007) Guideline on Clinical Trials in Small Populations. Committee for Medicinal Products for Human Use (CHMP).

Rogatko A, Schoeneck D, Jonas W, et al (2007) Translation of innovative designs into phase I trials. J Clin Oncol; 25:4982-6.

Spiegelhalter DJ, Abrams KR, Myles JP (2004) Bayesian Approaches to Clinical Trials and Health-Care Evaluation.

[redacted]

14.8 Appendix 7: Prohibited Medication

In general, the use of any concomitant medication deemed necessary for the care of the patient is permitted in this study, except as specifically prohibited in Section 6.4.2 and in Table 14-33 below. Combination administration of study drugs could result in drug-drug interactions (DDI) that could potentially lead to reduced activity or enhanced toxicity of the concomitant medication and/or BLZ945. Refer to the BLZ945 IB for more information on possible interactions with other drugs.

The following lists are based on the Oncology Clinical Pharmacology Drug-Drug Interaction Database (release date: January 2018), which was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table and supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (February 2012), and the University of Washington's Drug Interaction Database (February 2015) and QTdrugs lists from qtdrugs.org (November 2015). These lists are not comprehensive and are only meant to be used as a guide. Please contact the medical monitor with any questions. If a medication appears on both the list of prohibited and the list of medications to be used with caution, the medication is prohibited.

Table 14-33 List of prohibited medications during study drug treatment

Strong inhibitors of CYP2C8 and CYP3A are prohibited

Moderate inhibitors of CYP2C8 and CYP3A are prohibited only when used in combination with other moderate CYP3A or CYP2C8 inhibitors.

Mechanism of Interaction	Drug Name
Strong inhibitors[1] of CYP2C8	clopidogrel, gemfibrozil[9]
Moderate inhibitors[2] of CYP2C8[5] (NOTE: only when combined with moderate or strong CYP2C8 inhibitor and/or CYP3A inhibitor)	deferasirox, teriflunomide,
Strong inhibitors[1] of CYP3A	boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, eltegravir/ritonavir grapefruit juice[6a], indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, sequinavir/ritonavir, telaprevir, telithromycin, voriconazole, indinavir/ritonavir, tipranoavir/ritonavir, troleandomycin,
Moderate inhibitors[2] of CYP3A[5] (NOTE: only when combined with moderate or strong CYP3A inhibitor and/or CYP2C8 inhibitor)	amprenavir, aprepitant, atazanavir, casopitant, cimetidine, ciprofloxacin, crizotinib, cyclosporin, darunavir, diltiazem, dronedarone, erythromycin, fluconazole[8], fosamprenavir, grapefruit juice[6a], imatinib, lomitapide, netupitant, nilotinib, schisandra sphenanthera[6], tofisopam, verapamil
Moderate inducers[4] of CYP2C8 (NOTE: only when combined with moderate or strong CYP2C8 inducer and/or CYP3A inducer)	rifampin[5a]
Strong inducers[3] of CYP3A	avasimibe, carbamazepine, enzalutamide, mitotane, phenobarbital, phenytoin, rifampin, St. John's wort[6], rifabutin
Moderate inducers[4] of CYP3A (NOTE: only when combined with moderate or strong CYP3A inducer and/or Rifampin)	bosentan, efavirenz, etravirine, genistein[7], lersivirine, lopinavir, modafinil, nafcillin, ritonavir, semagacestat[10], talviraline[10], thioridazine, tipranavir
PPI[10]	dexlansoprazole, esomeprazole, ilaprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole
Medications with a known risk to prolong the QT interval and/or known to cause Torsades de Pointe TdP	amiodarone, anagrelide, arsenic trioxide, astemizole, azithromycin, chloroquine, chlorpromazine, cilostazol, ciprofloxacin, cisapride, citalopram, clarithromycin, disopyramide, dofetilide, domperidone, donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, gatifloxacin, halofantrine, haloperidol, ibutilide, levofloxacin, levomepromazine, levosulpiride, methadone, moxifloxacin, ondansetron, oxaliplatin, papaverine HCl (intra-coronary), pentamidine, pimozide, procainamide, propofol, quinidine, roxithromycin, sevoflurane, sotalol, sulpiride, sultopride, terlipressin, terodiline, thioridazine, vandetanib

Mechanism of Interaction	Drug Name
Medications with 'possible' risk to prolong the QT interval	alfuzosin, apomorphine, aripiprazole, artenimol+piperaquine, asenapine, atomoxetine, bedaquiline, bendamustine, bortezomib, bosutinib, buprenorphine, cabozantinib, capecitabine, ceritinib, clomipramine, clozapine, crizotinib, cyamemazine (cyamepromazine), dabrafenib, dasatinib, degarilix, delamanid, desipramine, dexmedetomidine, dolasetron, efavirenz, eliglustat, epirubicin, eribulin mesylate, ezogabine (retigabine), famotidine, felbamate, fingolimod, flupentixol, gemifloxacin, granisetron, hydrocodone-ER, iloperidone, imipramine (melipramine), isradipine, ketanserin, lapatinib, lenvatinib, leuprolide, lithium, melperone, midostaurin, mifepristone, mirabegron, mirtazapine, moexipril/HCTZ, necitumumab, nicardipine, nilotinib, norfloxacin, nortriptyline, nusinersen, ofloxacin, osimertinib, oxytocin, paliperidone, palonosetron, panobinostat, pasireotide, pazopanib, perflutren lipid microspheres, perphenazine, pilsicainide, pimavanserin, pipamperone, promethazine, prothipendyl, ribociclib, rilpivirine, risperidone, romidepsin, saquinavir, sertindole, sorafenib, sunitinib, tacrolimus, tamoxifen, telavancin, telithromycin, tetrabenazine, tiapride, tipiracil/trifluridine, tizanidine, tolterodine, toremifene, trimipramine, tropisetron, vardenafil, vemurafenib, venlafaxine, vorinostat, zotepine
Hematopoietic colony- stimulating growth factors	sargramostim , filgrastim, filgrastim-sndz, lenograstim, pegfilgrastim, molgramostim

[1] a strong inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by equal or more than 5-fold

[2] a moderate inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 5-fold but equal to or more than 2-fold

[3] a strong inducer for a specific CYP is defined as an inducer that decreases the AUC of a sensitive substrate for that CYP by equal or more than 80%

[4] a moderate inducer for a specific CYP is defined as an inducer that decreases the AUC of a substrate for that CYP by 50-80%

[5] combined treatment of a moderate CYP2C8 or CYP3A and a moderate CYP2C8 or CYP3A inhibitor will increase the exposure to BLZ945

[5a] combined use of rifampin and of an additional moderate CYP3A inducer will reduce exposure to BLZ945 and interfere with efficacy

[6] herbal product

[6a] the effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used

[7] food product

[8] fluconazole is listed as a strong CYP2C19 inhibitor based on the AUC ratio of omeprazole, which is also metabolized by CYP3A

[9] gemfibrozil also inhibits OATP1B1

[10] co-administration of a PPI with BLZ945 will reduce the systemic exposure to BLZ945. Due to the pH shift in the stomach caused by the PPI, BLZ945 is expected to precipitate and it will be less efficiently absorbed

[11] Medications with a known risk to prolong the QT interval and/or known to cause Torsades de Pointe TdP

14.9 Appendix 8: Medications to be used with caution

Table 14-34 List of medications to be used with caution during study drug treatment

Mechanism of Interaction	Drug Name
H2 antagonists[1] (refer to Section 6.4.3)	nizatidine, ranitidine
Antacids[1]	aluminum hydroxide, aluminum carbonate, calcium hydroxide, calcium carbonate, bismuth subsalicylate
Medications with 'conditional' risk to prolong the QT interval	amantadine, amisulpride, amitriptyline, amphotericin B, bendroflumethiazide (bendrofluazide), chloral hydrate, diphenhydramine, doxepin, fluoxetine, fluvoxamine, furosemide, galantamine, garenoxacin, hydrochlorothiazide, hydroxychloroquine, hydroxyzine, indapamide, ivabradine, loperamide, metoclopramide, metronidazole, olanzapine, paroxetine, piperacillin/tazobactam, quetiapine, quinine sulfate, ranolazine, sertraline, solifenacin, torsemide, trazodone, ziprasidone

[1] co-administration could lower the exposure to BLZ945 and have an impact on efficacy

[redacted]

14.10 Appendix 9: Guidelines for efficacy evaluation in Hodgkin and non-Hodgkin lymphoma studies

Author(s):	[redacted]
Document type:	TA Specific Guideline
Development phase	Modified from Final Version 04: 20-Apr-2018

Template version 4.0 (effective 20 Apr 2018)

[redacted]

14.10.1 Introduction

The purpose of this guideline is to provide working definitions and rules to evaluate efficacy in non-Hodgkin lymphoma (NHL) studies conducted by Novartis. This document is based on the International Working Group response criteria (Cheson et al 1999), the International Harmonization Project revised response criteria (Cheson et al 2007), and the revised Consensus of the International Conference on Malignant Imaging Working Group and the Lugano Classification (Barrington et al 2014; Cheson et al 2014), and it is intended for studies of radiographically measurable disease. For studies without measurable disease, e.g., studies of consolidation of complete response, maintenance treatment, or autologous stem cell transplantation, see Appendix A.

14.10.2 Methodologies

14.10.2.1 Computed tomography (CT)

The same method of assessment and technique should be used to characterize each identified and reported lesion throughout the study. Contrast-enhanced CT of neck, chest, abdomen and pelvis, from skull base through lesser trochanters ensuring complete coverage of the pelvis and inguinal areas, should be performed using a $\leq$ 5 mm slice thickness with a contiguous reconstruction algorithm. If a patient has a CT contrast allergy or develops it during the trial, non-contrast CT of the chest plus contrast-enhanced MRI of abdomen and pelvis are acceptable for a follow up. Chest MRI is not recommended due to respiratory artifacts.

14.10.2.2 Positron emission tomography (PET)

Studies of FDG-avid histologies require PET using the radiotracer ^{18}F-fluorodeoxyglucose (FDG) to confirm any new CR determined by CT. PET will not be required to confirm progression or relapse.

PET scans should cover the whole body from base of skull to mid-thigh. Examinations should be consistent across all time points including amount of tracer, location of injection, arm location, and scan delay. Information of height, weight, gender, administered dose, time between dose administration and imaging, duration of fasting and glucose level are required for each time point. PET images should be converted to SUV maps to support comparison across time points and to standardize viewing conditions.

14.10.2.3 PET-CT

Hybrid PET-CT may be used to acquire PET and CT images if CT images produced by the scanner are of diagnostic quality and include intravenous contrast. Non-diagnostic CT images acquired for attenuation purposes during PET-CT are NOT acceptable as the only images for the time point.

If diagnostic CT and PET are to be acquired on the same day, PET must be performed prior to CT with IV contrast to avoid compromising PET results.

[redacted]

Thus, any of the three following imaging methodologies are possible in a lymphoma study:

- PET-CT with diagnostic
- PET-CT with non-diagnostic CT and dedicated diagnostic CT
- Dedicated diagnostic CT and dedicated FDG PET

14.10.2.4 Magnetic resonance imaging (MRI) and PET-MRI

MRI or PET-MRI is an acceptable method of imaging if CT is contraindicated e.g., due to CT contrast allergy. If at baseline a patient is known to be allergic to CT contrast or develops allergy during the trial, the following change in imaging modality will be accepted for follow up: a non-contrast CT of the chest plus contrast-enhanced MRI of abdomen and pelvis (MRI of the chest is not recommended due to respiratory artifacts).

14.10.2.5 Five point scale (5PS)

To standardize PET interpretation, a simple reproducible scoring method called the five point scale (5PS) or the Deauville criteria has been implemented for initial staging and assessment of interim and end of treatment responses (Barrington et al 2014). The 5PS assesses the most intense uptake in a site of disease (Table 14-35).

Table 14-35 Five Point Scale (5PS)

Score	Findings
Score 1	No uptake above background
Score 2	Uptake ≤ mediastinum
Score 3*	Uptake > mediastinum, but ≤ liver
Score 4**	Uptake moderately > liver
Score 5**	Uptake markedly higher than liver and/or new lesions

- Score 3 will be considered PET negative unless otherwise specified in the protocol (e.g. de-escalation studies), in which case CMR will be based on 5PS of 1 or 2 only, and PMR/NMR/PMD will be based on 5PS of 3,4 or 5)
- ** Score 4 should be applied to uptake greater than the maximum standard uptake value (SUV) in a large region \ of normal liver and score 5 to uptake 2 times greater than the maximum SUV in the liver. PET images should be converted to SUV maps to support comparison across time points and to standardize viewing conditions.

(New) areas of uptake unlikely to be related to lymphoma will be marked as "X" (Barrington et al. 2014).

14.10.3 Definitions

14.10.3.1 Disease stage

Extent and involvement by lymphoma is described by the disease stage and is an important prognostic factor. Stage can also influence treatment decisions.

14.10.3.2 Baseline

Baseline examination should be as close as possible to the randomization/start of treatment (e.g., within 4 weeks prior to randomization/start of treatment). Longer periods may be allowed depending on the disease studied and the study design.

[redacted]

14.10.3.3 Nodal vs. extranodal lesion

A lesion can be categorized as:

- Nodal lesion (a lymph node or a nodal mass)
- Extranodal lesion (a lesion located in other organs, including spleen and liver)

14.10.3.4 Measurable disease

All anatomic measurements should be taken in two perpendicular dimensions and recorded in metric notation, using a ruler or calipers.

Throughout this document, a lesion will be called measurable if:

- It can be measured accurately in two perpendicular dimensions: longest diameter (LDi) (also known as transverse diameter), and short diameter (SDi), which is the longest diameter perpendicular to LDi (also known as perpendicular diameter). The LDi and SDi must be measured on the same slice.
- For a nodal lesion, LDi is greater than 15 mm, regardless of SDi
- For an extranodal lesion, if both LDi and SDi are greater than 10 mm

A lymph node not meeting the measurability criteria but with LDi greater than 15 mm (e.g. SDi cannot be measured accurately) will constitute a non-measurable nodal lesion if FDG-avid (for FDG-avid histologies).

A lymph node not meeting the measurability criteria but with LDi ranging from 11 mm to 15 mm and with SDi greater than 10 mm will be checked for relationship to disease as follows:

- If it is related to lymphoma, it will constitute a non-measurable nodal lesion (referred to as "involved node" in Cheson et al 2007)
- If not related to lymphoma and not FDG-avid, it will constitute an abnormal lymph node but neither a measurable nor a non-measurable nodal lesion for FDG-avid histologies

All lesions visible on PET but not on CT/MRI will be treated as non-measurable.

Bulky disease

Bulky disease is captured by means of the longest measurement by CT scan. The definition of bulky disease (a minimum size) should be included in the study protocol.

14.10.3.5 Assessable disease

Assessable disease refers to disease presentations that are consistent with lymphoma but are not suitable for measurement, e.g., pleural effusion, ascites, etc. Assessable disease will be followed qualitatively.

14.10.3.6 Index lesion

- Up to 6 of the largest nodes, nodal masses or other lymphomatous lesions, including extranodal lesions, measurable in two diameters (LDi and SDi)
- Should represent overall disease burden and include mediastinal and retroperitoneal disease, if involved

[redacted]

14.10.3.7 Non-index lesion

- All other lesions which are not selected as index lesions but are consistent with lymphoma
- Abnormal nodes and extranodal lesions, both measurable and non-measurable, such as cutaneous, gastrointestinal, and bone lesions, pleural or pericardial effusions, and ascites

14.10.3.8 New lesions

- Regrowth of previously resolved lesions
- A new nodal lesion > 15 mm in any axis
- A new extranodal lesion > 10 mm in any axis
- A new extranodal lesion ≤ 10 mm in any axis that is unequivocal and attributable to lymphoma
- A new assessable lesion attributable to lymphoma (e.g., ascites, pleural effusion)

14.10.4 Efficacy assessments

14.10.4.1 Eligibility

In general, patients should have at least one measurable nodal lesion (greater than 15 mm in the long axis) or at least one measurable extranodal lesion (with both LDi and SDi greater than 10 mm).

14.10.4.2 Methods of disease assessment

14.10.4.2.1 PET combined with diagnostic CT

The integration of PET into more frequently acquired CT evaluation does present a challenge to the way response is assessed in a clinical trial. The study protocol must clearly define the imaging intervals and imaging methods to be used at each imaging visit. PET scans should be performed at pre-specified times for example at randomization before treatment and at clearly defined times during and/or after the end of treatment. PET may also be acquired to confirm CT results.

The same CT imaging modality should be used at baseline and all post-baseline assessments in order to reduce the risk of false responses or progressions based on measurement error. A change in modality can be either a change in contrast use (i.e., with contrast versus without contrast) or a change in technique (e.g. from CT to MRI). Response assessments made after a change in imaging modality should be queried, and if the investigator or blinded central reviewer can provide sufficient justification, then the response can be accepted.

In order to calculate the sum of the product of the perpendicular diameters (SPD) of all index lesions, their size must be recorded throughout the study. Actual lesion measurements should be entered on the corresponding CRFs. If, during the course of the study, either of the perpendicular diameters of a lesion cannot be reliably measured because of its small size, it is recommended to enter the minimum limit of detection as the diameter size (e.g., 5 mm for spiral CT). In other cases when, during the course of the study, the diameter cannot be reliably measured for reasons other than its size (i.e., borders of the lesion are confounded by

[redacted]

neighboring anatomical structures), no measurement should be entered and the lesion cannot be evaluated.

If lesions become confluent over time, it is recommended to measure them as one lesion, report the overall diameters to one of the lesions and assign 0 mm × 0 mm to each of the other previously measured lesions. The PPD of the current confluent mass should be used to measure response, with more than 50% increase in the PPD of the confluent mass compared with nadir of the sum of individual nodes necessary to indicate progressive disease.

If a lesion splits into several discrete lesions, the individual product of the perpendicular diameters (PPDs) of each lesion should be summed together to represent the PPD of the split lesion; this PPD is added to the sum of the PPDs of the remaining lesions to measure response. If subsequent growth of any or all of these discrete nodes occurs, the nadir of each individual node is used to determine progression (as if each individual node was selected as an index lesion at baseline).

14.10.4.2.2 Bone marrow assessment

Bone marrow should be evaluated by biopsy or aspirate in all patients at baseline. If lymphoma involvement in bone marrow is observed at baseline, then biopsy or aspirate should be performed post-baseline to confirm radiological CR. Any deviation from this approach should be justified in the study protocol.

14.10.4.2.3 Physical examination

Skin lesions must be histologically confirmed for lymphoma involvement (the investigational site must document the histological confirmation (yes or no) on the corresponding CRF) and photographed including a ruler (color photography using digital camera). Response assessment of skin lesions will be performed and results will be recorded on the corresponding CRF at baseline and at the time of each radiological assessment.

14.10.4.3 Documentation of disease

For the evaluation of disease at baseline and throughout the study, the following will be recorded.

14.10.4.3.1 FGD uptake

FDG uptake in a nodal or extranodal site that is suggestive of lymphoma will be assessed using 5PS.

14.10.4.3.2 Index lesions

A minimum of one measurable index lesion and a maximum of six of the largest dominant nodal and extranodal lesions must be documented at baseline and assessed throughout the study in two dimensions. The lesions should come from different body regions representative of the patient's overall disease burden and should include mediastinal and retroperitoneal disease, if involved. Two perpendicular dimensions (LDi, SDi) must be recorded on the corresponding CRF at each assessment of a measurable lesion selected to be an index lesion.

[redacted]

Index nodal lesions

Index nodal lesions are selected from the measurable nodal lesions and should be documented at baseline and assessed throughout the study. Index nodal lesions should be from disparate regions of the body including mediastinal and retroperitoneal areas of disease whenever these sites are involved.

Index extranodal lesions

Other organs such as breast and lung can be occasionally involved by lymphoma. Such extranodal lesions (e.g. hepatic nodules) may be included (if measurable) in the six index lesions to be assessed throughout the study. In some cases histological examination may be necessary to confirm that these lesions represent lymphoma involvement (e.g. skin lesions).

14.10.4.3.3 Non-index lesions

Non-index nodal lesions

Nodal lesions not selected as index lesions (both measurable and non-measurable) are considered as non-index lesions. Non-index lesions should be documented at baseline and assessed throughout the study. Measurements of these lesions are not required to be documented on the CRF.

Non-index extranodal lesions

Measurable extranodal lesions not selected as index lesions and all non-measurable extranodal lesions (including non-measurable but assessable disease e.g. pleural effusion) will be documented at baseline and assessed throughout the study as non-index lesions. Measurements of these lesions are not required to be documented on the CRF.

14.10.4.3.4 Spleen involvement

Splenic involvement is determined by imaging: vertical (cranial to caudal) length > 13 cm is considered as involved, and spleen length must be assessed at each imaging time point. Intrasplenic lesions should be followed as index, non-index and new extranodal lesions.

14.10.4.3.5 Liver involvement

Given variability in physical habitus and the impact of numerous medical conditions, assessment of liver size is not considered a reliable measure of hepatic involvement and therefore liver assessment is not included in the Lugano 2014 classification. Intrahepatic lesions should be followed as index, non-index and new extranodal lesions.

14.10.4.3.6 Bone marrow involvement

Lymphoma involvement in bone marrow should be documented in the CRF as “Yes” or “No” at each bone marrow biopsy and/or aspiration.

[redacted]

14.10.4.4 Response evaluation

The efficacy variables in the statistical analysis are based on **overall disease response**, which is a combined evaluation of response based on both radiological and clinical findings, and is determined at each post-baseline assessment. The radiological response is first obtained from CT and PET studies according to the Lugano criteria (Table 14-36) and overall disease response is then determined by taking into account results of bone marrow biopsies and other clinical information (Table 14-37).

14.10.4.4.1 Radiological response

There are three separate components to radiological response, all of which should be collected on the CRF at each post-baseline assessment:

1. **CT response** based on anatomical measurements of index/non-index/new lesions and spleen length. The possible response outcomes are complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) as defined in Table 14-36.
2. **PET response** based on 5PS, changes in intensity or extent of standard uptake values (SUVs) and bone marrow assessments directly from the PET scan. The possible outcomes for PET response are complete metabolic response (CMR), partial metabolic response (PMR), no metabolic response (NMR), or progressive metabolic disease (PMD) as defined in Table14-36.
3. **Overall radiological response** combines CT response with PET response. The outcomes include CR, PR, SD, and PD. For time points when both CT and PET are available, PET response overrules CT response. Overall radiological response at a time point with CT only may also be affected by PET response obtained at a different time point.

   Example

   A CT response of PR at the same assessment as a PET response of CMR will constitute an overall radiological response of CR, and (i) a subsequent time point with CT only and CT response of PR will still constitute an overall radiological response of CR, (ii) a previous time point with CT only and CT response of PR may be upgraded to CR at the discretion of the investigator or blinded central reviewer.

Table 14-36 Radiological response assessment

		PET-based response	CT-based response
		Complete Metabolic Response (CMR) (All of the following)	**Complete Response (CR)** (All of the following)
Complete Response	**Index**	5PS† of 1, 2, or 3* with or without residual mass on 5PS	**Nodal lesion**: ≤ 15 mm in Ldi **Extranodal lesion**: Absent (0 mm x 0 mm)
	Non-index		Absent
	Spleen		Return to normal (≤ 13 cm)
	New lesions	None	None
	Bone marrow	No FDG-avid disease	Not applicable
		Partial Metabolic Response (PMR) (all of the following)	**Partial Response (PR)** (all of the following)

		PET-based response	CT-based response
		Complete Metabolic Response (CMR) (All of the following)	**Complete Response (CR)** (All of the following)
Partial Response	**Index**	5PS of 4 or 5 with reduced uptake compared to baseline with respect to SUV intensity or extent. This may apply to the specific hot spot and/ or overall the subject. It is expected that there will be residual mass(es) present.	≥ 50% decrease from baseline in SPD across all index lesions
	Non-index		No increase
	Spleen		≥ 50% decrease from baseline in enlarged portion of spleen ***Example:*** *If 16 cm, then enlarged portion is 3 cm. A decrease by 2 cm gives a 66.6% decrease*
	New lesions	None	None
	Bone marrow	● Residual uptake higher than uptake in normal marrow but reduced compared with baseline ● Persistent focal changes in the marrow with nodal response	Not applicable
		No Metabolic Response (NMR) (all of the following)	**Stable Disease (SD)** (all of the following)
Stable Disease	**Index**	5PS of 4 or 5 with no significant change in FDG uptake from baseline	● <50% decrease from baseline in SPD across all index lesions ● No criteria for PD are met
	Non-index		No progression
	Spleen		No progression
	New lesions	None	None
	Bone marrow	No change in FDG uptake from baseline	Not applicable
		Progressive Metabolic Disease (PMD (At least one of the following)	**Progressive Disease (PD)** (At least one of the following)
Progressive Disease	**Index**	5PS of 4 or 5 with increased uptake compared to the visually determined nadir with respect to SUV intensity or extent. This may apply to the specific hot spot and/ or overall the subject. and/or ● New FDG-avid foci consistent with lymphoma ● Consider biopsy or interval scan if etiology of new lesions uncertain	PPD Progression[#]: An individual node/lesion must be abnormal with: ● LDi > 15 mm AND ● Increase by >= 50% from PPD nadir AND ● An increase in LDi or SDi from nadir: ● ≥ 5 mm for lesions with LDi ≤ 20 mm at current assessment ● ≥ 10 mm for lesions with LDi > 20 mm at current assessment
	Non-index		Unequivocal Progression
	Spleen		● Progression (increase from baseline by >50% in enlarged portion). ***Example:*** *If 15 cm at baseline then enlarged portion is 2 cm and an increase by >1 cm would be progression* ● New splenomegaly (> 13 cm and

[redacted]

		PET-based response	CT-based response
		Complete Metabolic Response (CMR) (All of the following)	**Complete Response (CR)** (All of the following)
			increase by > 2 cm from normal at baseline) ● Recurrent splenomegaly (normalization followed by increase by > 2 cm from nadir reaching > 13 cm)
	New lesions		● Regrowth of previously resolved lesions ● New node > 15 mm in any axis ● New extranodal site > 10 mm in any axis ● New extranodal site ≤ 10 mm in LDi, unequivocal and attributable to lymphoma ● Assessable disease of any size Unequivocally attributable to Lymphoma
	Bone marrow	New/recurrent FDG-avid foci	Not applicable

Abbreviations: LDi Longest diameter; SDi Shortest diameter; PPD Product of perpendicular diameters; SPD Sum of the product of the perpendicular diameters.
* Score 3 will be considered PET negative unless otherwise specified in the protocol (e.g. de-escalation studies, in which case CMR will be based on 5PS of 1 or 2 only, and PMR/NMR/PMD will be based on 5PS of 3,4 or 5)
# In the context of an agent associated with a flare reaction, caution must be exercised not to confuse the possible tumor flare with progressive disease. It is recommended that either a biopsy be performed or the lesion be reassessed in at least 2 weeks, and if there is continued evidence of tumor progression, the date of progressive disease is the previous evaluation.
† PET 5PS 1: no uptake > background; 2: uptake ≤ mediastinum; 3: uptake > mediastinum but ≤ liver; 4: uptake moderately > liver; 5: uptake markedly > liver and/or new lesions; X: new areas of uptake unlikely to be related to lymphoma.

14.10.4.4.2 Overall disease response

Overall disease response is determined by assessing whether the combined radiological responses at each time point are appropriate, based on bone marrow biopsies and other clinical findings that may be available, such as cytology results, physical examination results of palpable lesions or skin lesions, and biopsies of lymph nodes or extra-nodal lesions (Table 14-37). The possible outcomes for overall disease response are CR, PR, SD, and PD.

For example, suppose there was lymphoma involvement in the baseline bone marrow biopsy, and the month 3 combined radiological response was CR (implying that PET-based bone marrow involvement at month 3 was negative). In that case, overall disease response could only be CR if there was a negative bone marrow biopsy otherwise overall disease response would be downgraded to PR. This is a case where the bone marrow biopsy results overrule the bone marrow findings on PET. Another example is when the combined radiological response is SD,

but cytology results of a pleural effusion show lymphoma involvement: this could lead to an overall disease response of PD.

Overall disease response at each post-baseline assessment should be captured on the CRF, along with the date of response. In addition, the source of any clinical data that affected the overall disease response should be documented.

Table 14-37 Overall disease response

Overall radiological response	Bone marrow biopsy/aspirate	Clinical findings	Overall disease response
CR/PR/SD	Negative at baseline or negative ± 28 days from assessment	Any except new or recurrent lymphoma involvement	CR/PR/SD
CR	Positive at baseline and either positive (without new or recurrent involvement) or not done ± 28 days from assessment	Any except new or recurrent lymphoma involvement	PR
PR/SD	Positive at baseline and either positive (without new or recurrent involvement) or not done ± 28 days from assessment	Any except new or recurrent lymphoma involvement	PR/SD
PD	Any	Any	PD
Any	New or recurrent involvement	Any	PD
Any	Any	New or recurrent lymphoma involvement	PD

14.10.4.5 Efficacy analysis definitions

14.10.4.5.1 Best overall response

The best overall response (BOR) is the best overall disease response recorded from randomization/start of treatment until progressive disease or start of new anticancer therapy, whichever comes first. The definition of new anticancer therapy may need to be defined in the study protocol (e.g., high-dose chemotherapy with autologous stem cell transplantation).

A patient will have a best overall response of CR if they have CR as overall disease response for at least one of the assessments.

A patient will have a best overall response of PR if at least one overall disease response of PR is available (and the patient does not qualify for CR).

A best overall response of SD will be declared when at least one overall disease response of SD is available at least 6 weeks after randomization/start of treatment (and the patient does not qualify for CR or PR). If SD is observed before this minimum follow-up period, and the patient does not qualify for CR, PR or PD, then the best overall response would be unknown (UNK). If a different minimum follow-up period for SD is more appropriate (e.g., if first post-baseline visit is at 28 days) then this must be specified in the Study Protocol.

[redacted]

A patient will have a best overall response of PD if overall disease response is PD between randomization/start of treatment and the second scheduled post-baseline assessment (and the patient does not qualify for CR, PR or SD).

For example, assuming 12 weeks between assessments and a permitted variation in visit timing of ± 1 week, this would mean during the first 25 weeks after randomization/start of treatment. If PD is observed after this maximum follow-up period, and the patient does not qualify for CR, PR or SD, then the best overall response would be UNK. If a different maximum follow-up period for PD is more appropriate then this must be specified in the Study Protocol.

A patient will have a best overall response of UNK if the patient does not qualify for CR, PR, SD or PD.

Overall disease response at a given assessment may be provided from different sources:

- Per Investigator: overall disease response based on local radiological assessments, using investigator choice of index lesions, measurements and assessments of lesion status and 5PS along with clinical findings
- Per Central Blinded Review, with or without blinded adjudication: based on central review of local radiological assessments, using central reviewer choice of index lesions, measurements and assessments of lesion status and 5PS, along with clinical findings

In studies that include a central blinded review, the Study Protocol should state which source will be used for the primary analysis.

Best overall response is summarized by calculating the **overall response rate (ORR)**, which is defined as the proportion of patients with a best overall response of CR or PR.

Similarly, the complete response rate is the proportion of patients with a best overall response of CR.

14.10.4.5.2 Time to event variables

Most of the time to event variables are defined in this section according to the revised International Working Group response criteria (Cheson et al 2007). Further details on dates and censoring rules are provided respectively in Section 14.10.4.5.3 and Section 14.10.4.5.4.

Overall survival

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

Progression-free survival

Progression-free survival (PFS) is defined as the time from the date of randomization/start of treatment to the date of event defined as the first documented progression (overall disease response = PD) or death due to any cause. If a patient has not had an event, PFS is censored at the date of the last adequate assessment as defined in Section 14.10.4.5.3.

[redacted]

Time to progression

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

Duration of response

Duration of response (DOR) applies only to patients with best overall disease response of CR or PR. It is defined as the time from the date of the first documented overall disease response of CR or PR to the date of first documented progression or death due to lymphoma. If a patient has not had an event, DOR is censored at the date of the last adequate assessment. It should be stated that this analysis might introduce a bias as it includes only responders.

Duration of complete response applies only to patients with best overall disease response of CR. It is defined as the time from the date of the first documented overall disease response of CR to the date of first documented progression or death due to lymphoma. If a patient has not had an event, duration of CR is censored at the date of the last adequate assessment. Duration of CR might be calculated in addition for studies in which a reasonable number of complete responders are seen.

The analysis of DOR should only be used as a descriptive analysis. If used as an inferential comparison between treatments, clear justification must be given in the study protocol.

Time to response

Time to response (TTR) is defined as the time from the date of randomization/start of treatment to the date of first documented overall disease response of PR or CR. Depending on the study design, this analysis could be based on all patients only, or on responders only, or both of these analysis populations may be used. The choice of analysis population for TTR should be stated in the study protocol.

For analysis using all patients, TTR will be censored for patients who did not achieve a PR or CR:

- 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 the date of the last adequate assessment otherwise

Time to complete response (TTCR) is defined similarly to TTR except using CR only instead of either PR or CR, and with this difference, the above rules and definitions for TTR also apply to TTCR.

Lymphoma specific survival

Lymphoma specific survival (LSS) is defined as the time from the date of randomization/start of treatment to the date of death documented as a result of lymphoma. If a patient has not had an event, LSS will be censored:

- at the date of last contact if the patient is not known to have died
- at the date of death if the patient died for reason other than lymphoma

[redacted]

Event-free survival

Event-free survival (EFS) may be appropriate in studies of advanced disease where early discontinuation is typically related to intolerance of the study drug. In some protocols, EFS may be considered as a sensitivity analysis for TTP. If a patient has not had an event, EFS is censored at the date of the last adequate assessment as defined in Section 14.10.4.5.3. The definition of event needs to be defined in the Study Protocol according to study design.

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

Assessment date

For each assessment, the assessment date is calculated as:

- the latest date of all radiological measurements (e.g. PET-CT, CT, or MRI), excluding bone marrow biopsy, if overall disease response at that assessment is CR/PR/SD/UNK
- the earliest date of all measurements (e.g. PET-CT, CT, or MRI), including bone marrow biopsy if overall disease response at that assessment is PD

Start date

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

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

- Date of first documented response is the assessment date of the first overall disease response of CR for duration of complete response or CR/PR for duration of response

End date

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

- Date of death as reported on the disposition CRF
- Date of last contact is defined as the last date the patient was known to be alive as derived from different CRF pages (see details in Section 14.10.5.2)
- Date of progression is the first assessment date at which the overall disease response was recorded as PD
- Date of last adequate assessment is the date of the last assessment with overall disease response of CR, PR or SD which was made before an event or a censoring reason occurred. If no post-baseline assessments are available (before an event or a censoring reason occurred) the date of randomization/start of treatment is used.
- Date of next scheduled assessment is the date of the last adequate assessment plus the protocol specified time interval between assessments. This date may be used if back-dating is considered when the event occurred beyond the acceptable time window for the next radiological assessment as per protocol.

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

- Date of treatment discontinuation is the last known date subject took study drug *(to be used, if applicable)*
- Date of new anti-cancer therapy is defined as the start date of first new antineoplastic therapy (including medication, radiotherapy, surgery or HSCT)

14.10.4.5.4 Censoring and sensitivity analyses

Censoring reasons

This section outlines the possible censoring reasons for each time to event variables. In order to summarize the various reasons for censoring, the following categories (Table 14-38) will be calculated for each time to event variable based on the information reported.

Table 14-38 Censoring reasons

Time to event variables	Possible censoring reasons
OS	• Alive • Lost to follow-up
PFS, EFS, TTP and DOR	• Ongoing without event • Lost to follow-up • Withdrew consent • Death due to reason other than lymphoma (only used for TTP and DOR) • New anti-cancer therapy added (except for EFS optional, see Table 14-39) • Event documented after two or more missing response assessments (optional, see Table 14-39) • Adequate assessment no longer available[1]
LSS	• Alive • Lost to follow-up • Death due to reason other than lymphoma

[1]Adequate assessment is defined in Section 14.10.4.5.3. This reason corresponds to any censoring reasons after two or more missing response assessments. This reason will also be used for censor in case of no baseline assessment

Event date, censoring date and sensitivity analyses

This section outlines the possible event and censoring dates for progression (Table 14-39), as well as addressing the issues of missing response assessments during the study. It is important that the protocol and analysis plan specify the primary analysis in detail with respect to the definition of event and censoring dates and also include a description of one or more sensitivity analyses to be performed.

Based on definitions outlined in Section 14.10.4.5.2, and using the draft FDA guideline on endpoints (FDA 2007) as a reference, the following analyses can be considered:

[redacted]

Table 14-39 Options for event dates used in PFS, EFS, TTP, DOR

Situation		Options for end-date (progression)[1] (1) = default unless specified differently in the protocol or analysis plan	Outcome
A	No baseline assessment	(1) Date of randomization/start of treatment[2]	Censor
B	Progression at or before next scheduled assessment	(1) Date of progression (2) Date of next scheduled assessment[1]	Event Event
C1	Progression or death due to any reason after exactly one missing assessments	(1) Date of progression (or death) (2) Date of next scheduled assessment[1]	Event Event
C2	Progression or death due to any reason after two or more missing assessments	(1) Date of last adequate assessment[1] (2) Date of next scheduled assessment[1] (3) Date of progression (or death)	Censor Event Event
D	No progression	(1) Date of last adequate assessment	Censor
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	(1) N/A (2) Date of discontinuation (visit date at which clinical progression was determined)	Ignored Event
F	New anticancer therapy given (except for EFS, in which this is always an event)	(1) Date of last adequate assessment (2) Date of new anticancer therapy (3) Date of secondary anti-cancer therapy (4) N/A	Censor Censor Event Ignored
G	Death due to reason other than lymphoma	(1) Date of last adequate assessment	Censor (only TTP and DOR)

[1] = Definitions can be found in Section 14.10.4.5.3

[2] = The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.

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

Situations C (C1 and C2): Progression or death after one or more missing assessments:

The primary analysis is usually using options (1) for situations C1 and C2, i.e.

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

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

Situation E: Treatment discontinuation due to 'Disease progression' without documented progression: By default, option (1) is used for situation E as patients without documented PD should be followed for progression after discontinuation of treatment. However, option (2) may be used as sensitivity analysis. If progression is claimed based on clinical deterioration instead of response assessment by e.g. CT-scan, option (2) may be used for indications with high early progression rate or difficulties to assess the response due to clinical deterioration.

[redacted]

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

Additional suggestions for sensitivity analyses

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for response assessments, e.g.:

- By assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in Table 14-39 the "Date of last adequate assessment" by the "Date of previous scheduled assessment (from baseline)", with the following definition:

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

The need for these types of sensitivity analyses will depend on the requirements for a specific study and disease area and have to be specified in the Study Protocol or RAP documentation.

14.10.5 Data handling and programming conventions

The following rules should be used and specified in the RAP documentation:

14.10.5.1 Calculation of 'time to event' variables

Time to event = enddate - startdate + 1 (in days)

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

14.10.5.2 Date of last contact

The date of last contact will be derived for patients alive using the latest complete date among the following:

- Assessment dates (e.g., vital signs assessment, performance status assessment, efficacy assessment, laboratory, pharmacokinetics assessment)
- Medication dates including study medication and antineoplastic therapies administered after study treatment discontinuation
- Adverse events dates
- Last known date subject alive collected on the 'Survival information' eCRF
- Randomization date

14.10.5.3 Date of new anti-cancer therapy

The date of new anti-cancer therapy is the date of the first antineoplastic therapy (including medicine, radiotherapy and surgery) reported on the post-treatment antineoplastic therapy CRF or from other sources (e.g., HSCT CRF).

[redacted]

14.10.5.4 Incomplete assessment dates

All investigation dates (e.g., PET-CT scan) must be completed with day, month and year. If one or more investigation dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date (and assessment date is calculated as outlined in Section 14.10.4.5.3). If all measurement dates have no day recorded, the 1st of the month is used.

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

14.10.5.5 Incomplete dates for last contact or death

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

14.10.6 References

Barrington SF, Mikhaeel NG, Kostakoglu L, et al (2014) Role of imaging in the staging and response assessment of lymphoma: Consensus of the International Conference on Malignant Lymphomas Imaging Working Group. J Clin Oncol 32 :3048-3058.

Cheson BD, Horning SJ, Coiffier B, et al (1999) Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. J Clin Oncol 17:1244-1253.

Cheson BD, Pfistner B, Juweid ME, et al (2007) Revised response criteria for malignant lymphoma. J Clin Oncol 25:579-586.

Cheson BD, Fisher RI, Barrington SF, et al (2014) Recommendations for initial evaluation, staging, and response assessment of Hodgkin and Non-Hodgkin lymphoma: The Lugano Classification. J Clin Oncol 32:3059-3067.

FDA Guideline (2007) Clinical trial endpoints for the approval of cancer drugs and biologics, May 2007.

14.10.7 Appendix A: Adaptation for use in maintenance/adjuvant settings

For study populations without measurable disease at baseline (e.g., maintenance), the event of interest is no longer progression but relapse, and the main endpoint is no longer progression-free survival but disease-free survival (see below).

Relapsed disease

Any of the following meets the definition of relapsed disease (RD):

- Any new nodal lesion > 15 mm in any axis (i.e. previously normal lymph node becoming >1.5 cm in any axis) on CT (or MRI) after baseline
- Any discrete extranodal lesion (including liver or spleen) reliably appearing on CT (or MRI) after baseline
- ≥ 50% increase in long axis from baseline of any residual lymph node or mass. A residual lymph node or mass is defined as a previously lymphoma-involved lymph node or mass

[redacted]

(>10 mm in short axis (without any upper limit)) that was PET negative at baseline and only reliably detected by baseline CT (or MRI). Note: If a residual lymph node or mass at baseline decreases in size during treatment and becomes normal (i.e. complete disappearance of extranodal mass or ≤ 10 mm in short axis and ≤ 15 mm long axis for nodal mass), then reappearance of an extranodal lesion at the same site or increase of the same nodal mass to > 15 mm in the long axis, will be considered RD and will be recorded as a new lesion.

- Any new bone marrow involvement
- Any new malignant effusion

Disease-free survival

Disease-free survival (DFS) is the time from date of randomization / start of treatment to the date of event defined as the first documented relapse of the disease or death due to any cause. If a patient has not had an event, DFS is censored at the date of the last adequate assessment. Similar censoring rules and reasons as the ones used for PFS can be applied.

[redacted]