NOVARTIS

Clinical Development

MBG453, PDR001

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

Statistical Analysis Plan (SAP) for the final CSR

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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
09-Dec-2015	Prior to DB lock	Creation of initial version	N/A - First version	NA
31-Aug-2021	Prior to DB lock	Creation of the SAP for the final CSR.	This version will be used for the final CSR	Structural update and various changes in wording, in order to align with the TCO SAP template (SAP_TCO_V3.0). Corrections and additions to reflect the latest amended protocol version (v6.0) considering also the SAP version used for the interim CSR: (CMBG453X2101_SAP_CSR_1_interim.docx). Wording added for the managment of the COVID-19 situation.
29-Sep-2022	Prior to DB lock	Creation of the SAP for the final CSR.	This amended version will be used for the final CSR	Update in the definition of the ADA determinants from the SAP version used for the interim CSR. Information on which outputs from MBG453 single agent will be presented in the CSR, updating or adding the MBG453 single agent information provided in the interim CSR.

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List of abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
BHLRM	Bayesian Hierarchical Logistic Regression Model
BLRM	Bayesian Logistic Regression Model
BOR	Best Overall Response
CI	Confidence Interval
CR	Complete Response
CRO	Contract Research Organization
SCLC	Small Cell Lung Cancer
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DAR	Dosage Administration Record
DBL	Database Lock
DDS	Dose-Determining Analysis Set
DI	Dose Intensity
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DMS	Document Management System
DOR	Duration of Response
DRL	Drug Reference Listing
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eCSR	Electronic Case Retrieval Strategy
FAS	Full Analysis Set
HGLT	High Group Level Term
HLT	High Level Term
IB	Investigator’s Brochure
iCSR	Interim CSR
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
IVR	Interactive Voice Response
IWR	Interactive Web Response
MTD	Maximum Tolerated Dose
MedDRA	Medical Dictionary for Drug Regulatory Affairs

NA	Not Assessed
NCI	National Cancer Institute
NMQ	Novartis MedDRA Query
NSCLC	Non-Small Cell Lung Carcinoma
ORR	Overall Response Rate
OS	Overall Survival
PAS	Pharmacokinetic Analysis Set
PD	Progressive Disease
PD	Pharmacodynamics
PD-1	Programmed Death-1
PD-L1	Programmed Death-Ligand 1
PDI	Planned Dose Intensity
PDS	Programming Datasets Specifications
PFS	Progression-Free Survival
PK	Pharmacokinetics
PPS	Per-Protocol Set
PR	Partial Response
PT	Preffered Term
QoL	Quality of Life
Q2W	Every 2 weeks
Q4W	Every 4 weeks
RAP	Reporting and Analysis Process
RCC	Renal Cell Carcinoma
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase II dose
ROW	Rest Of the World
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMQ	Standardized MedDRA Query
SOC	System Organ Class
TFLs	Tables, Figures, Listings
TIM-3	T-cell Immunoglobulin domain and Mucin domain-3
TIL	Tumor Infiltrating Lymphocytes
UNK	Unknown
WHO	World Health Organization

1 Introduction

This Statistical Analysis Plan (SAP) provides detailed statistical methodology for the analysis of data from study CMBG453X2101 that will be presented in the Clinical Study Report (CSR). The output shells (in-text and post-text) accompanying this document can be found in the Tables-Figures-Listings (TFL) shells document. The specifications for derived variable and datasets can be found in the Programming Datasets Specifications (PDS) document.

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

The SAP, TFL shells and PDS documents may also serve as a reference for the creation of any outputs required outside of the CSR, e.g., MTD/RP2D declaration, Investigator's Brochure (IB) updates, abstracts, posters, presentations, manuscripts and management updates. Data used for these analyses will have a status aligned to the database lock guidance.

1.1 Study design

This is a first-in-human, open-label, phase I-Ib/II multicenter study of parallel cohorts with single agent MBG453, MBG453 in combination with PDR001. The study consists of the following parts:

- A phase I dose escalation part with MBG453 as single agent (including a separate Japanese single agent dose escalation part) in advanced solid tumors. For the distinction of the different escalation parts the labels Japanese vs. rest of the world (ROW) will be used, as shown in Figure 1-1.
- 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.
- MBG453 and PDR001 will be administered i.v. Q2W or Q4W 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 should not discontinue treatment based on progressive disease per RECIST v1.1 unless clinical deterioration or increase in tumor markers is observed.
- Should signs of anti-tumor activity (defined as at least one confirmed objective Partial Response (PR) or Complete Response (CR)) be detected in the phase I-Ib dose escalation parts, a dose ranging part will be opened, in which different dose levels of MBG453 alone and/or in combination with PDR001 will be also evaluated.
- 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 1-1.

Should signs of anti-tumor activity (defined as at least one confirmed objective PR) be detected in the phase I dose escalation part, a phase II part will be opened to evaluate clinical efficacy of MG453 alone.

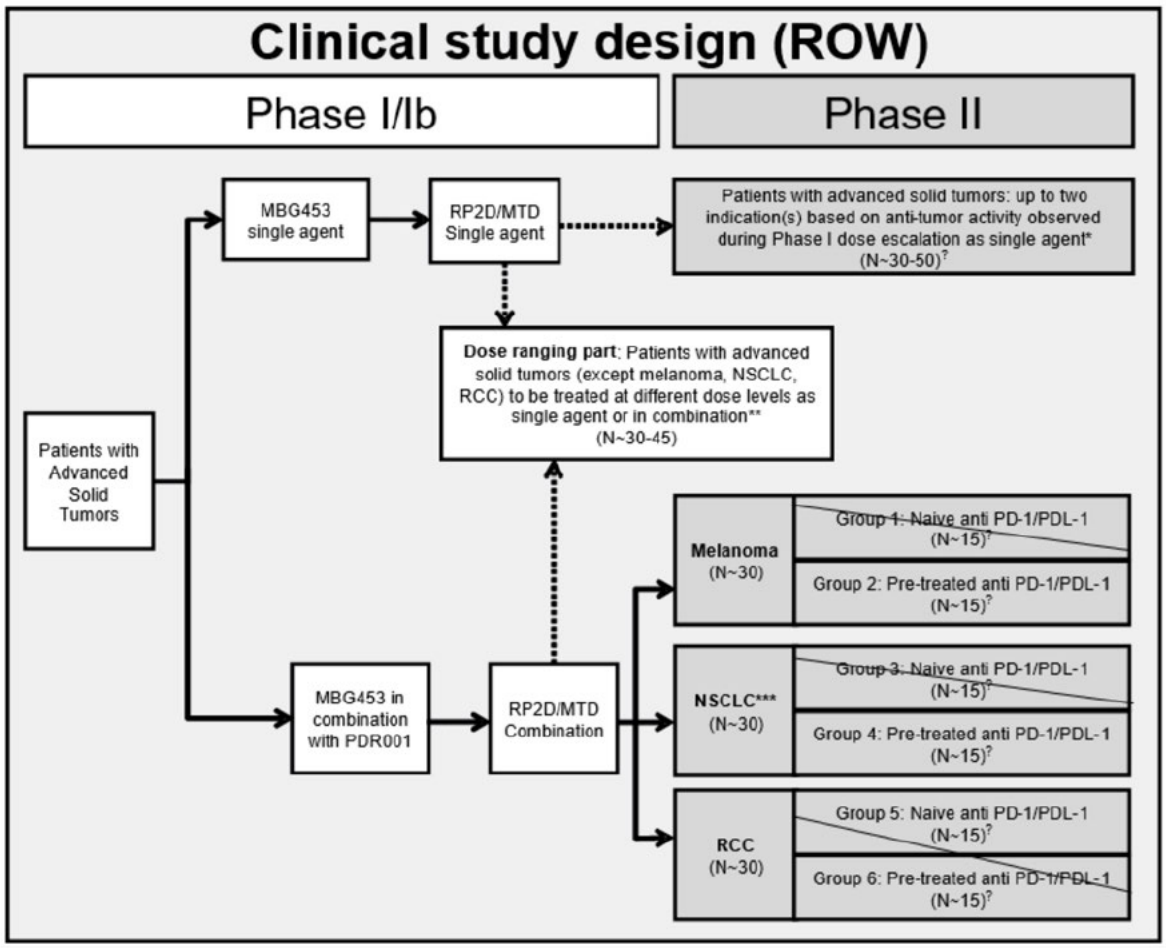
Japanese specific study design:

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. Dose escalation decisions will be guided by a separate 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.

For more information regarding the study desing see Section 4 of the protocol.

Figure 1-1 Study Design

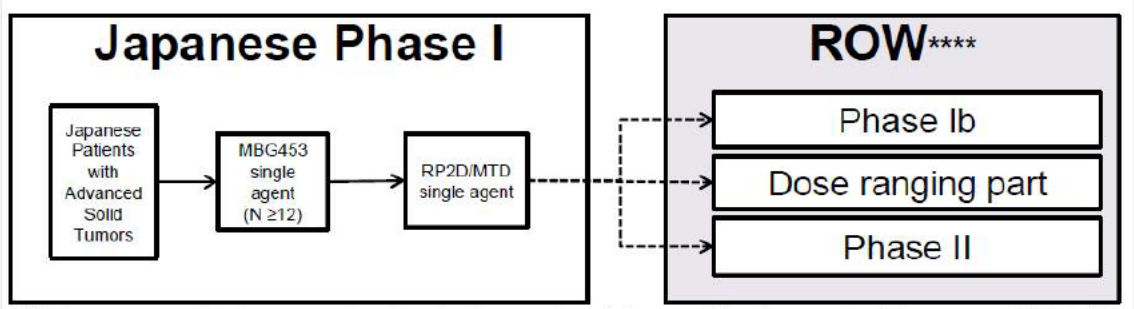


*This part will only be opened in relevant indications in the event that signs of anti-tumor activity (defined as either CR, PR or durable SD with tumor shrinkage that does not qualify for PR) to be observed in the phase I dose escalation part with MBG453 as single agent,

**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.



**** 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.

1.2 Study objectives and endpoints

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

Table 1-1 Objectives and related endpoints

Objective	Endpoint
Primary	
Phase I-Ib parts: To characterize the safety and tolerability of MBG453 as a single agent in rest of the world (ROW) and Japanese patients separately and in combination with PDR001 and identify recommended doses 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
Phase I-Ib dose ranging part: To further investigate the safety and tolerability of different doses of MBG453 as single agent and 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	Overall response rate (ORR) per RECIST v1.1
Secondary	
Phase I-Ib/II parts: To evaluate the preliminary anti-tumor activity of MBG453 as single agent and in combination with PDR001	Best Overall Response (BOR), Progression-free Survival (PFS) and Duration of Response (DOR) per RECIST v1.1; ORR and PFS per irRC
Phase II part (combination):	

Objective	Endpoint
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 and in combination with PDR001	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 and in combination with PDR001	Presence and/or concentration of anti-MBG453 and anti-PDR001 antibodies
Phase I-Ib/II parts: To assess potential predictors of efficacy of MBG453 single agent and in combination with PDR001 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 and in combination with PDR001 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 and in combination with PDR001 for each disease group	Overall survival (OS)
[redacted]	

2 Statistical methods

2.1 Data analysis general information

The data will be analyzed by Novartis personnel and/or designated CRO(s) using the most updated SAS® version, and for the Bayesian modeling the most updated versions for R (v 3.0.2 or later) and JAGs (v 4.0.0 or later). PK parameters will be calculated using non-compartmental methods available in Phoenix WinNonlin version 5.2.

The study data will be analyzed and reported in a final CSR based on all patients' data of the Phase I-Phase Ib and Phase II parts, up to the time when all patients have discontinued the study. The final CSR will include all outputs planned within the TFL shells document.

An interim CSR (iCSR) was prepared, as it was considered appropriate by the study team. Though the main focus of the iCSR was on the data and results of the phase I part of the study (MBG453 single agent treatment arm), it also included all outputs planned within the TFL shells document for all treatment arms with treated patients. Additional data for patients in the other parts of the study (phase Ib/II of MBG453 in combination with PDR001) past the data cutoff date of the iCSR, will be reported once all patients have discontinued the study in the final CSR.

Since there is no addition or update in the single agent data presented in the iCSR, no outputs will be produced for MBG453 single agent in the final analysis apart from the following:

- EUdraCT and clinicaltrials.gov requirements for AE and death summaries (see Section 2.9.3), as well as DSUR tables with subjects exposed by sex, age and race , as they were not included in the iCSR.
- Adverse events of special interest (AESIs; See Section 2.9.4), as they were not included in the iCSR .
- Listings for PK parameters , as this was considered important for publication issues and were not included in the iCSR.
- Table for demographic data for the whole number of patients of the study, as this is required for publication issues (clinicaltrials.gov).
- Immunogenicity analysis (IG), as there will be an update in the definitions of determinants (see Section 2.12).
- Tables of adverse events per system organ class and preferred term, as they will be used as source tables for the AESIs in-text tables.
- Biomarker analysis presented by treatment group, as per reporting requirements, though it was not initially considered appropriate due to the small number of patients per dose level.
- Duration of response outputs presented by treatment group, as per reporting activities, though it was not initially considered appropriate due to the small number of patients per dose level. Also listings of time to onset and duration of overall response, as those will be used as source listings for the duration of response.

- Protocol deviations outputs, as there were additional deviations included for MBG453 single agent after iterim data base lock.

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

Treatment group is defined by the study treatment, the dose level and the frequency of the study treatment (e.g. MBG453 80mg Q2W, MBG453 80mg Q2W + PDR001 240mg Q2W, etc.). Therefore, a treatment group may consist of more than one cohort.

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, 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 classified according to the patient group to which they were assigned at baseline based on the disease type.

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:

- 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.

Groups 1, 3, 5 and 6 were finally not populated and no patient was treated in a Q2W dosing at phase II. As a result, no outputs will be produced for those groups and the secondary phase II

objective "To make an initial comparison for MBG453 and PDR001 administered in combination on a Q2W and Q4W dosing schedules" will not be analyzed and presented.

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.

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

2.1.1 General definitions

Study drug and study treatment

Investigational drug will refer to MBG453 and PDR001. The terms investigational drug and study drug are used interchangeably.

Investigational treatment will refer MBG543 as single agent and MBG453 in combination with PDR001. The term investigational treatment may also be referred to as **study treatment**. For consistency across studies, the term study treatment will be used throughout this document.

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

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

Study day

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

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

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

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

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

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

Study day will be displayed in the data listings.

Time unit

A year length is defined as 365.25 days. A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in year, duration in days will be divided by 365.25.

Baseline

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

Baseline is the last available and valid assessment performed or value measured on or before the date of first administration of study treatment.

Baseline can also be the same day as first treatment administration if a pre-dose assessment/value is available (e.g., ECG, PK samples, samples for biomarkers).

- If time is recorded for the first treatment dose and for a specific assessment performed the day of first dose, this assessment will be considered as baseline only if it is actually performed before the first dose, as checked using both times.
- If time is not recorded, a specific assessment performed the day of first dose administration will be considered as baseline if, according to protocol, it should be performed before the first dose.

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

For pregnancy test, baseline will be within 72 hours before first administration of study treatment.

Computation of baseline for ECG are described in section 2.9.6.1.

On-treatment assessment/event

For all safety reporting the overall observation period will be divided into three mutually exclusive segments:

- *Pre-treatment period*: from day of patient's informed consent to the day before first dose of study medication
- *On-treatment period*: from day of first dose of study medication to 30 days after last dose of study medication
- *Post-treatment period*: starting at day 31 after last dose of study medication.

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

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (*treatment-emergent* AEs).

Last contact

The last contact date will be derived for patients not known to have died at the analysis cut-off using the latest complete date reported in the data base related to study visits or communication

with the patient on or before the data cut-off date. The cut-off date will not be used for last contact date, unless the patient was seen or contacted on that date.

The last contact date will be used for censoring of patients in the analysis of time to event endpoints.

New anticancer therapy

New anticancer therapy is defined as any therapy (medication, radiotherapy or surgery) given after the first study treatment administration. For more information on concomitant medication see Section 6.4 of the protocol.

The following categories of the eCRF "Antineoplastic Therapy Since Discontinuation of Study Treatment" shall be taken into consideration for the censoring of the patients in the analysis of the relevant endpoints (see Section 2.8.3):

- For medication, all cases with setting: adjuvant, neoadjuvant, prevention, palliative or other.
- For radiotherapy, all cases with setting: adjuvant, neoadjuvant, palliative or other.
- For surgery, all cases using the procedures: debulking, dissection, resection or excision/removal/ablation.

2.2 Analysis Set/ Patient Classification/Withdrawal of ICF/Subgroups

2.2.1 Analysis sets

2.2.1.1 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.

2.2.1.2 Safety Set

The Safety Set includes all patients from the FAS

Patients for the safety set 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.

The safety set will be used for the safety summary of the study.

2.2.1.3 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 (see Appendix 1 of the protocol).
- At least 2 post-baseline tumor assessments (unless disease progression as per RECIST v1.1 is observed before that time).
- For Group 1, 3 and 5, 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.
- Histologically documented advanced or metastatic solid tumors (for Groups 1-6).
- Baseline ECOG performance status ≤ 2.
- Phase II part (MBG453 single agent): pre-specified tumor type.
- Phase II part (MBG453 in combination with PDR001): melanoma, NSCLS or RCC.

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 of the protocol. If the PPS and the FAS are identical, then analyses described by the PPS below (Section 2.5.4) will not be performed.

2.2.1.4 Dose-determining analysis set (DDS)

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 dose limiting toxicity (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 $\geq$ 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 of the protocol.

Phase Ib part (MBG453 in combination with PDR001)

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 both MBG453 and PDR001 during Cycle 1.

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 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 of the protocol.

2.2.1.5 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 any or 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.

2.2.1.6 Immunogenicity analysis sets

The immunogenicity (IG) set includes two parts (IG prevalence set and IG incidence set) that will be defined for MBG453 (as single agent and in combination with PDR001) and PDR001 in combination with MBG453. Definitions of the IG sets are the following:

The IG prevalence set includes all subjects in the FAS with a determinant baseline IG sample or at least one determinant post-baseline IG sample.

The IG incidence set includes all subjects in the IG prevalence set with a determinant baseline IG sample and at least one determinant post-baseline IG sample.

See Section 2.12 for the definition of determinant.

2.2.2 Subject classification

Patients may be excluded from the analysis populations defined above based on the protocol deviations (PD) entered in the database and/or on specific classification rules defined in Table 2-1.

Table 2-1 Classification based on PDs and non-PD criteria

Analysis set	Protocol deviations leading to exclusion (DVSPID)	Non protocol deviation leading to exclusion
Full analysis set	No written inform consent (INCL19, INCL16)	No dose of study treatment (in both drugs for the combination arms) administered
Safety set	No written inform consent (INCL19, INCL16)	No dose of study treatment (in both drugs for the combination arms) administered
Dose-determining set	No written inform consent (INCL19, INCL16)	For MBG453 single agent: • Not all planned dose administered at cycle 1, or • Not followed up for ≥ 28 days after first dose administration, unless patient had a DLT during this period. For MBG453 + PDR001: • Not all planned dose of both drugs administered at cycle 1, or • Not at least one planned dose of both drugs was administered at cycle 2, unless patient had a DLT during 1st cycle, or Not followed up for ≥ 28 days after first dose administration of cycle 2, unless patient had a DLT during this period.patient

		had a DLT during this period.
Per-protocol set	• No written inform consent (INCL19, INCL16) • No presence of measurable and no measurable lesion for phase I/Ib parts or no presence of measurable lesion for phase I part according to RECIST v1.1 (INCL04, INCL06, INCL09). • For Groups 1, 3 and 5 (see Figure 1-1), patients previously treated with PD-1 or PD-L1 directed therapy (INCL21). For Group 2, 4 and 6 patients not previously treated with PD-1 or PD-L1 directed therapy. • Not histologically documented advanced or metastatic solid tumors (for Groups 1-6) (INCL09). • Baseline ECOG performance status > 2 (INCL12). • Phase II part (MBG453 single agent): not pre-specified tumor type. (INCL11). • Phase II part (MBG453 in combination with PDR001): no melanoma, NSCLS or RCC (INCL11).	• No dose of study treatment (in both drugs for the combination arms) administered. • Less than 2 post-baseline tumor assessments (unless disease progression is observed before that time).
PK Analysis Set	No written inform consent (INCL19, INCL16)	No blood sample providing evaluable PK data.
IG Analysis sets: • IG prevalence set • IG incidence set	No written inform consent (INCL19, INCL16)	• No dose of study treatment (in both drugs for the combination arms) administered • No determinant baseline IG sample and no determinant post-baseline IG sample, for the IG prevalence test. • No determinant baseline IG sample or no determinant post-baseline IG sample, for the IG incidence test.

2.2.3 Withdrawal of Informed Consent

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

Death events may be used in the analysis, if captured from public records (registers), given that local law and patient informed consent permits.

For more details on withdrawal of informed consent, please refer to Section 7.1.4 of the protocol.

2.2.4 Subgroup of interest

Not Applicable.

2.3 Patient disposition, demographics and other baseline characteristics

Unless noted otherwise, summaries and listings described in this section will be based on the FAS.

2.3.1 Patient disposition

The number and percentage of the patients included in the FAS, the ones who are still on treatment at the time of the data cut-off, the ones who discontinued the study phases, as well as the reason for discontinuation will be presented.

In particular, the following summaries will be provided (with % based on the total number of FAS patients):

- Number (%) of patients still on-treatment at the time of the data cut-off (based on non-completion of the 'End of Treatment' page)
- Number (%) of patients having discontinued the study treatment (based on completion of the 'End of Treatment' page with discontinuation date and reason entered)
- Primary reason for study treatment discontinuation (based on discontinuation reason entered in the 'End of Treatment' page)
- Number (%) of patients having discontinued the study (based on completion of the 'End of Post treatment Phase' page with discontinuation date and reason entered)
- Primary reason for study evaluation completion (based on discontinuation reason entered in the 'End of Post treatment Phase' page).

2.3.2 Demographics and other baseline characteristics

Demographic data including age, sex, race, ethnicity, height, and baseline weight and ECOG performance status as well as other baseline data including disease characteristics (primary site of cancer, histological grade, predominant histology/cytology, stage at initial diagnosis and stage at time of study entry) and metastatic sites will be listed and summarized descriptively. In addition, child bearing potential and pregnancy test results will be listed, and age (18- <65 years, 65- < 85 years, and ≥ 85 years) categories summarized.

These data will be summarized by frequency counts and percentages; the number and percentage of patients with missing data will be provided. Continuous data (e.g. age, weight, height) will be summarized by descriptive statistics (N, mean, median, standard deviation, minimum and maximum).

2.3.3 Medical history

Medical history and current (ongoing) medical conditions, including cancer-related conditions and symptoms will be summarized and listed. Separate summaries will be presented for current and historical medical conditions by primary system organ class and preferred term. Medical history and current medical conditions are coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) terminology available at the time of reporting.

2.3.4 Prior antineoplastic therapy

The number (%) of patients who received any prior anti-neoplastic medication, radiotherapy or surgery will be summarized.

The summary of prior anti-neoplastic medications will include the total number of regimens (note: there can be more than one medication per regimen), immuno-oncology therapeutic class at last treatment, setting at last treatment and best response at last treatment (defined to be the best response during the last treatment regimens recorded). Prior antineoplastic medications will also be summarized by Anatomical Therapeutic Chemical (ATC) class and preferred term.

The summary of prior anti-neoplastic radiotherapy will include the radiotherapy locations, (including all locations recorded for each Subject) and setting at last radiotherapy.

The summary of prior anti-neoplastic surgery will include the time (in months) between the last surgery (non-biopsy procedure) to start of study treatment, procedure at last surgery and residual disease at last surgery.

All prior anti-neoplastic medication, radiotherapy and surgery will be listed.

2.3.5 Diagnosis and extend of cancer

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

2.4 Protocol deviations

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

COVID-19 specific protocol deviations will be included in the protocol deviation listing. Details about COVID-19 impact are provided in Section 4.1.

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

2.5.1 Study treatment

The safety set will be used for all summaries and listings regarding study treatment.

2.5.1.1 Data handling

Imputation rules regarding last and first treatment administration of study drug can be found in Appendix, Section 5.1.1.

2.5.1.2 Duration of exposure to study treatment

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

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

The last date of exposure to study treatment is the latest of the last dates of exposure to the investigational drug of the treatment arm.

The definition of last date of exposure to investigational drug (days) is defined as follows:

- **For MBG453:** the date of last administration of a non-zero dose +
  - 13 days, for the Q2W treatment schedule
  - 27 days, for the Q4W treatment schedule.
- **For PDR001:** the date of last administration of a non-zero dose +
  - 13 days, for the Q2W treatment schedule
  - 27 days, for the Q4W treatment schedule.

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

Definition of date of last contact can be found in Section 2.1.1.Summary of duration of exposure of investigational drug will include categorical summaries (based on clinically meaningful time intervals) and continuous summaries (i.e. mean, standard deviation, etc.) using appropriate units of time.

2.5.1.3 Cumulative dose

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

The **planned cumulative dose** for a study treatment component refers to the total planned dose as per the protocol up to the last date of investigational drug administration.

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

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

2.5.1.4 Dose intensity and relative dose intensity

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

- For the Q4W regimens: DI (mg/28 days) = 28 * Actual cumulative dose (mg) / Actual duration of exposure = 28 * Actual cumulative dose (mg) / [Last dosing date – First dosing date + Dose interval (28 days)].
- For the Q2W regimens: DI (mg/14 days) = 14 * Actual cumulative dose (mg) / Actual duration of exposure = 14 * Actual cumulative dose (mg) / [Last dosing date – First dosing date + Dose interval (14 days)].

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

Planned dose intensity (PDI) is defined as follows:

- For the Q4W regimens: PDI (mg/28 days) = Planned dose (mg) per cycle (28 days).
- For the Q2W regimens: PDI (mg/14 days) = Planned dose (mg) per cycle (14 days).

Relative dose intensity (RDI) is defined as follows:

RDI = DI / PDI.

The duration of exposure considered for the derivation of the DI and the RDI will be derived from the start date of study treatment (first dosing date) to the end of the last cycle initiated (last dosing date + dose interval, where dose interval is 28 or 14 days for Q4W or Q2W schedule, respectively), irrespective of date of death, date of last contact and cut-off date.

DI and RDI (including categories: ≤ 75%, > 75% - ≤ 90%, > 90% - ≤ 110% and > 110%) will be summarized separately for each of the study treatment components, using the duration of exposure of each of the components.

2.5.1.5 Dose reductions, interruptions or permanent discontinuations

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

‘Dose changed’, ‘Dose interrupted’ and ‘Dose permanently discontinued’ fields from the DAR eCRF pages will be used to determine the dose reductions, dose interruptions, and permanent discontinuations, respectively. Dose reductions will be derived programmatically using the dosing information as described below.

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

A dose change is either ‘change in prescribed dose level’ or ‘dosing error’, ‘dispensing error’, etc., where actual dose administered is different from the prescribed dose.

Dose interruption: Actual dose equal to zero, between the first and last non-zero doses, following a non-zero actual dose.

For the purpose of summarizing interruptions and reasons, in case multiple entries for interruption that are entered on consecutive days/time periods with different reasons will be counted as separate interruptions. However, if the reason is the same in this mentioned multiple entries on consecutive days, then it will be counted as one interruption.
Intermediate interruptions that end up in a non-zero dose administration should not be considered dose interruptions.

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

2.5.2 Prior, concomitant and post therapies

Concomitant therapies are defined as any medications (excluding study treatment, prior antineoplastic treatments) and significant non-drug therapies (including physical therapy and blood transfusions) administered in the study and are recorded in the Concomitant Medications/significant non-drug therapies eCRF. These therapies will be coded using the WHO Drug Reference Listing (WHO DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (WHO ATC) classification system. The non-drug therapies will be coded using MedDRA.

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

Imputation rules regarding last and first treatment administration of concomitant therapies can be found in Appendix, Section 5.1.3.

2.6 Analysis of the primary objective

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.

Phase I-Ib dose ranging part

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

Phase II part

To estimate the anti-tumor activity of MBG453 as single agent and in combination with PDR001.

2.6.1 Definition of the primary endpoint

2.6.1.1 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
- Incidence of DLTs:
  - For MBG453 single agent, in the first cycle of treatment.
  - For MBG453 in combination with PDR001, in the first two cycles 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.

2.6.1.2 Phase I-Ib dose ranging part

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

2.6.1.3 Phase II part

Overall Response Rate (ORR): is 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 (see Appendix 1 of the protocol).

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

2.6.2 Statistical hypothesis, model, and method of analysis

2.6.2.1 Phase I-Ib parts

Safety and Tolerability

See Section 2.9 for details on safety 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 every two weeks (Q2W, stratum 1) and patients treated every four weeks (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:

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

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

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

where d denotes dose; 240 is a fixed reference dose for each respective strata; π_{Q2W}^{d} π_{Q4W}^{d}, and π_{PDR}^{d}, 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 $\theta_{Q2W} = \left(\log(\alpha_{Q2W}), \log(\beta_{Q2W})\right)$, $\theta_{Q4W} = \left(\log(\alpha_{Q4W}), \log(\beta_{Q4W})\right)$, 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 $\left(p_{Q2W}, 1 - p_{Q2W}\right)$, $\left(p_{Q4W}, 1 - p_{Q4W}\right)$, and $(p_{PDR}, 1 - p_{PDR})$ respectively.

- 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.

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

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

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) of the protocol. 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:

$$\text{logit}\left(\pi^{d}_{MBG,i}\right) = \log\left(\alpha_{MBG,i}\right) + \beta_{MBG,i}\log\left(d^{0.5}_{MBG,i}/240^{0.5}\right)$$

$$\text{logit}\left(\pi^{d}_{PDR,i}\right) = \log\left(\alpha_{PDR,i}\right) + \beta_{PDR,i}\log\left(d^{0.5}_{PDR,i}/240^{0.5}\right)$$

where i = 1 and 2 for Cycle 1 and 2, respectively; $\text{logit}(\pi^{d}_{\cdot}) = \log[\,\pi^{d}_{\cdot}/\{1-\pi^{d}_{\cdot}\}]$; 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

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

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:

$$\begin{aligned} odds^{d}_{MBG+PDR,i} &= \frac{\pi_{MBG+PDR,i}}{1-\pi_{MBG+PDR,i}} \\ &= \exp\left(\eta\, d^{0.5}_{MBG,i}\Big/240^{0.5}\, d^{0.5}_{PDR,i}\Big/240^{0.5}\right)\frac{\pi^{d}_{MBG,i} + \pi^{d}_{PDR,i} - \pi^{d}_{MBG,i}\pi^{d}_{PDR,i}}{(1-\pi^{d}_{MBG,i})(1-\pi^{d}_{PDR,i})} \end{aligned}$$

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 of the protocol), 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 of the protocol) 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:

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

For the MBG453 single agent and MBG453 in combination with 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.

Listing of DLTs

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

2.6.2.2 Phase I-Ib dose ranging part

Safety and Tolerability

See Section 2.9 for details on safety analysis.

2.6.2.3 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.

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.

Groups 1, 3, 5 and 6 were finaly not populated and no patient was treated in a Q2W dosing at phase II. As a result, no outputs will be produced for those groups.

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 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.

Operating characteristics of the design can be found in Table 3-2.

2.6.3 Handling of missing values/censoring/discontinuations

Patients in the dose escalation part who are ineligible for the DDS will be excluded from the BLRM 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 (see Appendix 1 of the protocol) and irRC (see Appendix 2 of the protocol).

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

2.6.4 Supportive analyses

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

For the phase II part, the primary analysis on ORR will be repeated using the PPS. Additional supportive [redacted] analyses will be conducted to support the primary objective, if considered appropriate.

2.7 Analysis of key secondary efficacy objective(s)

Not applicable.

2.8 Analysis of secondary efficacy objective(s)

Phase I-Ib parts

To evaluate the preliminary anti-tumor activity and the survival distribution of patients treated with MBG453 single agent or in combination with PDR001.

Phase II part

To evaluate the preliminary anti-tumor activity and the survival distribution of patients treated with MBG453 single agent or in combination with PDR001.

To make an initial comparison for MBG453 and PDR001 administered in combination on a Q2W and Q4W dosing schedules. As no patients were treated on a Q2W dosing schedule in phase II part of the study, this objective will not be analyzed.

2.8.1 Definition of secondary endpoints

2.8.1.1 Phase I-Ib/II parts

ORR per irRC, Best Overall Response (BOR) per RECIST v1.1and irRC, Progression-free Survival (PFS) per RECIST v1.1 and irRC and Duration of Response (DOR) per RECIST v1.1, Overall survival (OS).

Definitions of the relevant endpoints is given below:

- **Best Overall Response (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 4 weeks after the criteria for response are first met. Additionally, for irRC, progressive disease should be confirmed in a similar manner.
- **Overall Response Rate (ORR):** see Section 2.6.1.2.

- **Progression-free Survival (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 experienced an event at the time of the analysis or has started a new anticancer therapy, PFS will be censored at the date of the last adequate tumor evaluation before the start of a new anticancer therapy, if any.
- **Duration of Response (DOR):** is 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 ("study indication" - see section 0).
  If progression or death due to underlying cancer ("study indication") has not occurred or patient has started a new anticancer therapy, then the patient is censored at the date of last adequate tumor assessment before the start of a new anticancer therapy, if any.
- **Overall Survival (OS):** is defined as the time from date of start of treatment to date of death due to any cause.
  If a patient is not known to have died, OS time will be censored at the date of last contact.

2.8.1.2 Phase II part (combination)

ORR per irRC, BOR per RECIST v1.1 and irRC, PFS per RECIST v1.1 and irRC and DOR per RECIST v1.1 and OS (see definition of endpoints in 2.8.1.1).

2.8.2 Statistical hypothesis, model, and method of analysis

Individual lesion measurements and overall response assessments will be listed by patient and assessment date. BOR will be listed and tabulated. BOR will be summarized as observed proportion for each treatment group/patient group, and corresponding 90% exact CI.

The primary analysis of ORR will be as described in Section 2.6.2.3. Additionally, ORR will be summarized as point estimate and corresponding 90% exact confidence interval (CI) according to Clopper-Pearson method (Clopper and Pearson, 1934).

A Kaplan-Meier plot for PFS will be presented. Median PFS (in months) with corresponding 90% CI, 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997) and Kaplan-Meier estimated probabilities (PFS rate) with corresponding 90% CIs (Greenwood's formula, Kalbfleisch and Prentice 1980) at several time points (6, 12, 18 and 24 months) will be presented for each treatment group/patient group. The number (%) of progressions, deaths and censored patients will also be summarized.

OS data will be listed for all patients enrolled in the Phase I-Ib and Phase II parts. A Kaplan-Meier plot for OS will be presented. Median OS (in months) with corresponding 90% CI, 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997) and Kaplan-Meier estimated probabilities (OS rate) with corresponding 90% CIs (Greenwood's formula, Kalbfleisch and Prentice 1980) at several time points (6, 12, 18 and 24 months) will be presented for each treatment group/patient group. The number (%) of deaths and censored patients will also be summarized.

DOR will be listed for all patients who achieved a response of CR or PR. Only if there is a large enough number of patients achieving response (i.e. 10 or more patients), a Kaplan-Meier plot for DOR will be also be produced and presented. Median DOR (in months) with corresponding 90% CI, 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997) and Kaplan-Meier estimated probabilities (DOR rate) with corresponding 90% CIs (Greenwood's formula, Kalbfleisch and Prentice 1980) at several time points (6, 12, 18 and 24 months) will be presented. The number (%) of progressions, deaths due to underlying cancer ("study indication") and censored patients will also be summarized.

Construction of waterfall graphs

Waterfall graphs will be used to depict anti-tumor activity. These plots will display the best percentage change from baseline in the sum of diameters of target lesions for each patient for RECIST v1.1, and best percentage change from baseline in the Total Measured Tumor Burden (TMTB) for irRC. The FAS will be used.

2.8.3 Handling of missing values/censoring/discontinuations

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 (see Appendix 1 of the protocol) and irRC (see Appendix 2 of the protocol). If any new anticancer therapy (see Section 2.1.1) is taken while on study, any subsequent assessments will be excluded from the best overall response determination.

For the analysis of PFS, patients without documented disease progression or death due to any cause will be censored at the time of last adequate tumor assessment documenting non-progression (one of complete response, partial response, or stable disease) before the start of a new anticancer therapy (see Section 2.1.1), if any. Patients without any valid post-baseline tumor assessment response (one of CR, PR, SD, or PD) will be censored on the start date of treatment. Patients who have a PFS event (progression or death due to any cause) after two or more consecutive missing assessments from the last valid tumor assessment will be censored on the last valid tumor assessment (or on the start date of treatment among those without a postbaseline tumor assessment).

For the analysis of DOR, patient without documented disease progression or death due to underlying cancer ("study indication") will be censored at the date of last adequate tumor assessment documenting non-progression (one of complete response, partial response, or stable disease) before the start of a new anticancer therapy (see Section 2.1.1), if any.

For the analysis of OS, patient without an event (death) will be censored at the date of last contact.

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

2.9 Safety analyses

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

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

For all safety reporting the overall observation period and safety summaries will follow the instructions mentioned in section 2.1.1.

2.9.1 Adverse events (AEs)

Adverse events will be coded using the latest available version of the Medical dictionary for regulatory activities (MedDRA) and assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. If CTCAE grading does not exist for an AE, grades 1, 2, 3, or 4 corresponding to the severity of mild, moderate, severe, and life-threatening, respectively, will be used.

The following AE summaries will be produced:

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

Complete listings of AEs as well as AEs for not treated patients will also be provided.

2.9.2 Deaths

CTCAE grade 5 (death) will not be used in this study. Death information will be collected on the “Death” eCRF as well as on the following disposition eCRF pages: “End of screening”, “End of treatment” and End of post treatment phase” disposition).

The following summaries will be produced:

- On-treatment deaths with cause of death by preferred term
- All deaths with cause of death by primary system organ class and preferred term

2.9.3 EudraCT and clinicaltrials.gov requirements for AEs and Deaths summaries

- For the legal requirements of clinicaltrials.gov and EudraCT, two on-treatment tables are required.On-treatment deaths resulting from SAEs suspected to be study drug related and SAEs regardless of study drug relationship by SOC and PT.
- Non-serious AEs regardless of study drug relationship, with an incidence rate greater than 5% by SOC and PT.

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

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

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

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

2.9.4 Adverse events of special interest / grouping of AEs

An adverse event of special interest (AESI) is a grouping of adverse events that are of scientific and medical concern specific to compound MBG453. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), HGLTs (high group level terms), HLT (high level terms) and PTs (preferred terms). Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad. These searches will be defined in the eCRS (electronic Case Retrieval Strategy) in the DMS (Document Management System) and a listing of search terms will be provided in the CSR.

Especially for the MBG453X2101 study, the following two safety topics of interest will only be presented as they were considered relevant by the study team:

- Immune mediated disorders
- Infusion related reactions

For each specified AESI, number (%) of subjects with at least one event of the AESI occurring during on treatment period will be summarized together with the individual preferred terms in that grouping.

2.9.5 Laboratory data

Laboratory data will be converted into SI units and classified (by Novartis statistical programming) into CTC grades according to CTCAE v4.03. Grade 5 will not be used.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. For other cases, a Grade 0 CTC grade will be set when laboratory value is:

- Within LLN and ULN and grading in both direction,
- Below ULN and grading in hyper direction,
- Above LLN and grading in hypo direction.

Laboratory data for which a CTC grading does not exist will be classified into low, normal, or high based on local laboratory normal ranges as applicable.

Laboratory summaries will include all assessment available for the laboratory parameters collected no later than 30 days after the last study treatment administration date.

The following summaries will be produced for hematology and coagulation, biochemistry parameters:

- Worst post-baseline abnormalities
- For parameters with CTC grades: Worst post-baseline abnormalities based on CTC grades for hematology and biochemistry, as well as Shifts from baseline to the worst on-treatment CTC grade for hematology and biochemistry,
- For parameters with no CTC grades defined: Shifts from baseline to the worst on-treatment classification, using the low/normal/high classifications,

The following listings will be produced:

- Listing of patients with laboratory abnormalities of CTC grade 3 and 4
- Listing of patients with Virology parameter assessment

Table 2-2and Table 2-3 list all laboratory parameters that will be summarized.

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

Hematology and coagulation		Biochemistry	
White Blood Cells (WBC)	↑ ↓	Creatinine	↑
Hemoglobin	↓	Sodium	↑ ↓
Platelets counts	↓	Potassium	↑ ↓
Absolute Neutrophils	↓	Calcium (corrected for Albumine)	↑ ↓
Absolute Lymphocytes	↑ ↓	Magnesium	↑ ↓
APTT	↑	Albumin	↓
INR	↑	AST (SGOT)	↑
		ALT (SGPT)	↑

Total Bilirubin	↑
Inorganic Phosphate	↓
Glucose (fasting)	↑ ↓
Amylase	↑
Lipase	↑
Alkaline Phosphatase	↑

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

Table 2-3 Laboratory parameters (without CTCAE grades) for which lab reference ranges are defined

Hematology and coagulation	Biochemistry
Prothrombin time (PT)	Blood urea nitrogen (BUN) / Urea
Absolute Basophils	
Absolute Eosinophils	TSH
Absolute Monocytes	Total T4
Hematocrit	Direct bilirubin
	Indirect bilirubin
	Chloride
	Bicarbonate

2.9.6 Other safety data

2.9.6.1 ECG and cardiac imaging data

As described in Section 2.1.1, baseline is the last available and valid assessment performed or value measured on or before the date of first administration of study treatment. Especially for ECG, where study requires multiple replicates per timepoint, the average of all these available ECG measurements associated with the baseline assessment will be calculated. Scheduled study day 1 pre-dose ECGs will be considered to have been obtained prior to study drug administration if dosing time is missing.

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

ECG data will be reviewed and processed centrally by a specialist CRO.

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

- Number (%) of patients having notable ECG values according to Table 2-4.

Table 2-4 Criteria for notable ECG values

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

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

2.9.6.2 Vital signs

Vital sign parameters collected are systolic and diastolic blood pressure (mmHg), pulse rate (beats per minute), respiratory rate (breaths per minute), body temperature (°C), and weight (kg). Vital sign values considered notably abnormal are defined in Table 2-5.

Table 2-5 Criteria for notable vital sign values

Vital sign	Criteria for clinically notable vital sign values
Systolic blood pressure [mmHg]	High: ≥180 mmHg with increase from baseline of ≥20 mmHg Low: ≤90 mmHg with decrease from baseline of ≥20 mmHg
Diastolic blood pressure [mmHg]	High: ≥105 mmHg with increase from baseline of ≥15 mmHg Low: ≤50 mmHg with decrease from baseline of ≥15 mmHg
Pulse rate [bpm]	High: ≥100 bpm with increase from baseline of ≥25 bpm Low: ≤50 bpm with decrease from baseline of ≥25 bpm
Body temperature [°C]	High: ≥ 39.1 °C
Weight [kg]	High: ≥10% increase from baseline Low: ≥10% decrease from baseline

- Vital signs table based on values classified as notable low or notable high will be produced.
- Patients with any clinically notable vital sign value will be listed.

2.9.6.3 Tolerability

Tolerability of study treatment will be assessed by summarizing the number of dose interruptions and dose reductions by treatment group. Reasons for dose interruption and dose reductions will be listed by patient and treatment group and summarized by treatment group. Cumulative dose, dose intensity and relative dose intensity of study treatment (see Section 2.5) will be also be used to assess tolerability.

2.10 Pharmacokinetic endpoints

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

PK parameters will be calculated using noncompartmental methods and summarized as described in Table 2-6. The PK parameters considerd primary are AUClast, AUCtau, Cmax, and Tmax. Other PK parameters (CL, V, T1/2, AR) are considered as secondary. All PK parameters or as appropriate they will be summarized in tables and will be listed.

Concentration values below the lower limit of quantitation (LLOQ) (< 1.0 µg/mL) or missing data will be handled as zero in summary statistics and figures. PK concentration values will be fully listed.

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 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. All analyses will be reported either in the CSR or a stand-alone report.

Table 2-6 PK parameters – descriptive statistics

Parameters	Descriptive statistics
AUCtau, AUClast, Cmax	Mean, standard deviation, CV% mean, geometric mean, CV% geometric mean, median, minimum and maximum
Tmax	Median, minimum and maximum
CV% = coefficient of variation (%) = sd/mean*100 CV% geometic mean = sqrt (exp (variance for log transformed data)-1)*100	

Dose proportionality and day effect

Analysis of dose-proportionality will be performed if at least three doses of MBG453 are investigated. Same applies for the analysis of dose-proportionality of PRD001.

Cmax and AUC will be used for dose proportionality analysis using the power model (Gough 1995). The power model empirical relationship between a PK parameter and dose is of the form

$$PK = Exp(\alpha)(dose)^{\beta},$$

where "PK" represents the PK parameter AUCinf or Cmax. For analysis, this equation is log-transformed (natural log), obtaining the equation

$$\log_e(PK) = \alpha + \beta \log_e(Dose),$$

The slope beta measures the dose-proportionality between Dose and the PK parameter.

To test for dose proportionality, the confidence interval criteria for assessment of dose proportionality from Smith et al. (2000) will be used. The a *priori* acceptance range for the slope, according to Smith, is given by

$$1+\frac{Ln(0.8)}{Ln(dose\_ratio)} < \beta < 1+\frac{Ln(1.25)}{Ln(dose\_ratio)}$$

Where 1.25 and 0.8 are the critical *a priori* values suggested by regulatory authorities for any bioequivalence problem after a data log transformation, and "*dose_ratio*" is the ratio of the largest to the smallest dose. Dose proportionality can be claimed if the 90% confidence interval for the slope is entirely contained within this a *priori* range.

2.11 PD and PK/PD analyses

Pharmacodynamic markers, including TIL counts, [redacted] will be assessed using paired tumor samples at screening/baseline and on-treatment (several time points as detailed in Table 7-10 of the protocol). 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.

2.12 Immunogenicity

2.12.1.1 Sample ADA Status

Each IG sample is assesed in a three tiered anti-drug anti-body (ADA) testing approach. All IG samples are analyzed in the initial screening assay (first tier). Samples testing negative in the screening assay are not subject to a confirmatory assay. Samples testing positive in the screening assay are then subjected to the confirmatory assay to demonstrate that ADA are specific for the therapeutic protein product (second tier). The titer of confirmatory positive samples will be subsequently determined in the titration assay (third tier). Samples identified as positive in the confirmatory assay are considered ADA positive. Samples can test negative in either the screening or confirmatory assay but for analysis purposes they are not differentiated. The following properties of each sample will be provided in the source data:

- Result of assay according to pre-specified confirmatory cut point: ADA positive (yes) or ADA negative (no)
- Titer (for positive samples): numerical representation of the magnitude of ADA response
- When titer values are below the titer cut point with minimal required diluation (MRD) and the result is reported as 'Titer value 50 (MRD)', it is interpreted as a POSITIVE sample with titer equal to 50.
- Drug tolerance level: highest drug concentration that does not interfere in the ADA detection method
- Fold titer change (i.e. x-fold): threshold for determining treatment boosted

Determinant samples are defined as samples which are not unevaluable (where unevaluable = sample where assay is not available).

The following definitions apply only to determinant samples:

- *ADA-negative sample*: Determinant sample where assay is ADA negative. and PDR001 or MBG453 PK concentration at the time of IG sample collection is less than the drug tolerance level.
- *ADA-positive sample*: Determinant sample where assay is ADA positive.
- *ADA-inconclusive sample*: Sample where assay is ADA negative and PDR001 or MBG453 PK concentration at the time of IG sample collection is greater than or equal to the drug tolerance level or missing.

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

- *Treatment-induced ADA-positive sample:* ADA-positive sample post-baseline with ADA-negative sample at baseline.
- *Treatment-boosted ADA-positive sample:* ADA-positive sample post-baseline with titer that is at least *the fold titer change* greater than the ADA-positive baseline titer.
- *Treatment-unaffected ADA-positive sample*: ADA-positive sample post-baseline with titer that is less than *the fold titer change* greater than the ADA-positive baseline titer.

NOTE: PK concentrations which are flagged for exclusion will still be used to determine ADA-inconclusive and ADA-negative samples.

The following summaries of ADA sample status (n and %) will be provided using *Immunogenicity prevalence set*:

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

Listings will be provided of sample ADA status (including titer for positive samples).

2.12.1.2 Subject ADA status

Any IG sample collected after 150 days or more form the last dose administration of PDR001 or MBG453 will not be used for summaries or derivations and will only be included in the listing.

Subject ADA status is defined as follows:

- *Treatment-induced ADA-positive subject*: subject with ADA-negative sample at baseline and at least one treatment-induced ADA-positive sample.
- *Treatment-boosted ADA-positive subject*: subject with ADA-positive sample at baseline and at least one treatment-boosted ADA-positive sample.

- *Treatment-unaffected ADA-positive subject*: subject with ADA-positive sample at baseline, no treatment-boosted ADA-positive samples, and at least one treatment-unaffected ADA-positive sample.
- *Treatment-reduced ADA-positive subject*: subject with ADA-positive sample at baseline and at least one post baseline determinant sample, all of which are ADA-negative samples.
- *ADA-negative subject*: subject with ADA-negative sample at baseline and at least one post baseline determinant sample, all of which are ADA-negative samples.
- *Inconclusive subject*: subject who does not qualify as treatment-induced ADA-positive, treatment-boosted ADA-positive, treatment-unaffected ADA-positive, treatment-reduced ADA-positive, or ADA-negative.

The following summaries of ADA subject status (n and %) will be provided using *Immunogenicity incidence set*:

- Treatment-boosted ADA-positive subjects; denominator is the number of subjects with ADA-positive sample at baseline.
- Treatment-induced ADA-positive subjects; denominator is the number of subjects with ADA-negative sample at baseline.
- ADA-inconclusive subjects: denominator is the number of subjects in *Immunogenicity incidence set*.
- ADA-negative subjects: denominator is the number of subjects in *Immunogenicity incidence set*.
- ADA-positive subjects (i.e. ADA incidence): calculated as the number of treatment-boosted ADA-positive and treatment-induced ADA-positive subjects; denominator is the number of subjects in *Immunogenicity incidence set*.

Listings will be provided of subject ADA status.

Additional analyses of ADA vs. safety, efficacy, and/or MBG453 PK, if conducted, will be defined in a separate SAP and the results reported separately from the CSR.

2.13 Patient-reported outcomes

Not Applicable.

2.14 Biomarkers

2.14.1 Introduction

As a project standard, Novartis Oncology BDM will analyze only biomarkers collected in the clinical database. [redacted]

[redacted]

There may be circumstances when a decision is made to stop sample collection, or not perform or discontinue the analysis of blood / archival tumor samples / fresh tumor biopsies / fine needle aspirates due to either practical or strategic reasons (e.g. issues related to the quality and/or quantity of the samples or issues related to the assay). Under such circumstances, the number of samples may be inadequate to perform a rigorous data analysis and the available data will only be listed and potentially summarized.

2.14.2 Outline of the data analysis

Additional analyses that may be performed after the completion of the end-of-study 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 or the analysis of biomarkers generated from samples collected during the study but analyzed after the database lock and completion of the CSR. The data analysis will be described in an addendum of the SAP or in a stand-alone analysis plan document, as appropriate.

All patients with evaluable PD measurements during phase I-Ib/II will be included in the data analysis. Missing values will not be imputed and will not be included in the analysis.

2.14.3 Biomarker objectives

For biomarker objectives, please see Table 1-1.

A list of potential biomarker and purposes of analysis can be found in Table 2-7.

Table 2-7 Biomarkers and purpose of analysis

Biomarker	Purpose of analysis
PD-L1 expression, TIM-3 expression, CD163-expression, LAG-3 expression, FOXP3 expression	Potential predictors of efficacy
CD8+ expression (TIL counts)	Pharmacodynamic (Baseline)
[redacted]	
[redacted]	
CD8+ expression (TIL counts)	Pharmacodynamic effect (On-treatment)
[redacted]	
[redacted]	
Anti-PDR001 antibodies	Assess emergence of anti-PDR001 antibodies following one or more intravenous (i.v.) infusions of PDR001 and MBG453

All interpretable IHC biomarker data available will be listed. [redacted]

The following listings will be produced for interpretable data:

- CD8+ expression at screening
- PD-L1 expression at screening
- TIM-3 expression at screening
- LAG-3 expression at screening
- CD163 expression at screening
- FOXP3 expression at screening
- TILS intratumoral presence at screening

Usual descriptive statistics will be displayed for interpretable biomarker data:

- Mean, standard deviation, median, minimum, and maximum for quantitative data measured at baseline
- N, % in each category for categorical data

If there are post-baseline data available the following descriptive statistics will be presented:

- Mean, standard deviation, median, minimum, and maximum of raw data, absolute change from baseline and relative change form baseline (depending on the biomarker) for quantitative data measured at baseline and at different time points.

Descriptive statistics computed for each time point separately.

- In case we have more than one measurements on the same day, then the average of those measurements will be used. Reason for this is to acount for cases where more than one slides of the same patient and at the same time-point were analyzed.

[redacted]

2.16 Interim analysis

An interim analysis was performed and reported in an interim CSR (iCSR), as it was considered appropriate by the study team.

3 Sample size calculation

Phase I-Ib dose escalation parts

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 of the protocol. 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.

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 alone 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 3-1 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

Special AE of interest incidence rate	Number of patients			
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.

The operating characteristics of the design is shown in Table 3-2, 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 3-2 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

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.

4 Change to protocol specified analyses

Confidence intervals for all endpoints was set to 90% for consistency in the study results.

For DOR, summaries of estimates using the Kaplan-Meier method will be reported only if there is a large enough number of patients achieving response (i.e. 10 or more patients). Definition of the per-protocol analysis set was updated, as this was considered more relevant by the study team.

Additional analysis sets were included (immunogenicity prevalence set and immunogenicity incidence set) for the analysis of immunogenicity data. An update of the definitions of the sample determinants was decided by the study team in order be consistent across studies of the same program.After protocol amendment 6 (31-Aug-2020) the following changes have been implemented:

- For the phase Ib/II part of MBG453 in combination with decitabine, as it was decided by Novartis to not open enrolment, no outputs will be presented in the CSR.

[redacted]

Various minor changes were applied in the analysis described in the protocol, as considered appropriate by the study team.

All changes were defined in the statistical analysis plan before the data base lock.

4.1 Planned analysis due to COVID-19

The COVID COVID-19 pandemic had minimal impact on this study because at the start of the pandemic, the vast majority of subjects had discontinued the study treatment and completed the safety follow-up phase. COVID-19 specific protocol deviations will be included in the protocol deviation listing.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

Not applicable.

5.1.2 AE date imputation

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

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

	AEM MISSING	AEM < TRTM	AEM = TRTM	AEM > TRTM
AEY MISSING	No imputation	No imputation	No imputation	No imputation
AEY < TRTY	(D)	(C)	(C)	(C)
AEY = TRTY	(B)	(C)	(B)	(A)
AEY > TRTY	(E)	(A)	(A)	(A)

AEM: Month AE started; AEY: Year AE started

TRTM: Month treatment started; TRTY: Year treatment started

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

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

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

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

5.1.3 Concomitant medication date imputation

The imputation of a concomitant medication start date will follow the same conventions as for an AE start date (see Section 5.1.2). No imputation will be performed for concomitant medication end dates.

5.1.3.1 Prior therapies date imputation

Start date

The same rule which is applied to the imputation of AE/concomitant medication start date (see Section 5.1.2) will be used, with the exception that TRTSTD-1 will be used instead of TRTSTD+1.

End date

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

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

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

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

5.1.3.2 Post therapies date imputation

Start date

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

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

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

5.1.4 End date

No imputation.

5.1.5 Deaths

Due to the fact that the reason of death is inserted as a free text into the database, a wider categorization should be applied in order to be able to distinguish the cases where a death is considered an event for the endpoint "duration of SD" (namely deaths due to study indication). For this wider categorization, the preferred term of the primary reason of death will be used.

The two basic categories will be the following ones:

- "Study indication": for all cases where death is due to underlying cancer. This category will include the cases with following preferred terms:
  - Adenocarcinoma gastric
  - Adenocarcinoma pancreas
  - Bladder cancer
  - Cachexia
  - Disease progression
  - Glioblastoma
  - Hepatocellular carcinoma
  - Ileus
  - Leiomyosarcoma metastatic
  - Lung cancer metastatic
  - Malignant melanoma
  - Malignant neoplasm progression
  - Metastatic neoplasm
  - Metastatic renal cell carcinoma
  - Nasopharyngeal cancer
  - Neoplasm malignant
  - Neoplasm progression
  - Non-small cell lung cancer
  - Non-small cell lung cancer metastatic
  - Ovarian cancer
  - Pancreatic carcinoma
  - Synovial sarcoma
  - Rectal cancer
  - Renal cancer
  - Renal cell carcinoma
  - Small cell lung cancer extensive stage
  - Small cell lung cancer metastatic

- Synovial sarcoma

- "Other": for all other cases where death is not due to underlying cancer.

Regarding incomplete death dates, the following imputatioin rules will be used:

- When only the day of death is missing, then
  death date=max [(01-MMM-YYYY), min (last contact date + 1, cut-off date)].
- When day and month of death is missing, then
  death date=max[(01-JAN-YYYY, min (last contact date + 1, cut-off date)].

The imputed dates will not appear in the listings

5.1.6 Other imputations

For date of diagnosis and date of previous progression, when reconded as a partial date, the missing day is imputed to the 1st of the month (e.g., DEC2007 imputed to 01DEC2007), and if the day and month are both missing then to 1st of January of that year (e.g., 2007 imputed to 01JAN2007). Such imputed data will not appear in the listings.

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

In case there is an entry with a date completely missing (e.g. in tumor assessments, in prior therapies, in post-treatment therapies, etc.), no imputation will be performed and the entry will be ignored.

5.2 AEs coding/grading

Not Applicable.

5.3 Laboratory parameters derivations

CTC grading for blood differentials is based on absolute values.

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

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

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

Corrected calcium, can be derived using the reported total calcium value and albumin at the same assessment using the following formula:

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

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

5.4 Statistical models

5.4.1 Primary analysis

Not Applicable.

5.4.2 Key secondary analysis

Not Applicable.

5.5 Rule of exclusion criteria of analysis sets

See section 2.2.2.

6 Reference

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.

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