NOVARTIS

Clinical Development

MBG453, PDR001

Oncology Clinical Trial Protocol CMBG453X2101 / NCT02608268

A phase I-Ib/II, open-label, multi-center study of the safety and efficacy of MBG453 as single agent and in combination with PDR001 in adult patients with advanced malignancies

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List of abbreviations

Ab(s)	Antibody(ies)
AE	Adverse Event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
AUC	Area Under the Curve
BHLRM	Bayesian Hierarchical Logistic Regression Model
BLRM	Bayesian Logistic Regression Model
BOR	Best Overall Response
CEACAM1	Carcinoembryonic Antigen-Related Cell Adhesion Molecule 1
CI	Confidence Interval
CMO&PS	Chief Medical Office and Patient Safety
CNS	Central Nervous System
CR	Complete Response
CRO	Contract Research Organization
CRS	Cytokine Release Syndrome
CSF	Colony Stimulating Growth Factor
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
DC	Dendritic Cell
DDS	Dose Determining Set
DLT	Dose Limiting Toxicity
DOR	Duration of Response
eCRF	Electronic Case Report/Record Form
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELISA	Enzyme-Linked Immunosorbent Assay
EWOC	Escalation With Overdose Control
EOT	End of Treatment
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIH	First In Human
GLP	Good Laboratory Practice
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
hCG	Human Chorionic Gonadotropin
HED	Human Equivalent Dose
HIV	Human Immunodeficiency Virus
HNSCC	Head and Neck Squamous Cell Carcinoma
HNSTD	Highest Non-Severely Toxic Dose
IB	Investigator brochure
IEC	Independent Ethics Committee
IFN-γ	Interferon-gamma
IG	Immunogenicity
IHC	Immunohistochemistry
IL	Interleukin

[redacted]

INR	International Normalized Ratio
IRB	Institutional Review Board
irAE(s)	Immune-related Adverse Event(s)
irCR	Immune-related Complete Response
irPD	Immune-related Progressive Disease
irPFS	Immune-related Progression Free Survival
irPR	Immune-related Partial Response
irSD	Immune-related Stable Disease
irRC	Immune-related Response Criteria
i.v.	Intravenous(ly)
JP	Japan
LAG-3	Lymphocyte-activation gene-3
LLOQ	Lower Limit Of Quantitation
LMWH	Low Molecular Weight Heparin
mAb(s)	monoclonal Antibody(ies)
MDSCs	Myeloid-Derived Suppressor Cells
MTD	Maximum Tolerated Dose
NCCN	National Comprehensive Cancer Network
NSCLC	Non-Small Cell Lung Carcinoma
NK	Natural Killer
ORR	Overall Response Rate
PAS	Pharmacokinetic Analysis Set
PBMC(s)	Peripheral Blood Mononuclear cell(s)
PHI	Protected Health Information
PD	Progressive Disease
PD-1	Programmed Death-1
PD-L1	Programmed Death-Ligand 1
PD-L2	Programmed Death-Ligand 2
(m)PFS	(median) Progression Free Survival
PK	Pharmacokinetics
PPS	Per Protocol Set
PR	Partial Response
PtdSer	Phosphatidylserine
Q2W	Every 2 weeks
Q4W	Every 4 weeks
RAP	Report and Analysis Plan
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria In Solid Tumors
RO	Receptor Occupancy
ROW	Rest of the World
RP2D(s)	Recommended phase II dose(s)
SAE(s)	Serious Adverse Event(s)
SCLC	Small Cell Lung Cancer
SEB	Staphylococcal enterotoxin B
SEC	Safety Event Categories
SJS	Steven Johnson Syndrome
SD	Stable Disease

[redacted]

TADC(s)	Tumor-associated Dendritic cell(s)
TEN	Toxic Epidermal Necrosis
TIL(s)	Tumor Infiltrating Lymphocyte(s)
TIM-3	T-cell Immunoglobulin domain and Mucin domain-3
Th1	T helper 1
Tlast	Time to last measurable concentration
TLR	Toll-like Receptor
TNF-α	Tumor Necrosis Factor-alpha
TTP	Time to Progression
TTR	Time To Response
Tregs	Regulatory T cells
ULN	Upper Limit of Normal
UNK	Unknown

[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)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Personal Data	Patient information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes patient identifier information, study information and biological samples.
Subject/Patient Number (Patient No.)	A unique identifying number assigned to each subject/patient volunteer who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
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 a patient permanently discontinues 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.

[redacted]

Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints
Withdrawal of 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:

Protocol number	CMBG453X2101
Title	A phase I-Ib/II, open-label, multi-center study of the safety and efficacy of MBG453 as single agent and in combination with PDR001 in adult patients with advanced malignancies
Brief title	Phase I-Ib/II study of MBG453 as single agent and in combination with PDR001 in patients with advanced malignancies.
Sponsor and Clinical Phase	Novartis Phase I-Ib/II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this “first-in-human” study of MBG453 is to characterize the safety, tolerability, pharmacokinetics (PK), pharmacodynamics and antitumor activity of MBG453 administered i.v. as a single agent or in combination with PDR001 or decitabine in adult patients with advanced solid tumors. In addition, the safety, tolerability, pharmacokinetics and pharmacodynamics of MBG453 as single-agent and in combination with PDR001 in Japanese adult patients will be evaluated.
Primary Objective(s)	Phase I-Ib: To characterize the safety and tolerability of MBG453 as a single agent and in combination with PDR001 and to identify recommended doses for future studies.Phase I-Ib dose ranging: To further investigate the safety and tolerability of different doses of MBG453 as single agent or in combination with PDR001. To characterize the safety and tolerability of MBG453 in combination with decitabine in anti-PD-1/PD-L1 therapy naïve small cell lung cancer (SCLC) patients Phase II: To estimate the anti-tumor activity of MBG453 as single agent in patients with solid tumors, and in combination with PDR001or decitabine in selected disease indications (melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC) , small cell lung cancer (SCLC)).
Secondary Objectives	• Evaluate the preliminary anti-tumor activity of MBG453 as single agent and in combination with PDR001 or decitabine. • Make an initial comparison of safety, PK and efficacy for MBG453 and PDR001 administered in combination on a every 2 weeks (Q2W) and every 4 weeks (Q4W) dosing schedules. • Characterize the pharmacokinetic profile of MBG453 as single agent and in combination with PDR001 or decitabine. • Assess emergence of anti-MBG453 and anti-PDR001 antibodies. • Assess potential predictors of efficacy of MBG453 as single agent and in combination with PDR001 or decitabine in tumor samples. • Assess the pharmacodynamic effect of MBG453 as single agent and in combination with PDR001 or decitabine in tumor samples. • Describe the survival distribution of patients treated with MBG453 as single agent and in combination with PDR001 or decitabine for each disease group.

Study Design	This is a first-in-human (FIH), open label, phase I-Ib/II, multi-center study which consists of a phase I dose escalation part of MBG453 as single agent (including a separate Japanese single agent dose escalation part), and a phase Ib dose escalation part of MBG453 in combination with PDR001 that will commence after two cohorts in the dose escalation with single agent have been completed. Once the Maximum Tolerated Dose (MTD)/Recommended Phase 2 Dose (RP2D) of MBG453 as single agent and/or in combination with PDR001 is achieved, a Phase I/Ib dose ranging part, and a phase II part in patients with solid tumors (MBG453 as single agent), and in selected indications (MBG453 in combination with PDR001) will commence. In addition, MBG453 in combination with decitabine in anti-PD-1/PD-L1 therapy naïve SCLC patients will be explored in phase Ib followed by a phase II. MBG453 and PDR001 will be administered i.v. Q2W or Q4W, decitabine will be administered on Days 1-5 Q4W until a patient experiences unacceptable toxicity, progressive disease (PD) as per irRC and/or treatment is discontinued at the discretion of the Investigator or the patient. Patients should not discontinue treatment based on progressive disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 unless clinical deterioration or increase in tumor markers is observed
Population	• The phase I-Ib dose escalation and dose ranging parts of the study will be conducted in adult patients with advanced solid tumors. • The single agent phase II part of the study will be conducted in adult patients in indications showing preliminary signs of activity in the phase I dose escalation part. • The combination phase II part of the study will be conducted in adult patients enrolled in 3 distinct groups (melanoma, NSCLC and RCC). • The phase Ib-II of MBG453 in combination with decitabine will be conducted in anti-PD-1/PD-L1 therapy naïve SCLC patients.
Inclusion criteria (selected)	1. Histologically documented advanced or metastatic solid tumors. 2. **Phase I-Ib part (including dose ranging part)**: Patients with advanced/metastatic solid tumors, with measurable or non-measurable disease as determined by RECIST v1.1, who have progressed despite standard therapy or are intolerant of standard therapy, or for whom no standard therapy exists**.** 3. **Phase II part (MBG453 single agent)**: Patients with advanced/metastatic solid tumors in the indication in which at least one confirmed PR or CR was seen during the dose escalation phase I part. Patients must have measurable disease as determined by RECIST v1.1, have progressed despite standard therapy or be intolerant to standard therapy. 4. **Phase II part (MBG453 in combination with PDR001)**: Patients with advanced/metastatic tumors in the below selected indications, with at least one measurable lesion as determined by RECIST v1.1, who have received standard therapy and are intolerant of standard therapy or have progressed following their last prior therapy: • Melanoma (anti-PD-1/PD-L1 therapy naïve or pre-treated) • NSCLC (anti-PD-1/PD-L1 therapy naïve or pre-treated) • RCC (anti-PD-1/PD-L1 therapy naïve or pre-treated) 5. 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/baseline, and during therapy on the study. 6. **Phase Ib-II part for MBG453 in combination with decitabine :** anti-PD-1/PD-L1 therapy naïve SCLC patients who have failed no more than two lines of standard chemotherapy, including topotecan.

[redacted]

Exclusion criteria (selected)	1. Presence of symptomatic central nervous system (CNS) metastases. 2. History of severe hypersensitivity reactions to any ingredient of study drugs and other monoclonal antibodies (mAbs) and/or their excipients. 3. Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) infection. 4. Active autoimmune disease or a documented history of autoimmune disease, including ulcerative colitis and Crohn's disease or any condition that requires systemic steroids. 5. Systemic steroid therapy or any immunosuppressive therapy (≥10mg/day prednisone or equivalent). 6. Use of any vaccines against infectious diseases (e.g. varicella, pneumococcus) within 4 weeks of initiation of study treatment. 7. Pre-treatment with anti-CTLA4 antibodies (Abs) in combination with any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathway. 8. Participation in an interventional, investigational non-immunotherapy study within 2 weeks of the first dose of study treatment. 9. Prior participation in an interventional, investigational cancer vaccine or immunotherapy study except for an anti-PD-1/PD-L1 study.
Investigational and reference therapy	MBG453 ,PDR001 and decitabine
Efficacy assessments	Tumor assessment per RECIST v1.1 and per irRC.
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	• Serum PK parameters, [redacted] and Immunogenicity (IG). [redacted]
Data analysis	The study data will be analyzed and reported based on all patients' data of the Phase I-Ib and Phase II parts up to the time when all patients have completed at least six cycles of treatment or discontinued the study.
Key words	Phase I-Ib/II, MBG453, PDR001, decitabine, checkpoint inhibitor, PD-1, TIM-3.

[redacted]

Amendment 06 (31-Aug-2020)

Amendment rationale

The main purpose of this amendment is to communicate the decision by Novartis to not open enrolment in the SCLC arm for MBG453 in combination with decitabine. Importantly, this decision is made due to the rapidly evolving treatment landscape for SCLC patients and is not a consequence of any safety concern.

In addition, this protocol amendment revises the definition of end of study 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 an alternative treatment option to continue providing study treatment to these patients.

This amendment also includes the following changes

[redacted]

- Other minor corrections were made for consistency and/or clarifications.

Study status

As of 25-Jul-2019, a total of 252 patients have been treated with either MBG453 single agent or MBG453 in combination with PDR001. Of the 133 patients treated with MBG453 as a single agent, 132 have permanently discontinued study treatment. Of the 119 patients treated with MBG453 in combination with PDR001, 111 have permanently discontinued study treatment. As of the cut-off date, out of the 9 ongoing patients, 6 have been receiving study treatment for more than 2 years.

Changes to the protocol

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

- Section 2 Rationale for the study design: updated to reflect that enrolment for MBG453 in combination with decitabine will not open in SCLC patients.
- Section 3: Correction of a typo in Table 3-1, incidence of DLTs in second cycle for MBG453 in combination with decitabine has been removed.

[redacted]

- Section 4.1 Description of study design: updated to reflect that enrolment for MBG453 in combination with decitabine will not open in SCLC patients.
- Figure 4-1 was updated to reflect that MBG453 in combination with decitabine in SCLC patients will not open for enrolment.

[redacted]

- Section 4.3 Definition of end of study: addition of language to account for patients who would transfer into another study or an alternative treatment option to continue provision of study treatment.
- Section 6.1.1: Clarification that MBG453 administration has to be followed by a dextrose solution flush as described in the pharmacy manual.
- Section 7.1.2 Treatment period: clarification of language that patients will not continue treatment at the discretion of the investigator or the patient as described in Section 7.1.3 and Section 4.3.
- Section 7.1.3 Discontinuation of study treatment: addition of language to specify that patients who transfer to another study or an alternative treatment option to continue provision of study treatment will complete end of treatment procedures.
- Section 7.1.5 Follow-up period: addition of language to specify that patients who transfer into another study or an alternative treatment option to continue provision of study treatment will not complete the safety, disease progression and survival follow-up.
- Section 9.4: Clarification that the investigator will receive copies of the patient data for archiving at the investigational site.
- Section 10 Statistical methods and data analysis: updated to reflect that MBG453 in combination with decitabine in SCLC patients will not open for enrolment.
- [redacted]
- Section 10.8 Sample size calculation: updated to reflect that MBG453 in combination with decitabine in SCLC patients will not open for enrolment.

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 05 (04-Nov-2019)

Amendment rationale

The main purpose of this amendment is to explore a new treatment arm of MBG453 in combination with decitabine with the option, at disease progression, to add PDR001 in anti-PD-1/PD-L1 therapy naïve small cell lung cancer (SCLC) patients who have failed no more than two lines of standard chemotherapy including topotecan.

Recent data suggest that decitabine treatment in a mouse model of colon carcinoma enhanced both the activation of immune cells in the tumor and combined with anti-PD-1 therapy enhanced the anti-tumor immune response (Yu et al 2018). Decitabine enhanced the expression of type I interferon in murine cancer models (Stone et al 2017) and this has also been shown in *in vitro* with the treatment of myeloid derived suppressor cells (unpublished data). Moreover clinical data from this study and from the study done by Harding with an anti-TIM-3 monoclonal antibody LY3321367 (Harding et al 2019) suggest that TIM-3 inhibitors have preliminary efficacy in SCLC. Moreover clinical data from this study and a competitor study suggest that TIM-3 inhibitors have preliminary efficacy in SCLC. Taken together, these data provide the rationale to combine decitabine with an anti TIM-3/antiPD-1 in SCLC.

Enrolment in this new arm is applicable to potential study sites in Italy, South Korea, Netherlands, Switzerland and United States.

In addition, in consideration of the rapidly evolving landscape for treatment options in melanoma, NSCLC, and RCC, Novartis made the decision to not open the Phase II of the following expansion groups as per the enrolment halt letter dated 22-May-2018:

- MBG453 in combination with PDR001 in Melanoma, and NSCLC (naive to anti PD-1/PD-L1 therapy) (Group 1 and Group 3)
- MBG453 in combination with PDR001 in RCC (both pretreated and naive to anti PD-1/PD-L1 therapy) (Group 5 and Group 6)

This amendment also includes the following changes

- To add that certain exceptions for steroid use can be allowed after discussion with Novartis.
- To add that for patients ongoing after cycle 24, and after documented discussion with Novartis and the Investigator, a treatment break lasting up to 2 cycles may be granted.
- The withdrawal of consent language was revised to differentiate sample use after a patient withdraws consent based on different regulations/laws around the world.
- To align with the EMA standard term list, the PDR001 pharmaceutical form has been updated to “Powder for solution for infusion”.
- Other minor corrections were made for consistency and/or clarifications.

Study status

As of 25-Jul-2019, a total of 252 patients have been treated with either MBG453 single agent or MBG453 in combination with PDR001. Of the 133 patients treated with MBG453 as a single agent, 132 have permanently discontinued study treatment. Of the 119 patients treated with

[redacted]

MBG453 in combination with PDR001, 111 have permanently discontinued study treatment. As of the cut-off date, out of the 9 ongoing patients, 6 are on treatment for more than 2 years.

MBG453 single agent and MBG453 in combination with PDR001 are now closed for enrolment.

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.

Following sections throughout the protocol have been added or updated to introduce MBG453 in combination with decitabine.

- Protocol Summary
- Section 1 Background
- Section 1.1.1 TIM-3 overview
- Section 1.1.3 Decitabine overview
- Section 1.2.1.2 MBG453 clinical experience
- Section 1.2.2.2 PDR001 Clinical experience
- Section 1.2.3 Overview of decitabine
- Section 1.2.3.1 Clinical experience with decitabine
- Section 1.2.4 Overview of MBG453 , PDR001 and decitabine
- Section 1.2.4.2 Clinical experience with the combination of MBG453 and PDR001
- Section 1.2.4.3 Non clinical experience with MBG453 in combination with decitabine
- Section 1.2.4.4 Clinical experience with MBG453 in combination with decitabine and MBG453 in combination with decitabine and PDR001
- Section 1.2.4.5 Potential drug interaction
- Section 2.1 Study rationale and purpose
- Section 2.2 Rationale for the study design
- Section 2.3 Rationale for dose and regimen selection
- Section 3 Objectives and endpoints
- Section 4.1 Description of study design
- Section 4.2 Timing of interim analyses and design adaptations
- Section 5.1 Patient population
- Section 5.2 Inclusion criteria
- Section 5.3 Exclusion criteria
- Section 6.1 Study treatment
- Section 6.1.1 Dosing regimen
- Section 6.1.2 Ancillary treatments
- Section 6.1.3 Treatment duration
- Section 6.2.2 Provisional dose levels
- Section 6.2.3.1 MTD definition

[redacted]

- Section 6.2.3.2 Dose cohort modification
- Section 6.2.4 Definitions of dose limiting toxicities (DLTs) for MBG453 single agent and MBG453 in combination with PDR001
- Section 6.2.5 Definition of dose limiting toxicities (DLTs) for MBG453 in combination with decitabine
- Section 6.3.1 Dose modification and dose delay
- Section 6.3.2 Follow-up for toxicities
- Section 6.3.3 Anticipated risks and safety concerns of the study drug
- Section 6.4.2 Permitted concomitant therapy requiring caution and/or action
- Section 6.5.2 Treatment assignment or randomization
- Section 6.6 Study drug preparation and dispensation
- Section 6.6.2 Drug supply and storage
- Section 7.1 Study flow and visit schedule
- Section 7.1.2 Treatment period
- Section 7.1.3.1 Replacement policy
- Section 7.1.4 Withdrawal of consent
- Section 7.2.2.6 Cardiac assessments
- Section 7.2.3 Pharmacokinetics and immunogenicity assessments
- Section 7.2.3.1 Bioanalytics
- Section 7.2.3.2 PK, [redacted] and IG samples handling, labeling and shipping instructions
- Section 7.2.4 Biomarkers
- Section 7.2.4.1 Tumor collection
- Section 7.2.4.2 Blood sample collection
- Section 7.2.4.3 Additional biomarker assessments
- Section 8.1.1 Definitions and reporting
- Section 8.2 Serious adverse events
- Section 10 Statistical methods and data analysis
- Section 10.1.2 Safety Set
- Section 10.1.3 Per-protocol Set
- Section 10.1.4 Dose-determining analysis set
- Section 10.3 Treatments (study treatment, concomitant therapies, compliance)
- Section 10.4 Primary objective
- Section 10.4.1 Variable
- Section 10.4.2 Statistical hypothesis, model and method of analysis
- Section 10.5.2 Other secondary efficacy objectives
- Section 10.5.3 Safety objectives
- Section 10.5.4 Pharmacokinetics

[redacted]

[redacted]

- Section 10.7 Interim analysis
- Section 10.8 Sample size calculation
- Section 13 References

Additional changes

- Glossary of terms has been updated to add the "Personal data" term and revise the "Withdrawal of consent" term.
- Section 6.4.3 Prohibited concomitant therapy.
  - Added a statement that exceptions can be made for steroid use after discussion with Novartis.
- Section 6.6 Study drug preparation and dispensation.
  - To align with the EMA standard term list, the PDR001 pharmaceutical form has been updated to "powder for solution for infusion".
- Section 6.6.1 Study drug packing and labeling.
  - The pharmaceutical form for PDR001 was changed to "powder for solution for infusion".
- Section 7.1.4 Withdrawal of Consent.
  - The withdrawal of consent language was revised to differentiate sample use after a patient withdraws consent based on different regulations/laws around the world.
- Section 7.1.2 Treatment period.
  - To add that for patients ongoing after cycle 24, and after documented discussion with Novartis and the Investigator, a treatment break lasting up to 2 cycles may be granted.
- Section 8.2.2 Reporting and Section 8.3 Pregnancies.
  - The name of the Novartis Drug Safety and Epidemiology department was updated to Chief Medical Office and Patient Safety. In addition, clarification was added in the pregnancy section to specify that the follow-up of the newborn will be 12 months.
- Section 10.5.3.1 Analysis set and grouping for the analyses.
  - The on-treatment and post-treatment observation periods have been updated.
- Section 10.6.1 Biomarkers.
  - The wording using blood and plasma samples has been removed.

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]

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 04 (04-Sep-2018)

Amendment rationale

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

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/toxic epidermal necrolysis (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 table describing the criteria for dose reduction/interruption and re-initiation of treatment for adverse drug reactions

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 6.3.1: Dose modification and dose delay

- Instruction for dose modification was updated and Table 6-5 updated accordingly. The list of abbreviations was updated to add SJS and 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.

The changes in this amendment identified above as being related to the USM have already been implemented by a USM letter issued on 15 June 2018. These changes are required for patient safety (i.e. necessary to eliminate immediate hazards to the trial subjects ICH GCP 3.3.8). Therefore they were required to have been implemented prior to IRB/IEC approval of this amendment.

The 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 03 (18-Jul-2016)

Amendment rationale

Main purpose of the amendment:

The purpose of this amendment is to update the exclusion criterion 2 as requested by a regulatory authority. The exclusion criterion is modified to clarify that patients with a history of hypersensitivity to any ingredient of the study drugs are also excluded.

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 underlined for insertions.

- Section 5.3 Exclusion criteria
  - Update of the exclusion criterion 2.

IRB/IEC/HA 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.

[redacted]

Amendment 02 (06-Jun-2016)

Amendment rationale

Main purpose of the amendment:

The main purpose of this amendment is to include a Japanese dose escalation part for single-agent MBG453 with the goal of informing subsequent clinical development opportunities in Japan.

The single agent dose escalation part of this study is already underway globally with the exception of Japan. At the time of this protocol amendment patients are being treated with single-agent MBG453 at 80mg Q2W and at 240mg Q2W and Q4W.

In order to ensure that the safety and pharmacokinetic profiles of single-agent MBG453 are adequately characterized in Japanese patients at more than one MBG453 dose, a Japanese-specific MBG453 single agent dose escalation is being included in the protocol. The Japanese dose escalation will run separately from the ongoing dose escalation with a starting dose for single agent MBG453 in Japanese patients of 80mg Q2W. After the first cohort Japanese patients may be treated in two different dosing regimens (Q2W and Q4W). Dose escalation decisions will be guided by a BHLRM.

If the recommended dose of single agent MBG453 in Japanese patients is the same as in patients from the rest of the world (ROW), then Japanese patients may be enrolled into the phase II single agent part of the study.

In addition, if the recommended dose of PDR001 for Japanese patients in the single agent study (PDR001X1101) currently ongoing in Japan is the same as that determined in the single agent ROW study (PDR001X2101), Japanese patients may also enter the combination parts of the current MBG453 study at whichever dose is being tested at that time.

If any of the Japanese single agents (PDR001 and/or MBG453) RP2D and/or MTD is different than the ROW, a new clinical development plan will be required to investigate the combination treatment in Japanese patients.

Other objectives of the amendment:

To update eligibility criteria:

In addition to the inclusion of Japan within the study, below described eligibility criteria have been updated and a new exclusion criterion has been added.

- **The inclusion criterion 4** has been amended to allow inclusion in the phase I-Ib parts of patients who previously received therapy with PD-1/PD-L1 blocking agents, as it has been recently shown that TIM-3 is significantly up-regulated in T-cells of patients previously exposed to PD-1 blocking agents (Koyama et al 2016).
- As durable stable disease (SD) is also a characteristic of cancer immunotherapy, **the inclusion criterion 5** has been amended to be less stringent and allow opening of the phase II MBG453 single agent in indications in which durable tumor shrinkages that may not qualify for PR have been observed.

[redacted]

- **The exclusion criterion 5** (Excluding HIV, HBV or HCV positive patients at screening/baseline) has been amended to allow inclusion of patients who may be HBV and HCV infection positive without active disease. Considering the mechanism of action of TIM-3 and PD1 blockade, the risk of hepatitis reactivation further to study treatment is very low.
- Given that pneumonitis is a reported adverse event of PD-1 blockade therapy, patients with a history of drug-induced pneumonitis or current pneumonitis are excluded.

To update other aspects of the protocol:

- Based on latest information recently communicated on Nivolumab, the immune-related adverse events (irAEs) expected to be associated with all classes of checkpoint inhibitors including MBG453 have been updated to add "Encephalitis".
- In keeping with current medical procedures the possibility to allow limited-field palliative radiotherapy or surgery to non-target lesion(s) as concomitant therapy requiring caution and/or action has been introduced.
- Due to its higher specificity, Free T4 substitutes Total T4 analysis.
- Furthermore the baseline cytokine collection for safety assessment has been removed as it was a duplicate. Baseline cytokine levels can be assessed from the biomarker blood sample collected at pre-dose Cycle 1 day 1.
- With the available PK data obtained from the single agent first-in-human study [CPDR001X2101], an exploratory population PK (PopPK) analysis showed that the T1/2 of PDR001 in man is 20 [17, 23] days (mean [90% CI]). Therefore the protocol will be amended by increasing the duration of contraception and safety follow-up periods post PDR001 treatment from 90 days to 150 days. These changes are related to an Urgent Safety Measure communicated on 08-June-2016 to all investigators.
- Additional minor corrections/clarifications were also made. The details are provided in the below section "Changes to the protocol".

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 underlined for insertions.

- Section 1.2.1.2 MBG453 Clinical experience
  - Encephalitis has been added as an irAE expected to be associated with all classes of checkpoint inhibitors.
- Section 1.2.2.2 PDR001 Clinical Experience
  - Updated the summary of CPDR001X2101 study.
- Section 2.2 Rationale for the study design:
  - Added a statement to include a separate Japanese dose escalation with MBG453 single agent.
  - Added statements of recruitment of Japanese patients in the other phases of the study.
  - Language update on signs of anti-tumor activity.
- Section 4.1 Description of study design

[redacted]

  - The description of the study design was updated in order to include a separate Japanese dose escalation with MBG453 single agent and to describe the participation of Japanese patients in the other phases of the study.
  - Updated to align with the new duration of contraception and safety follow-up periods post treatment from 90 days to 150 days.
  - Figure 4-1 was updated to include a separate Japanese dose escalation with MBG453 single agent.
  - Figure 4-2 was updated to align with the new duration of contraception and safety follow-up periods post treatment from 90 days to150 days.
- Section 5.2 Inclusion criteria
  - Updated 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 for Japanese patients.
  - Language update in order to allow for patients pre-treated with PD1/PD L1 to be enrolled in the phase I-Ib parts.
  - Language update on signs of anti-tumor activity.
  - Inclusion criterion 9: life expectancy > 12 weeks, has been removed.
- Section 5.3 Exclusion criteria
  - Minor clarification on hypersensitivity reactions.
  - Update on HBV/HCV/HIV patients exclusion criteria.
  - Minor clarification on post-menopausal criteria.
  - Addition of an exclusion criterion for patients with a history of drug-induced pneumonitis or current pneumonitis.
  - Clarification of indolent malignancies.
  - Updated to align with the new duration of contraception and safety follow-up periods post treatment from 90 days to 150 days.
- Section 6.2.3.2 Dose cohort modification
  - Included dose escalation guidelines for Japanese patients.
  - Minor clarification on RP2D/MTD identification conditions.
- Table 6-5 Management of toxicities defined as study treatment-related only
  - Clarified language on management of Bilirubin, and AST or ALT toxicities.
  - Clarified language for discontinuation due to grade 3 and 4 CRS toxicity.
  - Minor clarification on any neurological disorder.
- Section 6.3.2 Follow-up for toxities
  - Updated to align with the new duration of contraception and safety follow-up periods post treatment from 90 days to 150 days.
- Section 6.4.2 Permitted concomitant therapy requiring caution and/or action
  - Clarified that limited-field palliative radiotherapy to non-target lesion(s) may be allowed after documented discussion with Novartis.
- Table 7-1 Visit evaluation schedule

[redacted]

  - Added statement that for Japan only, patients enrolled in dose escalation are required to be hospitalized during cycle 1.
  - Updated collection time points of cytokine samples for safety.
  - Updated to align with the new duration of contraception and safety follow-up periods post treatment from 90 days to 150 days and to include the urine pregnancy test during and at the end of the safety follow-up period.
- Section 7.1.2 Treatment period
  - A statement was added that for Japan only, patients enrolled in dose escalation are required to be hospitalized during the DLT evaluation period.
  - Clarified criteria on continuation / discontinuation of treatment.
- Section 7.1.5
  - Updated to align with the new duration of contraception and safety follow-up periods post treatment from 90 days to 150 days.
- Section 7.2.2.5.6 Cytokine analysis
  - Removed a duplicate baseline time point.
- Table 7-4 Local/Central clinical laboratory parameters collection plan
  - Total T4 analysis replaced by Free T4.
- Section 7.2.2.5.8 Pregnancy and assessments of fertility
  - Updated to align with the new duration of contraception and safety follow-up periods post treatment from 90 days to 150 days and to include the urine pregnancy test during and at the end of the safety follow-up period.
- Table 7-5 12-lead ECG collection plan
  - Clarification in the ECG schedule.
- Table 7-6 Pharmacokinetic blood collection log for MBG453 single agent and MBG453 and PDR001 combination, [redacted] and IG (all patients)
  [redacted]
- Table 7-7 and Section 7.2.4.2 Biomarker sample collection plan (tumor/blood samples)
  - Updated table with a statement regarding the use of Cycle1 Day1 cytokine level pre-dose sample.
- Section 8.1.1 Definitions and reporting
  - Updated to align with the new duration of contraception and safety follow-up periods post treatment from 90 days to 150 days.
- Section 8.2.2 Reporting
  - Specified SAE reporting guidelines for Japan.
  - Updated to align with the new duration of contraception and safety follow-up periods post treatment from 90 days to 150 days.

[redacted]

- Section 10: Statistical Methods and data analysis
  - Updated to include data analysis rules throughout the section; statistical hypothesis; model; and method of analysis for the Japanese-specific single agent MBG453 dose escalation.
  - Section 10.4.2 Phase II part: corrected values of observed ORR less than 10%.
  - Section 10.4.2 Listing of DLT: DLT summary table may be provided.
  - Section 10.5.3 Safety objectives
  - Updated to align with the new duration of contraception and safety follow-up periods post treatment from 90 days to 150 days.
- Section 14: Appendices.
  - Added a new Section 14.3.2: "Phase I part MBG453 single agent with Japanese patients".
  - Section 14.3.3: Operating characteristics: remove irrelevant text and correct typo.
  - Section 14.4 (Appendix 4): Recommended management algorithms for suspected toxicities: Corrected inconsistency in the algorithm tables for management of AEs.

IRB/IEC/HA 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. 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 01 (19-Oct-2015)

Amendment rationale

This amendment addresses the following revisions requested by a regulatory authority:

- Clarification in protocol to require discontinuation of study drug for Grade 3 treatment-related cardiac adverse events and for grade 3 treatment-related neurological events.
- To include assessment of vital signs during infusion of study drug as well as after. In addition, include requirements to observe patients for 1-2 hours post infusion of study drug.
- Clarification of wording in protocol to provide additional details concerning dose escalation decision and number of patients to include in the first cohort.
- Additional minor corrections/clarifications were also made. The details are provided in the below section Changes to the protocol.

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 underlined for insertions.

- Section 6.1.1, Section 6.2.3.2 and Table 6-4: corrections as requested by regulatory authority.
- Section 6.5.1: minor correction in wording.
- Table 7-1: changes in Vital signs as per requested by regulatory authority and correction of an extra sample not needed.
- Section 7.2.2.2: corrections as requested by regulatory authority.
- Table 7-6: minor correction of a missing timepoint.
- Section 8.1.1 and Section 8.2.2: new language added for electronic SAE process.
- Section 8.3: clarification of follow up pregnancy for female of male participant.
- Section 14.2.1: minor clarification.

IRB/IEC/HA 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. 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]

1 Background

The ultimate goal of cancer immunotherapy is to break tumor-induced immunosuppression and activate a powerful immune response against cancer. Since the approval of ipilimumab, an anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibody for patients with advanced melanoma, the blockade of immune checkpoints has been considered a promising approach to fight cancer. Immune checkpoints refer to a variety of inhibitory pathways that are crucial for maintaining self-tolerance and modulating the duration and amplitude of physiological immune responses in peripheral tissues in order to minimize collateral tissue damage (Shin and Ribas 2015).

During tumorigenesis, cancer cells from a wide range of tumor types exploit immune checkpoint pathways, such as the programmed death-1 (PD-1) / programmed death-ligand 1 (PD-L1) pathway, to avoid detection by the adaptive immune system (Murphy 2011). Blockade of the PD-1 pathway leads to increased numbers of effector T cells through induction or expansion, and improved anti-tumor cytolytic activity. Additionally, PD-1 blockade is associated with accumulation of effector T cells and a reduced numbers of regulatory T cells (Tregs) at the tumor site (Wang 2009, Mangsbo 2010, Mkrtichyan 2011, Rosenblatt 2011).

Blockade of the PD-1 pathway has demonstrated clinically relevant durable responses in melanoma (Robert 2015, Weber 2015), leading to the Food and Drug Administration (FDA) approval of both pembrolizumab and nivolumab. The durable responses observed in lung cancer (Brahmer 2015, Garon 2015) led to the approval of nivolumab and a priority review for pembrolizumab in this indication.

In metastatic melanoma, the anti PD-1 antibody pembrolizumab induced durable responses in 30–35% patients (Hamid 2013). In advanced NSCLC, data from the ongoing Phase Ib KEYNOTE-001 study showed an overall response rate (ORR) of 19.4% with the median duration of response (DOR) of 12.5 months in an unselected population (Garon 2015).

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

Furthermore, durable responses have been observed among patients with Hodgkin's disease (Ansell 2015), breast cancer (Homet Moreno and Ribas 2015), RCC (Michel Ortega and Drabkin 2015, Sunshine 2015), and bladder cancers (Powles 2014) treated with anti-PD-1 or anti-PD-L1 antibody monotherapy, representing a new and promising treatment approach for patients with advanced cancer.Recurrence in Small Cell Lung Cancer (SCLC) after second line treatment is inevitable. There are limited options at the time of progression including institution of best supportive care. In the subgroup of 109 SCLC patients enrolled in the CheckMate-032 study in third or later-line treatment receiving nivolumab monotherapy, the ORR was 11.9% and the 6-month PFS rate was 17.2% (Ready et al 2018). It is, therefore, important to investigate new strategies that might improve the antitumor response in this disease after failure of standard of care.

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The blockade of other negative immune regulators, such as T-cell immunoglobulin domain and mucin domain-3 (TIM-3) and lymphocyte-activation gene-3 (LAG-3), has also shown promising preclinical activity alone and synergistic activity when combined with anti-PD-1/ PD-L1. Blockade of TIM-3 has shown anti-tumor efficacy (moderate effect alone, and additively or synergistically in combination with PD-1 pathway blockade) in several preclinical cancer models, including CT26 colon carcinoma (Sakuishi 2010) and WT3 sarcoma and TRAMP-C1 prostate carcinoma (Ngiow 2011). In all models tested, efficacy was improved relative to single agent treatment by combination of PD-1 and TIM-3 pathway blockade.

Despite the clinical results seen to date, the majority of patients still do not respond to anti- PD-1/anti-PD-L1 blockade. It is therefore important to investigate new strategies and assess whether the concurrent blockade of other inhibitory pathways (such as TIM-3 and PD-1) might improve the objective response rate to single agent anti-PD-1 or anti-PD-L1 therapy, provide more durable responses than single agent checkpoint inhibition, or re-induce response in patients who progressed on or after anti-PD-1 or anti-PD-L1 monotherapy.

1.1 Overview of disease pathogenesis, epidemiology and current treatment

1.1.1 TIM-3 overview

The transmembrane immunoglobulin and mucin domain (TIM) family are characterized by an N-terminal Immunoglublin (Ig) domain of the V subset, followed by a mucin-like domain, single transmembrane domain and a cytoplasmic tail of variable length. The human genome contains three TIM genes, which encode the proteins TIM-1, TIM-3 and TIM-4.

Studies published thus far have indicated that TIM-3 has a widespread and complex role in immune system regulation. TIM-3 was initially described as a co-inhibitory protein expressed on activated T helper 1 (Th1) $CD4^+$ and cytotoxic $CD8^+$ T cells that secrete interferon-gamma (IFN-γ). TIM-3 protein is not expressed by naïve T cells, and little TIM-3 can be detected after several rounds of antigenic stimulation in the presence of interleukin (IL)-4. In contrast, repetitive *in vitro* re-stimulation of murine T cells in the presence of Th1-polarizing conditions (IL-12 and anti-IL-4) leads to an abundance of Th1 cells expressing TIM-3 (Monney 2002, Sánchez-Fueyo 2003). TIM-3 is largely co-expressed on $PD\text{-}1^+$ exhausted T cells and co-blockade of these pathways restores effector T cell function (IFN-γ secretion, proliferation) in several models as well as human PBMCs derived from metastatic melanoma patients and patients with HIV or HCV (Jones 2008, Golden-Mason 2009, Fourcade 2010).

TIM-3 is also enriched on FoxP3+ Tregs, which correlate with disease severity in NSCLC, hepatocellular and ovarian carcinomas (Gao 2012, Yan 2013). Intratumoral PD-1+ TIM-3+ FoxP3+ Tregs are highly suppressive, and *in vivo* co-blockade of TIM-3 and PD-1 pathways downregulates molecules associated with TIM-3+ Treg suppressor functions (Sakuishi 2013). Interestingly, TIM-3+ Tregs, unlike CTLA-4+ Tregs, are predominantly localized to the tumor microenvironment rather than peripheral circulation (Sakuishi 2013).

TIM-3 is also constitutively expressed on dendritic cells (DCs), monocytes/macrophages, and natural killer (NK) cells (Anderson 2007, Ndhlovu 2012), and blockade of TIM-3 has been shown to correlate with increased cytotoxicity in NK cells (da Silva 2014), increased secretion

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of IL-12/tumor necrosis factor-alpha (TNF-α) by monocytes/macrophages (Zhang 2011) and increased nuclear factor 'kappa-light-chain-enhancer' of activated B-cells expression in DCs (Anderson 2007). High expression of TIM-3 has been detected in tumor-associated DCs (TADCs), in tumor-bearing mice as well as tumor samples from patients. Critically, tumor cells as well as tumor-derived immunoregulatory factors (such as IL-10 and vascular endothelial growth factor) promote TIM-3 expression on immature bone marrow-derived DCs, which suggests that immunosuppressive factors in the tumor microenvironment induce DCs to express TIM-3. TIM-3 has also been shown to contribute to expansion of myeloid-derived suppressor cells (MDSCs) through an unknown mechanism (Dardalhon 2010). Constitutive expression of TIM-3 on macrophages is associated with less IL-12 secretion, and downregulation of TIM-3 post- Toll-like receptor (TLR) activation leads to enhanced IL-12 and subsequent effector T cell responses (Zhang 2011, Zhang 2012).Blockade of TIM-3 on antigen cross-presenting dendritic cells enhances activation and inflammatory cytokine/chemokine production (Chiba et al 2012, de Mingo Pulido et al 2018), potentially ultimately leading to enhanced effector T cell responses.

TIM-3 was found to be expressed on leukemic stem cells (CD34+CD38- LSCs) as well as CD34 positive leukemic blasts in the majority of AML subtypes (M0-M2; M4-M7) (Kikushige et al 2010). Upregulation of TIM-3 is also associated with leukemic transformation of pre-leukemic disease, include myelodysplastic syndromes (MDSs) and myeloproliferative neoplasms (MPNs), such as chronic myelogenous leukemia (CML) (Kikushige et al 2015, Asayama et al 2017). Preclinical evidence in AML murine models also suggests that disease progression may be associated with increased PD-1 expression on CD8-positive T-cells, and treatment with anti-PD-1 or anti-PD-L1 antibodies decreased AML burden and improved survival (Zhang et al 2009). Dual blockade of PD-1 and TIM-3 significantly reduced AML burden and prolonged survival in mouse syngeneic model of AML (Zhou et al 2011).

TIM-3 ligand usage and intracellular signaling pathways remain unclear. There are four proposed ligands for TIM-3: S-type lectin galectin-9 has been described in murine models to inhibit TIM-3-associated Th1 effector function and induce apoptosis on TIM-3-expressing T cells (Zhu 2005); phosphatidylserine (PtdSer), which binds a preserved cleft in all three human TIM family members (TIM-1, 3, 4), though functional effects of engagement of TIM-3 are unknown (DeKruyff 2010); DNA alarmin HMGB1, for which TIM-3 has been proposed to act as a 'sink,' preventing the HMGB1/RAGE interactions that stimulate innate immunity (Chiba 2012); and most recently, the carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1), proposed to interact with TIM-3 both in *cis* as a heterodimer on T cells and in *trans* as a ligand (Huang 2015). Co-blockade of TIM-3 and CEACAM1 in CT26 colon carcinoma showed similar efficacy to that seen for co-blockade of PD-L1 and TIM-3. The intracellular signaling pathways engaged downstream of TIM-3 remain largely unknown.

TIM-3 has a critical role in tumor-induced immune suppression as it marks the most suppressed or dysfunctional populations of CD8+ T cells in animal models of solid and hematologic malignancies (Sakuishi 2010, Yang 2012, Zhou 2011). TIM-3 blockade in these animal models has successfully demonstrated similar anti-tumor activity compared to PD-1 pathway blockade (Ngiow 2011, Zhou 2011), with greater efficacy with the combined use of TIM-3 and PD-1 blockade (Sakuishi 2010, Ngiow 2011). Increasing data support the relevance of TIM-3 blockade in human cancer as TIM-3+ NY-ESO-1 specific CD8+ T cells in patients with

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melanoma showed dysfunctional phenotypes. TIM-3 blockade restored IFN-γ and TNF-α production as well as the proliferation of these cells in response to antigenic stimulation (Fourcade 2010).

TIM-3 has now emerged as an immune checkpoint receptor with its selective expression in tumor tissue as well as its critical role in multiple immune suppressive mechanisms, which strongly supports TIM-3 targeted immunotherapies as single or combined modalities.

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, NKT cells, CD4+ Tregs, and some DC 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, NSCLC, RCC, breast cancer, bladder cancer and head and neck squamous cell cancer (HNSCC) with an acceptable and manageable safety profile (Topalian 2012, Hamid 2013, Topalian 2014, Lyford-Pike 2013, Powles 2014, Ansell 2015, Homet Moreno and Ribas 2015, Michel Ortega and Drabkin 2015, Sunshine 2015).

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1.1.3 Hypomethylation overview

The incorporation of the hypomethylating agent decitabine in place of 5-methylcytosine in DNA results in the inactivation of DNA methyltransferase 1 due to covalent bond formation between the 5-azacytosine ring of decitabine and this enzyme. The end result of this process is hypomethylation of DNA. Genes that are silenced by aberrant DNA methylation can be reactivated by treatment with decitabine. Both leukemic and tumor cells are very sensitive to the antineoplastic action of low concentrations of decitabine. In animal models of leukemia and cancer, decitabine shows curative potential (Momparler 2005). A pilot study on intense dose decitabine showed promising results in patients with metastatic NSCLC (Montparler et al 1997, Montparler and Ayoub 2001). However, subsequent clinical studies using low dose decitabine were not very effective against NSCLC and interest in this therapy diminished. Recently, interesting responses were observed in a patient with NSCLC following treatment with a combination of the related inhibitor of DNA methylation, 5-azacytidine, and an inhibitor of histone deacetylation. This finding has generated a renewed interest in the epigenetic therapy of lung cancer (Schrump et al 2006, Lemaire et al 2008). The delayed and prolonged epigenetic action of the hypomethylating agent has been taken into consideration and decitabine is dosed before MBG453.

1.2 Introduction to investigational treatments

1.2.1 Overview of MBG453

MBG453 is a high-affinity, ligand-blocking, humanized anti-TIM-3 IgG4 antibody (stabilized hinge, S228P) which blocks the binding of TIM-3 to PtdSer. MBG453 is cynomolgus monkey cross-reactive and shows functional activity.

1.2.1.1 MBG453 Non-clinical experience

MBG453 binds specifically and with high affinity to human TIM-3. In Biacore assays, the K_D of MBG453 for human TIM-3 is 0.167±0.008 nM and in cell binding assays, MBG453 binds human TIM-3 expressing cells with an affinity of 0.5±0.1nM. MBG453 does not cross-react with rat or mouse TIM-3, and therefore cannot be evaluated in murine tumor models. It does cross-react with cynomolgus monkey TIM-3 (affinity of 0.9±0.1nM on cynomolgus TIM-3-expressing cells), making cynomolgus monkey a relevant species and the only species for toxicology studies.

In order to assess potential off target binding of MBG453, a good laboratory practice (GLP) tissue cross reactivity study using frozen human and cynomolgus monkey tissues was conducted. Due to the low level of staining in healthy monkey compared to human tissues, lung and colon tissue from a monkey in which several inflammatory foci were observed was also included to increase the population of (active) mononuclear cells. In human tissues, positive membranous/cytoplasmic staining with MBG453 was primarily observed in interstitial round and occasionally spindle cells; consistent with mononuclear inflammatory cells in most tissues; binding was also observed in tissues with resident monocyte-macrophage lineage cells and at low level in some renal tubular epithelial cells. In monkeys, staining was limited to placenta, cerebellum, pituitary gland and spinal cord and staining intensity was lower compared to human tissues staining. Stained cells were similar to cells described above in the human tissues

[redacted]

(mononuclear cells probably consistent with resident macrophages). Positive staining was not observed in the tissues (lung and colon that had mononuclear cell infiltrations) from the diseased monkey.

Safety was evaluated in a limited panel in a PK study that included single and repeat dose arms as well as a five week repeat dose GLP toxicology study, both in cynomolgus monkeys. In the PK study, animals were dosed either once at 10 mg/kg i.v. or twice at 100 mg/kg i.v. one week apart. Clinical observations, clinical chemistry, and hematology endpoints were evaluated as part of an in-life assessment of safety in this study. There was no toxicity related to MBG453 administration and exposure to MBG453 was confirmed. The only effects noted were transient decreases in counts of CD4+ and CD8+ T cells, and monocytes with lowest levels observed 2 days after the second dose of 100 mg/kg. The biological significance of this is unclear.

In the five week GLP toxicology study, MBG453 was administered to monkeys weekly i.v. at 6, 25, and 100 mg/kg. There was no test article-related toxicity observed at any dose. In females only there were greater CD4+CD25+, CD8+CD25+ and CD8+CD25+FoxP3+T cell counts per gram weight at all MBG453 doses. Dose proportionality was observed for all three doses, with immunogenicity impacting all 6 mg/kg/week animals in week 5. The Highest Non-Severely Toxic Dose (HNSTD) was 100 mg/kg weekly i.v. MBG453 has a favorable safety profile in monkeys that supports the proposed human starting dose of 1 mg/kg.

For details please refer to [MBG453 Investigator's Brochure].

1.2.1.2 MBG453 Clinical experience

This is the FIH study with MBG453. Based on the clinical experience with the PD-1 blocking mAbs pembrolizumab and nivolumab, all classes of checkpoint inhibitors including MBG453 therapy are expected to be associated with immune-related adverse events (irAEs), including skin reactions, endocrinopathies (hypothyroidism, hyperthyroidism, diabetes, hypophysitis, and hypopituitarism), pneumonitis, colitis, hepatitis, encephalitis and nephritis (pembrolizumab US label, nivolumab US label).

As of 25-Jul-2019 in the current study, 133 patients have been treated with MBG453 single agent on a Q2W or Q4W regimen. No Dose Limiting Toxicities (DLTs) were reported for any patients treated with MBG453 as a single agent. The RP2D has been declared for MBG453 single agent at 800mg Q4W.

Of the 133 patients treated with MBG453 single agent on a Q2W or Q4W regimen, 125 patients (94%) experienced AEs of any grade, regardless of relationship to study drug, with the most frequent AEs (>10%) being fatigue (39 patients, 29%), nausea (34 patients, 26%), anemia (29 patients, 22%), constipation (26 patients, 20%), decreased appetite (23 patients, 17%), dyspnea (21 patients, 16%) abdominal pain (19 patients, 14%), vomiting (18 patients, 14%), diarrhea (17 patients, 13%) cough and pyrexia (16 patients each, 12%) and edema peripheral (14 patients, 11%).

For further details, refer to the most recent edition of the [MBG453 IB].

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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].

1.2.2.1 PDR001 Non-clinical experience

PDR001 binds specifically and with high affinity to human PD-1. In Biacore assays, the K_D of PDR001 on human PD-1 is 0.83 nM. 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.

[redacted]

Dose-dependent exposure to PDR001 in each dose group was confirmed. A pharmacodynamic *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 HNSTD dose in this study was 100 mg/kg.

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

1.2.2.2 PDR001 Clinical experience

PDR001 is being tested in a FIH, multi-center, open-label study [CPDR001X2101] starting with a phase I dose escalation part, followed by a phase II part. The study has completed enrolment. The dose escalation part of the study evaluated dose levels of 1, 3 and 10 mg/kg Q2W and 3 and 5 mg/kg Q4W. No subject experienced a dose limiting toxicity (DLT). The PK analysis of the dose escalation data using a population approach and the expected wide therapeutic index of PD-1 inhibitors support the use of flat dosing for PDR001 of 400 mg Q4W or 300 mg Q3W. The expected PDR001 Ctrough concentrations using either dosing regimen exceed the EC50 for PD-1 blockade by approximately 75-fold in an ex vivo assay in peripheral blood mononuclear cells (PBMCs). Based on the available PK and safety data, the RP2D of PDR001 has been declared as 400 mg i.v. Q4W or 300 mg i.v. Q3W for combination treatment regimens for which this may be more convenient.

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

Based on the preliminary data, PDR001 was well tolerated with a safety profile similar to those of other marketed anti-PD-1 antibodies. For additional information, please refer to the [PDR001 Investigator's Brochure].

1.2.3 Overview of decitabine

Decitabine (5-aza-2'-deoxycytidine) is a cytidine deoxynucleoside analogue that selectively inhibits DNA methyltransferases at low doses, resulting in gene promoter hypomethylation that can result in reactivation of tumor suppressor genes, induction of cellular differentiation or cellular senescence followed by programmed cell death. Decitabine is commercially available and indicated for the treatment of adult patients aged 65 years and above with newly diagnosed de novo or secondary AML, according to the WHO classification, who are not candidates for standard induction chemotherapy. Decitabine is also indicated for treatment of patients with MDS including previously treated and untreated, de novo and secondary MDS of all French-American-British subtypes and intermediate-1, intermediate-2, and high-risk iPSS groups in the U.S.

[redacted]

1.2.3.1 Clinical experience with decitabine

There is limited clinical experience with decitabine treatment in solid tumors.The use of decitabine (20 mg/m^2 daily for 5 days) has been evaluated in several studies, including an open-label, randomized, multicenter Phase III study (DACO- 016) in patients with newly diagnosed *de novo* or secondary AML according to the WHO classification. The most common adverse drug reactions reported during treatment with decitabine are neutropenia, thrombocytopenia and anemia. Neutropenia of any grade occurred in 90% of decitabine-treated patients with grade 3 or 4 occurring in 87% of patients. Thrombocytopenia of any grade occurred in 89% of patients with grade 3 or 4 occurring in 85% of patients. Grade 3 or 4 febrile neutropenia occurred in 23% of patients. Anemia of any grade occurred in 82% of patients (decitabine country-specific label). Other commonly occuring Grade 3/4 adverse drug reactions (≥20%) included pneumonia (21%), (Kantarjian et al 2012).

Decitabine exhibits linear PK, and following intravenous infusion, steady-state concentrations are reached within 0.5 hour post-infusion. The systemic half life is short (20 minutes) and there was no accumulation observed with this dosing regimen. Plasma protein binding of decitabine is negligible (< 1%).

For further details refer to the decitabine product insert and prescribing information.

1.2.4 Overview of MBG453, PDR001 and decitabine

1.2.4.1 Non-clinical experience with the combination of MBG453 and PDR001

The rationale for combining MBG453 with PDR001 is based on scientific evidence in preclinical models. Several reports have shown that the cancer-induced inhibitory modulation of T-cell activation is synergistically promoted by the concurrent blockade of TIM-3 and PD-1 (Sakuishi 2010, Ngiow 2011). Furthermore, blockade of TIM-3 not only restores T cell function, but also blocks inhibitory signals mediated by TIM-3+ FoxP3 regulatory T cells (Sakuishi 2013) and may also alleviate inhibitory signals from innate cells in the tumor microenvironment (Zhang 2011, Zhang 2012).

In preclinical models of colon carcinoma (CT26 and MC38) and the poorly immunogenic B16F10 melanoma model, TIM-3 blockade alone exhibits similar efficacy to PD-1 pathway blockade (Ngiow 2011). However, the combination of TIM-3 blockade with PD-1 pathway blockade is markedly more effective than either TIM-3 or PD-1 blockade alone (Anderson 2015, Ngiow 2011).

Internal data support the combination efficacy seen in the published models described above. Co-blockade of the PD-1/PD-L1 axis and TIM-3 in murine colon tumor models demonstrated partial anti-tumor activity. In the CT26 tumor model in BALB/cJ mice, co-blockade of PD-L1 with 10F.9G2, a rat anti-mouse IgG2b and TIM-3, with either RMT3-23 (a rat anti-mouse IgG2a), 2C12 (a rat anti-mouse isotype, rat IgG1) or 5D12 (a mouse anti-mouse isotype, IgG1), resulted in partial tumor growth delay. In the related COLON26 model, co-blockade of PD-1, with the rat anti-mouse IgG2a RMP1-14, and TIM-3, with either 5D12 or RMT3-23, resulted in partial tumor growth delay. Notably, 5 of 10 and 2 of 10 animals in each treatment group had durable complete regressions when treated with RMP1-14 and 5D12 or RMP1-14 and RMT3-23, respectively.

[redacted]

Moreover, TIM-3/PD-1 pathway co-blockade also drives the downmodulation of several genes associated with potent suppressor function such as Tregs, MDSC and TADC (reviewed in Anderson 2014). Thus, TIM-3 /PD-1 co-blockade abrogates two major mechanisms of immune suppression in tumor tissue, restoring function to dysfunctional CD8+ T cells and deprogramming potent intratumoral Tregs, TADC and MDSC.

TIM-3 deficient mice do not develop overt autoimmunity, suggesting that TIM-3 plays a more subtle role in modulating T cell function than either CTLA-4 or PD-1 (Sánchez-Fueyo 2003, Sabatos 2003).

1.2.4.2 Clinical experience with the combination of MBG453 and PDR001

As of 25-Jul-2019 in this FIH study, 119 patients have been treated with MBG453 in combination with PDR001 on a Q2W or Q4W regimen. One DLT (myasthenia gravis grade 4) was reported for a patient (metastatic thymoma) treated at 240mg MBG453 Q4W and 80mg PDR001 Q4W. The RP2D has been declared for MBG453 at 800mg Q4W in combination with PDR001 at 400mg Q4W

Of the 119 patients treated with MBG453 in combination with PDR001, 115 patients (97%) experienced AEs of any grade, regardless of relationship to study drug, with the most frequent AEs (>10%) being fatigue (33 patients, 28%), anemia (25 patients, 21%), cough (23 patients, 19%), constipation, nausea (22 patients each, 19%), abdominal pain pyrexia, dyspnea (19 patients each, 16%), diarrhea, back pain (18 patients each, 15%), decreased appetite (17 patients, 14%), vomiting (15 patients, 13%), pruritus (13 patients, 11%) aspartate aminotransferase increased (12 patients, 10%).For further details refer to the most recent edition of the [MBG453 IB]

1.2.4.3 Non-clinical experience with MBG453 in combination with decitabine

Decitabine has been shown to enhance the expression of type I interferon in murine cancer models (Stone et al 2017) and in a mouse model of colon carcinoma decitabine treatment enhanced both the activation status of immune cells at the tumor and combined with anti-PD-1 therapy enhanced the anti-tumor immune response (Yu et al 2018). The combination of MBG453 and decitabine was tested in two AML patient-derived xenograft models in immune deficient hosts where it was well-tolerated as measured both by body weight change monitoring and visual inspection of health status. While decitabine demonstrated efficacy to varying degrees in the two models, the addition of MBG453 did not enhance activity, likely due to the lack of immune cells, including key TIM-3-expressing T cells, NK cells, and myeloid cells. As MBG453 is not rodent cross-reactive, studies will be undertaken with murine surrogate antibodies in an immuno-competent setting (or with a human TIM-3-overexpressing murine AML line) to evaluate the role of the immune system in potential anti-TIM-3 activity in AML models.

1.2.4.4 Clinical experience with MBG453 in combination with decitabine and MBG453 in combination with decitabine and PDR001

MBG453 is being evaluated in CPDR001X2105, an ongoing phase Ib, multi-arm, open-label study of PDR001 and/or MBG453 in combination with/without decitabine in patients with acute myeloid leukemia (AML) or high risk myelodysplastic syndrome (MDS).

[redacted]

As of 26-Jul-2019, 157 patients with AML de novo, AML-Relapsed/Refractory or high risk MDS have been treated in the MBG453 single agent arm and in the combination arms (MBG453 in combination with decitabine (n=85), MBG453 in combination with PDR001 (n=11), MBG453 in combination with decitabine and PDR001 (n=19) and MBG453 in combination with Azacitidine (n=16)).

Four patients experienced DLTs during the first 2 cycles which included Grade 3 hepatitis (MBG453 in combination with decitabine), Grade 3 tubulointerstitial nephritis (MBG453 in combination with decitabine and PDR001), Grade 3 encephalitis (MBG453 in combination with PDR001) and Grade 2 uveitis (MBG453 in combination with decitabine and PDR001).

For further details refer to the most recent edition of the [MBG453 IB].

1.2.4.5 Potential drug interaction

Immunomodulators, such as MBG453 and PDR001, may regulate CYP enzymes and may cause DDI with small molecule drugs because of the potential to alter CYP mediated metabolism. However, Cytochrome P450 mediated degradation is minor for decitabine and DDI between PDR001, MBG453 and decitabine is not expected. When MBG453 was administered in combination with decitabine in Study CPDR001X2105, decitabine PK was similar to the decitabine country-specific label reported value.

For further details refer to the most recent edition of the [MBG453 IB].

2 Rationale

Any reference to MBG453 in combination with decitabine is not applicable in this study as the enrolment of SCLC patients in this treatment will not open.

2.1 Study rationale and purpose

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. Different checkpoint inhibitors, by signaling via distinct pathways, have demonstrated enhanced activity in combination. The combination of ipilimumab and nivolumab in melanoma has shown an increased objective response rate compared to the monotherapy of either agents (Postow 2015, Larkin 2015).

TIM-3 is a distinct co-inhibitory receptor which cooperates with PD-1 to dampen immune responses. The remarkable synergy of TIM-3/PD-1 pathway co-blockade in controlling tumor growth in experimental models of cancer could reflect the combined effects on modulating not only the functional phenotype of dysfunctional CD8+ effector T cells, but also inhibiting the suppressive activity of Tregs and deprogramming of other suppressor cells such as MDSC and TADC (Anderson 2014).

[redacted]

Taken together, these data suggest that TIM-3 blockade or the combined inhibition of TIM-3 and PD-1 in the clinic may have significant anti-tumor efficacy.

PD-1 blockade has proven clinical efficacy in various disease settings, such as melanoma, NSCLC and RCC. These indications also express high levels of TIM-3 and thus are ideally placed to test the anti-PD-1/anti-TIM-3 combination.

MBG453 in combination with decitabine

Hypomethylating agents have been shown to alter the immune microenvironment in both solid tumors and hematological malignancies. HMAs have been shown to: (1) increase the expression of killer-cell immunoglobulin-like receptors (KIR) and in some instances, the activity of NK cells, which may play a role in anti-tumor immunity; (2) increase the expression of major histocompatibility complex (MHC) class I on tumor cells; (3) increase expression of endogenous retroviral elements (ERVs); and (4) increase the expression of checkpoint proteins, including PD-1, PD-L1 and Cytotoxic T-Lymphocyte-Associated protein 4 (CTLA-4) (Sohlberg et al 2015, Yang et al 2014, Orskov et al 2015, Fazio et al 2018; reviewed in Lindblad et al 2017).

Decitabine can enhance the expression of type I interferon in murine cancer models (Stone et al 2017). Decitabine treatment in a mouse model of colon carcinoma enhanced both the activation of immune cells at the tumor and combined with anti-PD-1 therapy to enhance the anti-tumor immune response (Yu et al 2018). De novo DNA methylation promoted T-cell exhaustion and limited the efficacy of anti–PD-1 immunotherapy, whereas inhibition of methylation enhanced PD-1 blockade–mediated T-cell activity. (Ghoneim et al 2017, Pauken et al 2016).

In an open-label phase Ia/Ib study of LY3321367 a monoclonal antibody against TIM-3, 23 patients with histologically confirmed advanced relapsed/refractory solid tumors were treated with LY3321367 single agent including 2 patients with SCLC. Both patients experienced > 20% tumor regression, one of which was later confirmed as a RECIST v1.1 partial response (PR) (Harding et al 2019).

In this MBG453X2101 study, three SCLC patients were treated with MBG453 in combination with PDR001. One patient experienced stable disease (SD) and one patient experienced PR. Six SCLC patients were treated with MBG453 single agent, 2 patients experienced SD, including one ongoing for 2 years.

Taken together, these data suggest the combination of an immune modulatory agent that stimulates a cytotoxic immune response such as decitabine with the antiTIM-3 agent MBG453 is a rationale therapeutic approach to test in SCLC.

[redacted]

2.2 Rationale for the study design

This is an open-label, phase I-Ib/II study of parallel cohorts with single agent MBG453 or the combination of MBG453 and PDR001. The study consists of the following parts:

- Phase I-Ib ROW:

  A phase I dose escalation part with MBG453 as single agent in advanced solid tumors.

  A phase Ib dose escalation part with MBG453 in combination with PDR001 in advanced solid tumors. This part of the study will start after at least two cohorts of MBG453 as single agent have been completed and dose is assessed safe and tolerable.
- Phase II ROW:

  Should signs of anti-tumor activity [defined as either complete response (CR), partial response (PR) or durable stable disease (SD) with tumor shrinkage that does not qualify for PR] be detected in the phase I dose escalation part, a phase II part will open to evaluate clinical efficacy of MG453 as single agent.
- A phase II part to evaluate clinical efficacy of MBG453 in combination with PDR001 at the MTD or RP2D (if that is lower than MTD) in the selected study disease indications, as shown in Figure 4-1 will be opened. Dose ranging part (optional, ROW):

  Should signs of anti-tumor activity (defined as either CR, PR or durable SD with tumor shrinkage that does not qualify for PR) be detected in the phase I-Ib dose escalation parts, a dose ranging part will be opened, in which different dose levels of MBG453 as single agent and/or in combination with PDR001 will be also be evaluated.
- Phase I-Ib / II in Japanese patients:

  This is a separate phase I dose escalation part with MBG453 as single agent in Japanese patients with advanced solid tumors. The purpose of the Japanese dose escalation is to ensure that the safety and pharmacokinetic profiles of single-agent MBG453 are adequately characterized in Japanese patients at more than one MBG453 dose.

  If the recommended dose of single agent MBG453 is the same in Japanese patients and patients from the rest of the world, then Japanese patients may be enrolled in the Phase II single-agent part of the study.

  In addition, if the recommended dose of PDR001 for Japanese patients in the single agent study ([PDR001X1101]) currently ongoing in Japan is the same as that determined in the single agent ROW study ([PDR001X2101]), Japanese patients may also enter the combination parts of the current MBG453 study at whichever dose is being tested at that time.

  If any of the Japanese single agents (PDR001 and/or MBG453) RP2D and/or MTD is different than the ROW, a new clinical development plan will be required to investigate the combination treatment in Japanese patients.

Combination of MBG453 and decitabine

A safety run-in testing the combination of MBG453 with decitabine will be conducted in anti PD-1/PD-L1 therapy naïve SCLC patients.

Following the safety run-in, additional patients will be enrolled in a phase II part to further evaluate the clinical efficacy.

[redacted]

Patients will be given the option to add PDR001 (i.v Q4W) to the MBG453 and decitabine combination after confirmed disease progression per irRC. The first iv Q4W dose of PDR001 may be given at the next scheduled cycle on day 8 of MBG453 administration, after documented discussion with the Novartis medical monitor.

Objectives and related endpoints apply to all patients enrolled and treated unless otherwise stated.

The objective for the phase I-Ib dose escalation parts will be to determine the MTD and/or RP2D of MBG453 as single agent and in combination with PDR001 or decitabine.

The objectives for the phase I-Ib dose ranging part will be to further define safety and tolerability of MBG453 as single agent, or in combination with PDR001 or decitabine.

The objectives for the phase II part of the study, either with MBG453 as single agent or in combination with PDR001 will be:

- To assess if MBG453 as single agent or in combination with PDR001 is efficacious in indications with high expression levels of both TIM-3 and PD-L1.
- To compare with published data - assess if MBG453 as single agent or in combination with PDR001 is more efficacious than anti PD-1/PD-L1 alone in these indications.
- To assess if MBG453 as single agent or in combination with PDR001 is efficacious in patients who progressed on or after anti-PD-1/PD-L1 as single-agent.
- To make an initial comparison of safety, PK, and efficacy between Q2W and Q4W dosing schedules of MBG453 in combination with PDR001 in one tumor disease indication.

The MTDs/RP2Ds (as single agent and in combination) will be determined from the collective experience in the clinic considering the safety data, pharmacokinetic data, pharmacodynamic data and any early anti-tumor activity observed along with the statistical inference from the Bayesian Hierarchical Logistic Regression Model (BHLRM) in the phase I single agent dose escalation part, and from the Bayesian Logistic Regression Model (BLRM) in the combination dose escalation part. The BHLRM is a hierarchical adaptation of the BLRM.

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 1998, Neuenschwander 2008, Neuenschwander 2010), and its development and appropriate use is one aspect of the FDA's Critical Path Initiative.

In the Phase II part of the study, an estimation approach will be used for patients treated on the single agent and MBG453 in combination with PDR001 for patients in Group 1, 3 and 6 and MBG453 in combination with decitabine (Figure 4-1). A Bayesian design will be used in order to estimate the true ORR for MBG453 in combination with PDR001 for patients in Group 2, 4 and 5, as well as for MBG453 in combination with decitabine. In one group, to be selected based on feasibility of enrollment, an initial comparison of the safety, PK, and efficacy of Q2W and Q4W dosing schedules will be made. Patients within these groups will have their activity monitored and in addition to continue evaluation of safety.

[redacted]

Because TIM-3 plays a more subtle role in modulating T cell function than either CTLA-4 or PD-1 (Sánchez-Fueyo 2003, Sabatos 2003), it is not expected that MBG453 would have a relevant anti-tumor activity as single agent in the clinic. Therefore, a group of patients will be treated with MBG453, if evidence of anti-tumor activity is detected in the dose escalation Phase I part.

2.3 Rationale for dose and regimen selection

The starting dose of MBG453 in the clinical setting was determined from toxicology studies as well as observed toxicity and efficacy from agents in the clinic with the similar mechanism of action of checkpoint inhibition (e.g. CTLA-4 and PD-1 inhibitors). The HNSTD dose from the cynomolgus monkey for MBG453 was 100 mg/kg. As MBG453 will be administered i.v., and it is generally accepted that antibody therapeutics allometrically scale according to body weight, the human equivalent dose (HED) of the HNSTD is 100 mg/kg. Based on the ICH S9 guidance, a factor of six can be used to determine the maximum allowable starting dose, with an estimated maximum starting dose of 17 mg/kg administered weekly. MBG453 has a K_D for human at approximately 0.5, while cyno K_D is 0.9. There is a 44% difference in affinity between cyno and human, and so therefore the starting dose based on S9 guidance and the additional affinity difference was used to calculate a starting dose of 7.6 mg/kg. MBG453 will be administered via intravenous (i.v) infusion every 2 weeks, consistent with a schedule commonly used for humanized monoclonal antibodies with an expected half-life of approximately 10-20 days. Based on the pharmacologically active doses of 2-10 mg/kg in the clinic with agents having a similar mechanism of action (checkpoint inhibitors, CTLA-4 and PD-1 inhibitors, (Topalian 2014, Wolchok 2013, Robert 2014) and with the intent to fully characterize the safety, pharmacokinetics, pharmacodynamics and preliminary efficacy at multiple dose levels, the starting dose of MBG453 is planned 1 mg/kg (80 mg) every 2 weeks. Starting with flat dose of 80 mg that equals approximately 1 mg/kg is not expected to overdose patients above the exposure observed in monkeys at the achieved HNSTD dose of 100 mg/kg or the estimated maximum starting dose of 7.6 mg/kg (600 mg).

For the dose escalation in combination part, the starting dose of PDR001 will be one dose level below the RP2D determined in the [CPDR001X2101] study, and the starting dose for MBG453 will be at a dose level below the last dose tested in the single agent dose escalation and shown to satisfy the EWOC criterion. Planned starting dose is provisionally (20 mg for MBG453 and 80 mg for PDR001, with both drugs administered i.v. once every 2 weeks. The starting doses of MBG453 and PDR001 in the combination will be at least 3 fold lower than the doses that at time of start of the combination part of the study have been tested for either of the molecules as single agents. In addition, the doses will be more than 10-fold lower than the suggested starting dose level by the highest non severely toxic dose level.Decitabine has been explored in combination with MBG453 (up to 400mg Q2W and 800mg Q4W respectively) or MBG453 (up to 400mg Q2W) with PDR001 (400mg Q4W) in the CPDR001X2105 study (Section 1.2.4.4 and MBG453 IB). For the phase Ib safety run-in part of this study, decitabine will be administered at a dose of 20mg/m^2 by i.v. infusion over a period of 1hr on days 1-5 Q4W, as per the decitabine country-specific label.

[redacted]

In conclusion, patients will receive decitabine as per country-specific approved label (20mg/m^2 daily for 5 days), followed by MBG453 at the RP2D (800 mg Q4W) on day 8, until confirmed disease progression per irRC or patient experiences unacceptable toxicity, and/or treatment is discontinued at the discretion of the Investigator or the patient. At the time of disease progression, patients may continue with the combination therapy with the addition of PDR001 at the RP2D (400 mg Q4W) on day 8 of the next cycle (Section 6.2.2)

[redacted]

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below and apply to all patients enrolled and treated unless otherwise stated.

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4
Phase I-Ib parts: To characterize the safety and tolerability of MBG453 as a single agent in ROW and Japanese patients separately and in combination with PDR001 and to identify recommended doses for future studies. To characterize safety and tolerability of MBG453 in combination with decitabine and identify recommended dose for future studies.	• Safety: Incidence and severity of AEs and SAEs, including changes in laboratory parameters, vital signs and ECGs • Tolerability: Dose interruptions, reductions and dose intensity • The incidence of DLTs during the first cycle of treatment with single agent MBG453 • The incidence of DLTs during the first and second cycle of treatment with MBG453 in combination with PDR001 • The incidence of DLTs during the first cycle of treatment with MBG453 in combination with decitabine	
Phase I-Ib dose ranging part: To further investigate the safety and tolerability of different doses of MBG453 as single agent or in combination with PDR001	• Safety: Incidence and severity of AEs and SAEs, including changes in laboratory parameters, vital signs and ECGs • Tolerability: Dose interruptions, reductions and dose intensity	
Phase II part: To estimate the anti-tumor activity of MBG453 as single agent and in combination with PDR001 or in combination with decitabine	Overall response rate (ORR) per RECIST v1.1	

[redacted]

Objective	Endpoint	Analysis
Secondary		Refer to Section 10.5
Phase I-Ib/II parts: To evaluate the preliminary anti-tumor activity of MBG453 as single agent,in combination with PDR001 or in combination with decitabine	Best Overall Response (BOR), Progressive Free Survival (PFS) and Duration of Response (DOR) per RECIST v1.1; ORR and PFS per irRC	
Phase II part (combination): To make an initial comparison for MBG453 and PDR001 administered in combination on a Q2W and Q4W dosing schedules.	• Safety: Incidence and severity of AEs and SAEs, including changes in laboratory parameters, vital signs and ECGs • Tolerability: Dose interruptions, reductions and dose intensity • Serum PK parameters (e.g., AUC, Cmax, Tmax, half-life); Serum concentration vs. time profiles • ORR, BOR, PFS and DOR per RECIST v1.1; ORR and PFS per irRC	
Phase I-Ib/II parts: To characterize the pharmacokinetic profile of MBG453 as single agent, in combination with PDR001 or in combination with decitabine	Serum PK parameters (e.g., AUC, Cmax, Tmax, half-life); Serum concentration vs. time profiles	
Phase I-Ib/II parts: To assess emergence of anti-MBG453 and anti-PDR001 antibodies following one or more i.v. infusions of MBG453 single agent, in combination with PDR001 or in combination with decitabine	Presence and/or concentration of anti-MBG453 and anti-PDR001 antibodies	
Phase I-Ib/II parts: To assess potential predictors of efficacy of MBG453 as single agent, in combination with PDR001 or in combination with decitabine in tumor samples	Assess potential associations between expression of PD-L1 and other immunological markers such as, but not restricted to TIM-3, CD8, FoxP3 and anti-tumor activity	
Phase I-Ib/II parts: To assess the pharmacodynamic effect of MBG453 as single agent, in combination with PDR001 or in combination with decitabine in tumor samples	Tumor Infiltrating Lymphocytes (TIL) counts	
Phase I-Ib/II parts: To describe the survival distribution of patients treated with MBG453 as single agent, in combination with PDR001 or in combination with decitabine for each disease group	Overall survival (OS)	

[redacted]

[redacted]

[redacted]

4 Study design

4.1 Description of study design

This study is a FIH, open-label, phase I-Ib/II, multi-center study which consists of a phase I dose escalation part of MBG453 as single agent, and a phase Ib dose escalation part of MBG453 in combination with PDR001 that will commence after two cohorts in the dose escalation with single agent have been completed. Once the MTD/RP2D of MBG453 as single agent and/or in combination with PDR001 is achieved, a dose ranging part and a phase II part will commence.

MBG453 and PDR001 will be administered i.v. Q2W or Q4Wuntil a patient experiences unacceptable toxicity, progressive disease as per irRC and/or treatment is discontinued at the discretion of the Investigator or the patient. Patients should not discontinue treatment based on progressive disease per RECIST v1.1 unless clinical deterioration or increase in tumor markers is observed. The study design is summarized in Figure 4-1.

MBG453 in combination with decitabine (this study arm is applicable potentially to Italy, South Korea, Netherlands, Switzerland and United States)*

A phase Ib safety run- in /phase II part will be conducted in approximately 15 anti-PD-1/PD-L1 therapy naïve SCLC patients treated with MBG453 in combination with decitabine.

The phase Ib safety run-in part will be conducted in 6 evaluable patients for the Dose Determining analysis Set (Section 10.1.4) to evaluate DLTs, AEs and available PK, PD, and preliminary efficacy. In the event that the administered dose levels are considered toxic (≥2 DLTs out of 6 patients (Section 6.2.3.2)), an additional 6 evaluable patients will be accrued to a lower dose level of decitabine for the Dose Determining analysis Set. The data from the safety run-in will be reviewed by Novartis study personnel and Investigators and approximately 9 additional patients may be recruited in the phase II part of the study.

The combination of MBG453 and decitabine will be administered until a patient experiences unacceptable toxicity, progressive disease as per irRC and/or treatment is discontinued at the discretion of the Investigator or the patient.

Patients will be given the option to add PDR001 to the combination of MBG453 and decitabine after confirmed disease progression per irRC. The first i.v Q4W dose of PDR001 may be given at the next scheduled cycle on day 8 of MBG453 administration after documented discussion with Novartis medical monitor.Treatment will be as follows:

- Decitabine will be administered i.v. on days 1-5 of each Q4W cycle at the dose of 20mg/m2 each day.
- MBG453 will be administered i.v on day 8 of each Q4W cycle at the dose of 800mg.
- PDR001 may be administered i.v on day 8 of each Q4W cycle at the dose of 400mg after confirmed disease progression per irRC.

* Note: as of Protocol Amendment 6, this part will not open.

[redacted]

Japanese specific study design:

A separate dose escalation will be performed in Japan in order to ensure that the safety and pharmacokinetic profiles of single-agent MBG453 are adequately characterized in Japanese patients. The proposed starting dose for single-agent MBG453 in Japanese patients is 80mg Q2W. Dose escalation decisions will be guided by a BHLRM. After the first cohort Japanese patients may be treated in parallel with two different dosing regimens (Q2W and Q4W). Dose escalation decisions will be guided by a BHLRM. If the recommended dose of single agent MBG453 in Japanese patients is the same as in ROW patients, then patients enrolled in Japan may be recruited into the Phase II single-agent part of the study.

In addition, if the recommended dose of PDR001 for Japanese patients in the single agent study ([PDR001X1101]) currently ongoing in Japan is the same as that determined in the single agent ROW study ([PDR001X2101]), Japanese patients may also enter the combination parts of the current MBG453 study at whichever dose is being tested at that time.

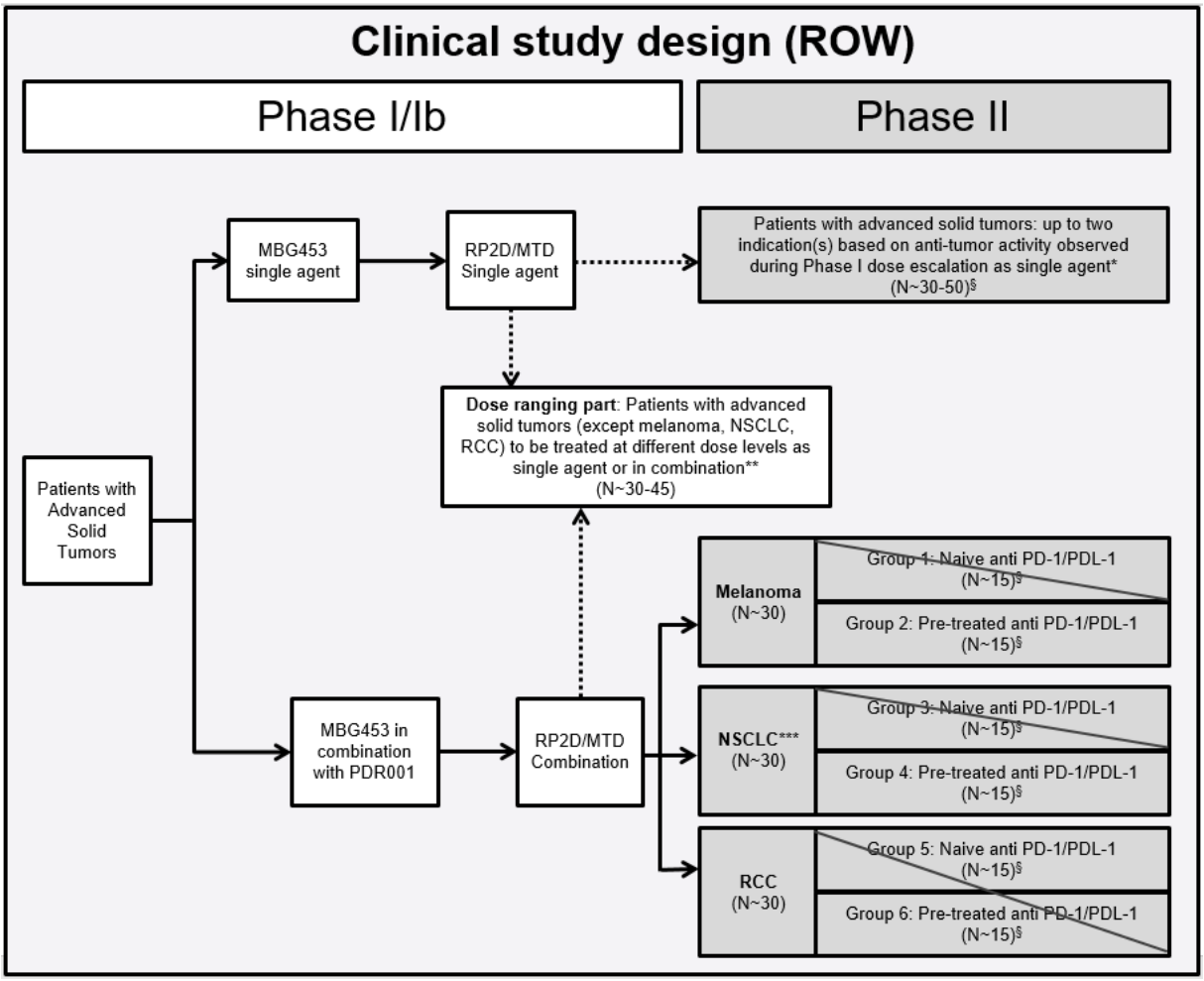
If any of the Japanese single agents (PDR001 and/or MBG453) RP2D and/or MTD is different than the ROW a new clinical development plan will be required to investigate the combination treatment in Japanese patients.

If Japanese patients have enrolled in the combination part and if during review of safety data (either in a Dose Escalation Meeting for Phase Ib or during a regular safety review for Phase II) Novartis and the enrolling Investigators consider the safety profile of Japanese patients treated in the current combination dose to be potentially worse than that of patients treated in the ROW, an additional 3 to 6 Japanese patients may be recruited in the Phase Ib part to a lower dose combination (previously studied in dose escalation) to further characterize the safety and tolerability of the combination in patients enrolled in Japan.

If after review of the safety data at the lower dose level, Novartis and the enrolling Investigators consider that re-escalation to a higher combination dose level is acceptable, Japanese patients may be treated at the same dose as ROW patients. If re-escalation is not acceptable, any additional Japanese patients recruited to the combination dose escalation will be treated at the lower dose. The combination dose escalation in the ROW may continue as planned.

[redacted]

Figure 4-1 Study Design



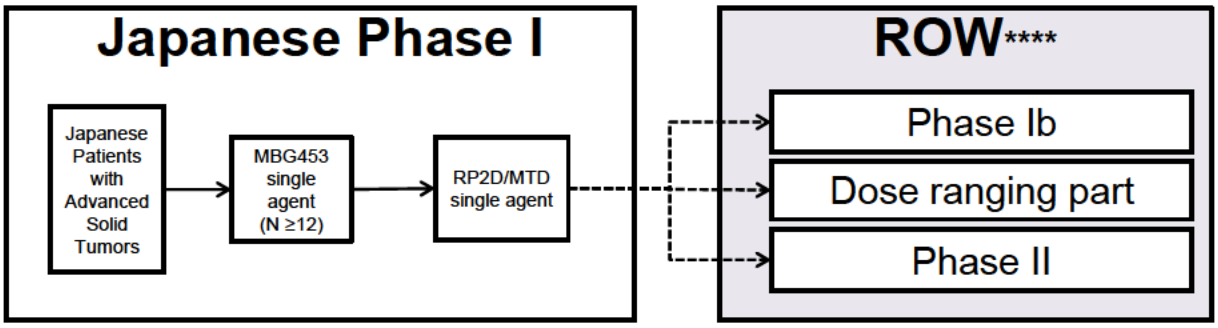
*This part will only be opened in relevant indications in the event that signs of anti-tumor activity (defined as either CR, PR or durable SD with tumor shrinkage that does not qualify for PR) to be observed in the phase I dose escalation part with MBG453 as single agent,

**Dose ranging part: Should signs of anti-tumor activity (defined as either CR, PR or durable SD with tumor shrinkage that does not qualify for PR) be observed in the phase I-Ib dose escalation parts, MBG453 as single agent or in combination with PDR001 will be tested at different doses levels.

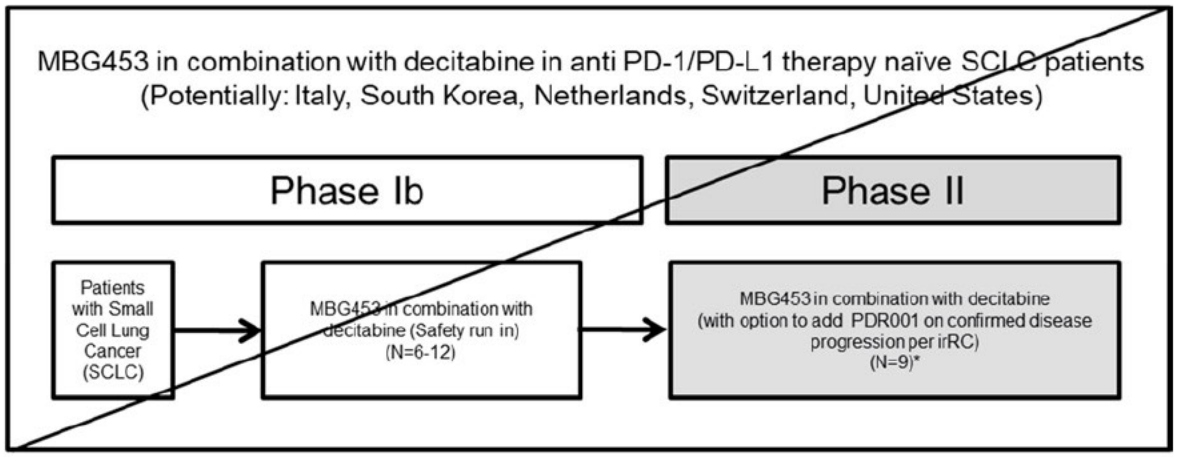
***Additional patients will be enrolled to test Q2W versus Q4W dosing schedule. The selection of the group will be based on enrollment feasibility.

§The number of patients enrolled per group could be reduced depending on enrollment feasibility, and they will be increased to 25 if 3 or more confirmed PRs or CRs are observed.

[redacted]



**** Japanese patients may enter the single agent and the combination parts of the current MBG453 study (at whichever dose is being tested at that time) if the single agent RP2Ds in Japanese patients for MBG453 and PDR001 (for combination parts only) are the same as in ROW.



* Total of 15 patients including safety run in

Phase I dose escalation part (MBG453 single agent)

In the phase I part of the study, cohorts of patients will be treated with MBG453 as single agent every 2 weeks (Q2W) until the MTD is reached or a lower RP2D is established. It is expected that a RP2D based on safety and PK data will be established before the MTD is reached, as this has been the case with other checkpoint inhibitors. To assure that the RP2D does not exceed the MTD, the dose escalation will also be guided by an adaptive Bayesian hierarchical logistic regression model (BHLRM) following the EWOC principle.

The MBG453 single agent dose escalation part in Japanese patients will run separately.

Testing of Q4W dosing schedule during the Phase I dose escalation part

A Q4W dosing schedule will be tested during the single agent MBG453 dose escalation part in the ROW and Japanese patients.The starting dose for the Q4W dosing schedule dose escalation will be no higher than the highest dose currently being tested in the Q2W dosing schedule and shown to satisfy the EWOC criterion. The dose for the Q4W dosing schedule may subsequently

[redacted]

be escalated in order to achieve similar exposure to that observed at the MTD/RP2D for the Q2W dosing schedule. In this dose escalation, patient's safety will continue to be monitored by the BHLRM following the EWOC principal, and will follow the same process as the Q2W dosing schedule at dose escalation.

Determination of MTD(s)/RP2D(s) for Phase I dose escalation part

MTDs/RP2Ds may be determined for the Q2W dosing schedule, the Q4W dosing schedule, or for both schedules. A minimum of 21 patients, treated on either Q2W or Q4W dosing schedules, are required during the single agent MBG453 dose escalation to define the MTD(s); however, fewer than 21 patients may be treated if the RP2D(s) is determined prior to reaching the MTD(s) (for further details see Section 6.2.3). A minimum of 12 patients are required during the single agent MBG453 dose escalation with Japanese patients to define the MTD(s) and/or RP2D(s).

Phase Ib dose escalation part (MBG453 in combination with PDR001)

The combination phase Ib part of the study will commence after at least two cohorts of MBG453 as single agent have been completed, and safety data suggests acceptable toxicity for patients to begin treatment in combination. The combination dose escalation will follow a Q2W dosing schedule. Treatment in combination will continue until the MTD is reached or a lower RP2D is established based on safety and PK data. The dose escalation will also be guided by an adaptive Bayesian logistic regression model (BLRM) following the EWOC principle.

Determination of MTD/RP2D for Phase Ib dose escalation part (MBG453 in combination with PDR001)

A minimum of 15 patients (including Japanese patients) are required during dose escalation in combination 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).

Optional: additional dose escalation using Q4W dosing schedule during Phase Ib dose escalation part (MBG453 in combination with PDR001)

Following identification of the MTD/RP2D for MBG453 and PDR001 in combination following a Q2W dosing schedule, a further dose escalation may open to identify the MTD/RP2D following a Q4W dosing schedule. This will be guided by a newly derived BLRM that will incorporate data from the Q2W dosing schedule dose escalation into an informative prior. The starting dose for the Q4W dosing schedule dose escalation will be no higher than the highest dose tested on the Q2W dosing schedule and demonstrated to satisfy the EWOC criterion. The dose for the Q4W dosing schedule may subsequently be escalated in order to achieve similar exposure to that observed at the MTD/RP2D for the Q2W dosing schedule.

[redacted]

Phase II part (MBG453 in combination with PDR001)

Once the MTD and/or RP2D have been declared for MBG453 in combination with PDR001, additional patients will be enrolled in the Phase II part in the selected indications (melanoma, NSCLC and RCC) in order to assess the preliminary anti-tumor activity. Japanese patients may enter the Phase II combination part only if each of their respective single agents' RP2D/MTD are identical to the RP2D and/or MTD in the ROW (MBG453 in the current study and PDR001 in PDR001X2101). Initially the phase II part will enroll approximately 15 patients to each of the defined patient groups (see Figure 4-1). Should enrollment for any of these groups not be feasible, then enrollment to that group may be closed before the 15 patients target is met. Based on current understanding of enrollment feasibility it is expected that full enrollment may be met for the benchmark diseases (melanoma and NSCLC) in pre-treated patients, since anti-PD-1 has been approved for these indications. For RCC, an indication for which anti-PD-1 has not been approved; it is expected to meet full enrollment in naïve patients.

If at least 3 patients out of the first 15 treated in any group have confirmed objective response (PR or CR) per RECIST v1.1 or irRC, then enrollment to that group may be extended to approximately 25 patients in order to better characterize efficacy.

A Bayesian design will be used in order to estimate ORR within each disease group. Details of the sample size calculations leading to the patient numbers are provided in Section 10.8.

Optional: testing of Q2W versus Q4W dosing schedule during Phase II part (MBG453 in combination with PDR001)

After a preliminary assessment of the Q4W dosing schedule in the phase I/Ib dose escalations, a decision may be made to further investigate the Q4W dosing schedule during the phase II combination part to further assess efficacy and safety. This comparison will take place within only one of the 6 identified patient groups included in the combination phase II, with the group to be used chosen based on enrollment feasibility.

The dose used for the Q4W dosing schedule will be either that recommended following the Q4W combination escalation, or in the event that Q4W dosing is not evaluated in the combination dose escalation, the dose for Q4W will be chosen so that it is no higher than the highest dose with which at least 6 patients were treated in the Q2W combination dose escalation that was demonstrated to satisfy the EWOC criterion.

To facilitate comparison between Q2W and Q4W dosing schedules in the chosen indication, patients will be randomized between the two dosing schedules.

In the event that the Q2W and Q4W dosing schedules are compared, then the two arms will be extended from 15 to 25 patients, if 3 or more objective confirmed responses are observed in either arm.

[redacted]

Optional: MBG453 single agent Phase II part

Should signs of anti-tumor activity (defined as either CR, PR or durable SD with tumor shrinkage that does not qualify for PR) be seen in the phase I dose escalation with MBG453 as single agent, a phase II part will open in order to further explore single agent efficacy at the recommended dose and schedule. Patients with tumor types that have been shown to respond to single agent MBG453 (maximum of two indications) will be enrolled. Up to 15 patients may be enrolled in each indication depending on feasibility. If the recommended dose of single agent MBG453 is the same in Japanese patients and ROW patients, then Japanese patients may be enrolled into the Phase II single agent part of the study.

Optional: dose ranging part

Following declaration of the MTDs/RP2Ds for single agent and combination, and only if efficacy has already been observed in the dose escalation parts (defined as either CR, PR or durable SD with tumor shrinkage that does not qualify for PR) an optional dose ranging part of the study may be opened. The dose ranging part will only enroll patients not eligible for the Phase II parts of the study. Japanese patients may also be enrolled in the dose ranging part.

The dose ranging part may include the testing of different dose levels to better understand the safety, tolerability and PK of MBG453 as single agent and in combination with PDR001. Further enrollment to achieve a target of approximately 15 patients per dose group will be based on the number of Grade 3 or Grade 4 treatment-related adverse events observed within the first 8 weeks of study treatment. All the Adverse event data (and any other data considered significant by Novartis or requested by the Investigators) will be reviewed by the Investigators and Novartis, prior to additional enrollment to the respective dose levels.

Because data from several PD-1 and PDL-1 inhibitors have demonstrated that PD-1 blockade at any dose above 0.3 mg/kg can result in tumor response across a broad range of solid tumors (Topalian et al 2012, Hamid and Carvajal 2013b, Seiwert et al 2014, Segal et al 2014, Powles et al 2014, Herbst et al 2014), doses below that recommended for the phase II part of the study may be explored in order to further understand safety, tolerability, and clinical efficacy.

The dose ranging part of the study will only use doses that have already been explored in the phase I and Ib dose escalation parts of the study, and demonstrated to be safe by satisfying the EWOC criterion under the relevant BLRM.

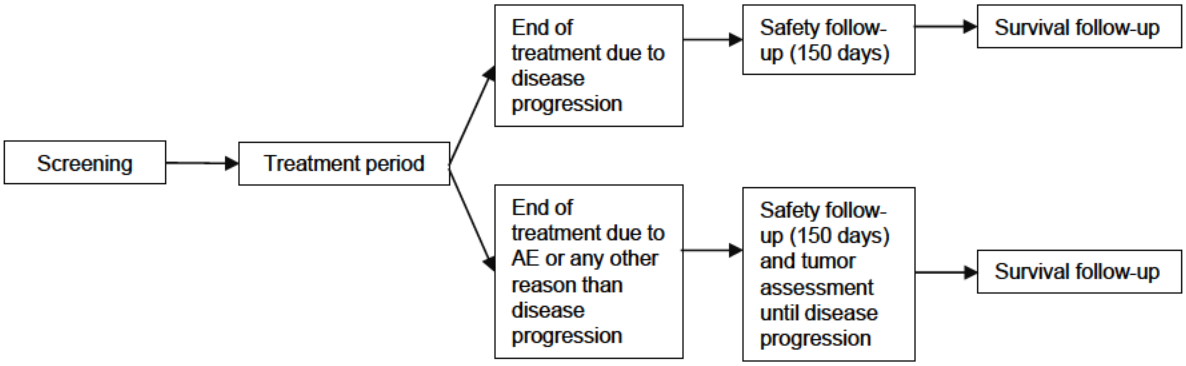
The assignment of a patient into a particular dose level will be coordinated by Novartis and will be based on the dose levels available at the time the patient consents the participation in the study.

[redacted]

Study flow

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

Figure 4-2 Study flow



4.2 Timing of interim analyses and design adaptations

No formal interim analyses are planned. However, in the phase I-Ib parts, the dose escalation design foresees that decisions based on the current data are taken before the end of the study. In the phase II part, the number of patients with tumor response will be monitored in each of the selected indications to decide if the enrollment should be extended from 15 to approximately 25 patients (this is not applicable to the SCLC patients treated with MBG453 in combination with decitabine) (Section 10.7).

4.3 Definition of end of the 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 150 days safety follow-up period,
- or if the study is terminated early
- or another clinical study becomes available that can continue to provide study treatment in this patient population; all patients ongoing are transferred to that clinical study and all discontinued patients have completed the safety follow-up period. The follow-up for disease progression and survival will not be performed or pursued (See Section 7.1.5).

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

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

[redacted]

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 7.1.3 and Section 7.1.4 for a discontinued or withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing Institutional Review Boards (IRBs) and/or independent ethics committees (IECs) of the early termination of the trial.

5 Population

5.1 Patient population

The phase I-Ib and dose ranging parts of the study will be conducted in adult patients with advanced solid tumors.

The phase II part of the study in combination with PDR001 will be conducted in adult patients with melanoma, NSCLC, RCC, either anti-PD-1/PD-L1 therapy naïve or pre-treated as outlined in Figure 4-1

In addition, the phase II part for single agent MBG453 will be conducted in adult patients with advanced solid tumors.

The Phase Ib safety run-in and Phase II part of the study of MBG453 in combination with decitabine will be conducted in anti-PD-1/PD-L1 therapy naïve SCLC patients.

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

5.2 Inclusion criteria

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

1. Written informed consent must be obtained prior to any procedures.
   For Japan only: written consent is necessary both from the patient and his/her legal representative if he/she is under the age of 20 years.
2. Age ≥ 18 years.
3. Histologically documented advanced or metastatic solid tumors.
4. **Phase I-Ib parts (including dose ranging part)**: Patients with advanced/metastatic solid tumors, with measurable or non-measurable disease as determined by RECIST v1.1 (refer to Appendix 1), who have progressed despite standard therapy or are intolerant of standard therapy, or for whom no standard therapy exists, and who did not receive prior anti-PD-1/PD-L1 treatment.
   Prior therapy with PD-1/PDL-1 inhibitors is allowed provided any toxicity attributed to priorPD-1 or PD-L1-directed therapy did not lead to discontinuation of therapy and after discussion between the Investigator and Novartis study medical representative.
5. **Phase II part (MBG453 single agent):** Patients with advanced/metastatic solid tumors in the indication in which signs of anti-tumor activity (CR, PR or durable SD with tumor

[redacted]

shrinkage that does not qualify for PR) were seen during the dose escalation study of MBG453 as single agent. Patients must have measurable disease as determined by RECIST v1.1 (refer to Appendix 1), have progressed despite standard therapy or be intolerant to standard therapy.

6. **Phase II part (MBG453 in combination with PDR001):** Patients with advanced/metastatic tumors in the below selected indications, with at least one measurable lesion as determined by RECIST v1.1 (refer to Appendix 1), who have received standard therapy or are intolerant to standard therapy, have progressed following their last prior therapy:
   - Melanoma (anti-PD-1/PD-L1 therapy naïve or pre-treated)
   - NSCLC (anti-PD-1/PD-L1 therapy naïve or pre-treated)
   - RCC (anti-PD-1/PD-L1 therapy naïve or pre-treated)
7. ECOG Performance Status ≤ 2.
8. 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/baseline, and during therapy on the study.
9. **For MBG453 in combination with decitabine (phase Ib/II):** anti-PD-1/PD-L1 therapy naïve SCLC patients who have failed no more than two lines of standard chemotherapy including topotecan.

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. Patients with treated brain metastases should be neurologically stable (for 4 weeks post-treatment and prior to study enrollment) and off of steroids for at least 2 weeks before administration of any study drug.
2. History of severe hypersensitivity reactions to any ingredient of study drugs and other mAbs 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
   - Total bilirubin > 1.5 x Upper Limit of Normal (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) > 3 x ULN, except for patients that have tumor involvement of the liver, who are excluded if ALT > 5 x ULN
   - Aspartate aminotransferase (AST) > 3 x ULN, except for patients that have tumor involvement of the liver, who are excluded if AST > 5 x ULN
   - Absolute neutrophil count (ANC) < 1.0 x 10^9/L
   - Platelet count < 75 x 10^9/L
   - Hemoglobin < 9 g/dL

[redacted]

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/baseline ECG or congenital long QT syndrome
   - Acute myocardial infarction or unstable angina pectoris < 3 months prior to study entry
5. HBV or HCV positive patients, with active disease or whose hepatitis is not controlled by therapy are excluded. HIV positive patients are 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 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.
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.
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.
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-CTLA4 antibodies in combination with any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathway.
14. Participation in an interventional, investigational non-immunotherapy study within 2 weeks of the first dose of study treatment.
15. Prior participation in an interventional, investigational cancer vaccine or immunotherapy study except for an anti-PD-1/PD-L1 study (please refer to Section 5.2 Inclusion criterion 6).
16. 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.

[redacted]

17. Use of hematopoietic colony-stimulating growth factors (e.g. G-CSF, GM-CSF, M-CSF) ≤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.
18. 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.
19. Pregnant or 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. In rare cases of an endocrine-secreting tumor, hCG levels may be above normal limits but with no pregnancy in the patient. In these cases, there should be a repeat serum beta-hCG test (with a non-rising result) and a vaginal/pelvic ultrasound to rule out pregnancy. Upon confirmation of results and discussion with the Novartis Medical representative, these patients may enter the study.
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 study treatment and for 150 days after the last dose of MBG453 as single agent or in combination with decitabine and/or PDR001 or 3 months after the last dose of decitabine or per decitabine country specific label, whichever is the longest. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least 6 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/baseline). 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 (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

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

Women are considered post-menopausal and not of child bearing potential if they have had over 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate [generally age from 40 to 59 years], history of vasomotor symptoms [e.g. hot flush]) in the absence of other medical justification or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least 6 weeks ago. In the case of oophorectomy

[redacted]

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 drug and for 150 days after stopping study treatment period or 3 months after the last dose of decitabine or per decitabine country specific label, whichever is the longest. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.
22. Patients with a history of drug-induced pneumonitis or current pneumonitis.
23. **For MBG453 in combination with decitabine (phase Ib/II)**: Hypersensitivity to decitabine or to any of the excipients, listed in decitabine country specific label.

6 Treatment

6.1 Study treatment

For this study, the investigational drugs are MBG453, PDR001 and decitabine. The study treatment is defined as MBG543 as single agent, MBG453 in combination with PDR001, or MBG543 in combination with decitabine with or without PDR001. All dosages prescribed and dispensed to patients and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

6.1.1 Dosing regimen

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Starting Dose	Frequency and/or Regimen
PDR001	Lyophilisate in vial for i.v. infusion	80 mg	Every 2 weeks (every 4 weeks if testing of a new dosing schedule) On day 8 (every 4 weeks) when in combination with MBG453 and decitabine
MBG453	Liquid in vial for i.v. infusion	80 mg (as single agent) 20 mg (when in combination with PDR001)	Every 2 weeks (every 4 weeks if testing of a new dosing schedule) On day 8 (every 4 weeks) when in combination with decitabine
Decitabine	i.v infusion	20mg/m2	Day1 to day5 (every 4 weeks)

MBG453 and PDR001 will be administered via i.v. infusion over 30 minutes (up to 2 hours, if clinically indicated) once every 2 weeks. When given in combination, both study drugs are to be administered on the same day, separate infusion bags and filters must be used for each infusion. MBG453 is to be administered first and promptly followed by a dextrose solution flush as described in the pharmacy manual for approximately 1 hour before starting the PDR001 infusion. There should be a period of at least one hour after the infusion where by the patient requires close observation.

[redacted]

Decitabine is commercially available. For details on preparation refer to the country-specific label instructions and/or decitabine package insert. Decitabine should be administered according to standard clinical practice. A standard dose of decitabine (20mg/m^2) will be given intravenously every day for five consecutive days (days 1-5) every 4 weeks (refer to local decitabine package insert), followed by MBG453 or MBG453 in combination with PDR001 on day 8. In order to maximize the potential immune priming effect and minimize the risk of toxicity with concomitant administration of decitabine, MBG453 infusions will be administered on day 8 every 4 weeks. If PDR001 is added as per Section 4.1, it will be administered after MBG453 administration on day 8.

Further instructions for the preparation and dispensation of MBG453 and PDR001 are described in the Pharmacy Manuals.

Next dose (as single agent or in combination) may be delayed by up to 7 days to recover from previous AEs. If the next dose (as single agent or in combination) cannot be administered within the above mentioned 7-days delay, then the dose should be skipped. Dosing will resume at the scheduled dose and assessment schedule will be shifted accordingly. Dose modifications should follow Section 6.3.1.

For MBG453 in combination with decitabine, if there are toxicities that prevent the patient from starting decitabine on day 1 of the next cycle, then the cycle should be resumed when the AE has resolved. For AEs occurring during a cycle that prevent the administration on day 8 of MBG453 (with or without PDR001), the dose may be delayed by up to 7 days to recover from the AEs.

6.1.2 Ancillary treatments

Patients should not receive pre-medication to prevent infusion reaction before the first infusion of MBG453 single agent or in combination with 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. Consider antiemetic premedication for nausea due to decitabine as specified in each decitabine country-specific label. 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 MBG453 and PDR001 infusion reactions are provided in Table 6-7.

The CTCAE category of “Infusion related reaction” should be used to describe MBG453 and PDR001 infusion reactions, unless the investigator considers another category, such as “Allergic reaction,” “Anaphylaxis,” or “Cytokine release syndrome” more appropriate in a specific situation.

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6.1.3 Treatment duration

All patients treated with either MBG453 single agent or in combination with PDR001 will begin study treatment on Cycle 1 Day 1. Each cycle will consist of 28 days.

Patients treated with MBG453 in combination with decitabine will receive decitabine from day 1 to day 5 and MBG453 will be administered on day 8. Each cycle will consist of 4 weeks.

A patient may continue treatment with MBG453 single agent or in combination with PDR001 or decitabine until the patient experiences unacceptable toxicity, confirmed disease progression per irRC and/or treatment is discontinued at the discretion of the investigator or the patient. Patients will not be withdrawn from the study due to progressive disease per RECIST v1.1. Refer to Section 7.1.3.

Patients will be given the option to add PDR001 to the combination of MBG453 and decitabine after confirmed disease progression per irRC

If more than 2 consecutive doses of MBG453 as single agent or in combination with PDR001 or 1 cycle of MBG453 in combination with decitabine have to be skipped due to study treatment-related toxicities, then the default position is that study drugs 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.

6.2 Dose escalation guidelines

6.2.1 Starting dose rationale

MBG453 cross reacts with monkey but not rodent TIM-3; therefore, the starting dose selected for this study is based on 5-week GLP toxicology studies performed in cynomolgus monkeys. MBG453 is a naked monoclonal antibody that does not have agonist activity, and will be administered to patients with advanced malignancies; therefore the starting dose is based on the ICH S9 guidance. The HNSTD was 100 mg/kg, administered i.v., once weekly. As MBG453 will be administered i.v. and it is generally accepted that antibody therapeutics allometrically scale according to body weight, the HED of the HNSTD is 100 mg/kg. Based on the ICH S9 guidance, a factor of six can be used to determine the maximum allowable starting dose, with an estimated maximum starting dose of 17 mg/kg administered weekly. MBG453 has a K_D for human at approximately 0.5, while cyno K_D is 0.9. There is a 44% difference in affinity between cyno and human, and so therefore the starting dose based on S9 guidance and the additional affinity difference was used to calculate a starting dose of 7.6 mg/kg. In order to evaluate the safety, PK and anti-tumor activity of MBG453 across a range of doses, the recommended starting dose as a single agent is 80 mg, i.v., every 2 weeks. Starting with flat dose of 80 mg that equals approximately 1 mg/kg is not expected to overdose patients above the exposure observed in monkeys at the achieved HNSTD dose of 100 mg/kg or the estimated maximum starting dose of 7.6 mg/kg (600 mg). The recommended starting dose of MBG453 in combination with PDR001 is 20 mg, i.v., every 2 weeks, which is well below the maximum permitted starting dose. The phase Ib combination part of the protocol will not begin until single agent safety for both MBG453 (up to 240 mg) and PDR001 (up to 800 mg) is established.

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6.2.2 Provisional dose levels

Table 6-2, Table 6-3 and Table 6-4 describe the starting dose for Phase I and Phase Ib parts, and the dose levels that may be evaluated during this trial.

Table 6-2 Provisional dose levels (Phase I part – MBG453 single agent)

Dose level	MBG453 Proposed dose*	Increment from previous dose
-1**	20 mg	-70%
1 (starting dose)	80 mg	Starting dose
2	240 mg***	300%
3	800 mg	333%

*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. Multiple dose levels below the MTD may be evaluated simultaneously in order to obtain PK and PD data across a range of doses.
**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.
***The escalation of Q4W dosing schedule will open at same dose as the current cohort of Q2W. Subsequent cohorts will have dose adjusted based on observed PK exposure.

Table 6-3 Provisional dose levels (Phase Ib part – MBG453 in combination with PDR001)

Dose level	MBG453 Proposed dose*	PDR001 Proposed dose*
-1**	20 mg	20 mg
1 (starting dose)	20 mg	80 mg
2	80 mg	80 mg
3	240 mg	80 mg
3a	80 mg	240 mg
4***	800 mg	80 mg
5***	240 mg	240 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. Multiple dose levels below the MTD may be evaluated simultaneously in order to obtain PK and PD data across a range of doses.
**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.
***Cohorts to be opened simultaneously.
****If Q4W dosing schedule is investigated, it will open at same dose as the current cohort of Q2W. Subsequent cohorts will have dose adjusted based on observed PK exposure.

[redacted]

Table 6-4 Provisional dose levels (MBG453 in combination with decitabine)

Dose level	Decitabine proposed dose	MBG453 dose	PDR001 dose **
-1*	10 mg/ m^2	800 mg	400mg
1 (starting dose)	20 mg/ m^2	800 mg	400mg

* If there are 2 or more DLTs within those 6 evaluable patients, 6 additional patients may be accrued to the -1 dose level. No dose reduction below dose level -1 is permitted for this study.

** for patients adding PDR001 to MBG453 in combination with decitabine

6.2.3 Guidelines for dose escalation and determination of MTD/RP2D

6.2.3.1 MTD definition

The MTD will be defined as follows in each of the phase I parts (as single agent or in combination):

- **MBG453 single agent**: the MTD is defined as the highest drug dosage not expected to cause DLT in 33% or more of the treated patients in the **first cycle (28 days)** of MBG453 treatment during the escalation part of the study.
- **MBG453 in combination with PDR001**: the MTD is defined as the highest combination drug doses not expected to cause DLT in 33% or more of the treated patients in the **first two cycles (56 days)** of treatment during the escalation part of the study. Co-blockade of CTLA4 and PD-1 has shown enhanced anti-tumor efficacy matched by an increased incidence of irAE, often with delayed onset (Wolchok et al 2013, Larkin et al 2015). For this reason the DLT safety profile will be followed for 2 cycles instead of one.

For MBG453 in combination with PDR001, since several possibilities may correspond to this definition, more than one MTD may be identified with different doses of the study drugs. One (or more) of these MTD(s) or a suitable lower dose combination will then be selected as the RP2D(s).

The applied adaptive Bayesian methodology provides an estimate of the single-agent MBG453 and the combinations of MBG453 and PDR001 not exceeding the MTD. Typically the MTD is a tested combination with maximum probability of targeted toxicity (DLT rate between 16% and < 33%). The use of the EWOC principle limits the risk that a potential next dose will exceed the MTD (Section 10.4.2). Adverse events and laboratory abnormalities considered to be DLTs are defined in Table 6-5 and Table 6-6.

- **MBG453 in combination with decitabine**: the MTD is defined as the highest drug dosage not expected to cause DLT in 33% or more of the treated patients who are evaluable for the dose determining set in the **first cycle (28 days)** of treatment (Section 6.2.4 and Section 10.1.4).

[redacted]

6.2.3.2 Dose cohort modification

For the purposes of dose escalation decisions (both Phase I and Phase Ib for MBG453 alone or in combination with PDR001), each cohort will consist of 3 to 6 newly enrolled patients who will be treated at the specified dose level. Should only two of these patients in the first cohort recruited to the study be considered evaluable (i.e., meet the criteria described below for a patient to be considered evaluable) and neither patient has experienced a treatment-related toxicity > CTCAE grade 1, then a dose escalation decision may be made following a dose escalation meeting between Novartis and Investigators. If however one, or both of these patients experiences a treatment-related toxicity > CTCAE grade 1, or if Novartis and Investigators decide additional information is required before making a dose escalation decision, then additional patients will be enrolled to this cohort to reach the minimum of 3 evaluable patients. Subsequent cohorts will have at least 3 evaluable patients. The first cohort will be treated with the starting dose of 80 mg of MBG453 as single agent and provisionally 20 mg of MBG453 and one dose level below RP2D for PDR001 for the combination.

The dose escalation will proceed as follows:

- **MBG453 single agent (ROW patients)**: 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 collectively between Novartis and the participating Investigators to escalate, the second cohort for the single agent will open. After all ongoing patients completed 1 cycle for the first two cohorts, combination dosing will begin at the planned starting dose in parallel to proceeding doses of the single agent cohorts.
- **MBG453 in combination with PDR001**: The combination dose escalation will proceed provided that the starting doses of the combination do not exceed the MTD of the single agents and the starting doses of the combination satisfy the EWOC criterion. Provisionally, the first cohort enrolled in the study will be treated with the starting dose for MBG453 at 20 mg in combination with PDR001 (a lower dose may be considered for starting the combination if emerging data support this, but will not be higher than 20 mg for MBG453 and 80 mg for PDR001; Section 6.2.1). Since the combination starting dose for MBG453 is anticipated to be below the efficacious range, and to be well tolerated, an initial assessment of DLT data in the first cohort may be made after all ongoing patients in the first cohort have completed a minimum of 1 cycle of treatment. Based on all existing data and after the dose escalation decisions with the Investigators and Novartis, a new cohort may be initiated at a higher dose satisfying the EWOC criteria. Once all patients in cohort 1 have completed cycle 2, the safety of the cohort 2 dose will be re-evaluated based on all available data at the confirmation decision with the Investigators and Novartis. Since cohort 2 can only open once all patients in cohort 1 have entered cycle 2, the confirmation of cohort 2 dose safety will be made before cohort 2 patients enter cycle 2. Should this dose no longer satisfy the EWOC criteria, then the dose for cohort 2 may be reduced before going into cycle 2. Subsequent cohorts will open in a similar fashion, with dose selected based on a minimum of one cycle's safety data from the previous cohort, and complete (2 cycle) data from earlier cohorts. In each case, where a cohort is opened based on incomplete data from the previous cohort, safety will be reconfirmed before patients begin the second cycle of treatment.

[redacted]

- **MBG453 single agent in Japanese patients:** For the purposes of dose escalation decisions, each cohort will consist of 1 to 6 newly enrolled patients who will be treated at the specified dose level. The first cohort of patients enrolled in the Japanese sub-population will be treated with the starting dose of 80 mg MBG453 Q2W as a single agent. When two patients (who may be in different cohorts) have experienced a toxicity of CTCAE grade 2 for which relationship to study drug cannot be ruled out; or when any single patient experiences a DLT or AE of CTCAE grade 3 or greater during Cycle 1, the minimum cohort size will be 3 evaluable patients for the current and subsequent cohorts. Once this cohort is complete and the dose escalation decision has been determined collectively between Novartis and the participating Investigators to escalate, the second cohort will open in a dose that satisfies the EWOC criterion. After the first cohort Japanese patients may be treated in two different dosing regimens (Q2W and Q4W). The dose escalation will then proceed until the MTD/RP2D is determined. The dose escalation in Japanese patients will run separately from the ROW. Dose escalation decisions will be guided by the BHLRM to estimate the MTD/RP2D in Japanese patients in the context of available safety and PK information.
- **MBG453 in combination with decitabine**: Provisionally, the first cohort of 6 patients enrolled in Phase Ib safety run-in of this treatment arm will be treated with the starting dose for MBG453 at 800 mg in combination with decitabine at 20 mg/m2. Since the starting dose of the specific combination is anticipated to be well tolerated, the assessment of DLT data will be made after all six patients evaluable for the dose determining analysis set (Section 10.1.4) have completed one cycle of treatment, unless they have experienced a DLT before. The safety of the combination will be evaluated based on all available data at the dose confirmation decision with the Investigators and Novartis. If there are 2 or more DLTs within those 6 evaluable patients, 6 additional evaluable patients will be accrued to the -1 dose level (Table 6-4). In case there are 2 or more DLTs within the 6 evaluable patients for the dose determining analysis set in the -1 dose level, then further enrolment will be halted in this treatment arm due to excessive toxicity.

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

- **MBG453 single agent**: Patients must complete a minimum of 1 cycle of treatment with the minimum safety evaluation and drug exposure (all planned doses of MBG453) or have had a DLT within the first cycle of treatment to be considered evaluable for dose escalation decisions (Section 10.1.4).
- **MBG453 in combination with PDR001:**
  - **Cycle 1 risk set**: For initial assessment of DLT data, patients must complete a minimum of 1 cycle of treatment with the minimum safety evaluation and drug exposure (all planned doses of study drugs) or have had a DLT within the first cycle of treatment to be considered evaluable for dose escalation decisions.
  - **Cycle 2 risk set**: For confirmation of DLT data, patients from the Cycle 1 risk set must receive at least one of their planned cycle 2 doses, and have completed minimum safety evaluation, or have had a DLT within cycle 2 to be considered evaluable for dose escalation decisions.
- Dose escalation decisions will occur when the cohort of patients has met these criteria. If only 2 patients in a cohort are evaluable and neither patient has experienced a treatment-

[redacted]

related toxicity > CTCAE grade 1, 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 (single agent) and Cycle 1 and 2 (combination), available PK, and PD data from evaluable patients. For the single agent dose escalation, the recommended dose for the next cohort of patients will be guided by the three separate BHLRMs (one for ROW patients and two for Japanese patients with Q2W and Q4W schedules) with EWOC principle evaluating the probability of DLT. For the combination dose escalation, the recommended dose for the next cohort of patients will be guided by the BLRM with EWOC principle evaluating the probability of DLT (Section 10.4.2).

- **MBG453 in combination with decitabine:** Patients must complete a minimum of 1 cycle of treatment with the minimum safety evaluation and drug exposure (all planned doses of study drugs) or have had a DLT within the first cycle of treatment to be considered evaluable for dose escalation decisions.

Bayesian logistic regression model of DLT rate (MBG453 single agent and MBG453 in combination with PDR001)

The adaptive Bayesian methodology provides an estimate of DLT rate for all dose levels of MBG453 as single agent and in combination with PDR001 that do not exceed the MTD and incorporates all accumulated DLT information from all dose cohorts for this estimation. The next dose will always satisfy the EWOC principle (less than 25% probability that the DLT rate is ≥ 33%) and will not exceed a 334% (1/2 log) increase from the previous dose (a standardly used escalation factor for mAb and immuno-oncology treatments). Smaller increases in dose may be recommended by the Investigators and Novartis 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 permissible under by the BLRM using the EWOC principle. If needed to better define the dose-toxicity relationship additional patients may be enrolled to the current dose level, to a preceding dose level, or to an intermediate dose level before proceeding with further dose escalation.

If 2 patients in a previously untested dose level experience a DLT, enrollment to that cohort will stop, the BHLRMs/BLRM will be updated and the next cohort will open at the next lower dose level or an intermediate dose level (see Table 6-2, Table 6-3 and Appendix 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

[redacted]

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 RP2D, which for single agent MBG453 is expected to occur before the MTD is reached.

The MTD and/or RP2D is identified when the following 3 conditions are met:

1. at least 6 patients have been treated at this dose or combination
2. this dose or combination satisfy 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
   b. minimum of 21 patients for the single agent in ROW or minimum of 15 patients for the combination or minimum of 12 patients for the single agent in Japanese patients have already been treated to identify the MTD. 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 or Ib 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 maximum 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 6.2.3.3.

6.2.3.3 Implementation of Dose Escalation/Confirmation Decisions

To implement dose escalation/confirmation decisions, the available toxicity information (including AEs and laboratory abnormalities that are not DLTs), the recommendations from the BLRM, and the available PK and pharmacodynamics 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.

6.2.4 Definitions of dose limiting toxicities (DLTs) for MBG453 single agent and MBG453 in combination with PDR001

A DLT is defined as an AE or abnormal laboratory value of CTCAE grade ≥ 3 assessed as unrelated to disease, disease progression, inter-current illness or concomitant medications, which occurs within the first cycle of treatment with MBG453 as single agent or in the first two cycles of treatment when MBG453 is given in combination with PDR001 during the dose escalation part of the study, with the exceptions described in Table 6-5.

[redacted]

National Cancer Institute Common Terminology Criteria for Adverse events 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. Adverse events meeting the criteria of DLT (please refer to Table 6-5) will be also collected in cycle 2 of MBG453 single agent, and will be used to derive prior distributions for the combination BLRM.

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

Table 6-5 Criteria for defining dose limiting toxicities (MBG453 single agent and MBG453 in combination with PDR001)

For the purpose of dose escalation and cohort expansion, DLT will be adjudicated as follows : **Any Grade 4 AEs will be adjudicated DLTs with the exception of:**	
	Neutropenia lasting <48 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.
	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.
The following Grade 2 AEs will be adjudicated as DLTs:	
	Total bilirubin with ≥ CTCAE grade 2 ALT.
	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.

6.2.5 Definition of dose limiting toxicities (DLTs) for MBG453 in combination with decitabine

A DLT is defined as an AE or abnormal laboratory value of CTCAE grade ≥ 3 assessed as unrelated to disease, disease progression, inter-current illness or concomitant medications, which occurs within the first cycle of treatment with MBG453 when is given in combination with decitabine during the safety run in part of the study, with the exceptions described in Table 6-6.

Myelosuppression is an expected toxicity for patients treated with decitabine and is managed with treatment interruption, dose reduction, growth factor support and anti-infective therapies as needed. AEs of myelosuppression are the most frequently reported with decitabine single agent (neutropenia of any grade in 90% of decitabine-treated patients with grade 3 or 4 occurring in 87% of patients; thrombocytopenia of any grade in 89% of patients with grade 3 or 4 in 85% of patients; grade 3 or 4 febrile neutropenia in 23% of patients; anemia of any grade in 82% of patients). Patients will be closely monitored for grade 3-4 hematological AEs as defined in the DLT criteria (Table 6-6). The dose -1 level of decitabine at 10 mg/m2 (days 1 to 5) might be considered after discussion and agreement between Novartis and the Investigators.

National Cancer Institute Common Terminology Criteria for Adverse events 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. Adverse events meeting the criteria of DLT (please refer to Table 6-6) will be also collected, and will be used to derive prior distributions for the combination BLRM.

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

Table 6-6 Criteria for defining dose limiting toxicities (MBG453 in combination with decitabine)

Any Grade 3 and 4 Hematological AEs will be adjudicated DLTs with the exception of:
Grade 3 or 4 Neutropenia lasting < 7 consecutive days that is not associated with fever or other clinical symptoms
Grade 3 thrombocytopenia without clinically significant bleeding
Grade 4 thrombocytopenia lasting < 7 consecutive days and without clinically significant bleeding
Grade 3 anemia
Grade 4 anemia lasting for < 7 consecutive days
Lymphopenia

Any Grade 4 AEs will be adjudicated DLTs with the exception of:	
	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.
	Nausea and vomiting persisting for < 2 days after optimal anti-emetic therapy.
	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.
The following Grade 2 AEs will be adjudicated as DLTs:	
	Total bilirubin with ≥ CTCAE grade 2 ALT.
	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 > 14 days in cycle 1.

6.3 Dose modifications

6.3.1 Dose modifications 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. The following guidelines need to be applied:

- If a patient experiences an AE meeting the criteria for DLT as outlined in Section 6.2.4 (including events occurring after cycle 1), treatment should be withheld. Dose modifications for toxicities related to MBG453 and PRD001 are summarized in Table 6-7. If decitabine treatment is deemed by the investigator to possibly have contributed to an observed adverse event, the dose or duration of decitabine treatment may be modified according to the country-specific label guiding decitabine use. Following resolution of the toxicity to grade 1 or to the patient's baseline value, the patient may resume study treatment at a lower dose level assessed to be safe (on the same dosing schedule), if there is no evidence of disease progression as per irRC. For patients in the dose escalation part receiving MBG453 in combination with PDR001, MBG453 dose level will be lowered except for the first two cohorts where PDR001 will be lowered instead.
- A decision to resume treatment with MBG453 as single agent or in combination with PDR001 or decitabine following the occurrence of a DLT is at the discretion of the Investigator. If the Investigator considers it to be in the patient's best interest to resume therapy before the toxicity has resolved to grade 1, or to resume without dose reduction, this may be permitted on a case by case basis, following discussion with Novartis.

[redacted]

- Dose reductions to doses below 20 mg are not permitted for MBG453 or PDR001. If more than 2 consecutive doses have to be skipped due to study treatment-related toxicities, then the patient must be discontinued from the study. If a patient who misses more than 2 consecutive doses due to 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.
- Patients who discontinue the study treatment for a study related AE or a study-related abnormal laboratory value must be followed as described in Section 6.3.2.

All interruptions or change to study drug administration must be recorded on the Dose Administration Record eCRF.

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.

An irAE is a clinically important AE of unknown etiology associated with the study drug exposure. irAEs are typically low grade and self-limited, often occurring after multiple doses, and most frequently involving the GI tract (diarrhea/colitis), skin (rashes), liver (hepatitis), and endocrine systems (a variety of endocrinopathies). Serologic, histologic (tumor sample) and immunological assessments should be performed as deemed appropriate by the Investigator, to verify the immune related nature of the AE, and exclude the neoplastic, infectious or metabolic origin of the AE. 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: [https://www.nccn.org/professionals/physician_gls/default.aspx#immunotherapy], the ASCO clinical practice guideline for Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy (Brahmer et al 2018) or the ESMO Clinical Practice Guidelines for Management of Toxicities from Immunotherapy (Haanen et al 2017)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, anti-DNA Ab, etc.) 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 150 days following the last dose of MBG453 single agent or in combination with PDR001.

Table 6-7 outlines the follow-up evaluation recommended for selected toxicities. For any irAEs/AEs Grade 1 and/or Grade 2, treatment with MBG453 and/or PDR001 should be maintained at the determined dose and schedule, unless otherwise specified in Table 6-6.

Decitabine treatment may be modified according to the country-specific label guiding decitabine use.

[redacted]

Table 6-7 Management of toxicities defined as study treatment-related only

Worst toxicity CTCAE v4.03 Grade (unless otherwise specified)	**Recommended dose interruption, delay and discontinuation for study treatment** **During a cycle of therapy**
Infusion/Hypersensitivity reactions	
Grade 1	• Decrease MBG453 or PDR001 infusion rate until recovery of the symptoms

Grade 2	• Stop MBG453 or PDR001 infusions immediately, and keep line open. Provide supplemental oxygen and fluids, as needed
	• Monitor vital signs (e.g. blood pressure, pulse, respiration, and temperature) every 15 ± 5 minutes until resolution
	• Administer medications for symptomatic relief as needed:
	  • **Urticaria**: Diphenhydramine (25 to 100 mg i.v.) as needed every 4 to 6 hours, or alternative as appropriate
	  • **Fever:** Acetaminophen/paracetamol (650-1000 mg by mouth) as needed every 4 to 6 hours, or alternative as appropriate
	  • **Rigors**: Meperidine 25 mg i.v. as needed every 6 hours or alternative as appropriate. Corticosteroids or bronchodilators may be administered, as needed
	• Resume MBG453 or PDR001 infusions once infusion reaction resolves (within 8 hours of initial start of infusion). Maintain dose level(s)
	• Administer oral pre-medication (e.g.1000 mg of acetaminophen/paracetamol, 50-100 mg diphenhydramine hydrochloride or alternative antihistamine), within 60 minutes of restarting the MBG453 or PDR001 infusion.
	• Restart MBG453 or 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

Grade 3 or Grade 4	• Discontinue MBG453 or 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
Hematology	
Neutropenia (ANC)	
Grade 3 (ANC < 1000 - 500/mm^3)	• Dose delay for study treatment-related Grade 3 until resolved to ≤ Grade 1
Grade 4 (ANC < 500/mm^3)	• Discontinue for study treatment-related Grade 4 > 7 days duration
Thrombocytopenia	
Grade 3 (PLT < 50,000 - 25,000/mm^3)	• Dose delay for study treatment-related Grade 3 until resolved to ≤ Grade 1 • Discontinue for study treatment-related Grade 3 > 7 days or associated with bleeding
Grade 4 (PLT < 25,000/mm^3)	• Discontinue for study treatment-related Grade 4

[redacted]

Worst toxicity CTCAE v4.03 Grade (unless otherwise specified)	**Recommended dose interruption, delay and discontinuation for study treatment** **During a cycle of therapy**
Febrile neutropenia	
(ANC < 1.0 x 10^9/L, fever ≥ 38.5°C)	• Dose delay for study treatment-related Grade 3 until resolved to ≤ Grade 1 • Discontinue for study treatment-related Grade 4
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 for study treatment-related Grade 4 until resolved to ≤ Grade 3 • Study treatment-related Grade 4 lymphopenia or leukopenia does not require discontinuation
Renal	
Serum creatinine	
Grade 2 (> 1.5 - 3.0 x ULN) Grade 3 (> 3.0 - 6.0 x ULN)	• Dose delay for study treatment-related ≥ Grade 2 until resolved to ≤ Grade 1
Grade 4 (> 6.0 x ULN)	• Discontinue for study treatment-related Grade 4
Hepatic	
Bilirubin*	
Grade 2 (> 1.5 - 3.0 x ULN)	• Dose delay for study treatment-related ≥ Grade 2 until resolved to ≤ Grade 1 • Baseline Grade 1 AST/ALT or Total bilirubin requiring dose delays for reasons other than a shift of 2 grades in AST/ALT or Total bilirubin may resume treatment in the presence of Grade 2 AST/ALT **OR** Total bilirubin
Grade 3 (> 3.0 - 10.0 x ULN) Grade 4 (> 10.0 x ULN)	• Discontinue for study treatment-related ≥ Grade 3 • Combined Grade 2 AST/ALT **AND** Total bilirubin values meeting discontinuation parameters (AST or ALT > 8 x ULN, Total bilirubin > 5 x ULN, concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN) should permanently discontinue treatment • If baseline total bilirubin is within normal limits, delay dosing for study treatment-related Grade ≥ 2 toxicity
AST or ALT	

Grade 2 (> 3.0 - 5.0 x ULN)	• If baseline total bilirubin is within the Grade 1 toxicity range, delay dosing for study treatment -related Grade ≥ 3 toxicity
	• Discontinue for:
	  • Concurrent AST or ALT > 3x ULN and total bilirubin > 2x ULN
	Dose delay for study treatment-related ≥ Grade 2 until resolved to ≤ Grade 1
	  • Baseline Grade 1 AST/ALT or Total bilirubin requiring dose delays for reasons other than a shift of 2 grades in AST/ALT or Total bilirubin may resume treatment in the presence of Grade 2 AST/ALT **OR** Total bilirubin

Grade 3 (> 5.0 - 20.0 x ULN) Grade 4 (> 20.0 x ULN)	• Discontinue for study treatment-related ≥ Grade 3 Combined Grade 2 AST/ALT **AND** Total bilirubin values meeting discontinuation parameters (AST or ALT > 8 x ULN, Total bilirubin > 5 x ULN, concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN) should permanently discontinued treatment

[redacted]

Worst toxicity CTCAE v4.03 Grade (unless otherwise specified)	**Recommended dose interruption, delay and discontinuation for study treatment During a cycle of therapy**
Asymptomatic amylase and/or lipase elevation**	
Grade 3 (> 2.0 - 5.0 x ULN) Grade 4 (> 5.0 x ULN)	• Any study treatment-related Grade ≥ 3 isolated amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay or discontinuation. The Novartis Medical representative should be consulted for such amylase or lipase abnormalities.
Cardiac General	
Grade 2	• Dose delay for study treatment-related ≥ Grade 2 until resolved to ≤ Grade 1
Grade 3 or Grade 4	• Discontinue for study treatment-related Grade 3 or Grade 4
Endocrinopathy	
Grade 2 or Grade 3	• Dose delay for study treatment-related ≥ Grade 2 until resolved to ≤ Grade 1 • Grade 3 study treatment-related endocrinopathies adequately controlled with only physiologic hormone replacement do not necessarily require discontinuation
Grade 4	• Grade 4 study treatment-related endocrinopathy adverse events, such as adrenal insufficiency, 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 require delays or discontinuation. Therapy can only be continued after discussion with and approval from the Novartis Medical representative.
Skin	
Grade 2	• In presence of study treatment-related Grade 2 skin toxicity, treatment may be resumed (even if patient experience before a study treatment -related Grade 3 toxicity)
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
Stevens-Johnson syndrome (SJS), or Lyell syndrome/toxic epidermal necrolysis (TEN)	• Permanently discontinue study treatment.
Gastrointestinal	
Diarrhea ***	
Grade 2	• Dose delay for study treatment-related ≥ Grade 2 until resolved to ≤ Grade 1. Resume treatment when resolved to baseline value.
Grade 3 or Grade 4	• Discontinue for study treatment-related Grade 3 lasting > 7 days or Grade 4
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 study treatment-related ≥ Grade 2 until resolved to ≤ Grade 1
Grade 3 or Grade 4	• Discontinue for study treatment-related Grade 3 or Grade 4

[redacted]

Worst toxicity CTCAE v4.03 Grade (unless otherwise specified)	Recommended dose interruption, delay and discontinuation for study treatment During a cycle of therapy
Ocular (uveitis, eye pain, blurred vision)	
Grade 2	• Dose delay for study treatment-related ≥ Grade 2 until resolved to ≤ Grade 1 • 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 within the re-treatment period 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, bronchospasm)	
Grade 1	• Patients with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by Novartis Medical representative
Grade 2	• Dose delay for study treatment-related ≥ Grade 2 until resolved to ≤ Grade 1
Grade 3 or Grade 4	• Discontinue for any study treatment-related Grade 3 pneumonitis of any duration • Discontinue for any study treatment-related Grade 3 lasting > 7 days or Grade 4
Cytokine release syndrome (CRS)	
Grade 2	• If CRS is suspected (very high fever and precipitous drops in blood pressure, myalgia, change in mental status) treat with corticosteroids. • Take blood for cytokine measurements immediately after the occurrence of the AE and during treatment. If very high levels of IL-6 can be confirmed, a more specific treatment may be used.
Grade 3 or Grade 4	• Discontinue for study treatment-related ≥Grade 3
Other non-laboratory adverse events	
Grade 2	• Dose delay for study treatment-related ≥ Grade 2 until resolved to ≤ Grade 1
Grade 3 or Grade 4	• Discontinue for study treatment-related Grade 3 lasting > 7 days or Grade 4
Any other laboratory adverse events	
Grade 3 or Grade 4	• Dose delay for study treatment-related ≥ Grade 3 until resolved to ≤ Grade 1
***Note**: If Grade 3 or 4 hyper-bilirubinemia is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level and continue treatment at the discretion of the investigator. ****Note**: A CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within 1 week of the first occurrence of any ≥ Grade 3 of amylase and/or lipase. If asymptomatic Grade 2 elevations of lipase and/or amylase occur again at the reduced dose, patients will be discontinued permanently from study treatment. *****Note**: antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea.	

6.3.3 Anticipated risks and safety concerns of the study drug

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 treatment for expected toxicities, including management of study-drug induced AEs, i.e. hematologic toxicity, infusion reaction, pneumonitis and other immune related toxicities, are provided in Section 6.3.2 and in the decitabine country-specific label.

[redacted]

Refer to preclinical toxicity data provided in the [PDR001 Investigator's Brochure] and [MBG453 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 Permitted concomitant therapy requiring caution and/or action

Treatment with hematopoietic colony-stimulating growth factors (e.g. G-CSF, GM-CSF, M-CSF) may not be taken during the study (with exception of the MBG453 in combination with decitabine arm). If a patient is using erythropoiesis stimulating agents (ESAs) 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 (LMWH) 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 MBG453 and/or 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.

Limited-field palliative radiotherapy or surgery to non-target lesion(s) may be allowed as concomitant therapy after documented discussion with Novartis. For the purpose of assessing response, a lesion treated with local therapy will be considered to have unequivocal progression of disease. Such local therapies administered during the study treatment must be listed on the Surgical and Medical Procedures eCRF.

6.4.3 Prohibited concomitant therapy

During the course of the study, patients may not receive other additional investigational 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 may 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 infusion reaction, irAEs or replacement-dose steroids in the setting of adrenal insufficiency (providing this is ≤ 10mg/day prednisone or equivalent) Additional exceptions may be discussed with Novartis. Systemic corticosteroids required for the control of infusion reactions or irAEs must be tapered and be at non-immunosuppressive doses (≤ 10 mg/day of prednisone or equivalent) before the next study drug administration. If more than 10 mg/day prednisone is used, study treatment should be suspended.

Topical, inhaled, nasal and ophthalmic steroids are 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.

6.5 Patient numbering, treatment assignment or randomization

6.5.1 Patient numbering

Each patient is identified in the study by a Patient Number (Patient No.),that is assigned when the patient is enrolled for screening/baseline. The Patient No. is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Patient 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 Patient 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 during Phase I-Ib parts will be coordinated by Novartis.

The assignment of a patient into testing one of the two dosing schedules during phase II part, and of a patient included for additional safety monitoring at different dose levels (dose ranging group), will be coordinated by Novartis and will be based on the dose levels available at the time the patient consents the participation in the study.

Randomization for Q2W versus Q4W comparison (Phase II part in combination only)

The investigator or designated staff will contact the Novartis Representative and provide the requested identifying information for the patient to register them. Once assigned, the Patient

[redacted]

No. must not be reused for any other Patient and the Patient No. for that individual must not be changed. If the patient is randomized but fails to start treatment for any reason, the reason will be entered into the End of Treatment phase Disposition eCRF and Novartis Representative must be notified within 2 days that the patient was not randomized.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased from patients and investigator staff. A patient randomization list will be produced by the Novartis Representative using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication randomization list will be produced by or under the responsibility of Novartis Global Clinical Supply using a validated system that automates the random assignment of medication numbers to medication packs containing each of the study treatments.

Prior to dosing, all patients who fulfill all inclusion/exclusion criteria will be randomized via Novartis Representative to one of the treatment arms (Section 4.1 and Section 6.1) in a ratio of 1:1. Randomization will not be stratified. The investigator or his/her delegate will call Novartis Representative and confirm that the patient fulfills all the inclusion/exclusion criteria. The Novartis Representative will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study treatment to be administered to the patient. The randomization number will not be communicated to the caller.

6.6 Study drug preparation and dispensation

MBG453

MBG453 (100 mg liquid in vial) will be administered i.v. Further instructions for the preparation and dispensation of MBG453 are described in the Pharmacy Manual.

All dosages for MBG453 prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

PDR001

PDR001 (100 mg powder for solution for infusion) will be administered i.v. Further instructions for the preparation and dispensation of PDR001 are described in the Pharmacy Manual.

All dosages for PDR001 prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

[redacted]

Decitabine

Decitabine is commercially available. For details on preparation refer to decitabine country-specific label instructions and/or decitabine package insert.

6.6.1 Study drug packaging and labeling

MBG453 100 mg liquid in vial and PDR001 100 mg powder for solution for infusion, will be supplied by Novartis to Investigator as open label bulk medication.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug but will not supply information about the patient.

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, MBG453 and PDR001 should be stored according to the instructions specified on the drug labels.

Decitabine will be sourced as local commercial supply (in the locally approved formulation and packaging configuration) and labeled in the country according to local practice and regulation.

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.

Study treatment will be administered to the patient by the study site staff. Compliance will be assured by administration of the study treatment under the supervision of investigator or his/her designee.

6.6.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment according to local institutional drug accountability processes. Drug accountability will be noted by the field monitor during site visits and at the completion of the study.

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.

[redacted]

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 lists all the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation. The table ("Category" column) indicates which assessments produce data to be entered into the clinical database (D) or remain in source documents only (S).

No eCRF will be used as a source document.

Screening/Baseline 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/baseline evaluations and within 3 days prior to the first dose of study treatment, are not required to be repeated on Cycle 1 Day 1. Laboratory and radiological assessments performed as part of standard of care prior to signing informed consent may be used if performed within the screening/baseline time window.

During the course of the study visits, test and/or procedures should occur on schedule whenever possible. A visit window of +/- 7 days is allowed. In case the infusion of MBG453 as single agent or in combination with PDR001 or decitabine cannot be administered at the scheduled visit, it has to be administered as soon as possible. If the delay is between 1 and 7 days the procedures at the original schedule visit should be performed. If the delay is longer than 7 days, the procedure of the following visit should be performed and subsequent visits will take place every 2 weeks. On PK collection days the windows are provided in Section 7.2.3.

Table 7-1 Visit evaluation schedule (MBG453 single agent and MBG453 in combination with PDR001)

			Screening/Baseline Phase	Treatment Phase															Follow-up		
Visit name	**Category**	**Protocol Section**	**Screening/Baseline**	**Cycle 1**					**Cycle 2**		**Cycle 3**					**Subsequent cycles[6]**		**EOT**	**150-Days Safety**	**Disease Progression**	**Survival**
Day of cycle			-28 to -1	1	2	8	11	15	1	15	1	2	8	11	15	1	15				
Obtain Informed Consent	D	7.1.1	X																		
Obtain additional biomarkers/biological sample 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	X	X			
Vital signs	D	7.2.2.2	X	X		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			

[redacted]

			Screening/Baseline Phase	Treatment Phase															Follow-up		
Visit name	**Category**	**Protocol Section**	**Screening/Baseline**	**Cycle 1**					**Cycle 2**		**Cycle 3**					**Subsequent cycles[6]**		**EOT**	**150-Days Safety**	**Disease Progression**	**Survival**
Day of cycle			-28 to -1	1	2	8	11	15	1	15	1	2	8	11	15	1	15				
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			
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			
HIV, HBV and HCV	D	7.2.2.5	X																		
Pregnancy test	D	7.2.2.5	X[1]						X		X					X		X	X		
Antineoplastic therapies since discontinuation of study treatment	D	7.1.5																	X	X	X
Tumor evaluation as per RECIST v1.1 and as per irRC	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 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. **EOT:** if a scan was not conducted within 30 days prior to end of study treatment.																
12-Lead ECG	D	7.2.2.6	X	X							X					X[2]		X			
Adverse events	D	8	X	Continuous																	

[redacted]

			Screening/Baseline Phase	Treatment Phase															Follow-up		
Visit name	**Category**	**Protocol Section**	**Screening/Baseline**	**Cycle 1**					**Cycle 2**		**Cycle 3**					**Subsequent cycles[6]**		**EOT**	**150-Days Safety**	**Disease Progression**	**Survival**
Day of cycle			-28 to -1	1	2	8	11	15	1	15	1	2	8	11	15	1	15				
Collection of new tumor sample	D	7.2.4	X								Any time during C3D1 and End of Treatment										
PDR001 infusion **(only in combination)**	D	6.1.1		i.v. every 2 weeks (every 4 weeks if testing of a new dosing schedule)																	
MBG453 infusion	D	6.1.1		i.v. every 2 weeks (every 4 weeks if testing of a new dosing schedule)																	
Blood sample for PK analysis[4]	D	7.2.3		X	X	X	X	X	X		X	X	X	X	X	X[3]		X			
Blood sample for soluble TIM-3 analysis[4]	D	7.2.3		X	X	X		X	X		X	X	X		X	X[3]		X			
Blood sample for IG analysis[4]	D	7.2.3		X					X		X					X[3]		X			
Blood sample for RO analysis	D	7.2.3		X	X	X		X	X		X	X	X		X	X[3]		X			
Blood sample for immunomonitoring	D	7.2.4		X		X			X	X											
Blood sample for cytokine analysis[5]	D	7.2.4		X		X			X	X											
Cytokines for safety (IFN-γ; IL-6, IL-1,TNF-α)[5]	D	7.2.2.5		Anytime for a suspected cytokine release syndrome, immediately after the AE, and one week after occurrence of the AE																	

[redacted]

			Screening/Baseline Phase	Treatment Phase														Follow-up		
Visit name	**Category**	**Protocol Section**	**Screening/Baseline**	**Cycle 1**					**Cycle 2**		**Cycle 3**					**Subsequent cycles[6]**		**EOT**	**150-Days Safety**	**Disease Progression**	**Survival**
Day of cycle			-28 to -1	1	2	8	11	15	1	15	1	2	8	11	15	1	15				
Survival contact (every 3 months)	D	7.1.5																			X

[1]To be performed within 72 hours before first dose.
[2]Cycle 6 Day 1 only.
[3]Cycles 4, 5 and 6 only.
[4] For PK, IG and soluble TIM-3 analysis, a single blood sample will be collected and then aliquoted into different tubes for each analyte and backups. For Japan only: Japanese patients enrolled in the dose escalation are required to be hospitalized during Cycle 1.
[5] The Cycle1 Day1 pre-dose biomarker cytokine sample will also be used as baseline for cytokine safety.
[6]After Cycle 24, in patients who are not experiencing grade 3 and 4 related toxicities, only visit at day1 of each cycle is required for patients at Q4W regimen.

[redacted]

Table 7-2 Visit evaluation schedule (MBG453 in combination with decitabine)

			Screening/ Baseline Phase	Treatment Phase																		Follow-up		
Visit name	**Category**	**Protocol Section**	**Screening/ Baseline**	**Cycle 1**						**Cycle 2**			**Cycle 3**						**Subsequent cycles**			**EOT**	**150-Days Safety**	**Disease Progression**	**Survival**
Day of cycle			-28 to -1	1	2	8	11	15	22	1	8	15	1	2	8	11	15	22	1	8	15				
Obtain Informed Consent	D	7.1.1	X																						
Obtain additional biomarkers/biological sample 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		X	X			
Vital signs	D	7.2.2.2	X	X		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			

[redacted]

			Screening/ Baseline Phase	Treatment Phase																		Follow-up		
Visit name	**Category**	**Protocol Section**	**Screening/ Baseline**	**Cycle 1**						**Cycle 2**			**Cycle 3**						**Subsequent cycles**			**EOT**	**150-Days Safety**	**Disease Progression**	**Survival**
Day of cycle			-28 to -1	1	2	8	11	15	22	1	8	15	1	2	8	11	15	22	1	8	15				
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			
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			
HIV, HBV and HCV	D	7.2.2.5	X																						
Pregnancy test	D	7.2.2.5	X[1]							X			X						X			X	X[5]		
Antineoplastic therapies since discontinuation of study treatment	D	7.1.5																					X	X	X
Tumor evaluation as per RECIST v1.1 and as per irRC	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 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. **EOT:** if a scan was not conducted within 30 days prior to end of study treatment.																					
12-Lead ECG	D	7.2.2.6	X	X		X																X			
Adverse events	D	8	X	Continuous																				X	X

[redacted]

			Screening/ Baseline Phase	Treatment Phase																			Follow-up		
Visit name	**Category**	**Protocol Section**	**Screening/ Baseline**	**Cycle 1**						**Cycle 2**			**Cycle 3**						**Subsequent cycles**			**EOT**	**150-Days Safety**	**Disease Progression**	**Survival**
Day of cycle			-28 to -1	1	2	8	11	15	22	1	8	15	1	2	8	11	15	22	1	8	15				
Collection of new tumor sample	D	7.2.4	X							X															
Decitabine infusion	D	6.1.1		on days 1-5 of every cycle (Q4W)																					
MBG453 infusion	D	6.1.1				X					X				X					X					
PDR001 infusion (only if in combination with Decitabine and MBG453)	D	6.1.1																		X[6]					
Blood sample for PK analysis[4]	D	7.2.3		X		X		X	X		X		X		X		X	X		X[3]		X			
Blood sample for soluble TIM-3 analysis[4]	D	7.2.3		X		X		X	X		X				X		X	X							
Blood sample for IG analysis[4]	D	7.2.3				X					X				X					X[3]		X			
Blood sample for immunomonitoring	D	7.2.4		X		X		X		X															
Blood sample for cytokine analysis	D	7.2.4		X		X		X		X															
Survival contact (every 3 months)	D	7.1.5																							X

[1]To be performed within 72 hours before first dose.
[2]Cycle 3 Day 1 and Day 8 only.

[redacted]

			Screening/ Baseline Phase	Treatment Phase																		Follow-up		
Visit name	**Category**	**Protocol Section**	**Screening/ Baseline**	**Cycle 1**						**Cycle 2**			**Cycle 3**						**Subsequent cycles**			**EOT**	**150-Days Safety**	**Disease Progression**	**Survival**
Day of cycle			-28 to -1	1	2	8	11	15	22	1	8	15	1	2	8	11	15	22	1	8	15				

[3]Cycles 4, 5 and 6 only.
[4] For PK, IG and soluble TIM-3 analysis, a single blood sample will be collected and then aliquoted into different tubes for each analyte and backups.
[5]A urine pregnancy test should be performed every month during safety follow-up period
[6]After confirmed disease progression per irRC on MBG453 in combination with decitabine

[redacted]

7.1.1 Screening/Baseline

The study IRC/IEC informed consent form must be signed and dated before any screening/baseline 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 or Table 7-2. Screening/Baseline assessments must be repeated if performed outside of the specified screening window. The screening failure reason will be entered on the Screening Phase Disposition eCRF.

Submission of a newly obtained tumor sample (formalin fixed, in ethanol) is requested from all patients at screening/baseline. For details refer to Section 7.2.4.

7.1.1.1 Information to be collected on screening failures

A patient who signed an Informed Consent Form but failed to be started on-treatment for any reason will be considered a screen failure. The screening failure reason will be entered on the Screening Phase Disposition eCRF.

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 SAE during screening/baseline (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 screening/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 MBG453 as single agent or in combination with PDR001 or decitabine

For Japan only; patients enrolled in dose escalation are required to be hospitalized during cycle 1.

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

- Patients with SD/irSD, PR/irPR, unconfirmed CR/irCR, and unconfirmed PD/irPD.

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

- Patients with confirmed PD/irPD, if the Investigator considers it to be in the patient's best interest to remain on the study, and after discussion with Novartis.

[redacted]

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

- Patients who experience unacceptable toxicity.
- Patients with confirmed PD/irPD. These patients will then enter the Safety follow-up period.
- Patients with an unconfirmed PD/irPD who show signs of clinical deterioration or toxicity. These patients will enter the Safety follow-up period, and will continue to be followed up until confirmed irPD or initiation of a new treatment.
- Patients who discontinued treatment at the discretion of the investigator or the patient as described in Section 7.1.3 and Section 4.3.

For MBG453 in combination with decitabine: patients will continue treatment until confirmed disease progression per irRC, or unacceptable toxicity and/or treatment is discontinued at the discretion of the Investigator or the patient. Only in the event of confirmed disease progression per irRC, the patient will have the option to add PDR001 to MBG453 in combination with decitabine based on investigator judgment and following a documented discussion with Novartis. The patient will continue treatment until confirmed disease progression per RECIST v1.1, or unacceptable toxicity and/or treatment is discontinued at the discretion of the Investigator or the patient.

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") (Wolchock 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 immune-related Response Criteria (irRC). An outline of the irRC is provided in Appendix 2.

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.

Optimal duration of immune therapy has not been established. There are some reports that indicate the durable response for the patients who have interrupted immunotherapy because of toxicity (Weber et al 2017). To improve patients' life who have been on therapy for more than 24 cycles and after documented discussion with Novartis and the Investigator, a treatment break lasting up to 2 cycles may be granted.

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

[redacted]

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)
- Confirmed Complete response (as per RECIST v1.1)
- Study terminated by Novartis
- Patient/guardian decision
- Protocol deviation
- Technical problems

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.

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.

Patients who transfer into another study or an alternative treatment option to continue provision of study treatment will perform the end of treatment procedures.

7.1.3.1 Replacement policy

Phase I-Ib dose escalation parts:

Patients will not be replaced on study. However, if a patient is considered to be 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 or at most the maximum number

[redacted]

of evaluable patients is achieved within the cohort. Minimum and maximum numbers of evaluable patients per cohort are defined in Section 6.2.3.

For MBG453 in combination with decitabine: if a patient is considered to be non-evaluable for the Dose Determining Set (DDS), enrollment of a new patient to the current cohort will be considered if there are less than 6 evaluable patients treated at this dose level, unless more than 2 DLTs are experienced in the specific dose level.

Phase II part:

During the phase II part no replacements will be needed.

7.1.4 Withdrawal of Consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient does not want to participate in the study anymore, and does not allow further collection of personal data.

In this situation, the investigator should make a reasonable effort (e.g. telephone calls, 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 RoW: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

[redacted]

7.1.5 Follow up period

All patients must have safety evaluations 150 days after the last dose of study treatment. Data collected should be added to the Adverse Events eCRF and the Concomitant Medications CRF.Patients who discontinue study treatment for any reason other than death, disease progression per confirmed irRC, 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 150 days 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.

Antineoplastic therapies since discontinuation of study drug will be collected during this follow-up period in the appropriate eCRF page.

For patients who transfer to another clinical study or an alternative treatment option to continue provision of study treatment, as described in Section 4.3, the follow-up for safety, disease progression and survival 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, e-mail, letters). 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 eCRF.

7.2 Assessment types

7.2.1 Efficacy assessments

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 1.1 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.

[redacted]

At screening/baseline, 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 7-3. 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.

Table 7-3 Disease assessment collection plan

Procedure	Screening/ Baseline	During Treatment/Follow-up
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. **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

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 AEs at every visit. For details on AE collection and reporting, refer to Section 8.

7.2.2.1 Physical examination

Physical examination will be performed according to Table 7-1 or Table 7-2.

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

After Cycle 1 Day 1 and onwards, a short physical examination will be performed. A short physical exam will include the examination of general appearance, vital signs (blood pressure and pulse) and body sites as directed by symptoms.

[redacted]

Significant findings that were present prior to the signature of the informed consent must be included in the Medical History eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event eCRF.

7.2.2.2 Vital signs

Vital signs (body temperature, pulse rate, blood pressure) must be performed before and during infusion at the visits indicated in Table 7-1 or Table 7-2. Vital signs should be assessed in the same position through the study.

There should be a period of at least one hour after the infusion where by the patient requires close observation.

More frequent examinations may be performed any time during the study 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 or Table 7-2 as per institutional standards.

7.2.2.4 Performance status

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

Table 7-4 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.

7.2.2.5 Laboratory evaluations

All laboratory parameters assessed for safety purposes will be evaluated locally (except cytokines and serology examinations that will be evaluated centrally). Refer to Table 7-5 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.

[redacted]

Table 7-5 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 (SGPT), AST (SGOT), 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 (BUN) or Urea
Coagulation	Prothrombin time (PT) or INR, Activated partial thromboplastin time (APTT)
Urinalysis	Bilirubin, Blood, Glucose, Ketones, pH, Protein, Specific Gravity, White Blood Cells
Thyroid	Free T4, TSH (Thyroid Stimulation Hormone)
Serology exam*	Anti-DNA antibodies (Abs), Anti-nuclear abs, Anti-phospholipid abs, Anti-mitochondrial abs, c-Reactive protein (CRP), Rheumatoid factor (RF)
Cytokines*	IFN-γ, IL-6, IL-1,TNF-α
Virology	HIV, HBV, HCV
Pregnancy	Serum samples only for women of childbearing potential
* To be performed by a Central laboratory. Details will be provided in the [CMBG453X2101 Laboratory Manual].	

7.2.2.5.1 Hematology

Hematology panel outlined in Table 7-5 will be performed as per the assessment schedule in Table 7-1 or Table 7-2.

7.2.2.5.2 Clinical chemistry

Clinical chemistry panel outlined in Table 7-5 will be performed as per the assessment schedule in Table 7-1 or Table 7-2.

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 7-5 will be performed as per the assessment schedule in Table 7-1 or Table 7-2.

7.2.2.5.4 Urinalysis

Abnormal findings will be followed up with a microscopic evaluation and/or additional assessments as clinically indicated. A microscopic evaluation (WBC/HPF, RBC/HPF, and any other evaluations depending on macroscopic findings) need only to be performed if the urinalysis result is significantly abnormal.

Urinalysis will be performed at screening/baseline and EOT visit.

7.2.2.5.5 Thyroid function and Serology exam

Thyroid and Serology panels outlined in Table 7-5 will be performed as per the assessment schedule in Table 7-1 or Table 7-2.

7.2.2.5.6 Cytokine analysis

Samples for the cytokine panel outlined in Table 7-5 will be collected at the following time points:

- Cytokine baseline level for safety purpose can be assessed from the biomarker blood sample (plasma) collected at pre-dose Cycle 1 day 1.
- On an ad-hoc basis in case a patient has an adverse event suspected to be a cytokine release syndrome (Table 7-1 or Table 7-2). In such case, this assessment should be performed at the following time points:
  a. within 5 hours (or as soon as possible) after the occurrence of the adverse event,
  b. one week after the occurrence of the adverse event.

7.2.2.5.7 Virology

Virology panel outlined in Table 7-5 will be performed as per the assessment schedule in Table 7-1 or Table 7-2.

7.2.2.5.8 Pregnancy and assessments of fertility

All females of childbearing potential will have a serum pregnancy test at screening/baseline and/or 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, and at EOT visit.

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

A urine pregnancy test should be performed every month during and at the end of the safety follow-up period. 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.

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 (or Table 7-2) and Table 7-6 (or Table 7-7). Blood samples scheduled at the same time point should be taken after the ECGs are completed. The ECGs on Day 1 of Cycles 1, 3 and 6 must be performed in triplicate.

The post-infusion ECGs in the Phase Ib combination part will be collected after the completion of the last infusion.

[redacted]

Table 7-6 12-lead ECG collection plan for MBG453 single agent and MBG453 in combination with PDR001

Cycle	Day	Time
Screening/Baseline	-28 to -1	Anytime
1	1	*Pre-infusion
1	1	*1hour (±5 min) post-infusion
3	1	*Pre-infusion
3	1	*1hour (±5 min) post-infusion
6	1	*Pre-infusion
6	1	*1hour (±5 min) post-infusion
EOT	-	Anytime
Unscheduled**	-	Anytime
*ECGs performed in triplicate. **A PK sample should be collected just after an ECG performed due to an unexpected cardiac signal.		

Table 7-7 12-lead ECG collection plan for MBG453 in combination with decitabine

Cycle	Day	Time
Screening	-28 to -1	Anytime
1	1	*Pre-decitabine infusion
1	1	*Right after completion of decitabine infusion
1	8	*Pre-MBG453 infusion
1	8	*1hour (±5 min) after completion of MBG453 infusion
EOT	-	Anytime during the EOT visit
Unscheduled**	-	Anytime if clinically indicated
*ECGs performed in triplicate **A PK sample should be collected just after an ECG performed due to an unexpected cardiac signal.		

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.

Clinically significant abnormalities present at screening/baseline should be reported on the Medical History eCRF. 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.

7.2.3 Pharmacokinetics and immunogenicity assessments

The following PK parameters will be determined for MBG453 as single agent, MBG453 in combination with PDR001 and PDR001 in combination with MBG453 using non-compartmental methods: Cmax, Tmax, AUC0-tlast (Cycle 1 Day 1 and Cycle 3 Day 1), time to last measurable concentration (Tlast), t1/2, and the accumulation ratio of MBG453 and PDR001.

[redacted]

The following PK parameters will be determined for MBG453 (in combination with decitabine) or decitabine (in combination with MBG453) using non-compartmental methods: Cmax, Tmax, AUC0-tlast (Cycle 1 Day 1 and Cycle 3 Day 1 for decitabine or Cycle 1 Day 8 and Cycle 3 Day 8 for MBG453), time to last measurable concentration (Tlast), t1/2, and the accumulation ratio of MBG453. Only trough level samples will be collected for PDR001 if applicable for patients treated with the MBG453 in combination with decitabine and PDR001.

The data will be analyzed- using WinNonlin Phoenix (Pharsight Corporation; Mountain View, CA).

PK profiles to assess PK properties of single agent MBG453 and MBG453 in combination with PDR001 or with decitabine will be collected from all enrolled patients. Please refer to Table 7-8 or Table 7-9 for details on PK and immunogenicity (IG) sample collections.

If the dosing of Cycle 3 Day 1 is delayed, the PK sampling for PK profile should be delayed accordingly to match the scheduled time points for cycle 3 as outlined in Table 7-8. PK and IG samples will be collected also at the End of Treatment Visit and in the event of a clinically significant AE (such as infusion reaction/anaphylaxis) or if IG is suspected, at which time those samples could be used to measure any relevant biomarkers, to understand the infusion reaction/adverse event better. After the primary Clinical Study Report (CSR) data cut-off date is reached, no additional PK and IG samples will be collected for the patients still on-going on the study.

[redacted]

Soluble TIM-3 and Receptor Occupancy (RO) for MBG453 will be assessed at the timepoints described in Table 7-8.

Table 7-8 Pharmacokinetic blood collection log for MBG453 single agent and MBG453 and PDR001 combination, for soluble TIM-3, RO and IG (all patients)

Cycle	Day	Scheduled Time Point (h)[b, c]	Analytes[a]
1	1	Pre-infusion of Cycle 1	mAb, soluble TIM-3, RO and IG
1	1	1h post-infusion (± 5 min)[b]	mAb, soluble TIM-3, RO
1	2	24h post-infusion (± 2h)	mAb, soluble TIM-3, RO[d]
1	8	168h post-infusion (± 8h)	mAb, soluble TIM-3, RO[d]
1	11	240h post-infusion (± 24h)	mAb
1	15	Pre-infusion of next dose / 336h post infusion (±24h)	mAb, soluble TIM-3, RO[d]
2	1	Pre-infusion of cycle 2/ 336h or 672h post infusion (±24h)	mAb, soluble TIM-3, RO and IG
2	1	1h post-infusion[b]	mAb
3	1	Pre-infusion of Cycle 3	mAb, soluble TIM-3, RO and IG
3	1	1h post-infusion (± 5 min)[b]	mAb, soluable TIM-3, RO[d]
3	2	24h post-infusion (± 2h)	mAb, soluble TIM-3, RO[d]

[redacted]

Cycle	Day	Scheduled Time Point (h)[b, c]	Analytes[a]
3	8	168h post-infusion (± 8h)	mAb, soluble TIM-3, RO[d]
3	11	240h post-infusion (± 24h)	mAb
3	15	Pre-infusion of next dose/336h post-infusion (±24h)	mAb, soluble TIM-3, RO[d]
4	1	Pre-infusion of cycle 4/ 336h or 672h post infusion (±24h)	mAb, soluble TIM-3, RO and IG
5	1	Pre-infusion of Cycle 5	mAb, soluble TIM-3, RO and IG
5	1	1h post-infusion (± 5 min)[b]	mAb
6	1	Pre-infusion of Cycle 6	mAb, soluable TIM-3, RO and IG
6	1	1h post-infusion (± 5 min)[b]	mAb
EOT		Anytime	mAb, soluble TIM-3, RO and IG
Unscheduled		Anytime	mAb, soluble TIM-3, IG and RO

a. IG samples associated with MBG453 and PDR001 are to be collected together with PK samples.

b. After completion of the infusion (during combination treatment, after completion of the last infusion)

c. PK samples will be collected from the arm opposite of infusion site. Alternatively, infusion site will need to be flushed with 10 mL of saline.

d. Applicable only for patients in the phase I-Ib dose escalation part.

Table 7-9 Pharmacokinetic blood collection log for MBG453 in combination with decitabine, for soluble TIM-3 and IG (patients treated with MBG453 and decitabine)

Cycle	Day	Scheduled Time Point (h)[2]	Analytes[1]
1	1	Pre-decitabine infusion[3]	Decitabine and soluble TIM-3
1	1	Right after completion of decitabine infusion	Decitabine
1	1	1h (± 5 min) after completion of decitabine infusion	Decitabine
1	8	Pre-MBG453 infusion[3]	MBG453, IG and soluble TIM-3
1	8	1h (± 5 min) after completion of MBG453 infusion	MBG453 and soluble TIM-3
1	15	168h (±2h) after completion of MBG453 infusion	MBG453 and soluble TIM-3
1	22	336h (±8h) after completion of MBG453 infusion	MBG453 and soluble TIM-3
2	8	Pre-MBG453 infusion[3]	MBG453, IG and soluble TIM-3
3	1	Pre-decitabine infusion[3]	Decitabine,
3	1	Right after completion of decitabine infusion	Decitabine
3	1	1h (± 5 min) after completion of decitabine infusion	Decitabine
3	8	Pre-MBG453 infusion[3]	MBG453, IG, soluble Tim-3
3	8	1h (± 5 min) after completion of MBG453 infusion	MBG453 and soluble TIM-3
3	15	168h (±2h) after completion of MBG453 infusion	MBG453 and soluble TIM-3
3	22	336h (±8h) after completion of MBG453 infusion	MBG453 and soluble TIM-3
4	8	Pre- MBG453 infusion[3]	MBG453 and IG

[redacted]

Cycle	Day	Scheduled Time Point (h)[2]	Analytes[1]
5	8	Pre- MBG453 infusion[3]	MBG453 (and PDR001 if applicable)[4] and IG
6	8	Pre-MBG453 infusion[3]	MBG453 (and PDR001 if applicable)[4] and IG
EOT		Anytime	MBG453 (and PDR001 if applicable)[4] and IG
Unscheduled		Anytime	PDR001[4], MBG453, decitabine and IG

[1]IG samples are to be collected together with PK samples. PDR001 PK, MBG453 PK and anti-PDR001 and anti-MBG453 antibodies
[2]Blood samples are to be collected from the arm opposite from the infusion site.
[3]Pre-infusion: blood samples should be collected prior to the start of the current infusion.
[4]if PDR001 is given to MBG453 in combination with decitabine

7.2.3.1 Bioanalytics

Bioanalysis for pharmacokinetic studies will employ 2 validated assays:

- The assay to quantify MBG453 and PDR001 will be a validated LC-MS. The details of the assay will be documented in the [CMBG453X2101 Laboratory Manual].
- The assay to quantify and assess the IG against MBG453 and PDR001 will be using a validated homogeneous ELISA. The details of the assay will be documented in the [CMBG453X2101 Laboratory Manual].
- Quantification of decitabine will be determined with a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay. The details of the assay will be documented in the [CMBG453X2101 Laboratory Manual].
- Bioanalysis for soluble TIM-3 will employ a validated ELISA. The details of the assay will be documented in the [CMBG453X2101 Laboratory Manual].
- Bioanalysis for RO will employ a validated assay. The details of the assay will be documented in the [CMBG453X2101 Laboratory Manual].

7.2.3.2 PK, Soluble TIM-3, RO and IG samples handling, labeling, and shipping instructions

Blood samples should be collected from the arm opposite from the investigational drug(s) infusion(s), or from another site. A total of 5 mL of blood will be collected at each time point. For time points when MBG453, decitabine and/or PDR001 (mAb) PK and IG are to be measured, a single blood sample will be collected for IG, soluble TIM-3, MBG453,decitabine and /or PDR001 PK. After clotting and centrifugation, the resulting serum will be separated in aliquots and will be stored frozen until analysis.

Samples for RO for MBG453 will be assessed using frozen PBMCs that will be generated from 7 mL of whole blood (separate blood collection).

Please see the [CMBG453X2101 Laboratory Manual] for detailed instructions about collection, handling and shipment of samples.

The actual collection date and time of each sample will be entered on the Pharmacokinetics/Immunogenicity/Soluble TIM-3/Receptor Occupancy Blood Collection eCRF pages.

[redacted]

7.2.4 Biomarkers

In this study biomarker analyses will be used to investigate the effect of the MBG453 single agent or in combination with PDR001 or decitabine at the molecular and cellular level as well as to determine how changes in the markers may relate to exposure and clinical outcomes PPD

While the goal of the biomarker assessments is to provide supportive data for the clinical study, 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). Detailed instructions for the collection, handling, and shipment of tumor samples are outlined in the [CMBG453X2101 Laboratory Manual].

Table 7-10 Biomarker sample collection plan for MBG453 single agent and MBG453 in combination with PDR001 (tumor/blood samples)

Sample Type	Visit/ Time point	Approx. volume (blood samples)	Marker*	Purpose
Tumor samples				
Newly obtained tumor sample	Screening/Baseline And During treatment (any time during C3D1 and End of Treatment)	Newly obtained formalin fixed tumor sample in ethanol (3-6 passes)	[redacted] IHC expression of markers such as: PD-L1 TIM-3 CD8, FoxP3 [redacted]	Assess expression status of potential predictors of efficacy. Pharmacodynamic markers
Blood samples				
[redacted]				

[redacted]

Sample Type	Visit/ Time point	Approx. volume (blood samples)	Marker*	Purpose
[redacted]				

Note: On days and time points when biomarker and pharmacokinetic blood samples are being collected, the PK sample must be drawn first.
*Markers are listed according to level of priority.
[redacted].

Table 7-11 Biomarker sample collection plan MBG453 in combination with decitabine (tumor/blood samples)

Sample Type	Visit/ Time point	Approx. volume (blood samples)	Marker*	Purpose
Tumor samples				
Newly obtained tumor sample	Screening/Baseline And C2D1	Newly obtained formalin fixed tumor sample in ethanol (3-6 passes)	[redacted]	Assess expression status of potential predictors of efficacy. Pharmacodynamic markers
			IHC expression of markers such as: PD-L1 TIM-3 CD8, FoxP3	
			[redacted]	
Blood samples				
[redacted]				

Note: On days and time points when biomarker and pharmacokinetic blood samples are being collected, the PK sample must be drawn first.
*Markers are listed according to level of priority.

[redacted]

7.2.4.1 Tumor Collection

7.2.4.1.1 Potential predictive markers

The status of immune checkpoint targets and cell populations will be analyzed in newly obtained tumor sample. Expression and localization of biomarkers including but not limited to PD-L1 and CD8+ TIL counts may be measured by immunohistochemistry (IHC) or using additional techniques deemed suitable. [redacted]

Submission of a newly obtained tumor sample (formalin fixed, then placed in ethanol) will be requested at screening/baseline unless agreed differently between Novartis and the Investigator.

7.2.4.1.2 Pharmacodynamic markers

Pharmacodynamic assessments in tumor samples

Collection of paired tumor samples is critical to assess the pharmacodynamic effect of MBG453 as a single agent and MBG453 in combination with either PDR001 or decitabine in the tumor. Newly obtained screening- and on-treatment paired tumor samples are required and are collected at screening and on-treatment as indicated in Table 7-10 and Table 7-11. Exceptions may be made on a case by case basis after discussion between Novartis and the Investigator.

The pre- and on-treatment paired tumor samples will be used to assess MBG453 single agent and in combination with either PDR001 or decitabine, target modulation with established immunohistochemical methods and RNA expression analysis.

[redacted]

7.2.4.2 Blood sample collection

Blood samples will be collected as specified in Table 7-10 or Table 7-11 to characterize markers of activation in immune cells and circulating levels of cytokines. [redacted]

All blood samples will be collected and processed as described in the [CMBG453X2101 Laboratory Manual].

[redacted]

[redacted]

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained. 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 of the patient's eCRF. Adverse event monitoring should be continued for at least 150days 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 seriousness criterion); rather, information about deaths will be collected through a Death form.

[redacted]

The occurrence of adverse events should be sought by non-directive questioning of the patient 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 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)
- Its duration (Start and end dates)
- Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
- Action taken with respect to study or investigational 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.

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 or as per RECIST), should not be reported as a serious adverse event.

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

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events 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 AE (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 RECIST or irRC. 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 only be reported if the event is suspected to be causally related to a study procedure as assessed by the investigator (e.g. an invasive procedure such as biopsy). 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 informed consent and until at least 150 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 150 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE 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.

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 [For Japan: sites participating in FIH studies must complete the SAE report form in English], and submit the completed form within 24 hours Novartis. Detailed instructions regarding the submission process and requirements for signatures are to be found in the investigator folder provided to each site.

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

If the SAE is not previously documented in the [PDR001 Investigator's Brochures] or [MBG453 Investigator's Brochures] or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, a Chief Medical Office and Patient Safety 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 outcomes should be collected for the female partners of any males who took study treatment in this study and the newborn will be followed up to 12 months after delivery date. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

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

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 formal data monitoring board will not be used for this study. This is an open-label, Phase I-Ib/II study in which patients will receive MBG453 as single agent or in combination 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 10.4.2).

[redacted]

During the phase II part of the study individual patient data will be reviewed on an ongoing basis and aggregate safety data and the primary endpoint 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 patient authorization informing the patient of the following:

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

In the event that a patient revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients 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 patient 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 (Patient 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 Patient Initials. Year of birth will be solicited (in the place of exact date of birth) to establish that the patient satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

[redacted]

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 eCRFs 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 eCRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, administered, 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 eCRFs 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 eCRF 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 eCRFs 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 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 Contract Research Organization (CRO) for central review when needed. Designated investigational site staff will enter the information required by the protocol into the appropriate eCRF and/or designated laboratory requisition forms. Field monitors will review the eCRFs and laboratory paper requisition forms for accuracy and completeness and instruct site personnel to make any required corrections or additions. One copy of the requisition form will be forwarded to each analytical laboratory with the respective sample(s) by the field monitor or by the designated investigational site staff; and one copy will be retained at the investigational site.

[redacted]

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 is required to respond promptly to queries and to make any necessary changes to the data.

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

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

For EDC studies, after database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

10 Statistical methods and data analysis

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

The study data will be analyzed and reported based on all patients' data of the dose escalation and Phase II parts up to the time when all patients have potentially completed at least six cycles of treatment or discontinued the study. 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. An interim CSR may also be prepared, if considered appropriate by the study team.

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

- For the phase I part, cohorts and patient groups treated with the same dose (dose levels and schedules) will be pooled into a single treatment group. Japanese patients and ROW patients will be separated into each of their respective single treatment group. All summaries, listings, figures and analyses will be performed by treatment group.
- For the phase Ib part (including optional dose ranging part), cohorts and patient groups 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. The additional phase Ib part referring to the SCLC patients (run-in part) will be analyzed separately.
- For the phase II part, all summaries, listings, figures for primary efficacy analysis and safety analyses will be presented by patient group. Patients from the phase II part will be

[redacted]

classified according to the patient group to which they were assigned at baseline based on the disease type. The additional phase II part referring to the SCLC patients (including the safety run-in part) will be analyzed separately.

Single agent phase I:

- Up to two indications for which response has been observed in the phase I dose escalation may be explored

Combination phase II (MBG453 in combination with PDR001):

- Group 1: Melanoma (naïve to anti-PD-1/PD-L1)
- Group 2: Melanoma (pre-treated with anti-PD-1/PD-L1)
- Group 3: NSCLC (naïve to anti-PD-1/PD-L1)
- Group 4: NSCLC (pre-treated with anti-PD-1/PD-L1)
- Group 5: RCC (naïve to anti-PD-1/PD-L1)
- Group 6: RCC (pre-treated with anti-PD-1/PD-L1)

Note that for one of the combination phase II groups an exploration of Q2W versus Q4W dosing may be conducted. The group to be used for this comparison will be chosen based on feasibility. Data from the two dosing schedules will be summarized separately.

Note: patients from the Phase I-Ib dose escalation parts and the Phase II part will not be pooled in any analyses unless otherwise specified. In addition, Japanese patients will not be pooled with ROW patients in any analyses unless otherwise specified in the RAP.

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.

Any reference to MBG453 in combination with decitabine is not applicable in this study as the enrolment of SCLC patients in this treatment will not open.

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 assigned single agent MBG453, or at least one full or partial dose of assigned combination of study drugs. 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 from the FAS who have received at least one dose of MBG453 or PDR001 or decitabine. Patients will be classified according to treatment 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.

[redacted]

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 FAS patients in the phase II part who meet the following criteria:

- Presence of at least one measurable lesion according to RECIST v1.1 as per Appendix 1;
- At least 2 post-baseline tumor assessments (unless disease progression is observed before that time);
- For Group 1, 3 and 5, as well as for the group treated with MBG453 in combination with decitabine, patients have not been previously treated with PD-1 or PD-L1 directed therapy. For Group 2, 4 and 6 patients must have previously received a PD-1 or PD-L1 directed therapy.

All major protocol deviations leading to exclusion from the PPS will be detailed in the RAP. 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

Phase I part (MBG453 single agent)

The DDS analysis 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. This constitutes an evaluable patient for the determination of MTD.

A patient is considered to have met the minimum exposure criterion if having received all planned doses of MBG453 during Cycle 1. Patients who do not experience a DLT during the first cycle are considered to have sufficient safety evaluations if they have been observed for ≥ 28 days following the first dose, and are considered by both Novartis and the Investigators to have enough safety data to conclude that a DLT did not occur.

Patients who do not meet these minimum dosing and safety evaluation requirements will be regarded as ineligible for the DDS and additional patients may be enrolled if required to meet the minimum cohort size for decision making, as described in Section 6.2.3.

Phase Ib part (MBG453 in combination with PDR001 or decitabine)

Cycle 1 risk set

The Cycle 1 risk set consists of all patients from the safety set in the dose escalation part who either meet the minimum exposure criterion for cycle 1 and have sufficient safety evaluations, or have experienced a DLT during Cycle 1.

A patient is considered to have met the minimum exposure criterion for Cycle 1 if they have received all planned dose of MBG453 with PDR001 or decitabine during Cycle 1.

[redacted]

For the cycle 1 risk set, 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 Novartis and the Investigators to have enough safety data to conclude that a DLT did not occur.

Cycle 2 risk set (for MBG453 single agent and MBG453 in combination with PDR001)

The Cycle 2 risk set consists of all patients in the cycle 1 risk set who (a) did not experience a DLT in Cycle 1, and (b) satisfy the minimum exposure criterion for Cycle 2 and have sufficient safety evaluations, or have experienced a DLT during Cycle 2.

A patient is considered to have met the minimum exposure criterion for Cycle 2 if they have received at least one planned dose of both MBG453 and PDR001 (at the same level as administered in Cycle 1) during Cycle 2.

For the Cycle 2 risk set, patients who do not experience a DLT during the second cycle are considered to have sufficient safety evaluations if they have been observed for ≥ 28 days following the first dose of Cycle 2, and are considered by both Novartis and the Investigators to have enough safety data to conclude that a DLT did not occur.

Patients who do not meet these minimum dosing and safety evaluation requirements will be excluded from the relevant risk set(s) and additional patients may be enrolled if required to meet the minimum cohort size for decision making, as described in Section 6.2.3.

10.1.5 Pharmacokinetic analysis set

The pharmacokinetic analysis set (PAS) consists of all patients who have at least one blood sample providing evaluable PK data. The PAS will be used for all PK analyses.

Note: Patients may be removed from the estimation of certain PK parameters on an individual basis depending on the number of available blood samples. These patients will be identified at the time of analysis.

10.2 Patient demographics/other baseline characteristics

Demographic and other screening/baseline data (including disease characteristics) will be listed in detail.

10.3 Treatments (study treatment, concomitant therapies, compliance)

For each of MBG453, PDR001 and decitabine, 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 MBG453, PDR001 or decitabine 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.

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 ATC term and treatment group.

[redacted]

The reason for discontinuation from treatment will be summarized and listed, along with dates of first and last doses of MBG453, PDR001 and decitabine (whatever is applicable), duration of exposure to MBG453, PDR001 and decitabine (whatever is 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-Ib parts

To characterize the safety and tolerability of MBG453 as a single agent and in combination with PDR001 or decitabine and to identify recommended doses for future studies.

Phase I-Ib dose ranging part (optional)

To further investigate the safety and tolerability of different doses of the MBG453 as single agent or in combination with PDR001.

Phase II part

To assess the anti-tumor activity of MBG453 as single agent or in combination with PDR001 or decitabine.

10.4.1 Variable

Phase I-Ib parts

- Safety: Incidence 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.

For MBG453 single agent, the primary variable is the incidence of DLTs in the first cycle of treatment.

For MBG453 in combination with PDR001, the primary variable is the incidence of DLTs in the first two cycles of treatment.

For MBG453 in combination with decitabine, the primary variable is the incidence of DLTs in the first cycle of treatment

Estimation of the MTD(s)/RP2D(s) will be based upon the estimation by the BHLRM (phase I) or BLRM (phase Ib) of the probability of a DLT in the DLT window for patients in the applicable analysis set.

For the SCLC group of patients, the MTD/RP2D will be based upon the rule defined in Section 10.4.2.

[redacted]

Phase I-Ib dose ranging part (optional)

- Safety: Incidence 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.

Phase II part

The primary variable is the Overall Response Rate (ORR), defined as the proportion of patients with a best overall response of CR or PR based on local Investigator assessment, as defined in RECIST v1.1 (Appendix 1).

Estimation of the true ORR in this part of the study will be based upon the observed ORR for patients in FAS, using a Bayesian analysis.

10.4.2 Statistical hypothesis, model, and method of analysis

Phase I part single agent MBG453 dose escalation

A Bayesian hierarchical logistical regression model (BHLRM) will be applied to estimate the relationship between dose and the probability of a patient experiencing a DLT for patients treated Q2W (stratum 1) and patients treated Q4W (stratum 2).

The standard Bayesian hierarchical model assumes full exchangeability of strata parameters; for the methodology and an application to binary data (Thall 2003, Chugh 2009). Here, we extend the standard Bayesian hierarchical model to dose-toxicity data, and exchangeable as well as non-exchangeable strata parameters.

In order to facilitate the inclusion of prior data in the model, a third stratum is added to the model. This additional stratum incorporated dose/DLT data from the dose escalation of PDR001, another checkpoint inhibitor expected to have a similar dose/toxicity profile to MBG453. By incorporating the prior data in this way the exchangeability (or otherwise) of the prior data with the on-study data will be assessed in an ongoing fashion, and if necessary the model will be able to compensate for differences between the prior data and data seen in the dose escalation of MBG453.

For the three patient strata, the probability of experiencing a DLT is modeled as follows:

$$\text{logit}\left(\pi_{Q2W}^{d}\right) = \log\left(\alpha_{Q2W}\right) + \quad_{Q2W} \log(d/240)$$

$$\text{logit}\left(\pi_{Q4W}^{d}\right) = \log\left(\alpha_{Q4W}\right) + \beta_{Q4W} \log(d/240)$$

$$\text{logit}\left(\pi_{PDR}^{d}\right) = \log(\alpha_{PDR}) + \beta_{PDR} \log(d/240)$$

[redacted]

where d denotes dose; 240 is a fixed reference dose for each respective strata; π^d_{Q2W} π^d_{Q4W}, and π^d_{PDR}, are the probability of a patient experiencing a DLT at dose d on the Q2W and Q4W dosing schedules, and in the [CPDR001X2101] study respectively; and the parameters $\theta_{Q2W} = \big(log(\alpha_{Q2W}), log(\beta_{Q2W})\big)$, $\theta_{Q4W} = \big(log(\alpha_{Q4W}), log(\beta_{Q4W})\big)$, and $\theta_{PDR} = (log(\alpha_{PDR}), log(\beta_{PDR}))$, describe the relationship between dose and toxicity for the three strata.

We further allow the parameters θ_{Q2W}, θ_{Q4W}, and θ_{PDR}, to be either exchangeable or non-exchangeable, with probability $\big(p_{Q2W}, 1 - p_{Q2W}\big)$, $\big(p_{Q4W}, 1 - p_{Q4W}\big)$, and $(p_{PDR}, 1 - p_{PDR})$ respectively.

1. Under exchangeability, the parameters θ_{Q2W}, θ_{Q4W}, and θ_{PDR} are assumed to follow a bivariate normal distribution:

$$\theta_{Q2W}, \theta_{Q4W}, \theta_{PDR} \sim BVN(m_{exch}, \mathrm{S}_{exch})$$

Prior distributions for the parameters m_{exch} and S_{exch} of the exchangeability distribution complete the model specifications for the exchangeability component of the model: $m_{exch} \sim F_m$, $\mathrm{S}_{exch} \sim G_S$

The prior distributions for m_{exch} will be normal and the prior distributions for the standard deviations and the correlation in S_{exch} will be log-normal and uniform, respectively.

1. Under non-exchangeability, the parameters θ_{Q2W} and θ_{Q4W}, and θ_{PDR} are assumed to have a weakly informative bivariate normal prior distribution.

$$\theta_{Q2W}, \theta_{Q4W}, \theta_{PDR} \sim BVN(m_w, \mathrm{S}_w)$$

All prior distributions will be defined before first patient first dose, and will be defined based on all available data at that time. The prior distributions will be fully described in the RAP.

Phase I part single agent MBG453 dose escalation with Japanese patients

Further, two BHLRM guided by EWOC principle will be used to make dose recommendations and estimate the MTD(s)/RP2D(s) during the dose escalation of the Japanese patients for both Q2W and Q4W schedules. Currently, available information about the dose-DLT relationships of single agent MBG453 in ROW patients will be used to inform the dose-DLT relationship of Japanese patients by taking into consideration of heterogeneity between Japanese patients (stratum 1) and ROW patients (stratum 2). For further details on the statistical model including the prior specification for the model parameters refer to Section 14.3 (Appendix 3). Data from the ROW patients will be updated in the model on an ongoing basis during the course of the study.

Phase Ib part combination of MBG453 and PDR001 dose escalation

For the combination phase Cycle 1 and Cycle 2, a 5-parameter model is used:

$$\mathrm{logit}\big(\pi^d_{MBG,i}\big) = \log\big(\alpha_{MBG,i}\big) + \beta_{MBG,i} \log\big(d^{0.5}_{MBG,i}/240^{0.5}\big)$$

$$\mathrm{logit}\big(\pi^d_{PDR,i}\big) = \log\big(\alpha_{PDR,i}\big) + \beta_{PDR,i} \log\big(d^{0.5}_{PDR,i}/240^{0.5}\big)$$

[redacted]

where i = 1 and 2 for Cycle 1 and 2, respectively; logit($\pi_{\cdot}^{d}$) = log[$\pi_{\cdot}^{d}$/{1- $\pi_{\cdot}^{d}$ }]; 240 is the reference dose of both MBG453 and PDR001.

Under independence, the odds of a DLT during cycle i at a given combination is

$$\frac{\pi_{MBG,i}^{d} + \pi_{PDR,i}^{d} - \pi_{MBG,i}^{d}\pi_{PDR,i}^{d}}{(1-\pi_{MBG,i}^{d})(1-\pi_{PDR,i}^{d})}$$

The possibility of synergism or antagonism between the safety profiles of the two drugs is then captured in modifying the odds by a dose-dependent factor:

$$odds_{MBG+PDR,i}^{d} = \frac{\pi_{MBG+PDR,i}}{1-\pi_{MBG+PDR,i}} = exp\left(\eta \, {d_{MBG,i}^{0.5}}\Big/{240^{0.5}} \, {d_{PDR,i}^{0.5}}\Big/{240^{0.5}}\right)\frac{\pi_{MBG,i}^{d} + \pi_{PDR,i}^{d} - \pi_{MBG,i}^{d}\pi_{PDR,i}^{d}}{(1-\pi_{MBG,i}^{d})(1-\pi_{PDR,i}^{d})}$$

Here,

- $\alpha_{MBG,i}$ and $\alpha_{PDR,i}$ are the odds of a DLT at the reference doses;
- $\beta_{MBG,i}$ and $\beta_{PDR,i}$ are the increase in the log-odds of a DLT by a unit increase in the log of the square root of dose;
- η is the interaction term.

The model is fitted to data from those patients eligible for the Cycle 1 and Cycle 2 risk sets (see Section 10.1.4), and provides estimates of the cumulative risk of DLT ($P_{MBG+PDR}$) up to the end of cycle 2 given doses $d_{MBG,i}$ and $d_{PDR,i}$ for i = 1,2. This cumulative risk is calculated as follows:

$$P_{MBG+PDR} = \pi_{MBG+PDR,1} + \left(1-\pi_{MBG+PDR,1}\right) \times \pi_{MBG+PDR,2}$$

No combination that exceeds the EWOC criteria (Section 6.2.3.1) will be considered for the next combination doses. A dose will not be tested in the Cycle 2 before having being studied successfully in Cycle 1. Any dose in Cycle 2 is always equal to or lower than the dose used in Cycle 1.

Optional: additional dose escalation using Q4W dosing schedule during Phase Ib dose escalation part

Should the optional dose escalation for MBG453 in combination with PDR001 following a Q4W dosing schedule take place, then a new model will be constructed. This model will follow the same functional form as that described above. Data from the Q2W dose escalation will be used to construct an informative prior distribution, which will be derived prior to first patient first treatment on the new dosing schedule. The priors will be fully documented in the RAP.

Dose recommendation

After each cohort of patients, the posterior distributions for the probabilities of DLT rates at different dose levels (or combinations) are 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:

[redacted]

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

For the single agent MBG453 and combination of MBG453 and PDR001 dose recommendation will also be guided by the EWOC principle, which mandates the dose for the next cohort and the full 2 cycle period for the combination to have less than 25% chance of excessive toxicity.

The final estimate of the MTD(s)/ RP2D(s) will also satisfy this condition.

Phase Ib part (run-in) combination of MBG453 and decitabine

A rule-based model is used for the group of the SCLC patients treated with MBG453 in combination with decitabine. Since the starting dose of the specific combination is anticipated to be well tolerated, the assessment of DLT data will be made after all six patients evaluable for the dose determining analysis set (Section 10.1.4) have completed one cycle of treatment, unless they have experienced a DLT before. The safety of the combination will be evaluated based on all available data at the confirmation decision with the Investigators and Novartis. If there are 2 or more DLTs within those 6 patients, 6 additional patients will be accrued to the -1 dose level (Table 6-4). In case there are 2 or more DLTs within the 6 evaluable for the dose determining analysis set patients in the -1 dose level, then this combination will stop due to excessive toxicity.

The dose level in which the two predefined rules are satisfied (less than 2 patients experiencing DLTs among the 6 patients evaluable for the dose determining analysis set) will be considered the final estimate of the MTD and will be used as the recommended dose for the phase II part of the study for the group of SCLC patients.

Listing of DLTs

DLTs will be listed and their incidence may be summarized by primary system organ class, worst grade based on the CTCAE version 4.03 and type of AE. The DDS will be used for these summaries.

Phase II part

A Bayesian design will be used in order to estimate ORR for each of the following patient groups. The primary analysis will be on ORR as defined under RECIST 1.1, with a secondary analysis on ORR as defined under irRC.

MBG453 single agent

- Up to two indications for which response has been observed in the phase I dose escalation

MBG453 in combination with PDR001

- Group 1: Melanoma (naïve to anti-PD-1/PD-L1)
- Group 2: Melanoma (pre-treated with anti-PD-1/PD-L1)
- Group 3: NSCLC (naïve to anti-PD-1/PD-L1)
- Group 4: NSCLC (pre-treated with anti-PD-1/PD-L1)

- Group 5: RCC (naïve to anti-PD-1/PD-L1)
- Group 6: RCC (pre-treated with anti-PD-1/PD-L1)

Note that for one of the combination phase II groups an exploration of Q2W versus Q4W dosing may be conducted. Data from the two dosing schedules will be summarized separately.

MBG453 in combination with decitabine

- SCLC (naïve to anti-PD-1/PD-L1 therapy)

Initially, approximately 15 patients will be enrolled to each of the above defined patient groups. Should enrollment for any of these groups not be feasible, then enrollment to that group may be closed before the 15 patient target is met. Should 3 or more responses be observed in any patient group, then enrollment to that group may be extended to 25 patients.

For the SCLC group of patients treated with MBG453 in combination with decitabine a total of approximately 15 patients will be enrolled at the MTD/RP2D (including the 6 patients treated at the same dose level in the Phase Ib part of the study).

For all patient groups, a minimally informative unimodal beta prior distribution of the true ORR is derived as follows. A priori it is assumed that the true mean of the ORR equals 20%. A true ORR of 20% is the midpoint between limited and moderate efficacy and serves as a compromise between a skeptical view assuming the treatment has only limited efficacy and an optimistic view assuming the treatment has moderate efficacy. The parameter of the minimally informative beta prior distribution of the ORR are then derived as $a = 1/4$ and $b = 1$.

At completion of the study, this prior distribution will be updated with all of the data available. Once updated, the estimate of ORR and probabilities that the true ORR lies in the following categories will be reported:

- [0, 10%) unacceptable efficacy
- [10%, 20%) limited efficacy
- [20%, 50%) moderate efficacy
- [50%, 100%] clinically relevant efficacy

For patient groups with a minimum of 15 patients, if the observed ORR is equal to or greater than 20%, then this will be considered as preliminary evidence of at least moderate efficacy in the respective patient group.

For $n = 15$, if the observed ORR is less than 10% (i.e. 1 CR or PR), then unacceptable efficacy will be concluded. If the observed ORR is greater than or equal to 20% (i.e. ≥ 3 CR or PR), then the true ORR has a posterior probability of 85.4% of at least limited efficacy.

For $n = 25$, if the observed ORR is less than 10% (i.e. < 3 CR or PR), then unacceptable efficacy will be concluded. If the observed ORR is greater than or equal to 20% (i.e. ≥ 5 CR or PR), then the true ORR has a posterior probability of 92.1% of at least limited efficacy.

See Table 10-3 for operating characteristics of the design.

[redacted]

10.4.3 Handling of missing values/censoring/discontinuations

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

Patients in the phase II part who have BOR of Unknown (UNK) or not assessed (NA) will be considered as a treatment failure in the primary analysis of ORR. Patients with individual scans of UNK or NA will be handled according to RECIST v1.1 (Appendix 1).

Other missing data will simply be noted as missing on appropriate tables/listings.

10.4.4 Supportive analyses

For the phase II part, the primary analysis on ORR may be repeated using the PPS. Additional supportive or exploratory analyses will be conducted to support the primary objective, if appropriate, and the details of these analyses will be defined in the RAP.

10.5 Secondary objectives

Please refer to Table 3-1 for the secondary objectives. The following subsections describe the analyses of related secondary objectives.

10.5.1 Key secondary objective(s)

Not applicable.

10.5.2 Other secondary efficacy objectives

Phase I-Ib parts

To assess the preliminary anti-tumor activity of MBG453 single agent or in combination with PDR001 or decitabine. The evaluations of tumor responses will be based on local investigator assessment according to RECIST v1.1 and irRC.

For all efficacy analysis in phase I-Ib parts, data will be listed, and may be summarized or analyzed by treatment group where applicable.

Phase II part

To assess the anti-tumor activity of MBG453 single agent or in combination with PDR001 or decitabine. The evaluations of tumor responses will be based on local investigator assessment according to RECIST v1.1 and irRC.

For all efficacy analysis in phase II part, data will be listed, summarized or analyzed by patient group (as defined in Section 10.4.2) for patients treated at the MTD(s)/RP2D(s).

The following endpoints and analyses will be used to assess the efficacy for phase I-Ib and phase II parts:

- BOR is defined as the best response recorded from the start of the treatment until disease progression/recurrence as defined for RECIST v1.1 and irRC. Complete and partial responses must be confirmed by repeat assessments that should be performed not less than

[redacted]

4 weeks after the criteria for response are first met. Additionally, for irRC, progressive disease should be confirmed in a similar manner.

- ORR, defined as the proportion of patients with best overall response of CR or PR.
- PFS:
  - For RECIST v1.1, PFS is 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.
  - For irRC PFS is defined as the time from the date of start of treatment to the date of the first documented and confirmed progression, or death due to any cause. Progressive disease should be confirmed by a repeat assessment that should be performed not less than 4 weeks after the criteria for progression are first met. The date of progression will then be the date of the first of these two assessments. For patients without a confirmation assessment, and with no subsequent assessments of SD, or better, a single assessment will be used as date of progression. If a patient has not had an event, PFS will be censored at the date of the last adequate tumor evaluation.
- OS, defined as the time from date of start of treatment to date of death due to any cause. If a patient is not known to have died, survival will be censored at the date of last known date patient alive.
- DOR, defined for responder as the time between the date of first documented response (CR or PR) and the date of first documented progression or death due to underlying cancer. If progression or death due to underlying cancer has not occurred, then the patient is censored at the date of last adequate tumor assessment.

Individual lesion measurements and overall response assessments will be listed by patient and assessment date. Best overall response (BOR) will be listed and tabulated.

The primary analysis of ORR will be as described in Section 10.4.2. Additionally ORR will be summarized as point estimate and corresponding 90% exact confidence interval (CI) according to Clopper-Pearson method (Clopper and Pearson 1934).

BOR will be summarized as observed proportion in each category, and corresponding 90% exact CI.

PFS will be analyzed using Kaplan-Meier estimates (Kaplan and Meier 1958) (including graphical representation) with CIs of median survival for each treatment group/patient group. In addition, median PFS and related 95% CI will be presented for each treatment group/patient group.

OS data will be listed for all patients enrolled in the Phase I-Ib and Phase II parts. Descriptive statistics for OS endpoint (e.g., median OS and 90% CI of the Kaplan-Meier estimates) will be provided as appropriate by treatment group and furthermore by disease group (melanoma, NSCLC and RCC) for patients treated at the MTD(s)/RP2D(s).

DOR and time to response (TTR) will be listed for all patients who achieved a response of CR or PR. 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.

Any additional analyses of efficacy endpoints will be described in the RAP.

[redacted]

10.5.3 Safety objectives

Another secondary objective is to characterize the safety and tolerability of MBG453 single agent and in combination with PDR001 or decitabine.

Incidence and severity of AEs and SAEs, changes in laboratory values, electrocardiograms and vital signs will be used to assess the safety of MBG453 single agent and combination with PDR001 or decitabine.

10.5.3.1 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.

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

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

10.5.3.2 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.

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

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). SEC will be specified in a case retrieval sheet (CRS) or in the RAP and finalized prior to database lock.

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

10.5.3.3 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.

[redacted]

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 (see below for details).
- Shift tables using CTCAE grades to compare baseline to the worst on-treatment value.
- Listing of all clinically relevant laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.

In addition to the above mentioned tables and listings, other exploratory analyses, for example figures plotting time course of raw or change in laboratory tests over time or box plots might be specified in the RAP.

10.5.3.4 Other safety data

ECG

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

Vital signs

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

- Shift table baseline to worst on-treatment result.

10.5.3.5 Supportive analyses for secondary objectives

Not applicable.

10.5.3.6 Tolerability

The tolerability of the study treatment will be assessed by summarizing the number of dose interruptions or changes. The reason for dose interruption and dose reduction and dose change will be listed by patient and summarized.

10.5.4 Pharmacokinetics

The pharmacokinetic parameters that will be assessed are presented in Table 10-1.

Table 10-1 Noncompartmental pharmacokinetic parameters

AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume-1)
AUCinf	The AUC from time zero to infinity (mass x time x volume-1)
AUCtau	The AUC calculated to the end of a dosing interval (tau) at steady-state (amount x time x volume-1)
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass x volume-1)
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)
T1/2	The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve (time). Use qualifier for other half-lives

[redacted]

CL	The total body clearance of drug from the plasma (volume x time-1)
V	The apparent volume of distribution during terminal phase (associated with λz) (volume)
AR	Accumulation Ratio = Cmax (multiple Dose)/Cmax (single dose)

PAS will be used in all pharmacokinetic data analysis and PK summary statistics.

Pharmacokinetic variables

The following pharmacokinetic parameters will be determined using non-compartmental method(s) for MBG453 single agent and in combination with PDR001 or deciatbine:

AUCinf, AUClast, Cmax, Tmax, T1/2, CL, V and accumulation ratio.

Bio-fluid concentrations will be expressed in mass per volume units. All concentrations below the limit of quantitation or missing data will be reported as such in the concentration data listings. Concentrations below the limit of quantitation will be treated as zero in summary statistics.

Descriptive statistics of all pharmacokinetic parameters will include arithmetic and geometric mean, median, SD, and CV, geometric CV, minimum and maximum. 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 given for this parameter.

Summary statistics will be presented for MBG453 and PDR001 serum concentrations at each scheduled time point. Descriptive graphical plots of individual serum concentration versus time profiles and mean concentration versus time profiles will be generated.

Further analyses may be conducted using population PK approaches. In addition, a model based approach may be used to explore the potential relationship between efficacy, safety, and/or biomarker endpoints (e.g., soluble receptor and/or receptor occupancy) and MBG453 and/or PDR001 concentration and/or exposure metrics. Any analyses performed will be specified either in the RAP or in a stand-alone analysis plan document. All analyses will be reported either in the CSR or a stand-alone report.

Dose proportionality

The analysis of dose proportionality will be conducted for AUC and Cmax of MBG453 single agent, MBG453 in combination with PDR001 and PDR001 in combination with MBG453 using a power model on log-transformed scale. The log-transformed PK parameters will each be regressed onto a fixed factor for log (dose). The 90% CI of the slope for each PK parameter will be computed from the model and presented in a summary table.

10.5.4.1 Data handling principles

Missing concentration values will be reported as is in data listings. Concentration values below Lower limit of quantitation (LLOQ) will be handled as zero in summary statistics, and reported as is in data listings. Any missing pharmacokinetic parameter data will not be imputed.

10.5.5 Biomarkers

[redacted]

[redacted]

If the number of samples is inadequate to perform a rigorous data analysis, then the available data will only be listed. Additional analyses that may be performed after the completion of the primary CSR will be documented in separate reports.

These analyses may include but are not limited to the meta-analysis of data from this study combined with data from other studies [redacted]. Any additional data analysis will be described in an addendum of the RAP modules or in a stand-alone analysis plan document, as appropriate.

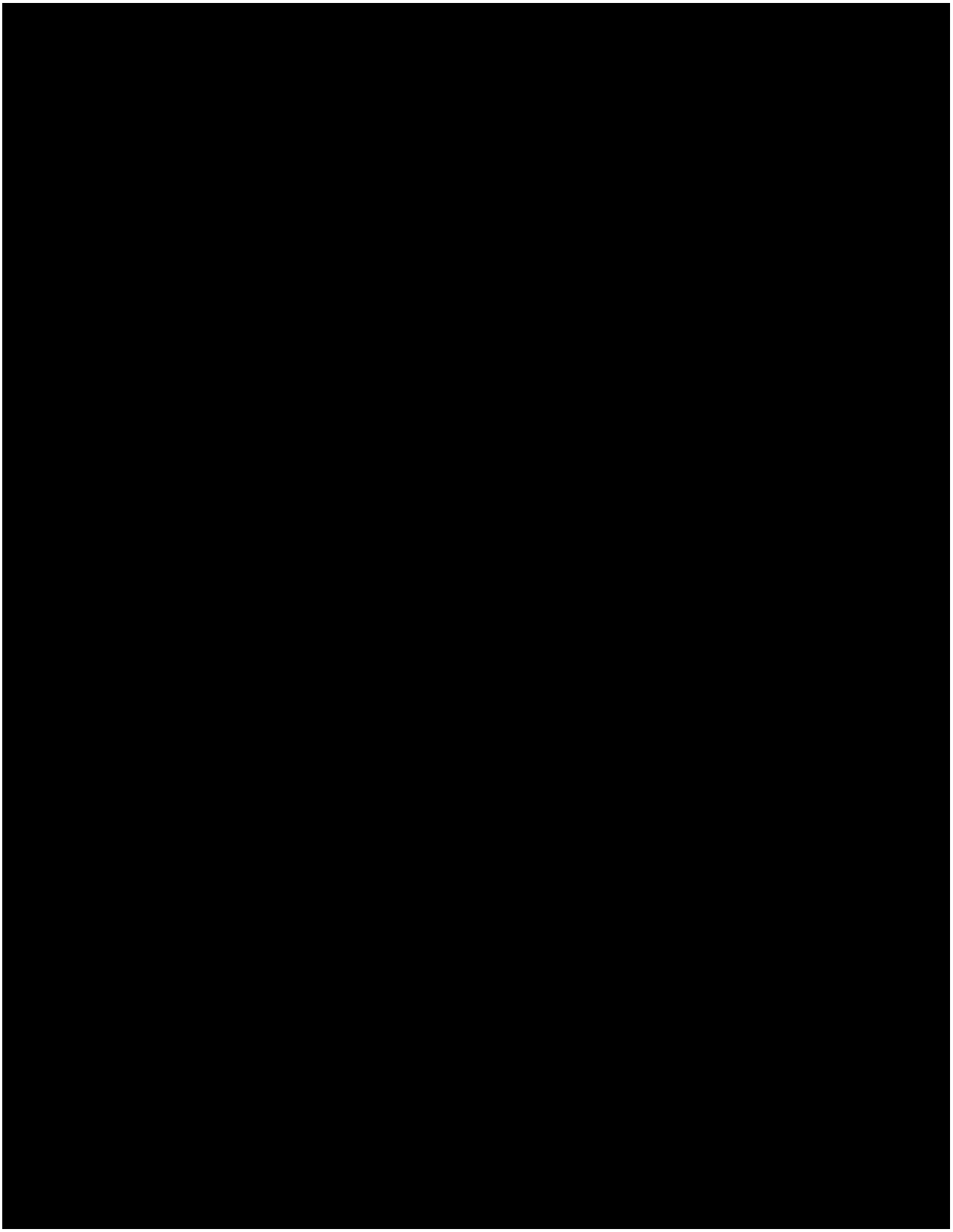
Potential predictor of efficacy

The expression level of PD-L1 and TIM-3, at screening/baseline will be listed and summarized. [redacted] Other immunological markers such as, CD8, FoxP3, CD68 may be listed and summarized [redacted]

Pharmacodynamic Markers

The pharmacodynamic marker, TIL counts will be assessed using paired tumor samples at screening/baseline and on-treatment (several time points as detailed in Table 7-10). Assessments at screening/baseline and on-treatment and change from baseline will be listed by patient and summarized (when sample size is sufficient) using descriptive statistics. Any association/correlation analyses with other endpoints (PK, early clinical activity) will be detailed in the RAP or in a stand-alone analysis plan document, as appropriate.

[redacted]



10.7 Interim analysis

No formal interim analyses are planned.

Phase I-Ib dose escalation part

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 of MBG453 as single agent or in combination with PDR001 has to be chosen depending on the observed data. Similar procedure will be followed after each dose level tested in the run-in part of the SCLC patients treated with MBG453 in combination with decitabine Details of this procedure and the process for communication with Investigators are provided in Section 6.2.3.

Phase II part

Data from patients will be reviewed on an ongoing basis to monitor the safety and tolerability of the RP2D part of the study. The sample size in any of the 6 groups may be extended to approximately 25 patients, if at least 3 patients have a response (PR or CR) per RECIST v1.1 or irRC (this is not applicable to the SCLC group of patient treated with MBG453 in combination with decitabine). The Investigators and Novartis study personnel will make the decision based on a synthesis of all relevant data available including safety, PK and PD information.

10.8 Sample size calculation

Any reference to MBG453 in combination with decitabine is not applicable in this study as the enrolment of SCLC patients in this treatment will not open.

Phase I-Ib dose escalation parts

ROW patients: Cohorts of 3 to 6 evaluable patients will be enrolled in the dose-escalation part including at least six patients at the MTD(s)/RP2D(s) level, as described in Section 6.2.3. Multiple cohorts may be sequentially enrolled to the same dose level. Additional cohorts of 1 to 6 patients may be enrolled at any dose level below the estimated MTD(s)/RP2D(s) for further elaboration of safety and pharmacokinetic parameters as required. At least 21 patients are expected to be treated in the single agent and 15 patients are expected to be treated in the

combination of in the dose escalation part, for the model to have reasonable operating characteristics relating to its MTD recommendation.

Japanese patients: Initially, cohorts of 1 to 6 evaluable patients will be enrolled in the single agent dose-escalation part with Japanese patients. Upon observation of specific toxicities (see Section 6.2.3 for details), minimum cohorts size of 3 evaluable patients will be enrolled including at least 6 patients at the MTD/RP2D level, as described in Section 6.2.3. Multiple cohorts may be sequentially enrolled to the same dose level. Additional cohorts of 1 to 6 patients may be enrolled at any dose level below the estimated MTD/RP2D for further elaboration of safety and pharmacokinetic parameters as required. At least 12 patients are expected to be treated in the single agent dose-escalation part with Japanese patients, for the model to have reasonable operating characteristics relating to its MTD recommendation.

Phase Ib run-in part for the SCLC patients

A cohort of 6 evaluable patients for the Dose Determining analysis Set (or twelve in total if the suggested dose level is considered toxic) will be enrolled in the run-in part including thus at least six patients at the MTD/RP2D level, as described in Section 6.2.3.

Phase I-Ib dose ranging part (optional)

A sample size of approximately 30-50 patients with advanced solid tumors will be treated at different dose levels of MBG453 as single agent or in combination with PDR001. The aim is to gain more information about the overall safety and tolerability, and to provide additional PK and PD data to guide the selection of dosing for future studies with the combination and identify anti-tumor activity. A minimum of 30 patients will result in 95.8% probability of detecting at least one special adverse event of interest with a true rate of 10%. This probability rises as the true adverse event rate increases.

There is no statistical hypothesis being tested for efficacy within this group. Patients within this group will have their activity monitored to assess if there is any indication of potential impact on tumor lesions, and the data will be used for internal decision making on the future development of the combination in alternative indications and dose levels.

Table 10-2 Probability to detect at least one special adverse event of interest

Special AE of interest incidence rate	Number of patients			
	10	20	30	50
10%	0.651	0.878	**0.958**	0.995
15%	0.803	0.961	0.992	1.000
20%	0.893	0.988	0.999	1.000

Phase II part

Approximately 15 patients will be initially enrolled to each of the patient groups. However, should enrollment for any of these groups not be feasible, then enrollment to that group may be closed before the 15 patient target is met. Any of the groups may be extended to approximately 25 patients in the event that 3 or more responses are observed. This extension is not applicable

to the SCLC group of patient treated with MBG453 in combination with decitabine.The operating characteristics of the design is shown in Table 10-3, including the probability of stopping the enrollment at 15 patients (fewer than 3 responses in the first 15 patients) and posterior probability of true ORR of at least limited efficacy. It was assessed how likely it is to wrongly declare activity as defined by observing at least "moderate efficacy" (i.e. seeing ≥ 5 responses out of 25 patients) given the true ORR = 10%, and how likely it is to correctly declare activity given the true ORR = 30% when 25 patients are evaluated.

- If the true ORR = 10%, the probability to wrongly declare activity is 9.8%.
- If the true ORR = 30%, the probability to correctly declare activity is 91.0%.

Table 10-3 Operating characteristics of the design for ORR

Pr(observe < 20% responses in N patients)						
N / True ORR	0.1	0.15	0.2	0.25	0.3	0.4
10	73.6	54.4	37.6	24.4	14.9	4.6
15	81.6	60.4	39.8	23.6	12.7	2.7
20	86.7	64.8	41.1	22.5	10.7	1.6
25	**90.2**	68.2	42.1	21.4	**9.0**	0.9
Posterior probability of a true ORR corresponding to at least limited efficacy (i.e. ≥10%)						
N / True ORR	0.1	0.15	0.2	0.25	0.3	0.4
10	44.7	64.5	79.5	89.3	94.9	99.1
15	45.5	69.2	**85.4**	94.1	98.0	99.8
20	46.0	72.8	89.4	96.7	99.2	100
25	46.4	75.8	**92.1**	98.1	99.6	100

Testing of Q2W versus Q4W dosing scheduling during the Phase II combination part of MBG453 in combination with PDR001

To facilitate comparison between Q2W and Q4W dosing in the chosen indication, patients will be randomized between the two dosing schedules. Initially 15 patients will be enrolled to each arm, should 3 or more responses be observed in either arm, then enrollment for both arms will be extended to 25 patients.

10.9 Power for analysis of key secondary variables

Not applicable.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

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

11.2 Responsibilities of the investigator and IRB/IEC/REB

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

11.3 Informed consent procedures

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

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 patient'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.

Additional consent form

Sub-studies [redacted] will have a separate consent form covering those studies. This form will be adapted for each Study based on a standard template used globally for all Studies. These informed consent forms will be submitted for ethical approval together with the Study Protocol and the main informed consent form of the Study. If a patient opts not to participate in the optional assessments, this in no way affects the patient's ability to participate in the main research study.

[redacted]

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 assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

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 patients. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of Novartis 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, patients' 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 patient files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The 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 eCRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic eCRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper eCRFs.

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.

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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 Novartis 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]

13 References (available upon request)

Anderson AC, Anderson DE, Bregoli L, et al (2007). Promotion of tissue inflammation by the immune receptor Tim-3 expressed on innate immune cells. Science.;318(5853):1141-3.

Anderson AC (2014). Tim-3: an emerging target in the cancer immunotherapy landscape. Cancer Immunol Res.;2(5):393-8.

Ansell SM, Lesokhin AM, Borrello I, et al (2015). PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med.;372(4):311-9.

Asayama T, Tamura H, Ishibashi M, et al (2017). Functional expression of Tim-3 on blasts and clinical impact of its ligand galectin-9 in myelodysplastic syndromes. Oncotarget; 8:88904-17.

Brahmer J, Reckamp KL, Baas P, et al (2015). Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med. ;373(2):123-35.

Brahmer JR, Lacchetti C, Schneider BJ et al (2018) Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol; Epub ahead of print.

Chiba S, Baghdadi M, Akiba H, et al (2012). Tumor-infiltrating DCs suppress nucleic acid-mediated innate immune responses through interactions between the receptor TIM-3 and the alarmin HMGB1.Nat Immunol.;13(9):832-42.

Chugh R, Wathen JK, Maki RG, et al (2009). Phase II multicenter trial of imatinib in 10 histologic subtypes of sarcoma using a bayesian hierarchical statistical model. J Clin Oncol.;27(19):3148-53.

Clopper CJ and Pearson ES (1934). The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. Biometrika.; 26,(4):404-13.

da Silva IP, Gallois A, Jimenez-Baranda S, et al (2014). Reversal of NK-cell exhaustion in advanced melanoma by Tim-3 blockade. Cancer Immunol Res.;2(5):410-22.

Dardalhon V, Anderson AC, Karman J, et al (2010). Tim-3/galectin-9 pathway: regulation of Th1 immunity through promotion of CD11b+Ly-6G+ myeloid cells. J Immunol.;185(3):1383-92.

DeKruyff RH, Bu X, Ballesteros A, et al (2010). T cell/transmembrane, Ig, and mucin-3 allelic variants differentially recognize phosphatidylserine and mediate phagocytosis of apoptotic cells. J Immunol. 15;184(4):1918-30.

de Mingo Pulido A, Gardener A, Hiebler S, et al (2018) TIM-3 regulates CD103+ dendritic cell function and response to chemotherapy in breast cancer. Cancer Cell; 33(1):60-74.

Fazio C, Covre A, Cutaia O, et al (2018). Immunomodulatory properties of DNA hypomethylating agents: selecting the optimal epigenetic partner for cancer immunotherapy. Front Pharmacol.; 9:1443.

[redacted]

Fourcade J, Sun Z, Benallaoua M, et al (2010). Upregulation of Tim-3 and PD-1 expression is associated with tumor antigen-specific CD8+ T cell dysfunction in melanoma patients. J Exp Med.;207(10):2175-86.

Francisco LM, Sage PT, Sharpe AH (2010). The PD-1 pathway in tolerance and autoimmunity. Immunol Rev.;236:219-42.

Gao X, Zhu Y, Li G, et al (2012). TIM-3 Expression Characterizes Regulatory T Cells in Tumor Tissues and Is Associated with Lung Cancer Progression. PLoS One.;7(2):e30676.

Garon EB, Naiyer AR, Rina Hui, MB et al (2015). Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer. N Engl J Med 2015; 372:2018-28.

Ghoneim HE, et al (2017) De novo epigenetic programs inhibit PD-1 blockade-mediated T cell rejuvenation. Cell; 170(1): 142–157

Golden-Mason, L, Palmer BE, Kassam N, et al (2009). Negative immune regulator Tim-3 is overexpressed on T cells in hepatitis C virus infection and its blockade rescues dysfunctional CD4+ and CD8. J. Virol. 83:9122–30.

Guideline on clinical trials in small populations available at:.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003615.pdf

Hamid O, Robert C, Daud A, et al (2013) Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. N Engl J Med.; 369:134–44.

Hamid O and Carvajal RD (2013b) Anti-programmed death-1 and anti-programmed death-ligand 1 antibodies in cancer therapy. Expert Opin Biol Ther.;13:847-61.

Haanen JBAG, Carbonnel F, Robert C et al (2017) Management of toxicities from Immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol; 28:iv119–iv142.

Harding J, Patnaik A, Moreno V et al (2019) A phase Ia/Ib study of an anti-TIM-3 antibody (LY3321367) monotherapy or in combination with and anti-PD-L1 antibody (LY33300054): Interim safety, efficacy, and pharmacokinetic findings in advanced cancers, J. clinical oncology; 37.8_suppl.12.

Herbst RS, Soria JC, Kowanetz M, et al (2014). Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature; 515:563-67.

Homet Moreno B, Ribas A (2015). Anti-programmed cell death protein-1/ligand-1 therapy in different cancers. Br J Cancer.;112(9):1421-27.

Huang YH, Zhu C, Kondo Y, et al (2015). CEACAM1 regulates TIM-3-mediated tolerance and exhaustion. Nature.;517(7534):386-90.

Jones, RB, Ndhlovu LC, Barbour JD, et al. (2008). Tim-3 expression defines a novel population of dysfunctional T cells with highly elevated frequencies in progressive HIV-1 infection. J. Exp. Med. 205:2763–79.

[redacted]

Kantarjian HM, Thomas XG, Dmoszynska A et al.(2012). Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia. J. Clin. Oncol.; 30(21):2670-7.

Kaplan, EL and Meier, P (1958). Nonparametric estimation from incomplete observations. Journal of the American Statistical Association.;53:457-81.

Keir, ME, Butte, MJ, Freeman, GJ, Sharpe AH (2008). PD-1 and its ligands in tolerance and immunity. Ann Rev Immunol.; 26:677–04.

Kikushige Y, Miyamoto T, Yuda J, et al (2010). TIM-3 is a promising target to selectively kill acute myeloid leukemia stem cells. Cell Stem Cell.; 7(6):708-17.

Kikushige Y, Shima T, Takayanagi S, et al (2015). A TIM-3/Gal-9 autocrine stimulatory loop drives self-renewal of human myeloid leukemia stem cells and leukemic progression. Cell Stem Cell.; 17(3):341-52.

Koyama S, Akbay Esra A, Li Y,Herter Sprie G et al (2016). Adaptive resistance to therapeutic PD-1 blockade is associated with upregulation of alternative immune checkpoints. Nature communications.

Larkin J, Chiarion-Sileni V, Gonzalez R, et al (2015). Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med.;373(1):23-34.

Lemaire M, Chabot GG, Raynal NJ,et al. (2008) Importance of dose-schedule of 5-aza-2'-deoxycytidine for epigenetic therapy of cancer. BMC Cancer 8:128.

Lindblad KE, Goswami M, Hourigan CS, et al (2017). Immunological effects of hypomethylating agents. Expert Rev Hematol. 10(8): 745–752

Lyford-Pike S, Peng S, Young GD, et al (2013). Evidence for a role of the PD-1:PD-L1 pathway in immune resistance of HPV-associated head and neck squamous cell carcinoma.Cancer Res.; 73(6):1733-41.

Mangsbo SM, Sandin LC, Anger K, et al (2010). Enhanced tumor eradication by combining CTLA-4 or PD-1 blockade with CpG therapy. J Immunother.; 33:225–35.

Michel Ortega RM, Drabkin HA (2015). Nivolumab in renal cell carcinoma. Expert Opin Biol Ther.;15(7):1049-60.

Mkrtichyan M, Najjar YG, Raulfs EC, et al (2011). Anti-PD-1 synergizes with cyclophosphamide to induce potent anti-tumor vaccine effects through novel mechanisms. Eur J Immunol.; 41: 2977–86.

Momparler RL, Bouffard DY, Momparler LF, et al.(1997) Pilot phaseI-II study on 5-aza-2'-deoxycytidine (decitabine) in patients with metastatic lung cancer. Anticancer Drugs 8:358–68.

Momparler RL, Ayoub J. (2001) Potential of 5-aza-2'-deoxycytidine (decitabine) a potent inhibitor of DNAmethylation for the therapy of advanced non-small cell lung cancer. Lung Cancer 334:S111–5.

[redacted]

Momparler RL (2005) Pharmacology of 5-aza-2′-deoxycytidine (decitabine). Semin Hematol 42S9–16 10.

Monney L, Sabatos CA, Gaglia JL, et al (2002). Th1-specific cell surface protein Tim-3 regulates macrophage activation and severity of an autoimmune disease. Nature.;415(6871):536-41.

Murphy K (2011). Janeway's Immunobiology. 8th ed; New York: Garland Science.

Ndhlovu LC, Lopez-Vergès S, Barbour JD, et al (2012). Tim-3 marks human natural killer cell maturation and suppresses cell-mediated cytotoxicity. Blood.;119(16):3734-43.

Neuenschwander B, Michael Branson M, Gsponer T (2008). Critical aspects of the Bayesian approach to phase I cancer trials Article first published online: Statistics in Medicine 27 (13): 2420–39.

Neuenschwander B, Capkun-Niggli G, Branson M, et al (2010) Summarizing historical information on controls in clinical trials. Clin Trials; 7:5-18.

Ngiow SF, von Scheidt B, Akiba H, et al (2011). Anti-TIM3 antibody promotes T cell IFN-γ-mediated antitumor immunity and suppresses established tumors. Cancer Res.;71(10):3540-51.

Nivolumab US label; available at:.accessdata.fda.gov/drugsatfda_docs/label/2015/125527s000lbl.pdf

Okazaki T, Chikuma S, Iwai Y, et al (2013). A rheostat for immune responses: the unique properties of PD-1 and their advantages for clinical application. Nat Immunol.;14(12):1212-18.

Orskov A, Treppendahl MB, Skovbo A, et al (2015). Hypomethylation and up-regulation of PD-1 in T cells by azacytidine in MDS/AML patients: a rationale for combined targeting of PD-1 and DNA methylation. Oncotarget; 6(11):9612-26.

Pauken KE, Sammons MA, Odorizzi PM, et al (2016). Epigenetic stability of exhausted T cells limits durability of reinvigoration by PD-1 blockade. Science ; 354(6316): 1160–1165Paz-Ares L, Horn L, Borghaei et al (2015). Phase III, randomized trial (CheckMate 057) of nivolumab (NIVO) versus docetaxel (DOC) in advanced non-squamous cell (non-SQ) non-small cell lung cancer (NSCLC). J Clin Oncol (Meeting Abstracts); 33: LBA109.

Pembrolizumab US label; available at:.accessdata.fda.gov/drugsatfda_docs/label/2014/125514lbl.pdf

Postow MA, Chesney J, Pavlick AC, et al (2015). Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med.;372(21):2006-17.

Postow MA, Chesney J, Pavlick AC, et al (2015). Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med.;372(21):2006-17 (supplementary appendix).

Powles T, Eder JP, Fine GD, et al (2014). MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature; 515:558-62.

[redacted]

Ready N, Farago AF, de Braud F, et al (2018). Third-line nivolumab monotherapy in recurrent SCLC: CheckMate 032. J Thorac Oncol.;14(2):237-44

Robert C, Ribas A, Wolchok JD, et al (2014) Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. Lancet; 384:1109-17.

Robert C, Schachter J, Long GV, et al (2015). Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med.;372(26):2521-32.

Rosenblatt, J, Glotzbecker B, Mills H, et al (2011). PD-1 blockade by CT-011, anti-PD-1 antibody, enhances ex vivo T-cell responses to autologous dendritic cell/myeloma fusion vaccine. J Immunother; 34:409–18.

Sabatos CA, Chakravarti S, Cha E, et al (2003). Interaction of Tim-3 and Tim-3 ligand regulates T helper type 1 responses and induction of peripheral tolerance. Nat Immunol.;4(11):1102-10.

Sakuishi K, Apetoh L, Sullivan JM, et al (2010). Targeting Tim-3 and PD-1 pathways to reverse T cell exhaustion and restore anti-tumor immunity. J Exp Med.;207(10):2187-94.

Sakuishi K, Ngiow SF, Sullivan JM, et al (2013). TIM3+FOXP3+ regulatory T cells are tissue-specific promoters of T-cell dysfunction in cancer. Oncoimmunology.;2(4):e23849.

Sánchez-Fueyo A, Tian J, Picarella D, et al (2003). Tim-3 inhibits T helper type 1-mediated auto- and alloimmune responses and promotes immunological tolerance. Nat Immunol.;4(11):1093-101.

Schrump DS, FischetteMR, NguyenDM, et al. (2006) PhaseI study of decitabine-mediated gene expression in patients with cancers involving the lungs, esophagus,or pleura. Clin CancerRes 12:5777–85.

Segal, NH, Hodi FS, Sanborn RE, et al (2014). A phase I dose escalation and cohort expansion study of lirilumab (anti-KIR; BMS-986015) in combination with nivolumab (anti-PD-1; BMS-936558, ONO-4538) in advanced solid tumors. J Clin Oncol (Meeting Abstracts):TPS3115.

Seiwert TY, Burtness B, Weiss J, et al (2014). A phase Ib study of MK-3475 in patients with human papillomavirus (HPV)-associated and non-HPV–associated head and neck (H/N) cancer. J Clin Oncol (Meeting Abstracts); 32(15s):6011.

Shin DS, Ribas A. (2015) The evolution of checkpoint blockade as a cancer therapy: what's here, what's next? Curr Opin Immunol.;33:23-35.

Sohlberg E, Pfefferle A, Andersson S, et al (2015). Imprint of 5-azacytidine on the natural killer cell repertoire during systemic treatment for high-risk myelodysplastic syndrome. Oncotarget; 6(33):34178-90.

Stone ML, Chiappinelli KB, Li H, et al (2017). Epigenetic therapy activates type I interferon signaling in murine ovarian cancer to reduce immunosuppression and tumor burden. PNAS 114(51) E10981-E10990.

Sunshine J, Taube JM (2015). PD-1/PD-L1 inhibitors. Curr Opin Pharmacol.;23:32-38.

[redacted]

Thall PF, Wathen JK, Bekele BN, et al (2003). Hierarchical Bayesian approaches to phase II trials in diseases with multiple subtypes. Stat Med.;22(5):763-80.

Topalian SL, Hodi SF, Brahmer JR, et al (2012) Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer. N Engl J Med.; 366: 2443-54.

Topalian SL, Sznol M, McDermott DF (2014) Survival, Durable Tumor Remission, and Long-Term Safety in Patients With Advanced Melanoma Receiving Nivolumab. J Clin Oncol.; 32:1020-31.

Wang W, Lau R, Yu D, et al (2009) PD-1 blockade reverses the suppression of melanoma antigen-specific CTL by CD4+ CD25(Hi) regulatory T cells. Int. Immunol.; 21,1065–77.

Weber JS, D'Angelo SP, Minor D, et al (2015). Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol.;16(4):375-84.

Weber, JS, Hodi, FS, Wolchok, JD, et al (2017) Safety profile of nivolumab monotherapy: a pooled analysis of patients with advanced melanoma. J Clin Oncol; 35: 785–792

Wolchok JD, Kluger H, Callahan MK, et al (2013). Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med.;369:122–33.

Yan J, Zhang Y, Zhang JP, et al (2013). Tim-3 Expression Defines Regulatory T Cells in Human Tumors. PLoS One.; 8(3): e58006.

Yang H, Bueso-Ramos C, DiNardo C, et al (2014). Expression of PD-L1, PD-L2, PD-1 and CTLA4 in myelodysplastic syndromes is enhanced by treatment with hypomethylating agents. Leukemia.; 28(6): 1280–1288.

Yang ZZ, Grote DM, Ziesmer SC, et al (2012). IL-12 upregulates TIM-3 expression and induces T cell exhaustion in patients with follicular B cell non-Hodgkin lymphoma. J Clin Invest.;122(4):1271-82.

Yu G, Wu Y, Wang W, et al (2018) Low-dose decitabine enhances the effect of PD-1 blockade in colorectal cancer with microsatellite stability by re-modulating the tumor microenvironment.Cellular and Molecular Immunology; 16:401–409.

Zacks, S., Rogatko, A. and Babb, J. (1998). Optimal Bayesian-feasibile dose escalation for cancer phase I trials. Statist. Probab. Lett. 38:215–20.

Zhang L, Gajewski TF, Kline J (2009) PD-1/PD-L1 interactions inhibit antitumor immune responses in a murine acute myeloid leukemia model. Blood.; 114(8):1545-52.Zhang Y, Ma CJ, Ni L, et al (2011). Cross-talk between programmed death-1 and suppressor of cytokine signaling-1 in inhibition of IL-12 production by monocytes/macrophages in hepatitis C virus infection. J Immunol.;186(5):3093-103.

Zhang Y, Ma CJ, Wang JM, et al (2012). Tim-3 regulates pro- and anti-inflammatory cytokine expression in human CD14+ monocytes. J Leukoc Biol.;91(2):189-96.

[redacted]

Zhou Q, Munger ME, Veenstra RG, et al (2011). Coexpression of Tim-3 and PD-1 identifies a CD8+ T-cell exhaustion phenotype in mice with disseminated acute myelogenous leukemia. Blood.;117(17):4501-10.

Zhu C, Anderson AC, Schubart A, et al (2005). The Tim-3 ligand galectin-9 negatively regulates T helper type 1 immunity.Nat Immunol. 2005;6(12):1245-52.

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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.

[redacted]

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.

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]

[1] SOD for CR may not be zero when nodal lesions are part of target lesions

[2] Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10 mm in size. In this case, the target lesion response is CR

[3] Methodology change See Section 14.1.2.2.

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.

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

[redacted]

- 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.

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

14.1.3 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.

[redacted]

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.

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)

[redacted]

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.

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.

[redacted]

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.

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.

[redacted]

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).

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.

[redacted]

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 assign the worst possible censoring time which could be observed in the study which is equal to the maximum follow-up time (i.e. time from FPFV to LPLV)
- at last adequate tumor assessment date otherwise. In this case patients have not yet progressed so they theoretically still have a chance of responding

Time to overall complete response (CR) is the time between dates of randomization/start of treatment until first documented CR. Similar analysis considerations including (if appropriate) censoring rules apply for this endpoint described for the time to overall response endpoint.

[redacted]

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 complete response) 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).

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.

[redacted]

- 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.

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.

[redacted]

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
F	New anticancer therapy given	(1) Date of last adequate assessment (2) Date of secondary anti-cancer therapy (3) Date of secondary anti-cancer therapy (4) N/A	Censored Censored Event Ignored
G	Deaths due to reason other than deterioration of 'Study indication'	(1) Date of last adequate assessment	Censored (only TTP and duration of response)

[1]=Definitions can be found in Section 14.1.3.2.7.

[2]=After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 14.1.3.2.7.

[3]=The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.

The primary analysis and the sensitivity analyses must be specified in the protocol. Clearly define if and why options (1) are not used for situations C, E and (if applicable) F.

[redacted]

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:

- **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).

[redacted]

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

[redacted]

- 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.

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.

[redacted]

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

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

[redacted]

*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.

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 diameters of the previously existing target lesions, and the sum of 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 10 lesions in total.

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 diameters for all target lesions is calculated (at baseline and throughout the study). The diameters of any new measurable lesions are included in the sum of diameters at each assessment to provide the total tumor burden. At each assessment, percent change in the sum of 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 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 irCR, and irPD in the case of unequivocal progression, as shown below in Table 14-6.

Like in RECIST 1.1, irCR and irPR must be confirmed at a new assessment after at least 4 weeks. Unlike RECIST 1.1, 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 measurable 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.
- 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 have not been assessed or have been assessed using a method significantly different from baseline that prevents reasonable comparison to the prior assessments.

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	Absent/Stable/not evaluated	irPR[a]
>-30 and<+20	Absent/Stable/not evaluated	irSD
≥+20	Any	irPD[a]
Any	Unequivocal progression	irPD[a]

*the diameter of new measurable lesions is included in the calculation of the sum of diameters.
[a] To be confirmed after at least 4 weeks.

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.

[redacted]

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 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; 19:3936-43.

[redacted]

14.3 Appendix 3: Statistical details of Bayesian regression models, priors, design operating characteristics and hypothetical dose escalation scenarios

14.3.1 Phase I part MBG453 single agent

A Bayesian hierarchical logistic regression model (BHLRM) guided by the escalation with overdose control (EWOC) principle will be used in the MBG453 single agent phase I part to establish the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) of MBG453 in patients with solid tumors. This section provides details of the statistical model, the derivation of prior distributions for the model parameters, and the properties of the adaptive design (dose recommendations for hypothetical data scenarios).

14.3.1.1 Statistical model and prior distributions

Section 10.4.2 outlined the model description for the BHLRM, here the derivation of the priors for that model is described as follows:

- Prior distributions for the exchangeability and non-exchangeability model components are derived.
- For each stratum (Q2W, Q4W, PDR001), the weight of the exchangeable and non-exchangeable mixture components are defined.
- Prior summaries for DLT rates at different dose levels are shown.

Prior for the non-exchangeable case

Under non-exchangeability, the parameter vectors θ_{Q2W}, θ_{Q4W}, and θ_{PDR} are assumed to have a weakly informative bivariate normal prior distribution,

$$\theta_{Q2W}, \theta_{Q4W}, \theta_{PDR} \sim BVN(\mathbf{m}_w, \mathbf{S}_w)$$

where $\mathbf{m}_w = (m_{w1}, m_{w2})$ and $\mathbf{S}_w = \begin{pmatrix} \tau_{w1}^2 & c\tau_{w1}\tau_{w2} \\ c\tau_{w1}\tau_{w2} & \tau_{w2}^2 \end{pmatrix}$ are the mean vector and covariance matrix.

For the purposes of setting the prior for the BLRM model, the median DLT rate at 80 mg Q2W is assumed to be at 5%, and the median DLT rate at 800 mg Q2W is assumed to be 10%. For the remaining doses, median DLT rates a priori are assumed linear in the logit-scale as a function of log-dose.

Based on the above specified medians for the DLT rate and wide prior confidence intervals, the optimal parameters of the bivariate normal distribution can be obtained following the procedure described by Neuenschwander 2008. This leads to the BVN distribution defined by $\mathbf{m}_w$ = (-2.692, -1.26), $\tau_{w1} = 2.484$, $\tau_{w2} = 0.745$ and $c = -0.765$.

To provide a simple, flexible prior, the same mean is retained, but the correlation is set to zero, and the standard deviations for $\log(\alpha)$ and $\log(\beta)$ approximated by 2 and 1, respectively, the prior for the non-exchangeable case is set to $\mathbf{m}_w$ = (-2.692, -1.26), $\mathbf{S}_w = \begin{pmatrix} 2^2 & 0 \\ 0 & 1^2 \end{pmatrix}$.

[redacted]

Prior for the exchangeable case

Under exchangeability, the parameters θ_{Q2W}, θ_{Q4W}, and θ_{PDR} are assumed to follow a bivariate normal distribution:

$$\theta_{Q2W}, \theta_{Q4W}, \theta_{PDR} \sim BVN(\boldsymbol{m}_{exch}, \mathbf{S}_{exch}),$$

where $\boldsymbol{m}_{exch} = (\mu_{e1}, \mu_{e2})$ and $\mathbf{S}_{exch} = \begin{pmatrix} \tau_{e1}^2 & \rho\tau_{e1}\tau_{e2} \\ \rho\tau_{e1}\tau_{e2} & \tau_{e2}^2 \end{pmatrix}$ are the mean vector and covariance matrix.

Prior specifications are as follows:

1. μ_{e1} and μ_{e2} are given prior normal distributions. Assume that prior means of μ_{e1} and μ_{e2} are the same as prior means for non-exchangeable case, m_{w1} and m_{w2}, respectively.
2. τ_{e1} and τ_{e2} are given log-normal distributions with $\tau_{e1} \sim LN(\log(0.5), (\log(2)/1.96)^2)$ and $\tau_{e2} \sim LN(\log(0.25), (\log(2)/1.96)^2)$. This allows for substantial between-strata standard deviations for the logistic parameters, $\log(\alpha)$ and $\log(\beta)$, respectively.
3. Assume that the marginal (total) variance of parameter θ follows normal distribution with the prior mean of $\mu \sim \mathrm{N}(m_\mu, s_\mu^2)$ and the prior standard deviation of $\tau \sim \mathrm{LN}(m_\tau, s_\tau^2)$.

   Under these assumptions, the marginal (total) variance of θ, V(θ), is calculated by

   $$\begin{aligned} \mathrm{V}(\theta) &= \mathrm{E}[\mathrm{V}(\theta|\mu,\tau^2)] + \mathrm{V}[\mathrm{E}(\theta|\mu,\tau^2)] = \mathrm{E}(\tau^2) + \mathrm{V}(\mu) \\ &= \{\exp(s_\tau^2) - 1\}\exp(2m_\tau + s_\tau^2) + \{\exp(m_\tau + s_\tau^2/2)\}^2 + s_\mu^2 \\ &= \exp(2m_\tau + 2s_\tau^2) + s_\mu^2. \end{aligned}$$

   As a result,

   $$s_\mu^2 = \mathrm{V}(\theta) - \exp(2m_\tau + 2s_\tau^2) \qquad (1)$$

   In this study, assume that the marginal (total) variances of parameters log(α) and log(β) are the same as those for non-exchangeable case, τ_{w1}^2 and τ_{w2}^2. Since step 1 and step 2 above and by applying (1), the prior variance of μ_{e1} and μ_{e2}, $\mathrm{V}(\mu_1)$ and $\mathrm{V}(\mu_2)$, are calculated by

   $$\begin{aligned} \mathrm{V}(\mu_1) &= \tau_{w1}^2 - \exp\{2 \cdot \log(0.5) + 2 \cdot (\log(2)/1.96)^2\} \\ \mathrm{V}(\mu_2) &= \tau_{w2}^2 - \exp\{2 \cdot \log(0.25) + 2 \cdot (\log(2)/1.96)^2\}. \end{aligned}$$

4. The correlation ρ is uniformly distributed between -1 and 1.

Prior probability of exchangeability

Let $p_{Q2W} = 1$, $p_{Q4W} = 0.5$ and $p_{PDR} = 0.1$, hence Stratum 2 (Q4W) has 50% prior probability to be exchangeable with Stratum 1 (Q2W). Stratum 3 (PDR) has 10% prior probability to be exchangeable with Stratum 1 (Q2W).

Summary of priors

The prior specifications are summarized in Table 14-7. Table 14-9 summarizes the associated prior distribution of the DLT rates at different dose levels for the three strata.

[redacted]

Table 14-7 Prior specifications for model parameters

Non-exchangeable case	
Model parameter	Bivariate normal prior distribution
$\mathbf{m}_w$	$(-2.692 \ -1.26)$
$\mathbf{S}_w$	$\begin{pmatrix} 2^2 & 0 \\ 0 & 1^2 \end{pmatrix}$
Exchangeable case	
Model parameter	Prior distribution
μ_{e1}	$\mathrm{N}(-2.692, 1.918^2)$
μ_{e2}	$\mathrm{N}(-1.26, 0.959^2)$
τ_{e1}	$\mathrm{LN}(\log(0.5), (\log(2)/1.96)^2)$
τ_{e2}	$\mathrm{LN}(\log(0.25), (\log(2)/1.96)^2)$
ρ	$\mathrm{U}(-1, 1)$
Probability of membership of exchangeable component for Q2W p_{Q2W}	1
Probability of exchangeability for Q4W p_{Q4W}	0.5
Probability of exchangeability for PDR001 p_{PDR}	0.1

The following data was included in stratum 3 of the model.

Table 14-8 Data from CPDR001X2101 as of 18-Jun-2015

Cohort	Dose level (mg/kg) / mg	No. of evaluable patients	No. of DLTs in cycle 1
1	1 / 80	6	0

[redacted]

14.3.1.1.1 Summary of priors

Table 14-9 Summary of prior distribution of DLT rates with CPDR001X2101 data **

Dose level (mg)	Prior probabilities that P(DLT) is in interval:					Quantiles		
	[0, 0.16)	[0.16, 0.33)	[0.33, 1]	Mean	SD	2.5%	50%	97.5%
Q2W								
20	0.827	0.091	0.082	0.091	0.158	0	0.024	0.61
80*	0.774	0.112	0.115	0.119	0.181	0.001	0.039	0.695
240	0.704	0.136	0.159	0.153	0.206	0.001	0.061	0.775
800	0.608	0.153	0.239	0.211	0.251	0.002	0.098	0.887
Q4W								
20	0.827	0.091	0.082	0.092	0.159	0	0.024	0.618
80	0.771	0.115	0.113	0.119	0.181	0.001	0.04	0.695
240	0.701	0.14	0.159	0.154	0.206	0.001	0.063	0.775
800	0.601	0.158	0.241	0.213	0.252	0.002	0.101	0.891
PDR001								
20	0.978	0.02	0.002	0.026	0.043	0	0.01	0.151
80	0.956	0.039	0.005	0.039	0.056	0	0.018	0.203
240	0.899	0.079	0.022	0.062	0.086	0.001	0.03	0.313
800	0.784	0.128	0.088	0.116	0.173	0.001	0.051	0.687

* Starting dose level

** as in Table 14-8

14.3.1.2 Hypothetical on-study data scenarios

Table 14-10 Hypothetical scenarios

Scenario	Cohort	Dose level (mg) stratum	Ntox / Npat	Next dose level (NDL) (mg) stratum	P(target) at NDL	P(over) at NDL	Median at NDL
1	1	80 Q2W	0/3	240 Q2W	0.088	0.037	0.030
				240 Q4W	0.118	0.105	0.043
2	1	80 Q2W	1/3	80 Q2W	0.288	0.210	0.159
3	1	80 Q2W	2/3	STOP			
4	1	80 Q2W	0/3	800 Q2W	0.090	0.052	0.033
	2	240 Q2W	0/3	800 Q4W	0.108	0.063	0.039
	2	240 Q4W	0/3				
5	1	80 Q2W	0/3	800 Q2W	0.147	0.073	0.060
	2	240 Q2W	0/3	240 Q4W	0.278	0.192	0.147
	2	240 Q4W	1/3				
6	1	80 Q2W	0/3	240 Q2W	0.296	0.099	0.129
	2	240 Q2W	1/3	240 Q4W	0.330	0.146	0.153
	2	240 Q4W	1/4				
7	1	80 Q2W	0/3	80 Q2W	0.373	0.182	0.179

[redacted]

Scenario	Cohort	Dose level (mg) stratum	Ntox / Npat	Next dose level (NDL) (mg) stratum	P(target) at NDL	P(over) at NDL	Median at NDL
	2	240 Q2W	2/3	80 Q4W	0.316	0.177	0.158
	2	240 Q4W	1/3				
8	1	80 Q2W	0/3	240 Q2W	0.380	0.185	0.184
	2	240 Q2W	1/3	20 Q4W	0.280	0.165	0.138
	2	240 Q4W	2/4				
9	1	80 Q2W	0/3	80 Q2W	0.383	0.222	0.201
	2	240 Q2W	2/3	20 Q4W	0.293	0.188	0.152
	2	240 Q4W	2/4				
10	1	80 Q2W	1/3	240 Q2W	0.282	0.124	0.128
	2	80 Q2W	0/4	240 Q4W	0.190	0.153	0.092
11	1	80 Q2W	1/3	80 Q2W	0.406	0.206	0.198
	2	80 Q2W	1/4				
12	1	80 Q2W	0/3	800 Q2W	0.036	0.002	0.021
	2	240 Q2W	0/3	800 Q4W	0.086	0.042	0.030
	2	240 Q4W	0/3				
	3	800 Q2W	0/5				
13	1	80 Q2W	0/3	800 Q2W	0.177	0.030	0.081
	2	240 Q2W	0/3				
	2	240 Q4W	0/3				
	3	800 Q2W	1/5				
14	1	80 Q2W	0/3	800 Q2W	0.235	0.109	0.113
	2	240 Q2W	1/3				
	2	240 Q4W	1/4				
	3	240 Q2W	0/6				
	3	240 Q4W	0/6				
15	1	80 Q2W	0/3	240 Q2W	0.503	0.145	0.199
	2	240 Q2W	1/3	800 Q4W	0.342	0.186	0.169
	2	240 Q4W	1/4				
	3	240 Q2W	2/6				
	3	240 Q4W	0/6				

Overall, the model is showing appropriate behaviors, in agreement with clinical sense and decision making process. The dose levels investigate correspond to the provisional dose levels specified in Section 6.2.2.

[redacted]

14.3.1.3 Operating characteristics

14.3.1.3.1 Scenarios

In order to investigate the performance of the model, 4 hypothetical scenarios are considered:

1. Scenario 1 represents a scenario which is in line with the prior for both Q2W and Q4W, i.e. the true underlying toxicity is set to the mean values of the prior.
2. Scenario 2 represents a scenario assuming high toxicity for Q2W strata whilst the toxicity for Q4W is in line with the prior.
3. Scenario 3 represents a scenario when both toxicity profiles for Q2W and Q4W are equally high.
4. Scenario 4 represents a scenario when both toxicity profiles for Q2W and Q4W are equally low.

Table 14-11 True underlying probabilities of DLT for different scenarios

Scenario 1				
Stratum / Dose level	20mg	80mg	240mg	800mg
Q2W	0.091	0.119	0.153	0.221
Q4W	0.092	0.119	0.154	0.213
Scenario 2				
Stratum / Dose level	20mg	80mg	240mg	800mg
Q2W	0.091	0.185	0.280	0.366
Q4W	0.092	0.119	0.154	0.213
Scenario 3				
Stratum / Dose level	20mg	80mg	240mg	800mg
Q2W	0.091	0.185	0.280	0.366
Q4W	0.091	0.185	0.280	0.366
Scenario 4				
Stratum / Dose level	20mg	80mg	240mg	800mg
Q2W	0.024	0.040	0.100	0.175
Q4W	0.024	0.040	0.100	0.175

- Grey shaded cells indicate True probability fall within target interval (0.16, 0.33]

14.3.1.3.2 Simulation details

1000 trials were simulated for each scenario and the total minimum number of DLT to control the declaration of MTD was fixed to one. For the simulated escalation, the next dose selected is the one maximizing the probability of the true DLT rate being in the targeted toxicity interval (16%, 33%] whilst fulfilling the EWOC criterion.

The starting dose was chosen as 80mg Q2W and 240mg Q4W.

[redacted]

Dose escalation continued until MTD was identified, that is, the following conditions were met:

- At least 6 patients have been treated at the dose, and
- The dose satisfies one of the following conditions:
  - The posterior probability of targeted toxicity at this dose exceeds 50% and is the highest among potential doses, or
  - A minimum of 21 patients have already been treated on the trial.

Otherwise, a trial could stop before MTD declaration if all dose levels did not satisfy the EWOC criterion or the maximum number of patients defined below had been treated.

The number of patients to treat in each stratum was defined as:

- Minimum cohort size a fixed number of 3 patients in Q2W and Q4W
- Minimum number of patients treated: 15 in Q2W and 6 in Q4W
- Maximum number of patients treated: 40 in Q2W and 40 in Q4W

14.3.1.3.3 Simulation results

Metrics to assess operating characteristics

Operating characteristics are reviewed based on the simulation results under the three scenarios. The metrics reviewed are:

1. Average number of patients receiving a target dose on study (I).
2. Average number of patients receiving a dose with true P(DLT) ≥ 33% on study (II).
3. Average number of patients receiving a dose with true P(DLT) < 16% on study (III).
4. Probability of recommending a target dose as the MTD (correct final decision) (IV).
5. Probability of recommending a dose with true P(DLT) ≥ 33% as the MTD (patient risk) (V).
6. Probability of recommending a dose with true P(DLT) < 16% as the MTD (VI).
7. Probability of stopping a trial before declaring MTD because all doses levels are too toxic (Stopped).

[redacted]

Operating characteristics

Table 14-12 below summarizes the operating characteristics of the design under the four scenarios.

Table 14-12 Simulation results

Scenario	Stratum	% start Q4W cohort	Metrics I	II	III	IV (Target MTD)	V (Overdose MTD)	VI (Under-dose MTD)	V Stopped (all too toxic)
1	Q2W	-	4.0	0	9.1	54.6	0	37.8	7.6
	Q4W	81.5	6.0	0	6.3	62.6	0	31.0	6.4
2	Q2W	-	8.9	2.0	1.5	43.3	18.5	20.9	17.3
	Q4W	65.0	5.4	0	7.1	53.8	0	39.4	6.8
3	Q2W	-	9.2	1.9	1.6	44.5	15.9	22.6	17.0
	Q4W	65.0	8.0	2.4	1.2	51.7	12.5	15.1	20.8
4	Q2W	-	7.1	0	8.3	79.5	0	20.2	0.3
	Q4W	96.5	5.0	0	4.5	77.0	0	20.6	2.4

Metric IV, indicates that the model is typically identifying an appropriate MTD with high probability. Scenario 1 (Q2W and Q4W), and Scenario 4 (Q4W) have a high probability of identifying an MTD with toxicity below the target range, however this is accounted for by the inclusion in these scenarios of a dose with P(DLT)=0.154, marginally below the lower limit of the target range, 0.16. Similarly, for Scenario 2 (Q2W) and Scenario 3 (Q2W and Q4W) there is an appreciable probability of identifying a dose with P(DLT) lying above 0.33, this is accounted for by the inclusion in these scenarios of a dose with a probability of DLT of 0.366, marginally above the target range.

The simulation results show that the BHLRM performs reasonably well under the investigated hypothetical scenarios.

14.3.2 Phase I part MBG453 single agent with Japanese patients

Similarly, the BHLRM guided by the EWOC principle (Section 14.3.1) will be used in Japanese patients for MBG453 single agent phase I part to make dose recommendations and estimate the MTD and/or identify the RP2D. This section provides details of the statistical model, the derivation of prior distributions for the model parameters, and the properties of the adaptive design (dose recommendations for hypothetical data scenarios).

[redacted]

14.3.2.1 Statistical model and prior distributions

Section 10.4.2 outlined the model description for the BHLRM, here the derivation of the priors for that model is described as follows:

- Prior distributions for the exchangeability and non-exchangeability model components are derived.
- For each stratum (Japanese patients and ROW patients), the weight of the exchangeable and non-exchangeable mixture components are defined.
- Prior summaries for DLT rates at different dose levels are shown.

Prior for the non-exchangeable case

Under non-exchangeability, the parameter vectors θ_{jp} (Japanese patients) and θ_{gp} (ROW patients) are assumed to have a weakly informative bivariate normal prior distribution,

$$\theta_{jp}, \theta_{gp} \sim BVN(\mathbf{m}_w, \mathbf{S}_w)$$

where $\mathbf{m}_w = (m_{w1}, m_{w2})$ and $\mathbf{S}_w = \begin{pmatrix} \tau_{w1}^2 & c\tau_{w1}\tau_{w2} \\ c\tau_{w1}\tau_{w2} & \tau_{w2}^2 \end{pmatrix}$ are the mean vector and covariance matrix.

For the purposes of setting the prior for the BLRM model, the median DLT rate at 80 mg Q2W is assumed to be at 5%, and the median DLT rate at 800 mg Q2W is assumed to be 10%. For the remaining doses, median DLT rates a priori are assumed linear in the logit-scale as a function of log-dose.

Based on the above specified medians for the DLT rate and wide prior confidence intervals, the optimal parameters of the bivariate normal distribution can be obtained following the procedure described by Neuenschwander et al 2008. This leads to the BVN distribution defined by $\mathbf{m}_w =$ (-2.692, -1.26), $\tau_{w1} = 2.484$, $\tau_{w2} = 0.745$ and $c = -0.765$.

To provide a simple, flexible prior, the same mean is retained, but the correlation is set to zero, and the standard deviations for $\log(\alpha)$ and $\log(\beta)$ approximated by 2 and 1, respectively, the prior for the non-exchangeable case is set to $\mathbf{m}_w =$ (-2.692, -1.26), $\mathbf{S}_w = \begin{pmatrix} 2^2 & 0 \\ 0 & 1^2 \end{pmatrix}$.

Prior for the exchangeable case

Under exchangeability, the parameters θ_{jp} and θ_{gp} are assumed to follow a bivariate normal distribution:

$$\theta_{jp}, \theta_{gp}, \sim BVN(\boldsymbol{m}_{exch}, \mathbf{S}_{exch}),$$

where $\boldsymbol{m}_{exch} = (\mu_{e1}, \mu_{e2})$ and $\mathbf{S}_{exch} = \begin{pmatrix} \tau_{e1}^2 & \rho\tau_{e1}\tau_{e2} \\ \rho\tau_{e1}\tau_{e2} & \tau_{e2}^2 \end{pmatrix}$ are the mean vector and covariance matrix.

Prior specifications are as follows:

[redacted]

1. μ_{e1} and μ_{e2} are given prior normal distributions. Assume that prior means of μ_{e1} and μ_{e2} are the same as prior means for non-exchangeable case, m_{w1} and m_{w2}, respectively.
2. τ_{e1} and τ_{e2} are given log-normal distributions with $\tau_{e1}\sim LN(\log(0.5), (\log(2)/1.96)^2)$ and $\tau_{e2}\sim LN(\log(0.25), (\log(2)/1.96)^2)$. This allows for substantial between-strata standard deviations for the logistic parameters, $\log(\alpha)$ and $\log(\beta)$, respectively.
3. Assume that the marginal (total) variance of parameter θ follows normal distribution with the prior mean of $\mu\sim \mathrm{N}(m_\mu, s_\mu^2)$ and the prior standard deviation of $\tau\sim \mathrm{LN}(m_\tau, s_\tau^2)$.

   Under these assumptions, the marginal (total) variance of θ, V(θ), is calculated by

$$\begin{aligned}\mathrm{V}(\theta) &= \mathrm{E}[\mathrm{V}(\theta|\mu,\tau^2)] + \mathrm{V}[\mathrm{E}(\theta|\mu,\tau^2)] = \mathrm{E}(\tau^2) + \mathrm{V}(\mu)\\ &= \{\exp(s_\tau^2) - 1\}\exp(2m_\tau + s_\tau^2) + \{\exp(m_\tau + s_\tau^2/2)\}^2 + s_\mu^2\\ &= \exp(2m_\tau + 2s_\tau^2) + s_\mu^2.\end{aligned}$$

   As a result,

$$s_\mu^2 = \mathrm{V}(\theta) - \exp(2m_\tau + 2s_\tau^2) \qquad (1)$$

   In this study, assume that the marginal (total) variances of parameters log(α) and log(β) are the same as those for non-exchangeable case, τ_{w1}^2 and τ_{w2}^2. Since step 1 and step 2 above and by applying (1), the prior variance of μ_{e1} and μ_{e2}, $\mathrm{V}(\mu_1)$ and $\mathrm{V}(\mu_2)$, are calculated by

$$\mathrm{V}(\mu_1) = \tau_{w1}^2 - \exp\{2\cdot\log(0.5) + 2\cdot(\log(2)/1.96)^2\}$$
$$\mathrm{V}(\mu_2) = \tau_{w2}^2 - \exp\{2\cdot\log(0.25) + 2\cdot(\log(2)/1.96)^2\}.$$

4. The correlation ρ is uniformly distributed between -1 and 1.

Prior probability of exchangeability

Let $p_{jp} = 1$, $p_{gp} = 0.5$, hence Stratum 2 (ROW patients) has 50% prior probability to be exchangeable with Stratum 1 (Japanese patients).

Summary of priors

The prior specifications are summarized in Table 14-13. Table 14-15 summarizes the associated prior distribution of the DLT rates at different dose levels for the two strata.

Table 14-13 Prior specifications for model parameters

Non-exchangeable case	
Model parameter	Bivariate normal prior distribution
$\mathbf{m}_w$	$(-2.692 \ -1.26)$
$\mathbf{S}_w$	$\begin{pmatrix}2^2 & 0\\ 0 & 1^2\end{pmatrix}$
Exchangeable case	
Model parameter	Prior distribution
μ_{e1}	$\mathrm{N}(-2.692, 1.918^2)$
μ_{e2}	$\mathrm{N}(-1.26, 0.959^2)$
τ_{e1}	$\mathrm{LN}(\log(0.5), (\log(2)/1.96)^2)$
τ_{e2}	$\mathrm{LN}(\log(0.25), (\log(2)/1.96)^2)$

[redacted]

ρ	$\mathrm{U}(-1,1)$
Probability of membership of exchangeable component for Japanese patients p_{jp}	1
Probability of exchangeability for ROW patients p_{gp}	0.5

The following data was included in stratum 2 of the model.

Table 14-14 Data from ROW patients CMBG453X2101 as of 07-Mar-2016

Cohort	Dose level mg	Schedule	No. of evaluable patients	No. of DLTs in cycle 1
1	80	Q2W	4	0

Testing of Q4W dosing schedule

Similarly, the BHLRM of the same functional form and same prior specification as described above was used to set up the dose escalation for Q4W of dose-escalation with Japanese patients. However, since no data is currently available for the Q4W global population, no data was included in stratum 2 of the model for this schedule. Table 14-15 summarizes the associated prior distribution of the DLT rates at different dose levels for the two strata.

14.3.2.1.1 Summary of priors

Table 14-15 Summary of prior distribution of DLT rates with ROW patient data **

Dose level	Prior probabilities that P(DLT) is in interval:					Quantiles		
(mg)	[0, 0.16)	[0.16, 0.33)	[0.33, 1]	Mean	SD	2.5%	50%	97.5%
Japanese patients (Q2W)								
20	0.887	0.064	0.049	0.066	0.130	0	0.016	0.493
80*	0.841	0.090	0.069	0.088	0.150	0.001	0.028	0.587
240	0.773	0.123	0.104	0.119	0.175	0.001	0.047	0.688
800	0.658	0.155	0.187	0.180	0.228	0.002	0.081	0.860
ROW patients (Q2W)								
20	0.963	0.032	0.005	0.032	0.055	0	0.011	0.194
80	0.931	0.057	0.012	0.047	0.070	0	0.020	0.252
240	0.866	0.100	0.034	0.073	0.100	0.001	0.034	0.374
800	0.746	0.140	0.114	0.131	0.182	0.002	0.058	0.714
Japanese patients (Q4W)								
20	0.829	0.090	0.081	0.091	0.159	0	0.024	0.625
80	0.773	0.114	0.112	0.119	0.181	0.001	0.040	0.702
240	0.700	0.142	0.158	0.154	0.206	0.001	0.063	0.778
800	0.598	0.160	0.242	0.214	0.252	0.002	0.102	0.895
ROW patients (Q4W)								
20	0.829	0.089	0.081	0.092	0.160	0	0.024	0.633
80	0.773	0.114	0.113	0.119	0.182	0.001	0.040	0.709
240	0.699	0.142	0.159	0.155	0.207	0.001	0.063	0.779
800	0.598	0.159	0.242	0.215	0.253	0.002	0.102	0.894

[redacted]

Dose level (mg)	Prior probabilities that P(DLT) is in interval: [0, 0.16)	[0.16, 0.33)	[0.33, 1]	Mean	SD	Quantiles 2.5%	50%	97.5%
* Starting dose level								
** as in Table 14-14								

14.3.2.2 Hypothetical on-study data scenarios

Table 14-16 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
Q2W							
1		80 ROW	0/4	240 JP	0.106	0.038	0.035
	1	80 JP	0/2				
2		80 ROW	0/4	240 JP	0.107	0.042	0.035
	1	80 JP	0/3				
3		80 ROW	0/4	80 JP	0.251	0.160	0.126
	1	80 JP	1/3				
4		80 ROW	0/4	STOP			
	1	80 JP	2/3				
5		80 ROW	0/4	240 JP	0.272	0.114	0.119
	1	80 JP	1/6				
6		80 ROW	0/4	800 JP	0.096	0.053	0.033
	1	80 JP	0/2				
		240 ROW	0/6				
	2	240 JP	0/3				
7		80 ROW	0/4	800 ROW	0.125	0.062	0.053
	1	80 JP	0/2	240 JP	0.264	0.117	0.188
		240 ROW	0/6				
	2	240 JP	1/3				
8		80 ROW	0/4	800 ROW	0.128	0.075	0.049
	1	80 JP	0/2	80 JP	0.323	0.232	0.182
		240 ROW	0/6				
	2	240 JP	2/3				
9		80 ROW	0/4	800 ROW	0.307	0.182	0.156
	1	80 JP	0/2	240 JP	0.293	0.106	0.130
		240 ROW	1/6				
	2	240 JP	1/3				
10		80 ROW	0/4	800 ROW	0.290	0.181	0.150
	1	80 JP	0/2	800 JP	0.297	0.205	0.161
		240 ROW	1/6				
	2	240 JP	1/6				
11		80 ROW	0/4	800 ROW	0.195	0.024	0.090
	1	80 JP	0/2	800 JP	0.192	0.017	0.088
		240 ROW	1/6				
	2	240 JP	1/6				
		800 ROW	0/3				

[redacted]

Scenario	Cohort	Dose level (mg)	Ntox / Npat	Next dose level (NDL) (mg)	P(target) at NDL	P(over) at NDL	Median at NDL
	3	800 JP	0/4				
12		80 ROW	0/4	800 ROW	0.319	0.080	0.130
	1	80 JP	0/2	240 JP	0.415	0.080	0.159
		240 ROW	1/6				
	2	240 JP	1/6				
		800 ROW	0/3				
	3	800 JP	2/4				

Scenario	Cohort	Dose level (mg)	Ntox / Npat	Next dose level (NDL) (mg)	P(target) at NDL	P(over) at NDL	Median at NDL
Q4W							
1		240 ROW	0/5	800 ROW	0.092	0.046	0.035
	1	240 JP	0/4	800 JP	0.100	0.053	0.035
2		240 ROW	0/5	800 ROW	0.165	0.084	0.068
	1	240 JP	1/4	240 JP	0.260	0.125	0.121
3		240 ROW	0/5	STOP			
	1	240 JP	2/4				
4		240 ROW	0/5	800 ROW	0.160	0.070	0.066
	1	240 JP	1/6	800 JP	0.273	0.165	0.137
5		240 ROW	0/5	800 ROW	0.046	0.006	0.023
	1	240 JP	0/4	800 JP	0.046	0.006	0.023
		800 ROW	0/3				
	2	800 JP	0/3				
6		240 ROW	0/5	800 ROW	0.092	0.011	0.042
	1	240 JP	0/4	800 JP	0.216	0.082	0.095
		800 ROW	0/3				
	2	800 JP	1/3				
7		240 ROW	0/5	800 ROW	0.135	0.032	0.052
	1	240 JP	0/4	240 JP	0.285	0.081	0.121
		800 ROW	0/3				
	2	800 JP	2/3				

[redacted]

14.3.2.3 Operating characteristics

14.3.2.3.1 Scenarios

In order to investigate the performance of the model, 4 hypothetical scenarios are considered:

1. Scenario 1 represents a scenario which is in line with the prior, i.e. the true underlying toxicity is set to the mean values of the prior.
2. Scenario 2 represents a scenario which the true probability of DLT is incremented in comparison to the prior, i.e. the true underlying toxicity is set to values between (0.16, 0.33]
3. Scenario 3 represents a scenario which the true probability of DLT is under-dose, i.e. the true underlying toxicity is set to values between [0, 0.16).
4. Scenario 4 represents a scenario assuming extremely high toxicity, i.e. the true underlying toxicity is set to values between 0.4 and 0.5.

Table 14-17 True underlying probabilities of DLT in Japanese patients stratum for different scenarios

Scenario / Dose level	20mg	80mg	240mg	800mg
1	0.066	0.088	0.119	0.180
2	0.185	0.230	0.280	0.300
3	0.024	0.040	0.100	0.130
4	0.410	0.430	0.450	0.470

- Grey shaded cells indicate True probability fall within target interval (0.16, 0.33]

14.3.2.3.2 Simulation details

1000 trials were simulated for each scenario and the total minimum number of DLT to control the declaration of MTD was fixed to one. For the simulated escalation, the next dose selected is the one maximizing the probability of the true DLT rate being in the targeted toxicity interval (16%, 33%] whilst fulfilling the EWOC criterion.

The starting dose was chosen as 80mg Q2W for the Japanese patients and 80mg Q2W for the ROW patients. Simulation is based on 1 ROW patient cohort at 80mg Q2W.

Dose escalation continued until MTD was identified, that is, the following conditions were met:

- At least 6 patients have been treated at the dose, and
- The dose satisfies one of the following conditions:
  - The posterior probability of targeted toxicity at this dose exceeds 50% and is the highest among potential doses, or
  - A minimum of 12 patients have already been treated on the trial.

Otherwise, a trial could stop before MTD declaration if all dose levels did not satisfy the EWOC criterion or the maximum number of patients defined below had been treated.

The number of patients to treat in each stratum was defined as:

- Minimum cohort size: 1 to 3 patients and may increase to 3 to 6 patients
- Minimum number of patients treated: 6 patients

[redacted]

- Maximum number of patients treated: 20 in Japanese patients and 4 in ROW patients

14.3.2.3.3 Simulation results

Metrics to assess operating characteristics for Japanese strata

Operating characteristics are reviewed based on the simulation results under the four scenarios. The metrics reviewed are:

I. Average number of patients receiving a target dose on study (I).
II. Average number of patients receiving a dose with true P(DLT) ≥ 33% on study (II).
III. Average number of patients receiving a dose with true P(DLT) < 16% on study (III).
IV. Probability of recommending a target dose as the MTD (correct final decision) (IV).
V. Probability of recommending a dose with true P(DLT) ≥ 33% as the MTD (patient risk) (V).
VI. Probability of recommending a dose with true P(DLT) < 16% as the MTD (VI).
VII. Probability of stopping a trial before declaring MTD because all doses levels are too toxic (Stopped).

Operating characteristics

Table 14-18 below summarizes the operating characteristics of the design under the four scenarios.

Table 14-18 Simulation results

Scenario	Metrics						
	I	II	III	IV (Target MTD)	V (Overdose MTD)	VI (Under-dose MTD)	V Stopped (all too toxic)
1	7.9	0	7.5	74.3	0	19.1	1.7
2	14.7	0	4.8	69.1	0	0	21.5
3	0	0	14.7	0	0	97.5	0.5
4	0	10.3	0	0	18.4	0	77.2

Scenario 4 displays the results of the simulation of extremely high toxicity at all dose levels. Results of the simulation should be interpreted with caution as this simulation does not allow for dose escalation decisions taken outside of the model based rules for dose selection which dooesn't reflect dose selection in practice following clinical review of all available data. In particular, if 2 patients experience a DLT at a previously untested dose, recruitment to that cohort will cease and either the next cohort will be enrolled at a lower dose, or the dose escalation will end if no dose is identified as safe by the BHLRM along with EWOC. For this reason, the scenario is considered liable to overestimate the proportion of trial in which a dose in excessive target interval is wrongly declared as MTD. Even with this limitation, it is notable that the average proportion of patients expected to be treated on trial is low (10), and the model correctly identifies in a high proportion of cases (77.2%) that the dose escalation should be stopped.

[redacted]

Overall, the simulation results show that the BHLRM performs reasonably well under the investigated hypothetical scenarios.

14.3.3 Phase Ib part MBG453 in combination with PDR001

An adaptive Bayesian logistic regression model (BLRM) guided by the escalation with overdose control (EWOC) principle will guide the dose-escalation of the MBG453 in combination with PDR001 to its MTD(s) and/or recommended phase 2 dose (RP2D) of MBG453 in patients with solid tumors. This section provides details of the statistical model, the derivation of prior distributions for the model parameters, and the properties of the adaptive design (dose recommendations for hypothetical data scenarios).

14.3.3.1 Statistical model and prior distributions

Section 10.4.2 outlined the model description for the BLRM, here the derivation of the priors for that model is described as follows:

- The single-agent prior distribution for PDR001 is derived.
- The single-agent prior distribution for MBG453 is derived.
- The prior distribution for the interaction parameter is derived.
- Numerical values and summary statistic at different dose levels are shown.

Prior for PDR001 parameters

A weakly informative bivariate normal prior for the model parameters $\left(\log(\alpha_{PDR,i}), \log(\beta_{PDR,i})\right)$ for cycle $i = 1,2$ is obtained as follows:

- The prior mean given by $\text{mean}(\log(\alpha_{PDR}), \log(\beta'_{PDR})) = (-2.692, -0.567)$. This is given the fact that, the corresponding slope in square-rooted scale is given by $\log(\alpha_{PDR}) + \beta_{PDR}\log(d/240) = \log(\alpha_{PDR}) + \beta'_{PDR}\log(d^{0.5}/240^{0.5})$. Therefore, $\beta'_{PDR} = 2\beta_{PDR}$, i.e. $\log(\beta'_{PDR}) = \log\left(2 \times \exp(-1.26)\right)$.

  The prior standard deviation was set to $\text{sd}(\log(\alpha_{PDR}), \log(\beta_{PDR})) = (2,1)$, which allows for considerably prior uncertainty for the dose-toxicity profile. The correlation was set to, $\text{corr}(\log(\alpha_{PDR}), \log(\beta_{PDR})) = 0$.
- Data from 6 patients eligible for the dose determining set of the ongoing study [CPDR001X2101] were used to update the dose-toxicity profile (refer to Table 14-8).
- Heterogeneity between the historical and current study was incorporated by between-trial standard deviations and τ_1 and τ_2 for $\log(\alpha_{PDR})$ and $\log(\beta_{PDR})$. Both τ_1 and τ_2 were set to follow a log-normal distribution. Mean log(0.25) and standard deviation log(2)/1.96 was chosen for τ_1 and mean log(0.125) and standard deviation log(2)/1.96 was chosen for τ_2, which correspond to moderate between-trial variability.
- The corresponding predicted distribution is given by a mixture of two components as detailed in Table 14-19.

Since risk over cycle is assumed to be constant for PDR001. Therefore, the mixture of two components with equal weight was used for both cycles.

[redacted]

Prior for MBG453 parameters

A weakly informative bivariate normal prior for the model parameters $\left(\log\left(\alpha_{MBG,i}\right), \log\left(\beta_{MBG,i}\right)\right)$ for cycle $i = 1,2$ is obtained as follows:

- A prior distribution is derived considering the possible similarities in toxicity from PDR001. The prior mean given by $\text{mean}(\log(\alpha_{MBG}), \log(\beta'_{MBG})) = (-2.692, -0.567)$. This is given the fact that, the corresponding slope in square-rooted scale is given by $\log(\alpha_{MBG}) + \beta_{MBG}\log(d/240) = \log(\alpha_{MBG}) + \beta'_{MBG}\log(d^{0.5}/240^{0.5})$. Therefore, $\beta'_{MBG} = 2\beta_{MBG}$, i.e. $\log(\beta'_{MBG}) = \log\left(2 \times \exp(-1.26)\right)$.
  The prior standard deviation was set to $\text{sd}(\log(\alpha_{MBG}), \log(\beta_{MBG})) = (2,1)$, which allows for considerably prior uncertainty for the dose-toxicity profile. The correlation was set to, $\text{corr}(\log(\alpha_{MBG}), \log(\beta_{MBG})) = 0$.
- After all ongoing patients completed 1 cycle for the first two cohorts of the single agent MBG453 dose escalation; combination dosing will begin at the planned starting dose. For the purposes of illustration, it is assumed here that in the single agent dose escalation there are 3 evaluable patients in each of the first two cohorts (doses 80mg and 240mg) and 0 DLTs are observed. Note, the prior specification of the model will be updated based on actual data prior to first patient enrolling onto the combination part.
- Heterogeneity between the historical and current study was incorporated by between-trial standard deviations and τ_1 and τ_2 for $\log(\alpha_{PDR})$ and $\log(\beta_{PDR})$. Both τ_1 and τ_2 were set to follow a log-normal distribution. Mean log(0.25) and standard deviation log(2)/1.96 was chosen for τ_1 and mean log(0.125) and standard deviation log(2)/1.96 was chosen for τ_2, which correspond to moderate between-trial variability.
- The corresponding predicted distribution is given by a mixture of two components as detailed in Table 14-19.
- In order to increase robustness to the model, a further component was added to the mixture prior to represent the risk of increased toxicity for MBG453 in combination. The $\text{mean}(\log(\alpha_{MBG}), \log(\beta_{MBG})) = (\log(0.5), 0)$, i.e. the median DLT rate at the reference dose was assumed 0.5 and a doubling in dose was assumed to double odds of DLT by a unit increase in the log of the square root of dose. To complete the specification, the prior standard deviation was set to $\text{sd}(\log(\alpha_{MBG}), \log(\beta_{MBG})) = (2,1)$, which allows for considerably prior uncertainty for the dose-toxicity profile and the correlation was set to, $\text{corr}(\log(\alpha_{MBG}), \log(\beta_{MBG})) = 0$.

Since risk in cycle 2 is assumed to be higher than cycle 1 for MBG453. The mixture weights of the three components were set differently for the prior for first cycle toxicity, to that for the second cycle toxicity. See detail in Table 14-19.

Prior for the interaction parameter η

A weakly informative prior reflecting the current uncertainty about the toxicity of the combination treatment is used for η. A normal prior distribution for the interaction parameter η is used, in order to allow for the potentiality of both synergy and antagonism of the safety profiles. Given that, exposure drug-drug interaction (PK DDI) is expected to be negligible, the following assumption is made for the interaction parameter:

[redacted]

- η is normally distributed and median = 0 i.e. no increase in odds of DLT i.e. independence at the anticipated combination reference dose of 240 and 240.
- 97.5th percentile of η is $\left(\log(4.5)\, {d_{MBG,i}^{0.5}}/{240^{0.5}}\, {d_{PDR,i}^{0.5}}/{240^{0.5}}\right)$, i.e. 4.5-fold increase in odds of DLT at the combination reference dose of 240 and 240.

Therefore, the prior mean for η is 0 and the prior standard deviation is 0.767.

Table 14-19 Prior distribution of model parameters

Parameter	Means	Standard deviations	Correlation	Weight
Cycle 1 risk for PDR001	-4.127, -0.472	1.560, 0.984	0.041	0.65
$(\log(\alpha_{PDR,1}), \log(\beta_{PDR,1}))$	-2.532, -0.418	1.126, 1.129	0.334	0.35
Cycle 2 risk for PDR001	-4.127, -0.472	1.560, 0.984	0.041	0.65
$(\log(\alpha_{PDR,2}), \log(\beta_{PDR,2}))$	-2.532, -0.418	1.126, 1.129	0.334	0.35
Cycle 1 risk for MBG453	-0.693, 0	2, 1	0	0.10
$(\log(\alpha_{MBG,1}), \log(\beta_{MBG,1}))$	-4.220, -0.525	1.557, 1.009	0.025	0.61
	-2.729, -0.522	1.033, 1.056	0.117	0.29
Cycle 2 risk for MBG453	-0.693, 0	2, 1	0	0.20
$(\log(\alpha_{MBG,2}), \log(\beta_{MBG,2}))$	-4.220, -0.525	1.557, 1.009	0.025	0.54
	-2.729, -0.522	1.033, 1.056	0.117	0.26
η	0	0.767	NA	NA

[redacted]

14.3.3.1.1 Summary of priors

Table 14-20 Summary of prior distribution of DLT rates

MBG453 Dose level (mg)	Prior cumulative probabilities that P(DLT) is in interval:					Quantiles		
	[0, 0.16)	[0.16, 0.33)	[0.33, 1]	Mean	SD	2.5%	50%	97.5%
	PDR001 80 mg							
20	0.670	0.191	0.139	0.164	0.192	0.005	0.094	0.780
80*	0.599	0.215	0.186	0.198	0.216	0.008	0.119	0.867
240	0.509	0.230	0.261	0.248	0.248	0.010	0.155	0.944
800	0.417	0.203	0.380	0.332	0.306	0.010	0.217	0.995
	PDR001 240 mg							
20	0.577	0.221	0.201	0.203	0.211	0.008	0.127	0.822
80	0.514	0.234	0.252	0.238	0.234	0.010	0.153	0.896
240	0.442	0.224	0.334	0.291	0.270	0.011	0.193	0.960
800	0.383	0.170	0.446	0.379	0.334	0.007	0.267	0.998

* Starting dose level

Grey shaded rows indicate dose not meeting the overdose criterion, that the risk of excessive toxicity must not exceed 25%.

14.3.3.2 Hypothetical on-study data scenarios

Table 14-21 Hypothetical scenarios

Scenario	Cohort	Dose combination MBG453 / PDR001 by cycle	Npat	Ntox	Next dose combination (NDC)	Pr(over) in NDC
1	1	20, - / 80, -	3, -	0, -	80 / 80	0.142
2	1	20, - / 80, -	3, -	1, -	20 / 80	0.208
3	1	20, 20 / 80, 80	3, 3	0, 1	20 / 80	0.175
4	1	20, 20 / 80, 80	3, 3	0, 0	80 / 80	0.065
5	1	20, 20 / 80, 80	3, 3	0, 0	240 / 80	0.123
	2	80, - / 80, -	3, -	0, -		
6	1	20, 20 / 80, 80	3, 3	0, 0	80 / 80	0.121
	2	80, - / 80, -	3, -	1, -		
7	1	20, 20 / 80, 80	3, 3	0, 0	20 / 80	0.174
	2	80, - / 80, -	3, -	2, -		
8	1	20, 20 / 80, 80	3, 3	0, 0	240 / 80	0.080
	2	80, 80 / 80, 80	3, 3	0, 0		
9	1	20, 20 / 80, 80	3, 3	0, 0	20 / 80	0.188
	2	80, 80 / 80, 80	3, 3	0, 2		
10	1	20, 20 / 80, 80	3, 3	0, 0	800 / 80	0.225
	2	80, 80 / 80, 80	3, 3	0, 0		
	3	240, - / 80, -	3, -	0, -		

[redacted]

Scenario	Cohort	Dose combination MBG453 / PDR001 by cycle	Npat	Ntox	Next dose combination (NDC)	Pr(over) in NDC
11	1	20, 20 / 80, 80	3, 3	0, 0	240 / 80	0.136
	2	80, 80 / 80, 80	3, 3	0, 0		
	3	240, - / 80, -	3, -	1, -		
12	1	20, 20 / 80, 80	3, 3	0, 0	240 / 80	0.122
	2	80, 80 / 80, 80	3, 3	0, 0		
	3	240, 240 / 80, 80	3, 3	0, 1		
13	1	20, 20 / 80, 80	3, 3	0, 0	80 / 80	0.102
	2	80, 80 / 80, 80	3, 3	0, 0		
	3	240, - / 80, -	3, -	2, -		
14	1	20, 20 / 80, 80	3, 3	0, 0	800 / 80	0.170
	2	80, 80 / 80, 80	3, 3	0, 0		
	3	240, 240 / 80, 80	3, 3	0, 0		
15	1	20, 20 / 80, 80	3, 3	0, 0	80 / 80	0.101
	2	80, 80 / 80, 80	3, 3	0, 0		
	3	240, 240 / 80, 80	3, 3	0, 2		
16	1	20, 20 / 80, 80	3, 3	0, 0	800 / 80	0.247
	2	80, 80 / 80, 80	3, 3	0, 0		
	3	240, 240 / 80, 80	3, 2	1, 0		
	4	240, - / 80, -	6, -	0, -		
17	1	20, 20 / 80, 80	3, 3	0, 0	800 / 80	0.233
	2	80, 80 / 80, 80	3, 3	0, 0		
	3	240, 240 / 80, 80	3, 2	1, 0		
	4	240, 240 / 80, 80	4, 4	0, 0		
18	1	20, 20 / 80, 80	3, 3	0, 0	240 / 80	0.127
	2	80, 80 / 80, 80	3, 2	1, 0		
	3	80, 80 / 80, 80	3, 3	0, 0		

Overall, the model is showing appropriate behaviors, in agreement with clinical sense and decision making process. The dose levels investigate correspond to the provisional dose levels specified in Section 6.2.2.

14.3.3.3 Operating characteristics

14.3.3.3.1 Scenarios

In order the design performs, 5 hypothetical scenarios are investigated:

8. Scenario 1 represents a scenario which is in line with the prior, i.e. the true underlying toxicity is set to the median values of the prior.
9. Scenario 2 represents a scenario assuming high toxicity for both compounds
10. Scenario 3 represents a scenario assuming low toxicity for both compounds
11. Scenario 4 represents a scenario assuming high toxicity occurs in cycle 1 risk set
12. Scenario 5 represents a scenario assuming high toxicity occurs in cycle 2 risk set

[redacted]

Table 14-22 True underlying cumulative probabilities of DLT for different scenarios

Scenario 1				
PDR001 / MBG453	20mg	80mg	240mg	800mg
80 mg	0.090	0.113	0.145	0.199
240 mg	0.122	0.146	0.182	0.248
Scenario 2				
PDR001 / MBG453	20mg	80mg	240mg	800mg
80 mg	0.179	0.208	0.281	0.367
240 mg	0.226	0.278	0.331	0.460
Scenario 3				
PDR001 / MBG453	20mg	80mg	240mg	800mg
80 mg	0.045	0.065	0.076	0.088
240 mg	0.062	0.075	0.088	0.126
Scenario 4				
PDR001 / MBG453	20mg	80mg	240mg	800mg
80 mg	0.132	0.155	0.210	0.273
240 mg	0.178	0.207	0.246	0.351
Scenario 5				
PDR001 / MBG453	20mg	80mg	240mg	800mg
80 mg	0.130	0.168	0.223	0.302
240 mg	0.163	0.211	0.275	0.374

- Grey shaded cells indicate True probability fall within target interval (0.16, 0.33]

14.3.3.3.2 Simulation details

1000 trials were simulated for each scenario and the total minimum number of DLT to control the declaration of MTD was fixed to one. For the simulated escalation, the next dose selected is the one maximizing the probability of the true DLT rate being in the targeted toxicity interval (16%, 33%] whilst fulfilling the EWOC criterion.

The starting dose was chosen as 20mg MBG453 and 80mg PDR001.

Dose escalation continued until MTD was identified, that is, the following conditions were met:

- At least 6 patients have been treated at the dose, and
- The dose satisfies one of the following conditions:
  - The posterior probability of targeted toxicity at this dose exceeds 50% and is the highest among potential doses, or
  - A minimum of 15 patients have already been treated on the trial.

Otherwise, a trial could stop before MTD declaration if all dose levels did not satisfy the EWOC criterion or the maximum number of patients defined below had been treated.

[redacted]

The number of patients to treat was defined as:

- Minimum cohort size a fixed number of 3 patients
- Minimum number of patients treated: 15
- Maximum number of patients treated: 60

14.3.3.3.3 Simulation results

Metrics to assess operating characteristics

Operating characteristics are reviewed based on the simulation results under the three scenarios. The metrics reviewed are:

I. Average number of patients receiving a target dose on study (I).
II. Average number of patients receiving a dose with true P(DLT) ≥ 33% on study (II).
III. Average number of patients receiving a dose with true P(DLT) < 16% on study (III).
IV. Probability of recommending a target dose as the MTD (correct final decision) (IV).
V. Probability of recommending a dose with true P(DLT) ≥ 33% as the MTD (patient risk) (V).
VI. Probability of recommending a dose with true P(DLT) < 16% as the MTD (VI).
VII. Probability of stopping a trial before declaring MTD because all doses levels are too toxic (Stopped).

Operating characteristics

Table 14-23 below summarizes the operating characteristics of the design under the four scenarios.

Table 14-23 Simulation results

Scenario	I	II	III	IV (Target MTD)	V (Overdose MTD)	VI (Under-dose MTD)	V Stopped (all too toxic)
1	40.5	0	40.7	74.2	0	22.3	3.5
2	50.0	16.5	0	53.6	22.8	0	23.6
3	0	0	84.0	0	0	99.1	0.9
4	46.7	5.4	20.9	64.6	10.5	12.6	12.3
5	70.6	5.4	0	78.2	10.3	0	11.5

Scenario 3 represents a scenario in which all doses have P(DLT) below the target range, hence in this case metric IV is zero. In all other cases, metric IV indicates a high probability of identifying an MTD within the target range. In scenario 2, metric V is slightly inflated the inclusion of a dose for which P(DLT)=0.331, slightly above the upper limit of the target range, 0.33.

In conclusion, the simulation results show that the BLRM performs reasonably well under the investigated hypothetical scenarios.

[redacted]

14.3.4 References (available upon request)

Neuenschwander B, Michael Branson M, Gsponer T (2008). Critical aspects of the Bayesian approach to phase I cancer trials Article first published online: Statistics in Medicine 27 (13): 2420–39.

[redacted]