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TITLE: TIM3 Inhibition with MBG453 for Patients with Lower Risk MDS: an Adaptive Two-Stage Phase II Clinical Trial

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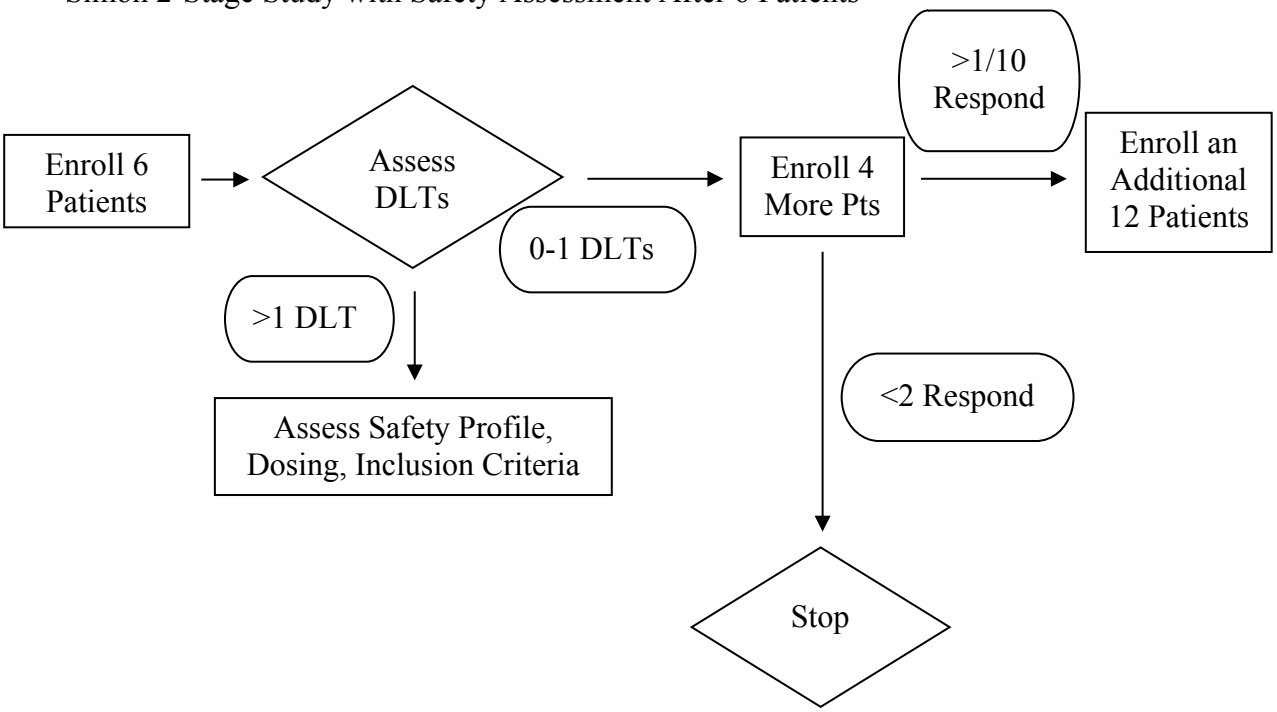
SCHEMA

Simon 2-Stage Study with Safety Assessment After 6 Patients



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1. OBJECTIVES

The objective of this study is to assess whether there is activity of MBG-453, a humanized monoclonal antibody targeting TIM-3, in the treatment of patients with lower-risk MDS.

1.1 Study Design

This is an adaptive two-stage phase II clinical trial to assess the activity of the anti-TIM-3 antibody, MBG453, in patients with lower-risk MDS, not eligible for or progressing on frontline therapy. We will evaluate the overall response rate (ORR) using international working group criteria. Patients will receive MBG453 dosed at the recommended phase II dose of 800mg and administered on day 1 of a 28 day cycle.

In this study, we seek to test MBG453 monotherapy in patients with lower-risk MDS unresponsive to or progressive after standard initial therapy. We will include patients progressing on prior ESA therapy or those that have an EPO level > 500, as well as patients with MDS who have cytopenias that require treatment and who are not felt to be candidates for or lack other treatment options.

This is an adaptive two-stage Phase II trial. We will plan to treat patients with MBG453 on day 1 of a 28 day cycle. Patients will be treated with MBG453 dosed at 800mg every 28 days. AEs will be assessed, with particular attention paid to monitoring for immune mediated adverse events. The primary endpoint, ORR, will be assessed as the best response within the first 6 months of treatment. Patients may stay on treatment until progression. The study will assume a historical null response rate of 0.15 (e.g. based on MEDALIST) and will be powered to detect an ORR of 0.35 with MBG453.

Simon's two-stage design (Simon, 1989) will be used. The null hypothesis that the true response rate is 0.15 will be tested against a one-sided alternative. In the first stage, 10 patients will be accrued. If there are no more than 1 responses in these 10 patients, the study will be stopped. Otherwise, 12 additional patients will be accrued for a total of 22. The null hypothesis will be rejected if 6 or more responses are observed in 22 patients. This design yields a type I error rate of 0.09 and power of 0.80 when the true response rate is 0.35.

The study will collect adverse events during the first 28 days of treatment for the first 6 patients treated on study to assess for dose-limiting toxicities (DLTs). DLTs will be defined as grade 3 or higher non-hematologic toxicities that are possibly, probably, or definitely related to the study drug (see section 5.4 for more detail). Low blood counts will not be considered DLTs; however, in the setting of persistent grade 4 cytopenias thought possibly, probably, or definitely related, and not resolving within 14 days, a bone marrow is recommended. If the bone marrow is absent of disease then this would be considered a DLT. If more than one of the first six patients enrolled experiences a DLT, enrollment will stop and safety will be assessed for this population prior to further enrollment.

Serious adverse events (SAEs) will be monitored; these preliminarily include deaths, life-threatening AEs, hospitalization, birth defects, or important medical events. SAEs should undergo expedited reporting to the IRB/FDA and Novartis, as appropriate. Patients will be followed for

survival up to 12 months after stopping MBG453

1.1 Primary Objectives

- The primary objective of this study is to evaluate the overall response rate (ORR) within first 6 months of treatment of MBG453 in patients with lower-risk MDS

1.2 Secondary Objectives

- To assess rates and severity of adverse events associated with MBG453 in lower risk MDS
- To evaluate rates of 1-year overall survival (OS), progression free survival (PFS), time to disease progression, and duration of response to therapy with MBG453.
- To characterize the response to therapy according to pretreatment disease and patient characteristics, monitoring disease-specific molecular, immunophenotypic, and cytogenetic evolution during treatment (exploratory analysis).
- To describe changes in cell surface marker expression, Immune cell subsets, and molecular clonal evolution during treatment and at the time of progression (exploratory analysis).

2. BACKGROUND

2.1 Study Disease(s)

Myelodysplastic syndromes (MDS) comprise a spectrum of advanced hematologic malignancies characterized by ineffective clonal hematopoiesis and the risk of progression to acute myeloid leukemia. Patient disease risk is characterized according to the presence and depth of cytopenias, recurrent cytogenetic abnormalities, and the number of blasts, typically using the IPSS or IPSS-R risk scores (Greenberg et al Blood 1997, 2012). In general, patients are divided into "lower-risk" and "higher-risk" disease based on overall survival and AML progression; patients with higher-risk disease generally proceed to disease modifying therapy with hypomethylating agents or transplant, while those with lower-risk disease generally receive symptom-directed therapy, most commonly toward RBC transfusion needs but also for thrombocytopenia and neutropenia.

The most commonly employed therapy for patients with lower-risk MDS is erythropoiesis stimulating agent (ESA) therapy, using epoetin alfa or darbepoetin alfa (Davidoff et al, Leuk Res 2013). These agents may alleviate red blood cell (RBC) transfusion requirements in 40-60% of patients, and a number of variables may predict for a higher chance of response, including a serum erythropoietin level < 100 IU/mL, limited prior transfusion history, and having lower-risk disease. Unfortunately, many patients will have limited responses to ESAs, have features such as an EPO level > 500 IU/mL and be unlikely to respond, or become transfusion dependent again after an initial response (Buckstein et al Am J Hematol 2017). These patients represent a significant unmet clinical need; although their MDS may not progress or transform for years, transfusion dependence is a significant burden on quality of life and can result in complications including iron overload and the formation of antibodies to blood products. For patients with thrombocytopenia or neutropenia, isolated or associated with anemia, therapies are lacking, and they may trial immunosuppressive agents or hypomethylating agents, but currently there is no standard of care. Such cytopenias are associated with bleeding complications or recurrent infectious complications.

New approaches to transfusion dependence and symptomatic cytopenias in lower-risk MDS are desperately needed. Historically, rates of blood count improvement are low without treatment; in the recent MEDALIST trial (Fenaux et al., 2020), which compared therapy with luspatercept to supportive care alone (placebo), 13% of patients receiving placebo achieved the primary endpoint, and this serves as a historical comparator in identifying new active compounds.

Currently, the only curative therapy for MDS is allogeneic transplant; the mechanism by which allogeneic transplant is effective in MDS is thought to be immune mediated through graft vs. leukemia effect, particularly when using a reduced intensity conditioning regimen (Weisdorf et al., 2012). Even in the absence of allogeneic transplantation, immune checkpoint dysregulation may contribute to disease progression for patients with MDS, CMML, and AML (Aggarwal et al., 2011). T-cell immunoglobulin and mucin domain containing molecule-3 (TIM-3) which is expressed on T-cells as well as on leukemic stem cells in MDS (Asayama et al., 2015; Kikushige et al., 2014, 2010; Tao et al., 2014). Interestingly, while TIM-3 is aberrantly expressed on leukemic blasts, it does not appear to be present on normal hematopoietic stem cells. TIM-3 is expressed on T-cells and plays a role in immune checkpoint control; upon encountering galectin-9 on tumor cells, TIM-3 is phosphorylated and downregulates the T-cell response against the tumor.

2.2 IND Agent: MBG453

MBG453 is a humanized monoclonal antibody targeting TIM-3, and acts as an immune checkpoint inhibitor. TIM-3 may have activity as monotherapy and in conjunction with hypomethylating agent treatment in MDS, both due to direct activity against leukemic stem cells, as well as enhancement of immune response toward myelodysplastic cells. Previous studies have explored TIM3 inhibition with MBG453 in MDS and AML (NCT03066648) but to date it has not been explored in lower-risk disease.

MBG453 is a humanized IgG4 antibody which interferes with the binding site of phosphatidylserine to the TIM-3 receptor. Primate studies were performed to assess PK and tolerability; doses of 10mg/kg to 100mg/kg administered intravenously each week showed safe administration with transient declines in CD4+ and CD8+ T cells, and monocytes. No other toxicity was noted. MGB453 was also studied for its potential to induce cytokine release in human donor blood *in vitro*; these studies, compared to an IgG4 isotype control and positive control antibodies, did not show an effect on cytokine release.

MBG453 was evaluated in patients with solid tumors; as of July 2019 252 patients had been treated with MBG453 as monotherapy or in combination with an anti-PD1 IgG4 antibody in a first in human clinical trial for patients with solid tumors, 133 of which received it as monotherapy. PK parameters demonstrate dose-proportional increases in exposure between 80mg and 1200mg, with moderate accumulation using either every 2 week or every 4 week dosing. No DLTs were observed with MBG453 monotherapy. Among patients treated with MNG453 in combination with the anti-PD1 antibody PDR001, PK data for MBG453 appeared comparable to monotherapy; one DLT of myasthenia gravis was reported in a patient with thymoma treated at a dose of 240mg MBG453 + 80mg PDR001 every 4 weeks.

MBG453 has also been studied in hematologic malignancies, specifically in patients with AML or MDS. A total of 152 patients were treated as of July 2019; 26 patients received MBG453 as monotherapy, while others received it in combination with decitabine, azacitidine, and/or PDR001. There were similar PK data as seen in the solid tumor study. Four patients treated with MBG453 in combination with decitabine experienced DLTs during the first 2 cycles which included Grade 3 hepatitis (Arm 2: MBG453 240 mg Q2W + Decitabine 20 mg/m2), Grade 3 tubulointerstitial nephritis (Arm 3: PDR001 400 mg Q4W + MBG453 160 mg Q2W + Decitabine 20 mg/m2), Grade 3 encephalitis (Arm 5: PDR001 400 mg Q4W + MBG453 240 mg Q2W) and Grade 2 uveitis (Arm 3: PDR001 400 mg Q4W + MBG453 400 mg Q2W + Decitabine 20 mg/m2).

Of the 26 patients with MDS or AML treated with MBG453 as a single agent, 24 patients (92%) experienced AEs of any grade, regardless of relationship to study drug, with the most frequent AEs (>10%) being abdominal pain and febrile neutropenia (6 patients each, 23%), constipation, decreased appetite, diarrhea, dyspnea, nausea and pyrexia (5 patients each, 19%), dizziness, peripheral edema, and platelet count decreased (4 patients each, 15%), anemia, fatigue, headache, pain and pneumonia (3 patients each, 12%). A total of 17 patients (65%) experienced SAEs of all grades, regardless of relationship to study drug. SAEs which occurred in more than one patient included febrile neutropenia (6 patients, 23%), pneumonia and pyrexia (3 patients each, 12%). A total of 10 patients experienced a grade 3 or higher AE possibly related to the study drug: hypertension (n=2), neutropenia (n=2), thrombocytopenia (n=4), rash (n=2).

Potential immune mediated toxicities have been monitored with MBG453. Approximately 6-15% of patients have experienced skin-related AEs, the majority being grade 1 or 2 and reversible. A total of three patients with grade 3 rashes have been reported across both the solid tumor study and the MDS/AML study to date. Hepatic AEs have also been observed; these have predominately been AST or ALT elevations, typically grade 1-2; no bilirubin increase has been noted. Periodic monitoring of liver enzymes is required. In the MBG453 study evaluating MDS and AML several possible immune-related toxicities were noted: one patient with myositis with MBG monotherapy. When combined with the PD1 inhibitor PDR001, one case of tubulointerstitial nephritis was noted and two cases of encephalitis. In combination with decitabine, one case each was noted for inflammatory arthritis, pericarditis, stomatitis, and one possible hemophagocytic lymphohistiocytosis that was possibly immune related and in the setting of active disease.

For complete information, please refer to the current Investigator's Brochure: MBG453 Investigator's Brochure, Edition 5.1, Release Date 11-Dec-2019.

2.3 Rationale

T-cell immunoglobulin and mucin domain containing molecule-3 (TIM-3) is expressed on T-cells as well as on leukemic stem cells in MDS (Asayama et al., 2015; Kikushige et al., 2014, 2010; Tao et al., 2014). TIM-3 has been characterized as an immune checkpoint in that it is a negative regulator of T-cell immunity, and is overexpressed on immune cells in cancer samples. TIM-3 expressed on T-cells plays a role in immune checkpoint control; upon encountering galectin-9 on

tumor cells, TIM-3 is phosphorylated and downregulates the T-cell response against the tumor. TIM-3 appears to be co-expressed with PD-1 and represent T-cell exhaustion; it is proposed as a possible mechanism of escape from immune checkpoint blockade (Anderson et al., 2016; Datar et al., 2019).

TIM-3 expression can be found on a number of hematologic cells, including monocytes and NK cells, and may be involved in regulating the inflammatory response (da Silva et al., 2014; Leavy, 2008). Further studies have identified TIM-3 expression on leukemic blasts; TIM-3 expression appears to be aberrantly increased on malignant leukemic blasts and not present on normal hematopoietic stem cells (Jan et al., 2011). In a murine xenograft model of serial transplantation of AML cells, administering an anti-TIM-3 antibody resulted in blocked engraftment, suggesting that TIM-3 inhibition may target leukemic precursors directly (Kikushige et al., 2010). The exact signaling mechanism of TIM-3 in leukemic precursors is under investigation.

In the previous study of MBG453 monotherapy for patients with relapsed and refractory AML or MDS, a number of patients exhibited hematologic responses (Borate, 2019), including decreased RBC transfusion needs and improvement in platelet and neutrophil counts. Several patients exhibited sustained blood count responses after multiple prior lines of treatment for refractory disease, suggesting that there may be a role of TIM-3 inhibition in hematopoiesis (Figure 1).

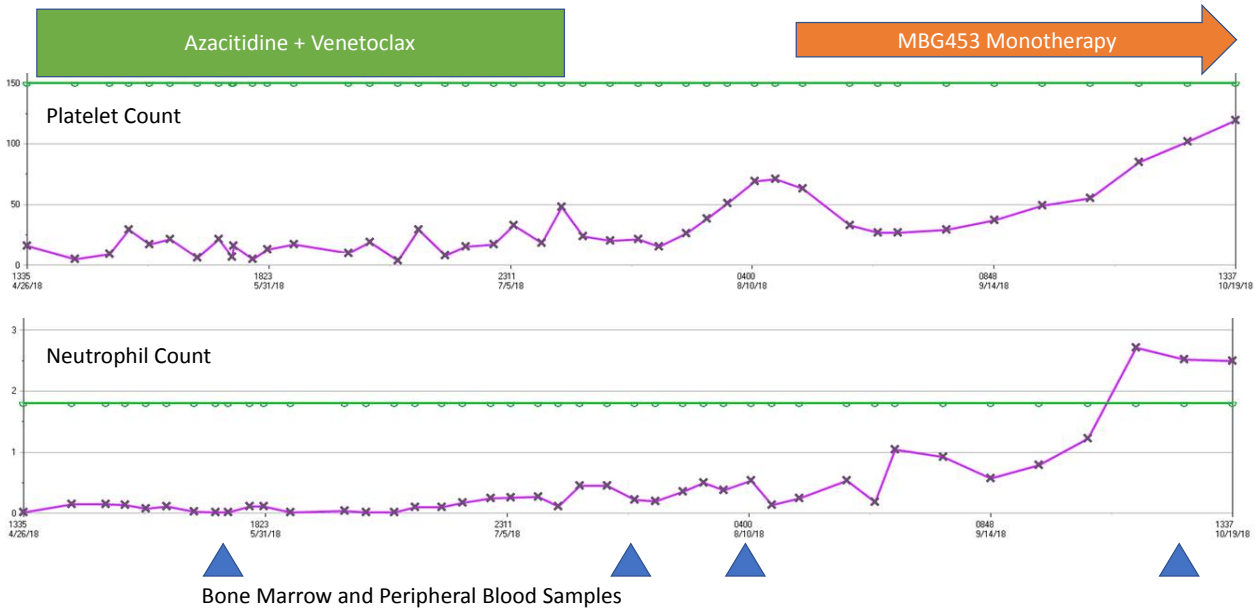

Figure 1. Example of a hematologic response seen in a patient on MBG453 monotherapy. The patient experienced neutrophil and platelet recovery.

Given the evidence of blood count responses in patients with advanced myeloid disease, and the favorable toxicity profile of MBG453 monotherapy, there is rationale to study MBG453 monotherapy for the treatment of lower-risk MDS. For those patients who are RBC transfusion dependent, they must have progressed after ESA therapy or be unlikely to respond to ESA therapy,

characterized by an EPO level >500, who are not felt to be candidates for or lack other treatment options. In addition, given early activity, there is particular interest in neutrophil and platelet responses to MBG453. These remain significant complications of MDS, with infectious and bleeding events identified as common causes of death from MDS. Therefore, patients with lower-risk MDS characterized by other cytopenias are also eligible if they require therapy, have cytopenias that can be assessed for IWG response, and are not eligible for or have progressed on other standard therapy.

2.4 Correlative Studies Background

Throughout the study, at designated time points, patient blood and marrow samples will be collected for correlative analysis. Specifically, we will viably cryopreserve peripheral blood and bone marrow samples serially at baseline, during treatment, and at the end of treatment/time of progression. We will collect blood samples just prior to each infusion of MBG453 during cycles 1-3, and a bone marrow assessment will be performed at baseline, after cycle 2, after cycle 4, and then per the treating investigator. Peripheral blood and bone marrow samples will be collected at end of treatment or progression.

We propose correlative studies to better characterize the effect of TIM3 inhibition on the MDS progenitor cells as well as T-cell subsets. We have previously developed a mass cytometry panel that assesses peripheral blood T-cells, myeloid components, and bone marrow cells with specific attention to markers relevant to MDS and immune checkpoint targets (Preliminary Markers, Table 1).

Immune Monitoring Panel	Tumor/LSC Marker Panel
CD3, CD4, CD8, CD11b, CD11c, CD14, CD16, CD19, CD20, CD25, CD27 CD28, CD38, CD44, CD45, CD45RA, CD45RO, CD56, CD57, CD62L, CD95 (Fas), CD123, CD127, CD134 (Ox40), CD137 (41BB), CD152 (CTLA4), CD161, CD195 (CCR5), CD197 (CCR7), CD223 (LAG3), CD278 (ICOS), CD279 (PD-1), CD366 (TIM3), HLA-DR	CD3, CD7, CD11b, CD11c, CD14, CD15, CD16, CD19, CD33, CD34, CD38 CD44, CD45, CD64, CD99, CD117, CD123, CD135, CD163, CD184, CD206, CD366 (TIM3), CD371, HLA-DR

The primary aim of this correlative will be to use mass cytometry to better characterize intra-patient changes in T-cell and myeloid cell populations during treatment with MBG453. This work will be done in coordination with the laboratory of Patrick Reeves (MGH Vaccine and Immunotherapy Center).

We will also perform serial NGS myeloid somatic mutation testing to characterize subclonal MDS changes during treatment. We will use these correlatives studies to explore the biological response to this drug combination including emerging mutations as putative escape mechanisms. We will collect standard tumor characteristics including tumor subtype, cytogenetics, cell surface markers, molecular abnormalities, both at study entry and during treatment. We will analyze whether certain

MDS characteristics are associated with a specific response to therapy or change in cell populations.

3. PARTICIPANT SELECTION

The purpose of this study will be to evaluate the activity of MBG453 in the treatment of patients with lower-risk MDS.

3.1 Eligibility Criteria

3.1.1 Lower risk MDS patients (IPSS-R score ≤3.5 at diagnosis) who have progressed or are refractory to/intolerant of prior therapy and meet one of the following categories:

- RBC transfusion dependent according to IWG criteria must either be unresponsive to prior ESA therapy or have an EPO level > 500
- Prior HMA therapy
- Patients with the following cytopenias who otherwise are felt to require treatment per the treating physician:
    - Platelets < 50k/uL
    - ANC < 500 cells/uL
- Patients with MDS with isolated del(5q) ("5q- syndrome") must have progressed on or not tolerated lenalidomide
- Patients who are not felt to be candidates for or lack other standard treatment options. Patients with prior luspatercept exposure are eligible.
- Patients with dysplastic type CMML (WBC < 13,000 cells/uL) meeting the above criteria are eligible; responses will be assessed using MDS criteria

3.1.2 Age ≥18 years. Because no dosing or adverse event data are currently available on the use of MGB453 in participants <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

3.1.3 ECOG performance status ≤2 (see Appendix A).

3.1.4 Participants must have adequate organ and marrow function as defined below within 21 days of treatment:

– Total bilirubin	≤ 2 mg/dL (unless due to Gilbert's in which case it must be <3 mg/dL)
– AST(SGOT)/ALT(SGPT)	≤3 × institutional ULN
– Creatinine clearance	≥30 mL/min/1.73 m^2 (by MDRD calculation)

3.1.5 Human immunodeficiency virus (HIV)-infected participants on effective anti-retroviral therapy with undetectable viral load over the prior 6 months are eligible for this trial.

3.1.6 Participants with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible

for this trial, participants should be class 2B or better.

3.1.7 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Participants who have had chemotherapy or radiotherapy within 14 days or five half-lives, whichever is shorter, prior to the first dose of study treatment.

3.2.2 Participants who are receiving any other investigational agents; a washout of 14 days or 5 half-lives, whichever is longer, is required. The washout period for biologic agents should be 28 days since the last dose.

3.2.3 Prior exposure to a TIM-3 inhibitor.

3.2.4 Active autoimmune disease requiring > 10 mg per day of prednisone or the equivalent. Inactive or controlled autoimmune disease is allowed.

3.2.5 Prior solid organ transplant is exclusionary. Patients with prior hematopoietic cell transplant are eligible if they are over 6 months from transplant and not on any related immunosuppressive therapy.

3.2.6 History of allergic reactions attributed to compounds of similar chemical or biologic composition to MBG453.

3.2.7 Active untreated or concurrent malignancy that is distinct in primary site or histology, excluding:

- The following will not be exclusionary: non-melanoma skin cancer, noninvasive colonic polyps, superficial bladder tumors, cervical cancer in-situ, ductal carcinoma in situ of the breast, monoclonal B-cell lymphocytosis, or monoclonal gammopathy of undetermined significance.
- Hormonal therapy is allowed.
- History of other malignancy is allowed if not requiring active management.
- Other malignancies that were treated with curative intent at least 1 year prior to study screening and without evidence of active disease will be allowed.
- Participants with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial pending discussion with the principal investigator.

3.2.8 Participants with uncontrolled intercurrent illness.

3.2.9 Participants must not have clinically active HBV or HCV; testing is not required

3.2.10 Receipt of a live vaccination within 28 days of cycle 1 day 1

3.2.11 Participants with psychiatric illness/social situations that would limit compliance with study requirements.

3.2.12 Female contraception is required. Pregnant women are excluded from this study because MBG453 is an agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with MBG453, breastfeeding should be discontinued. Women of child-bearing potential should use highly effective methods of contraception during treatment and for 150 days after the last dose of MBG453.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

4 REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of any protocol-specific therapy or intervention. Any participant not registered to the protocol before protocol-specific therapy or intervention begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol-specific therapy and/or intervention. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If the subject does not receive protocol therapy following registration, the subject must be taken off study in the CTMS (OnCore) with an appropriate date and reason entered.

4.2 Registration Process for DF/HCC Institutions

Applicable DF/HCC policy (REGIST-101) must be followed.

5. TREATMENT PLAN

5.1. Treatment Regimen

We will plan to treat patients with MBG453 on day 1 of a 28-day cycle. Patients will be treated with MBG453 dosed at 800mg every 28 days. AEs will be assessed, with particular attention paid to monitoring for immune mediated adverse events. The primary endpoint, ORR, will be assessed as the best response during the first 6 months of treatment. Patients may stay on treatment until progression. The study will assume a historical null response rate of 0.15 (e.g. based on MEDALIST) and will be powered to detect an ORR of 0.35 with MBG453.

MBG453 will be administered on day 1 of each cycle, where 28 consecutive days is defined as a treatment cycle. Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

Patients should not receive pre-medication to prevent infusion reactions before the first infusion of MBG453, in order to determine if pre-medication is necessary. If a patient experiences an infusion reaction he/she may receive pre-medication on subsequent dosing days. The pre-medication should be chosen per institutional standard of care, at the discretion of the treating investigator. Acute allergic reactions should be treated as per institutional standard of care. In the event of anaphylactic/anaphylactoid reactions, this includes any therapy necessary to restore normal cardiopulmonary status. If a patient experiences a Grade 3 anaphylactic/anaphylactoid reaction, the patient will be discontinued from the study. Patients should be treated at a facility equipped for cardiopulmonary resuscitation. Appropriate resuscitation equipment should be available at the bedside and a physician readily available.

5.2. Pre-Treatment Criteria

5.2.1. Cycle 1, Day 1

Patients should have C1D1 labs that meet inclusion criteria and otherwise be clinically stable per the treating investigator, prior to starting treatment on C1D1. These labs include total bilirubin, creatinine, and ALT/AST (Section 3.1.4).

5.2.2. Subsequent Cycles

Treatment-related AEs meeting DLT criteria should resolve baseline or Grade 1 to proceed to the next cycle (see section 6). Patients may remain on therapy until progression of MDS per IWG revised criteria, or excess/unresolved toxicity as noted below. Therapy is intended to be given consecutively every 28-day cycle without interruption between cycles. Given the nature of MDS and CMML, patients may delay the start of a cycle for up to 28 days for concurrent illness or ongoing toxicity, drug-related or not, that is grade 3 or higher and is felt to prohibit the initiation of therapy according to the treating investigator (see section 6, Management of IP related toxicities

and dose reductions).

Patients should avoid the use of immunosuppressive medication while on study treatment (exceptions are allowed, see section 5.5). If steroids are administered for immune-related AEs during the period on study treatment, patients should be on doses no greater than 10 mg/day prednisone or equivalent prior to the next treatment.

Treatment delays beyond 28 days for toxicity are not permitted and the patient should be discontinued from the study medication. Patients that are deriving clinical benefit but require a treatment delay beyond 28 days for non-toxicity events should be discussed with the principal investigator.

Patients will be assessed for response to therapy after 2 cycles of treatment, via a bone marrow biopsy performed on day 1 of cycle 3 (± 3 business day window). The findings of this marrow are not required to proceed to the next cycle but may be used by the treating investigator as clinically indicated. This will be repeated after cycle 4, on cycle 5 day 1 (± 3 business day window). A bone marrow assessment and peripheral blood should also be tested at the end of treatment. Any additional marrow assessments are per the treating investigator. The results of these marrows are not required to proceed to the next cycle unless there is a reason to delay per the treating investigator.

5.3. Agent Administration

5.3.1. MBG453

MBG453 100 mg/1 mL and 400 mg/4 mL Liquid in vial. MBG453 100 mg/1 mL Concentrate for solution for infusion is used for intravenous administration from a dose of 12 mg up to a maximal dose of 2400 mg.

Administration:
MBG453 is administered as an intravenous infusion given over 30 minutes, but which may be given over up to 2 hours, if clinically indicated. The maximum administration time is 120 min ± 10 min.

> Shorter infusion times can be applied, since longer infusion times are considered worst-case with regards to potential protein adsorption. The selection of infusion speed within that requirement is in the responsibility of the project-responsible clinician and needs to comply with the specifications given by the infusion pump.

When administration is complete, flush the line with at least 25 mL of 5% dextrose solution to guarantee that all the MBG453 solution for infusion remaining in the infusion line has been administered.

Dosing:
MBG453 will be administered at a dose of 800mg on day 1 of a 28-day cycle.

Drug, Tubing and Filtration:

Only the materials (infusion bags, infusion syringes, infusion lines and in-line filter) specified below should be used for administration of the study medication. The solution for infusion must be infused through a 0.2 micron in-line filter. The infusion sets including the intravenous filter set have to be prepared according to the instructions supplied by the manufacturers.

The infusion set materials listed below are compatible with MBG453. The following materials are accepted to be used in clinical trials for administration of MBG453 Solution for infusion prepared in 5 % dextrose solution (100 mL bags).

Compatible materials of infusion sets components (doses from 40mg to 2400):

- *100 mL 5% Dextrose infusion bag materials in contact with the drug product:* PolyVinyl Chloride (all plasticizers); PolyEthylene

- *Infusion line materials, material in contact with the drug product (maximum length: 300 cm):* PolyVinyl Chloride (all plasticizers); PolyEthylene

- *Infusion filter materials membrane type:* Positively charged Polyamide, Positively charged PolyEtherSulfone, Neutral PolyEtherSulfone

The infusion set (bag, line, and filter) selected for the study should be approved according to local regulation.

Special Equipment:
Infusion pumps are used according to the recommendation given by the supplier and should be suitable to administer MBG453. The combination of bag, line, filter and pump should be tested in advance to ensure that each connection works properly, without any leak.

Hydration:
There is no prespecified hydration recommendation

Observation Period
There should be a period of at least 1 hour after the infusion whereby the patient requires close observation.

Infusion Reactions:
Infusion reactions (typically consisting of flushing, fevers, chills, and less commonly rigors, dyspnea and hypotension) can occur in patients receiving monoclonal antibody therapies. To reduce the risk of infusion-related reactions, MBG453 should be administered by intravenous infusion over at least 30 min and should not be administered as a bolus injection.

Infusion reactions should be treated promptly with medications directed at relief of symptoms, such as antihistamines and antipyretics, and medications and other interventions needed to maintain cardiovascular and pulmonary function. MBG453

infusion should be interrupted for infusion-related reactions of Common Terminology Criteria for Adverse Events (CTCAE) grade 2 or worse.

5.3.2. Other Modality(ies) or Procedures

N/A.

5.4. Definition of Dose-Limiting Toxicity (DLT)

This phase II study will include a safety lead-in to ensure there is no excess toxicity in this patient subgroup. The study will collect adverse events during the first cycle (initial 28 days) of treatment for the first 6 patients treated on study to assess for dose-limiting toxicities (DLTs). If more than one of the first six patients enrolled experiences a DLT, enrollment will pause and safety will be assessed for the lower-risk MDS population prior to further enrollment. At that point any further enrollment would depend upon discussions with the sponsor and treating investigators regarding the event, and whether to stop the study or consider amending the protocol to explore lower doses and alternative dose schedules.

DLTs should be possibly, probably, or definitely related to the study drug. The following AEs will be defined as dose-limiting toxicities if considered to be related to MBG453:

Non-hematologic toxicities:

- Grade 3 non-hematologic toxicities unless attributable to persistent MDS or CMML and excluding toxicities secondary to cytopenias (e.g. febrile neutropenia, infection due to MDS-associated neutropenia, bleeding due to thrombocytopenia).
    - The following will *not* be considered DLTs:
        - Grade 3 fatigue, asthenia, fever, anorexia, or constipation.
        - Grade 3 nausea, vomiting or diarrhea not requiring tube feeding, total parenteral nutrition, or requiring or prolonging hospitalization, and that resolve to grade 1 with appropriate treatment within 7 days
        - Grade 3 or 4 tumor lysis syndrome (TLS) if it is successfully managed clinically and resolves within 72 hours without end-organ damage. Grade 4 TLS lasting >72 hours is a DLT.
        - Grade 3 or 4 isolated electrolyte abnormalities that last < 72 hours.
- All Grade 4 non-hematologic toxicities (excluding toxicities attributable to neutropenia and thrombocytopenia due to active MDS or CMML). Conversely, complications of cytopenias including febrile neutropenia, bleeding, and infections, will be considered DLTs in the absence of evidence of active disease, as well as if the baseline for a given cell line (neutrophils, platelets) is above the threshold where such events would be expected due to disease alone.
- CTCAE grade ≥ 3 immune-related adverse events persisting > 7 days after treatment with corticosteroids (if it improves to < grade 3 it is not considered a DLT)
- CTCAE grade ≥ 2 eye pain or reduction of visual acuity that does not respond to topical therapy and does not improve to grade 1 severity within 2 weeks of initiating topical therapy or requiring systemic treatment

- Treatment-related deaths

Hematologic toxicities:

- ≥ Grade 3 hematologic toxicities attributed to active MDS will not be considered DLTs, including complications attributed to cytopenias from disease such as infections during neutropenia or bleeding events during thrombocytopenia. As above this does not include such events in the absence of disease or if occurring at a baseline cell count where such events would be expected.
- Grade 4 neutropenia or thrombocytopenia lasting more than 14 days, and associated with a marrow absent features of MDS, is considered a DLT. A bone marrow assessment is recommended if there is suspicion of drug-related cytopenias.
- In the setting of new grade 4 cytopenias thought possibly, probably, or definitely related, and not resolving to grade 3 or better within 14 days, a bone marrow is recommended. If the bone marrow is absent of disease then this would be considered a DLT.

Management and dose modifications associated with the above adverse events are outlined in Section 6.

5.5. General Concomitant Medication and Supportive Care Guidelines

MBG453 is a monoclonal antibody and is not metabolized by cytochrome P450 (CYP450) enzymes, or transported by P-glycoprotein (Pgp) or related ABC membrane transporters, and drug-drug interactions are not anticipated. Cytokines produced by activated lymphocytes may impact the levels of Pgp and the activity of CYP450 enzymes. The clinical relevance of MBG453 immune modulation and potential cytokine production that could impact Pgp and CYP450 is unknown; a clinically relevant drug-drug interactions is considered highly unlikely.

Because a primary goal of the study is to evaluate for hematologic responses, growth factors (including G-CSF, GM-CSF, epoi etin, darbepoietin, etc) should not be used during the study period. If a patient is deemed by the treating investigator to urgently require growth factor support e.g. G-CSF in the setting of a life-threatening infection, this may be considered but should also be relayed to the overall PI. Such treatments should not be administered chronically, only during the time of acute illness, if indicated.

While the patient is receiving study therapy, they may not receive other investigational drugs or chemotherapy. They also may not receive other approved chemotherapy drugs, with the exception of short duration growth factor support as noted.

Because MBG453 is thought to work in part through activation of the immune system, patients should not receive systemic immunosuppressive medication at doses greater than 10mg/day of prednisone or equivalent, with the following exceptions:

- Prophylactic use for subjects with imaging contrast dye allergy
- Premedication for transfusions or for other infusions, as clinically indicated.

- Replacement-dose steroids (defined as up to 10 mg/day of prednisone or equivalent dose of corticosteroids) in the setting of adrenal insufficiency. Short course "sick doses" are permitted as long as the dose is reduced to 10 mg/day prior to the next treatment.
- Transient exacerbations of chronic inflammatory conditions such as chronic obstructive pulmonary disease (COPD). Steroids must be reduced to 10 mg/day (or lower dose) of prednisone or equivalent dose of corticosteroids prior to the next treatment with MBG453.
- Acute illness e.g. "stress dose" steroids may be administered but should be tapered prior to the next dose of MBG453
- Upon treatment of MBG453 infusion reactions or MBG453-related irAEs, steroids must be reduced to 10 mg/day (or lower dose) of prednisone or equivalent dose of corticosteroids prior to the next treatment with MBG453.

Topical, inhaled, nasal and ophthalmic steroids are allowed.

The use of live vaccines is not allowed through the duration of the study. Inactivated vaccines are allowed.

5.6. Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue for until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable treatment-related adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the medication regimen and/or study requirements
- Participant and/or treating investigator decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant. If MBG453 becomes commercially available and reimbursable, patients may choose to transition off protocol therapy to commercial product.

In the event of unusual or life-threatening complications, treating investigators should immediately notify the Overall PI, Dr. Andrew Brunner at (617) 724-1124 or paged at (617) 280-3886.

When a participant is removed from protocol therapy and/or is off of the study, the participant's status must be updated in OnCore in accordance with REGIST-OP-1.

5.7. Duration of Follow Up

Participants will be followed for 12 months after removal from protocol therapy (30, 150, 250 days, and at 12 months, ±7-day window) or until death, whichever occurs first. Follow-up will assess for survival and progression and may be done in person or via phone/electronically. If three consecutive follow-ups are missed the patient will be considered lost to follow up and censored at the last verified date of clinical follow up (in person or electronically verified). Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.8. Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). In addition, the study team will ensure the participant's status is updated in OnCore in accordance with REGIST-OP-1.

6. DOSING DELAYS/DOSE MODIFICATIONS

MBG453 may be delayed due to toxicities. Doses may be delayed for up to 28 days for toxicity; toxicities that result in more than 28 days delay should result in discontinuation from the study medication. Patients that are deriving clinical benefit but require a treatment delay beyond 28 days for non-toxicity events should be discussed with the principal investigator.

Dosing may be resumed once an AE has resolved to baseline or to Grade 1. If a treating investigator considers it in the patient's best interest to resume therapy before resolution of an AE or to resume without dose modification this may be considered on a case-by-case basis after discussion with the overall PI of the trial.

Dose modifications of MBG453 may be accomplished through dose reduction or altering the treatment interval; provisional dose levels are shown below.

Dose delays and modifications will be made as indicated in the following table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Dose Level	**Dose**
-2	240 mg every 28 days
-1	400 mg every 28 days
0	800 mg every 28 days

If the patient experiences an AE meeting the criteria for DLT as outlined in section 5.4, including events outside the DLT period, treatment should be held. Patients may resume treatment after resolution to Grade 1 or to the patient's baseline value. If this event occurs during the first cycle (whether or not they are among the first 6 patients being evaluated for DLT assessment) a dose modification must be made. If this event occurs after the first cycle the patient may resume at the same or a lower dose at the discretion of the investigator. Specific guidance is provided below.

Infusion Reaction	**Management/Next Dose for MBG453**
≤ Grade 1	Decrease infusion rate until recovery
Grade 2	Stop Infusion. Before restarting, pre-medicate according to local institutional guidelines. Restart infusion at 50% of previous rate under continuous observation. Ensure that there is a minimum observation period of 1 hour prior to restarting the infusion(s). If the AE recurs at the reinitiated slow rate of infusion, and despite oral pre-medication, then discontinue treatment
Grade 3	Discontinue treatment
Grade 4	Discontinue treatment
*Participants requiring a delay of >28 days should go off protocol therapy. **Participants requiring > two dose reductions should go off protocol therapy.	
Recommended management: antihistamines, antipyretics, steroids, cardiopulmonary monitoring.	

GI Immune AEs	**Management/Next Dose for MBG453**
≤ Grade 1 (diarrhea < 4 stools/day, or asymptomatic colitis)	Continue treatment Symptomatic treatment as indicated
Grade 2 (diarrhea <4 stools/day over baseline, or colitis with pain/blood in stool)	Hold until ≤ Grade 1. Resume at same dose level. Symptomatic treatment as indicated
Grade 3 lasting > 7 days (>6 stools/d over baseline, IV fluids>24h) or colitis with medical intervention indicated	Hold* until < Grade 2. Resume at one dose level lower, if indicated.** Consider 1-2mg/kg/day methylprednisolone or equivalent Consider antibiotic treatment including prophylaxis Consider lower endoscopy
Grade 4 (life threatening)	Discontinue protocol therapy Consider 1-2mg/kg/day methylprednisolone or equivalent Consider antibiotic treatment including prophylaxis Consider lower endoscopy
*Participants requiring a delay of >28 days should go off protocol therapy.	

GI Immune AEs	**Management/Next Dose for MBG453**
**Participants requiring > two dose reductions should go off protocol therapy.	
Recommended management: assess for other causes, empiric corticosteroids, assessment of immune-related organ dysfunction as indicated	

Renal Immune AEs	**Management/Next Dose for MBG453**
≤ Grade 1 (Cr <1.5x baseline)	Continue treatment Symptomatic treatment as indicated
Grade 2-3 (Cr >1.5x baseline to 6x ULN)	Hold until ≤ Grade 1. Resume at same dose level. Symptomatic treatment as indicated Consider renal biopsy to confirm immune related Consider 0.5-1.0mg/kg/day methylprednisolone or equivalent with slow taper (>1 mo) if responds
Grade 4 (Cr > 6x ULN)	Discontinue protocol therapy Consider 1-2mg/kg/day methylprednisolone or equivalent with slow taper (>1 mo) if responds Consider nephrology input and monitor creatinine daily Consider renal biopsy
*Participants requiring a delay of >28 days should go off protocol therapy. **Participants requiring > two dose reductions should go off protocol therapy.	
Recommended management: assess for other causes, empiric corticosteroids, assessment of immune-related organ dysfunction as indicated	

Pulmonary Immune AEs	**Management/Next Dose for MBG453**
≤ Grade 1 (radiographic changes only)	Continue treatment; consider delay Symptomatic treatment as indicated, monitor every 2-3 days
Grade 2 - 3 (mild-moderate symptoms, hypoxia)	Hold until ≤ Grade 1. Resume at same dose level. Consider involving ID and pulmonary consults Monitor daily symptoms, consider hospitalization Consider bronchoscopy, lung biopsy Consider 1.0mg/kg/day methylprednisolone or equivalent with slow taper (>1 mo) if responds
Grade 4 (life threatening)	Discontinue protocol therapy Consider 2-4mg/kg/day methylprednisolone or equivalent with slow taper (at least 6 weeks) if responds Hospitalization, involvement of pulmonary and/or ID Consider antibiotic treatment including prophylaxis Consider bronchoscopy, lung biopsy
*Participants requiring a delay of >28 days should go off protocol therapy. **Participants requiring > two dose reductions should go off protocol therapy.	
Recommended management: assess for other causes, empiric corticosteroids, assessment of immune-related organ dysfunction as indicated	

Hepatic Immune AEs	**Management/Next Dose for MBG453**
≤ Grade 1 (AST/ALT ULN - 3.0x ULN and/or Tbili ULN – 2 x ULN)	Continue treatment Symptomatic treatment as indicated
Grade 2 (AST/ALT 3-5x ULN and/or Tbili 2-3x ULN)	Hold until ≤ Grade 1. Resume at same dose level. Increase monitoring frequency Symptomatic treatment as indicated
Grade 3 lasting < 7 days (AST/ALT >5-8x ULN and/or Tbili 3-5x ULN)	Hold* until < Grade 2. Resume at one dose level lower, if indicated.** Consider 1-2mg/kg/day methylprednisolone or equivalent Consider antibiotic treatment including prophylaxis Consider liver biopsy and gastroenterology consult
Grade 3 lasting > 7 days Grade 4 (AST or ALT >8x ULN and/or Tbili > 5x ULN)	Discontinue protocol therapy Consider 2mg/kg/day methylprednisolone or equivalent Consider antibiotic treatment including prophylaxis Consider liver biopsy and gastroenterology consult
*Participants requiring a delay of >28 days should go off protocol therapy. **Grade 3 hepatic imAEs that do not improve within 7 days on steroids should come off protocol therapy. Consideration should be given for additional immunosuppression e.g. mycophenolate mofetil 1gm BID. Participants requiring > two dose reductions should go off protocol therapy.	
Recommended management: assess for other causes, empiric corticosteroids, assessment of immune-related organ dysfunction as indicated	

Skin Immune AEs	**Management/Next Dose for MBG453**
≤ Grade 1-2 (<30% BSA)	Continue treatment Symptomatic treatment as indicated (antihistamines, topical steroids) If persists or recurs consider delay in therapy, consider 0.5-1.0mg/kg/d methylprednisolone or equivalent
Grade 3-4 (>30% BSA or with life threatening consequences)	Delay or discontinue protocol therapy Consider skin biopsy Consider dermatology involvement Consider 1.0-2.0mg/kg/day methylprednisolone or equivalent with slow taper (>1 mo) if responds
SJS/TEN	Discontinue protocol therapy Consider 1-2mg/kg/day methylprednisolone or equivalent with slow taper (>1 mo) if responds Consider dermatology involvement, skin biopsy
*Participants requiring a delay of >28 days should go off protocol therapy. **Participants requiring > two dose reductions should go off protocol therapy.	
Recommended management: assess for other causes, empiric corticosteroids, assessment of immune-related organ dysfunction as indicated	

Neurological Immune AEs	**Management/Next Dose for MBG453**
≤ Grade 1 (asymptomatic/mild)	Continue treatment Symptomatic treatment as indicated
Grade 2 (Moderate, limiting iADLs)	Hold until ≤ Grade 1. Resume at same dose level. Symptomatic treatment as indicated Consider neurology involvement Consider 0.5-1.0mg/kg/day methylprednisolone or equivalent
Grade 3-4 (Cr > 6x ULN)	Delay and dose reduce (for fully reversible grade 3) or discontinue protocol therapy Consider 1-2mg/kg/day methylprednisolone or equivalent with slow taper (>1 mo) if responds Consider neurology consult and additional immunosuppressive therapies as indicated
*Participants requiring a delay of >28 days should go off protocol therapy. **Participants requiring > two dose reductions should go off protocol therapy.	
Recommended management: assess for other causes, empiric corticosteroids, assessment of immune-related organ dysfunction as indicated	

Endocrine Immune AEs	**Management/Next Dose for MBG453**
TSH elevation (asymptomatic)	Continue treatment Symptomatic treatment as indicated, consider endocrinology
Symptomatic endocrinopathy	Evaluate for endocrine function Consider endocrinology consult Consider pituitary imaging If symptomatic, delay in treatment and 1-2mg/kg/day methylprednisolone or equivalent with slow taper (>1 mo) if responds Appropriate hormone replacement therapy
Adrenal crisis	Delay or discontinue protocol therapy Evaluate for sepsis IV fluids, stress dose IV steroids with mineralocorticoid activity Consider endocrinology consult
*Participants requiring a delay of >28 days should go off protocol therapy. **Participants requiring > two dose reductions should go off protocol therapy.	
Recommended management: assess for other causes, empiric corticosteroids, assessment of immune-related organ dysfunction as indicated	

Other Immune-Related Toxicities	**Management/Next Dose for MBG453**
≤ Grade 1	Continue treatment
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3 lasting < 7 days	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 3 lasting > 7 days	Discontinue protocol therapy

Other Immune-Related Toxicities	**Management/Next Dose for MBG453**
Grade 4	
*Participants requiring a delay of >28 days should go off protocol therapy. **Grade 3 imAEs that do not improve within 7 days on steroids should come off protocol therapy. Consideration should be given for additional immunosuppression. Participants requiring > two dose reductions should go off protocol therapy.	
Recommended management: assess for other causes, empiric corticosteroids, assessment of immune-related organ dysfunction as indicated (e.g. thyroid testing, pituitary testing, GI/pulmonary evaluation, neurological assessment).	

Non-Hematologic Toxicities	**Management/Next Dose for MBG453**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy
*Participants requiring a delay of >28 days should go off protocol therapy. **Participants requiring > two dose reductions should go off protocol therapy.	
Recommended management: assess for other underlying/secondary causes	

Hematologic Toxicities	**Management/Next Dose for MBG453**
≤ Grade 1	No change in dose
Grade 2	No change in dose
Grade 3	Hold* until < Grade 2 (or baseline if baseline was grade 2). If persistent cytopenia beyond day 42 of the cycle, or as indicated, evaluate with a bone marrow biopsy. Resume at one dose level lower, if indicated.**
Grade 4	Hold* until < Grade 2 (or baseline if baseline was grade 2). If persistent cytopenia beyond day 42 of the cycle, or as clinically indicated, evaluate with a bone marrow biopsy. If no evidence of MDS, discontinue therapy.
*Participants requiring a delay of >28 days should go off protocol therapy. **Participants requiring > two dose reductions should go off protocol therapy.	

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1. Expected Toxicities

Toxicities associated with MBG453 are based on prior experience with this drug used both as a single agent and in other chemotherapy combinations, in both solid tumors and in hematological malignancies, as presumed based on the current knowledge including the mechanism of action and the available pre-clinical and clinical safety data.

7.1.1. Potential immune mediated toxicities

Based on the reported experience, toxicity associated with MBG453 as single agent or in combination treatment is expected to include AEs of a potential immune-mediated etiology. Despite important clinical benefits, checkpoint inhibition is associated with a unique spectrum of side effects termed immune-related adverse events (irAEs) or, occasionally, adverse events of special interest. IrAEs include dermatologic, gastrointestinal, hepatic, endocrine, kidney, respiratory, neurological and other less common inflammatory events. IrAEs are believed to arise from general immunologic enhancement, and temporary immunosuppression with corticosteroids, tumor necrosis factor-alpha antagonists, hormone replacement or other agents can be an effective treatment in most cases.

In general, treatment of moderate or severe irAEs requires interruption of the checkpoint inhibitor and the use of corticosteroid immunosuppression. Treatment is based upon the severity of the observed toxicity.

Serologic, immunologic and histologic (biopsy) data should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

7.1.2. Skin Toxicity

Twelve out of 133 patients (9%) and 18 out of 119 (15%) patients experienced skin related adverse events with MBG453 as single agent or in combination with PDR001 (PD1 inhibitor) in the solid tumor study, respectively. The majority of these AEs were Grade 1 or 2 and were manageable and reversible. One case of drug related rash maculopapular of Grade 3 was reported in MBG453 in combination with PDR001.

In the MDS/AML study, MBG453 was associated with skin related adverse events as follows: for single agent MBG453 (arm 4) in two out of 26 patients (8%), for MBG453 in combination with decitabine (arm 2) in seven out of 81 patients (9%), for MBG453 in combination with azacitidine (arm 6) in one out of 16 patients (6%), for MBG453 in combination with PDR001 (arm 5) in one out of 11 patients (9%), and for MBG453 in combination with PDR001 and decitabine (arm 3), no patients experienced skin related adverse events.

The majority of the AEs in the MDS/AML study were Grade 1 or 2 and were manageable and reversible. There was one case of Grade 3 drug related rash reported in Arm 2, one case of Grade 3 drug related rash reported in Arm 4 and one case of Grade 3 drug related rash reported in Arm 5.

Patients should be monitored carefully for any skin toxicity or mucositis. Specific guidance on management of skin toxicity includes discontinuation of study treatment for any suspected case of SJS/TEN.

7.1.3. Hepatotoxicity

Hepatic adverse events have been observed with MBG453 as a single agent and in combination. Abnormalities in hepatic enzymes are common in patients with cancer, who often have multiple possible etiologies for liver toxicities including concomitant medications, infections, liver metastases, obstruction, and prior hepatotoxic therapies.

Of the 133 patients treated with MBG453 single agent in the solid tumor study, 3 patients (2%) reported drug related AST increase and 1 patient (1%) reported drug related ALT increase. No grade 3 or grade 4 AST or ALT increase have been reported. Of the 119 patients treated with MBG453 and PDR001 combination, 7 patients (6%) reported drug related AST increase and 5 patients (4%) reported drug related ALT increase. Of these, 1 patient reported grade 3 AST elevation and 1 patient reported grade 3 ALT elevation. No cases of drug related bilirubin elevation were reported associated with AST and ALT elevation. Two serious cases of immune mediated hepatitis were reported from the combination study with PDR001 and considered as suspected to be related to study drug combination.

In the MDS/AML study, investigation related adverse events have been detailed by treatment arm. For patients treated with single agent MBG453 (arm 4), one patient experienced drug-related ALT increase (4%) and one patient experienced drug-related AST increase (4%), both of which were below grade 3. For MBG453 in combination with decitabine (arm 2), four patients (5%) experienced ALT increase (1 of these was a grade 3 drug related case) and 2 patients (3%) experienced AST increase (both of these were drug related and none were grade 3 or higher). For MBG435 in combination with azacitidine, one patient experienced drug related AST increase (6%) below grade 3. For MBG453 in combination with PDR001, there were no reported cases of drug related ALT or AST increase. For MBG453 in combination with PDR001 and decitabine, there were no reported drug-related grade 3 ALT increase, but 1 patient (5%) experienced drug related AST increase. In the MDS/AML study, no cases of drug related bilirubin elevation were reported associated with AST and ALT elevation.

Evaluation of patients with enzyme abnormalities should assess alternative possibilities to the extent possible before attributing the event to study treatment and initiating immunosuppressive therapy. Periodic monitoring of liver enzymes is required.

7.1.4. Other potential immune mediated toxicities

Single agent MBG453 was not associated with any ADRs considered as possibly immune mediated in the solid tumor study, but in the MDS/AML study, in patients with AML and higher-risk MDS, single agent MBG453 (Arm 4) was associated with myositis in one patient that was suspected to be immune-mediated.

In the solid tumor study, MBG453 in combination with PDR001 was associated with a few adverse events that were considered to be possibly immune-mediated, including the development

of hypothyroidism in two patients (2%) and myasthenia gravis in one patient with thymoma (1%).

In the MDS/AML study there were several adverse events that were considered to be possibly immune-mediated, as follows: for MBG453 single agent (arm 4), myositis in one patient (4%), for MBG453 in combination with decitabine (arm 2), one case (1%) each of acute inflammatory arthritis, pericarditis, stomatitis, and possible hemophagocytic lymphohistiocytosis, for MBG453 in combination with PDR001 and decitabine (Arm 3), a biopsy-confirmed tubulointerstitial nephritis in one patient (5%), for MBG453 in combination with PDR001 (Arm 5), encephalitis reported in two (18%) patients, one of these patients experienced the event 28 days after the last dose of study treatment.

These events may represent immune-mediated toxicities characteristic of other immune checkpoint inhibitors. It is unclear to what extent the above events were attributable to TIM-3 inhibition alone or in combination with other agents, including PD-1 inhibition, as opposed to PD-1 inhibition alone.

7.1.5. Infusion-related reactions

Infusion reactions (typically consisting of flushing, fevers, chills, and less commonly rigors, dyspnea and hypotension) can occur in patients receiving mAb therapies. To reduce the risk of infusion-related reactions, MBG453 should be administered by i.v infusion over at least 30 min, and should not be administered as a bolus injection. Infusion reactions should be treated promptly with medications directed at relief of symptoms, such as antihistamines and antipyretics, and medications and other interventions needed to maintain cardiovascular and pulmonary function. Typically, MBG453 infusion should be interrupted for infusion-related reactions of Common Terminology Criteria for Adverse Events (CTCAE) grade 2 or worse. Among all of the patients treated with MBG453, there was only one serious suspected case of an infusion reaction manifesting as shaking chills reported in a patient treated with single agent MBG453.

7.1.6. Adverse Events Lists

7.1.6.1. Adverse Event List(s) for MBG453

Of the 26 patients with MDS or AML treated with MBG453 as a single agent, 24 patients (92%) experienced AEs of any grade, regardless of relationship to study drug, with the most frequent AEs (>10%) being abdominal pain and febrile neutropenia (6 patients each, 23%), constipation, decreased appetite, diarrhea, dyspnea, nausea and pyrexia (5 patients each, 19%), dizziness, peripheral edema, and platelet count decreased (4 patients each, 15%), anemia, fatigue, headache, pain and pneumonia (3 patients each, 12%). A total of 17 patients (65%) experienced SAEs of all grades, regardless of relationship to study drug. SAEs which occurred in more than one patient included febrile neutropenia (6 patients, 23%), pneumonia and pyrexia (3 patients each, 12%). A total of 10 patients experienced a grade 3 or higher AE possibly related to the study drug: hypertension (n=2), neutropenia (n=2), thrombocytopenia (n=4), rash (n=2).

Potential immune mediated toxicities have been monitored with MBG453. Approximately 6-

15% of patients have experienced skin-related AEs, the majority being grade 1 or 2 and reversible. A total of three patients with grade 3 rashes have been reported across both the solid tumor study and the MDS/AML study to date. Hepatic AEs have also been observed; these have predominately been AST or ALT elevations, typically grade 1-2; no bilirubin increase has been noted. Periodic monitoring of liver enzymes is required. In the MBG453 study evaluating MDS and AML several possible immune-related toxicities were noted: one patient with myositis with MBG monotherapy. When combined with the PD1 inhibitor PDR001, one case of tubulointerstitial nephritis was noted and two cases of encephalitis. In combination with decitabine, one case each was noted for inflammatory arthritis, pericarditis, stomatitis, and one possible hemophagocytic lymphohistiocytosis that was possibly immune related and in the setting of active disease.

Refer to Tables in the Investigator Brochure for further AE information.

7.2. Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3. Adverse Event Reporting

7.3.1. In the event of an unanticipated problem or life-threatening complications treating investigators must immediately notify the Overall PI.

7.3.2. Investigators **must** report to the Overall PI any adverse event (AE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

7.3.3. DF/HCC Adverse Event Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

Attribution	DF/HCC Reportable Adverse Events(AEs)				
	Gr. 2 & 3 AE Expected	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days#	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days#	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within 1 business day of learning of the event.					

7.3.4. Serious Adverse Events

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

Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event. Please also see below for reporting exclusions.

All patients must be followed for safety for 150 days after the last dose of MBG453.

After the 30-Day on-site safety follow-up visit, patients may be followed via telephone call (or onsite visit if patient happens to be visiting the site) up to 150 days after the last dose of MBG453.

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

Any SAE experienced after 150 days of the last dose of MBG453 will only be reported to Novartis Safety if the investigator suspects a relationship to the study treatment.

Progression of malignancy (including fatal outcome), if documented by use of an appropriate method (for example per IWG guidelines (Cheson et al 2006)), should not be reported as an SAE except if the investigator considers the progression of malignancy is related to the study treatment.

7.3.5. Protocol-Specific Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting to the Overall PI or the DFCI IRB. However, they still must be reported through the routine reporting mechanism (i.e. case report form). Grade 1-2 hematologic toxicities do not need to be reported as AEs unless felt clinically relevant.

- Hematologic toxicity of any grade does not need expedited reporting unless felt to meet criteria in Section 5.4 and be related to MBG453.
- Electrolyte abnormalities (K, Na, HCO3, Chloride, Phosphorus, Magnesium) that are not felt to be clinically significant and/or improve to grade < 3 within 72 hours.

Events not considered to be SAEs are hospitalizations for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition
- The administration of blood or platelet transfusion as routine treatment of studied Indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.

- A procedure that is planned (i.e., planned prior to starting of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of or an elective procedure for a pre-existing condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE Case Report Form and the SAE Report Form must be completed. For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to study drugs, action taken regarding study drugs, and outcome.

7.4. Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.5. Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports, sentinel events or unanticipated problems that require reporting per institutional policy.

7.6. Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must <u>also</u> be reported in routine study data submissions.**

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 7.1. Please also refer to the current Investigator's Brochure and Pharmacy Manual.

8.1. MBG453

8.1.1. Description

MBG453 is a humanized monoclonal antibody against human TIM-3 (T-cell immunoglobulin) domain and mucin domain containing protein 3). MBG453 is expressed in a Chinese hamster ovary cell line (CHO-C8TD) and belongs to the IgG4/κ isotype subclass. The theoretical average molecular mass of MBG453 based on the amino acid

composition as deduced from DNA sequence is 144644 Da.

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

MBG453 binds specifically and with high affinity to human TIM-3. In Biacore assays, the KD of MBG453 for human TIM-3 is 0.167±0.008 nM and in cell binding assays, MBG453 binds human TIM-3 expressing cells with an affinity of 0.5±0.1nM.

Approximately dose-proportional increases in MBG453 Area Under the Curve (AUC) exposure (Cycle 1 $AUC_{0\text{-}336hr}$ for Q2W or $AUC_{0\text{-}672h}$ for Q4W)) were observed from 80 mg to 1200 mg Q2W. The $AUC_{0\text{-}336h}$ for Q2W and the $AUC_{0\text{-}672h}$ for Q4W during cycle 3 were higher than during cycle 1 indicating a moderate accumulation of MBG453, although this observation is based on limited preliminary data. The observed median half-life for MBG453 ranges from 5.21 to 15.3 days. A relatively short half-life was observed at low dose levels (e.g. 80 mg) of MBG453 potentially due to soluble target (sTIM-3) mediated drug disposition in the blood circulation.

Specific studies to investigate drug-drug interactions (DDI) have not been conducted. Monoclonal antibodies such as MBG453 are eliminated through protein catabolism and target-mediated disposition, and are not metabolized by cytochrome P450 (CYP450) enzymes or transported by P-glycoprotein (PgP) or related ABC membrane transporters. Therefore, the potential for drug-drug interaction is considered low and consistent with preliminary data observed from ongoing studies.

8.1.2. Form

The formulation of MBG453 is a clear to opalescent, colorless to slightly yellowish or slightly brownish solution in a glass vial containing 100 mg/mL MBG453 concentrate for solution for infusion for administration by intravenous infusion. In addition to the drug substance, the vial contains, L-histidine/L-histidine.HCl monohydrate, polysorbate 20, sucrose and water for injection and complies with pharmacopoeia standards. The vial contains a 20% overfill to allow accurate withdrawal of the dose.

8.1.3. Storage and Stability

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access.

MBG453 Concentrate for solution for infusion must be stored as per information provided on the label. Protect from light and do not freeze. Storage facilities must be carefully controlled in accordance with regulations governing investigational medicinal

products and local regulations. The recommended storage conditions of the drug product is 2-8 °C. Protect from light.

8.1.4. Compatibility

Only the materials (infusion bags, infusion syringes, infusion lines and in-line filter) specified should be used for administration of the study medication. The infusion sets including the intravenous filter set have to be prepared according to the instructions supplied by the manufacturers.

The following materials are accepted to be used in clinical trials for administration of MBG453 Solution for infusion prepared in 5 % dextrose solution (100 mL bags). Do NOT use 0.9 % sodium chloride solution.

Compatible materials of infusion set components (doses from 40mg to 2400)

100 mL 5% Dextrose infusion bag materials in contact with the drug product	**Infusion line materials, material in contact with the drug product (maximum length: 300 cm)**	**Infusion filter materials membrane type**
PVC (all plasticizers)	PVC (all plasticizers)	Positively charged PA
PE	PE	Positively charged PES
		Neutral PES

PVC: PolyVinyl Chloride; PE: PolyEthylene; PA: Polyamide; PES: PolyEtherSulfone
The infusion set (bag, line, and filter) selected for the study should be approved according to local regulation.

Infusion pumps to be used
Infusion pumps are used according to the recommendation given by the supplier and should be suitable to administer MBG453. The combination of bag, line, filter and pump should be tested in advance to ensure that each connection works properly, without any leak.

8.1.5. Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

The preparation and handling of the infusion bags shall comply with the guidance given in the USP but is limited to the physico-chemical stability demonstrated as follows: Chemical and physical in-use stability of the MBG453 Concentrate for solution for infusion and MBG453 Solution for infusion has been demonstrated for up to 24 hours at 2 to 8°C (of which 8 hours at room temperature, representing a worst case condition, and 16 hours at 2 to 8°C).

8.1.6. Availability

MBG453 100 mg liquid in vial will be supplied by Novartis to Investigator as open label bulk medication and will be packed and labeled under the responsibility of Novartis Drug Supply Management. Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug but will not supply information about the patient.

8.1.7. Preparation

The compounding instructions outlined are for preparation of one solution dose of MBG453 per patient. Each liquid formulation thus prepared is dedicated to one subject i.e. one vial serves ONLY one subject, note that multiple vials may be required for one dose. Allow drug product vials of MBG453 to equilibrate to room temperature.

Only qualified and trained personnel in the preparation procedure will promptly prepare the study drug ensuring that aseptic technique is followed during handling and preparation in a continuous process.

MBG453 is available as a histidine buffered solution, containing sucrose and polysorbate 20. The formulation does not contain a preservative as it is to be used for single-dose administration only.

Compounding of MBG453 Solution for Infusion (intravenous administration)

MBG453 100 mg/1 mL Concentrate for solution for infusion can be used for the preparation of the solution for infusion from a dose of 12 mg up to a maximal dose of 2400 mg. The vial contains a total final volume of 1.2 mL from which 1.0 mL can be withdrawn. The Concentrate for solution for infusion is subsequently diluted in an infusion bag using 5 % dextrose.

Since MBG453 is a protein, the Concentrate for solution for infusion may contain a few translucent particles. The solution for infusion must therefore be infused through a 0.2 micron in-line filter (see above).

- Each vial is to be used once. Discard any remaining MBG453 Concentrate for Solution for infusion in vials which have been used.
- Do NOT use these vials for other dilutions/other subjects.
- Do NOT use 0.9 % sodium chloride solution.

Volume Calculations

To obtain the volume [V] of MBG453 Concentrate for solution for infusion, which is needed for dosing, the intended dose is to be divided by the concentration of the Solution for infusion, as stated in the equation below:

$$Volume\ [mL][\boldsymbol{V}] = \frac{Target\ dose\ [mg]}{concentration\ of\ solution\ for\ injection\ [\frac{mg}{mL}]}$$

- Example: Volume Calculation for a target dose of 450 mg:

$$\text{Volume [mL][}\mathbf{V}\text{]} = \frac{450\ \text{mg}}{100\ \text{mg/mL}}$$

Example of dose calculation for a target dose of 450 mg

Dose	**450 mg**
Concentration of MBG453 Solution for Injection	100 mg/mL
Calculated volume required from equation **[V]**	4.50 mL
Vials of MBG453 100 mg/1 mL needed	5

Preparation of the infusion bag

IMPORTANT: Only materials specified in Section 2.3 of this document must be used for dose administration.

- Calculate the volume **[V]** of MBG453 to be added to the infusion bag, for each individual subject, according to the defined dose (Section 3.2.1.1).
- Calculate the number of vials needed according to calculated total volume.
- Choose an appropriate syringe size. Prepare only one syringe containing the dosing solution.
- Carefully withdraw the calculated total volume [**V**] of MBG453 Concentrate for solution for infusion into the selected syringe. Withdraw the volume left in the needle into the syringe. With the needle pointing upward, gently tap the syringe to move any air bubbles to the top and remove the needle.
- Ensure that the pooled volume matches the target calculated volume **[V]** using the disposable syringe graduation marking.
- Take an appropriate infusion bag and remove the equivalent of the later to be added volume **[V]** of the MBG453 concentrate for solution for infusion from the bag with a syringe and discard it.
- Slowly inject into the 100 mL infusion bag the pooled volume [**V**] of MBG453 Concentrate for solution for infusion.
- Mix the combined solution by gently agitating the infusion bag (**DO NOT SHAKE**).
- Label the bag with a local label.

8.1.8. Administration

- Infuse the filling volume of the infusion bag with a maximum administration time of 120 min ± 10 min. The solution for infusion must be infused through a 0.2 micron in-line filter (see filter requirements in 5.3.1).

  Remark: Shorter infusion times can be applied, since longer infusion times are considered worst-case with regards to potential protein adsorption. The selection of infusion speed within that requirement is in the responsibility of the project-responsible clinician and needs to comply with the specifications given

by the infusion pump.

- When administration is complete, flush the line with at least 25 mL of 5% dextrose solution to guarantee that all the MBG453 solution for infusion remaining in the infusion line has been administered.

8.1.9. Ordering

Novartis will supply MBG453 in individual, vacuum sealed, 6 mL glass vials each containing nominally 100 mg/1 mL MBG453 as a liquid. Vials contain an overfill of 20% to allow a complete withdrawal of the labeled amount of MBG453.

8.1.10. Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.1.11. Destruction and Return

Any unused product or waste material should be disposed of in accordance with local requirements.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1. Laboratory Correlative Studies

Throughout the study, at designated time points, patient blood and marrow samples will be collected for correlative analysis. Specifically, we will viably cryopreserve peripheral blood and bone marrow samples serially at baseline, during treatment, and at the end of treatment/time of progression. We will collect blood samples just prior to each infusion of MBG453 during cycles 1-3, and a bone marrow assessment will be performed at baseline, after cycle 2, after cycle 4, and then per the treating investigator. Peripheral blood and bone marrow samples will be collected at end of treatment or progression.

9.1.1. Correlative Study 1: Characterize the impact of TIM-3 Inhibition on MDS progenitor and T-cell subsets

Background: We propose an exploratory correlative study to characterize the effect of TIM3 inhibition on the MDS progenitor cells as well as T-cell subsets. We have previously developed a mass cytometry panel that assesses peripheral blood T-cells, myeloid components, and bone marrow cells with specific attention to markers relevant to MDS and immune checkpoint targets. The primary aim of this correlative will be to use mass cytometry to better characterize intra-patient changes in T-cell and myeloid cell

populations during treatment with MBG453. This work will be done in coordination with the laboratory of Patrick Reeves (MGH Vaccine and Immunotherapy Center).

9.1.1.1. Collection of Specimen(s)

- Bone marrow biopsies will be performed at baseline (screening), after cycle 2 of treatment, and at EOT. Approximately 10cc of bone marrow aspirate should be collected locally in an EDTA-containing tube(s).
- Peripheral blood will be collected at baseline and just prior to each infusion of MBG453 day 1 of cycles 2, 3, and 5, on day 15 of cycles 1-4, and at EOT. Peripheral blood should be collected in 2 10ml EDTA-containing tubes

9.1.1.2. Handling and Shipping of Specimens(s)

Samples will be packaged and shipped per instructions in the laboratory manual. Samples should be shipped Monday through Thursday to ensure Friday receipt.

9.1.1.3. Site(s) Performing Correlative Study

This work will be done in the laboratory of Patrick Reeves (MGH Vaccine and Immunotherapy Center).

9.1.2. Correlative Study 2: Exploring genetic factors associated with response and progression

Background: We will perform serial NGS-based testing for recurrent myeloid somatic mutations to characterize subclonal MDS changes during treatment. We will use these data to explore the biological response to MBG453 including mutations that confer sensitivity to treatment, and emerging mutations as putative escape mechanisms. We will collect standard tumor characteristics including tumor subtype, cytogenetics, cell surface markers, molecular abnormalities, both at study entry and during treatment. We will analyze whether certain MDS characteristics are associated with a specific response to therapy or change in cell populations. NGS-based testing will be performed per local institutional standards at with bone marrow biopsies at Baseline, C3D1, and End of Treatment (EOT). In the event of a dry tap, peripheral blood may be substituted.

10. STUDY CALENDAR

All screening evaluations must be conducted within 21 days of the start of protocol therapy. If the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. Assessments must be performed prior to administration of any study agent. Study assessments and agents should be administered within $\pm$ 3 days of the protocol-specified date, unless otherwise noted.

Standard safety assessments will be conducted at screening, during the study treatment and as scheduled during the safety follow up period. A visit should be planned at EOT and end of the safety follow up period (150 days after last dose of MBG453).

Local clinical laboratories can be used for the analysis of scheduled hematology, chemistry and other

blood specimens collected as part of safety monitoring. It is preferable to use the same laboratory for all the assessments performed.

- **Troponin-T** should be included among the regular blood chemistry parameters to monitor for cardiac toxicity.
- To monitor **thyroid** toxicity, TSH, Free-T3 and Free-T4 should be measured at screening. TSH should be monitored regularly (at selected visits) during treatment and as clinically indicated. If TSH is abnormal, then test free-T3 and free-T4.
- MDRD equation should be used to calculate eGFR at screening.
- Amylase and lipase should be monitored with serum chemistries

Local ECGs should be planned among regular safety assessment (vitals and physical examination) pre-dose on D1 of each cycle and at EOT, and may be stored as source documents.

		Cycles 1 - 2				**Cycles 3 - 4**		**Cycle 5 onwards**	**End of Treatment[d]**	**Safety / Survival**	**EDC Timepoints**
	Screening	**Day 1[h]**	**Day 8 ± 3 days**	**Day 15 ± 3 days**	**Day 22 ± 3 days**	**Day 1**	**Day 15 ± 3 days**	**Day 1**	**30 days after last dose**	**30, 150, 250 days, 1 year**	
MBG453		X				X		X			Day 1 of every cycle
Informed consent	X										N/A
Demographics	X										Screening
Medical history	X										Screening
Concurrent meds, including transfusion history	X	X---------- X									N/A
Physical exam	X	X				X		X	X		Screening
Vital signs	X[g]	X	X	X	X	X	X	X	X		Screening
Height	X										Screening
Weight	X	X				X		X	X		Screening
Performance status (ECOG)	X	X				X		X			Screening
CBC w/diff, plts	X	X	X	X	X	X	X	X	X		Screening, C1-2 day 1, 8, 15, 22, C3-4 day 1, 15, the day 1 of every cycle, and EOT/each follow up
Serum chemistry[a]	X	X	X	X	X	X	X	X	X		Screening, C1-2 day 1, 8, 15, 22, C3-4 day 1, 15, the day 1 of every cycle, and EOT/each follow up
Troponin-T	X	X	X	X	X	X		X	X		Screening, C1-2 day 1, 8, 15, 22, C3-4 day 1, 15, the day 1 of every cycle, and EOT/each follow up
TSH, free T3, free T4[j]	X	X[j]				X[j]		X[j]	X[j]		Screening, day 1 of every cycle, EOT
PT/INR, PTT, fibrinogen, ddimer	X										Screening
ECG	X	X				X		X	X		Screening, day 1 of every cycle, EOT
Adverse event evaluation		X---------- X								X[i]	During all visits
Transfusions administered	Assess prior 16 week transfusions	X---------- X									
B-HCG	X[b]	X				X		X	X	X	Screening, day 1 of every cycle, EOT, safety
Serum EPO level	X										Screening
Bone Marrow Biopsy[c]	X					C3D1		C5D1[e]	X		Screening, cycle 3 day 1, cycle 5 day 1, EOT, and any additional marrow

											assessments while on treatment
NGS (Rapid Heme Panel)[k]	X					X				X	With bone marrow biopsies at screening, cycle 3 day 1, and EOT/progression
Peripheral Blood for correlatives	X	C2D1 only		X		C3D1	X	C5D1[e]	X		
Bone marrow aspirate for correlatives[f]	X					C3D1		C5D1[e]	X		
Follow up										X[i]	Safety/Survival

a: Albumin, alkaline phosphatase, total bilirubin, direct bilirubin, bicarbonate or CO2, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, magnesium, total protein, SGOT [AST], SGPT [ALT], sodium, uric acid, amylase, lipase.

b: Serum pregnancy test (women of childbearing potential, WOCP). At screening, a serum pregnancy test (serum ß-HCG) must be performed within 3 days before the first dose for WOCP. During the study, a urine / serum pregnancy test should be done at Day 1 of each cycle for WOCP (except Cycle 1 if a pregnancy test had been performed within 72 hours of the first dose) and at EOT visit. A pregnancy test (serum or urine) should be performed every month during the safety follow-up period for WOCP (until day 150). If the patient is not coming to the clinic during the safety follow-up, it can be performed at home or at a local doctor's office, and the results will be communicated to the site staff.

c: Bone marrow biopsy and aspirate should be performed at baseline, cycle 3 day 1 ±3 days, and then within 7 days of cycle 5 day 1, at end of treatment, and as clinically indicated. Standard institutional testing including cytogenetics and molecular testing is recommended.

d: Off-treatment evaluation. The in-person visit has a window of ±3 days; additional safety follow-up is required through day 150. Note: for IND/IDE trials, follow up visits or other contact are required in order to identify SAEs during the 30 days following the end of study treatment. After end of treatment visit, patients should be followed per section 5.7 for survival and progression.

e: Bone marrow assessment for cycle 7 and cycle 11 may be done up to 7 days prior to the start of the treatment cycle. If a patient has a bone marrow assessment within 1 cycle of the planned assessment (e.g. cycle 6 or cycle 10) this may be used for the study assessment. A bone marrow for research samples will be performed on cycle 1 day 3 (window day 3-6).

f: Bone marrow samples for correlative studies will be collected at baseline, at cycle 3 day 1, and EOT for both NGS testing and for cytof analysis.

g. Blood pressure, heart rate, and temperature will be performed at screening and then as clinically indicated. . Bone marrow biopsy on cycle 5 day 1 will only require Cytof samples to be obtained.

h. On C1D1, total bilirubin, direct bilirubin, creatinine, SGOT [AST], SGPT [ALT], and INR should continue to meet inclusion criteria. Baseline values will be those assessed on C1D1

i. Follow up to evaluate for progression and survival may be ±7 days from those noted (day 30, 150, 250, and 1 year). Safety evaluations must be through 150 days after the last dose of MBG453. The safety follow up can be done by telephone call or visit. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 7.3. Documentation of attempts to contact the subject should be recorded in the source documentation.

j. TSH, free T3, and free T4 should be obtained during screening. TSH should be monitored regularly (at selected visits) during treatment and as clinically indicated. If TSH is abnormal, then test free-T3 and free-T4.

k. Rapid Heme Panel for NGS should be collected as part of standard of care with bone marrow biopsies at screening, C3D1 (+/-3 days), and EOT/progression. In the event of a dry tap, peripheral blood may be substituted.

11. MEASUREMENT OF EFFECT

Response to therapy will be assessed based on the proposal for the modification of the International Working Group (IWG) response criteria in myelodysplasia (Cheson et al., 2006), but modified to include complete remission with partial hematologic improvement CRh (Bloomfield et al., 2018), and the 2018 proposed update for hematologic responses and transfusion independence (TI) (Platzbecker et al., 2019). Patients with dysplastic-type CMML will use MDS risk-stratification and response assessment criteria.

11.1. Antitumor Effect – MDS

Complete remission (CR): patients must have a bone marrow with ≤ 5% myeloblasts and with normal maturation of all cell lines. Persistent dysplasia may be noted. Blood counts over a duration of at least 4 weeks should show a hemoglobin ≥ 11 g/dL, platelets ≥ 100,000/uL, and absolute neutrophil count ≥ 1000/uL, without circulating blasts in the peripheral blood.

Partial remission (PR): over a duration of at least 4 weeks, all CR criteria (if abnormal prior to treatment) except:

1. Bone marrow blasts have decreased ≥ 50% over pre-treatment levels but are still > 5%, if elevated at baseline
2. Cellularity and morphology are not considered relevant

Marrow Complete Remission (mCR): over a duration of at least 4 weeks, bone marrow showing ≤ 5% myeloblasts and with a decreased of ≥ 50% over pre-treatment levels. If the peripheral blood counts show evidence of hematologic improvement responses, these will be noted in addition to the marrow CR.

Complete Remission with Partial Hematologic Recovery: < 5% blasts in the bone marrow and partial recovery of peripheral blood counts (platelets > 50 × 109/L and ANC > 0.5 × 109/L).

Stable disease (SD): failure to achieve at least PR, but without evidence of progression for > 8 weeks.

Hematologic Responses According to the 2006 Hematologic Response Criteria:

Hematologic Improvement: HI is assessed in addition to CR/PR/mCR/SD.

1. Erythroid response: pretreatment level < 11 g/dL, showing a hemoglobin increase by ≥ 1.5 g/dL over at least 8 weeks
2. Platelet response: pretreatment level < 100,000/uL; showing:
    a. Absolute increase ≥ 30,000 if baseline > 20,000
    b. Absolute increase > 20,000 and by at least 100% increase if baseline < 20,000
3. Neutrophil response: pretreatment level < 1000/uL, showing an absolute increase > 500/uL and at least a 100% increase

Transfusion Independence: pretreatment requirement of at least 4U RBC within an 8 week period for a Hgb < 9 g/dL, no transfusions needed over an 8 week period

Hematologic Responses According to Proposed 2018 Hematologic Response Criteria:

We will also collect responses according to the proposed 2018 criteria. Patients will be categorized at baseline based on transfusion needs in the prior 16 weeks into three groups:

1. Non-transfusion Dependent (NTD): 0-2 RBCs in 16 weeks
2. Low Transfusion Burden (LTB): 3-7 RBCs in at least 2 transfusion episodes, maximum of 3 in a given 8 week period
3. High Transfusion Burden (HTB): ≥8 RBCs in 16 weeks, ≥4 in 8 weeks

IWG 2018 hematologic responses will include:

1. Erythroid Response: pretreatment Hgb level < 10 d/dL
    a. NTD: At least 2 consecutive Hgb measurements ≥1.5 g/dL for a period of minimum 8 weeks in an observation period of 16 to 24 weeks compared with the lowest mean of 2 Hgb measurements (apart from any transfusion) within 16 weeks before treatment onset

   b. LTB: HI-E in LTB patients corresponds to transfusion independence, defined by the absence of any transfusions for at least 8 weeks in an observation period of 16-24 weeks, compared with 16 weeks prior to treatment
   c. HTB:
      i. Major response: Major HI-E response in HTB patients corresponds to transfusion independence, defined by the absence of any transfusions over a period of minimum 8 weeks in an observation period of 16-24 weeks compared with 16 weeks prior to treatment
      ii. Minor response: Minor HI-E response in HTB patients is defined as a reduction by at least 50% of RBCs over 16 weeks
2. Platelet response: pretreatment level < 100,000/uL; showing:
   a. Absolute increase ≥ 30,000 if baseline > 20,000
   b. Absolute increase > 20,000 and by at least 100% increase if baseline < 20,000

   Increments of platelets will be reported for patients with pretreatment platelets >100k
3. Neutrophil response: pretreatment level < 1000/uL, showing an absolute increase > 500/uL and at least a 100% increase. Increments of neutrophils will be reported for patients with a pretreatment ANC > 1000.

Overall Response Rate
The overall response rate (ORR) will be defined as CR + PR + CRh + HI + TI. It will be reported using both the 2006 and 2018 criteria above but the primary endpoint will be based on the 2006 criteria.

Patients not meeting one of the above criteria are considered to have a failed response (see "Failure," below).

The following response measures may be assessed in addition to/subsequent to the above.

Cytogenetic response:
1. Complete response is the disappearance of the chromosomal abnormality without the appearance of new ones
2. Partial response is at least 50% reduction of the chromosomal abnormality

Progression of disease:
1. For patients with <5% blasts: ≥ 50% increase in blasts to > 5% blasts
2. 5-10% blasts: ≥ 50% increase in blasts to > 10% blasts
3. 10-20% blasts: ≥ 50% increase in blasts to > 20% blasts
4. Progression/relapse from HI:
   a. Reduction in hemoglobin by ≥ 1.5 g/dL
   b. ≥ 50% decrease from maximum response in granulocytes or platelets
   c. Transfusion dependence

Relapse after CR or PR: at least 1 of the following:
1. Return to pre-treatment bone marrow blast percentage
2. ≥ 50% decrease from maximum response in granulocytes or platelets

3. Reduction in hemoglobin by ≥ 2 g/dL or transfusion dependence

Failure:
Death during treatment, or disease progression characterized by worsening of cytopenias, increased bone marrow blasts, or progression to a more advanced MDS subtype than pretreatment.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1. Data Reporting

12.1.1. Method

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

12.1.2. Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the Office of Data Quality (ODQ) in accordance with DF/HCC policies.

12.2. Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of medical oncologists, research nurses, pharmacists and biostatisticians with direct experience in cancer clinical research. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year with the frequency determined by the outcome of previous reviews. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3. Collaborative Agreements Language

N/A

13. STATISTICAL CONSIDERATIONS

Patients with MDS progressing after or unlikely to respond to front-line therapeutic options have limited salvage treatment options. This study seeks to determine whether MBG453 has activity in this setting.

The primary outcome will be the overall response rate within the first 6 months of treatment, which will be a composite endpoint of complete remission (CR), partial remission (PR), hematologic improvement (HI), transfusion independence (TI), and complete remission with incomplete hematologic recovery (CRh). We will assume that the null response rate is 0.15 based on prior studies (Fenaux et al., 2020; Garcia-Manero et al., 2020; Giagounidis et al., 2014; Oliva et al., 2017; Santini et al., 2016). Although patients may have received HMA prior to enrollment, we will plan to analyze the post-HMA group as a distinct subgroup. Secondary outcomes include adverse event monitoring, duration of response, number of patients receiving MBG453 and duration of treatment, overall survival, progression-free survival, and toxicities. Descriptive statistics will be used for patient and treatment characteristics and for correlative studies. We will estimate OS, PFS, and duration of response using the method of Kaplan and Meier. Toxicities will be presented using descriptive statistics, evaluated according to the NCI criteria, and summarized by patient as well as by type and grade.

13.1. Study Design/Endpoints

The primary objective is to evaluate the ORR of MBG453 in lower-risk MDS after standard front-line therapy. The ORR will be comprised of CR, PR, HI, TI, and CRh, as described in section 11.1. We will assess response as the best overall response within the first 6 months of treatment.

Secondary endpoints include:

- The rates and severity of adverse events associated with MBG453 in lower risk MDS
- The rates of 1-year overall survival (OS), progression free survival (PFS), time to disease progression, and duration of response to therapy with MBG453.
- Response to therapy according to pretreatment disease and patient characteristics, monitoring disease-specific molecular, immunophenotypic, and cytogenetic evolution during treatment (exploratory analysis)
- Changes in cell surface marker expression, Immune cell subsets, and molecular clonal evolution during treatment and at the time of progression (exploratory analysis)

This study will follow a Simon's Optimal Two-Stage Phase II design. The null hypothesis that the true response rate is P=0.15 will be tested against a one-sided alternative. In the first stage, 10 patients will be accrued. If there are no more than 1 responses in these 10 patients, the study will be stopped. Otherwise, 12 additional patients will be accrued for a total of 22. The null hypothesis will be rejected if 6 or more responses are observed in 22 patients. This design yields a type I error rate of 0.09 and power of 0.80 when the true response rate is 0.35.

In order to closely monitor for signals of toxicity in the lower-risk MDS cohort, we will assess

the first six patients who are enrolled for dose limiting toxicities (DLTs) during the first 28 days of treatment. If more than 1 of the first 6 patients experiences a DLT the study enrollment will stop and reviewed for safety prior to further enrollment. The following table provides the probability that no more than 1 in 6 patients experiences a DLT and the study proceeds without interruption, given the true but unknown rate of DLT:

	True but unknown probability of experiencing a DLT				
	0.10	0.20	0.30	0.40	0.50
Pr(success)	0.89	0.66	0.42	0.23	0.11

Follow-up will be planned 1 year after end of treatment or death, whichever occurs first. The toxicities will be measured according to NCI-CTC version 5.0 (http://ctep.info.nih.gov), and tabulated according to the stage of dose escalation.

13.2. Sample Size, Accrual Rate and Study Duration

A maximum of 22 patients will be accrued on this study. We anticipate that these patients will be accrued over an 18 month period across centers, for a total study duration of 18 months of accrual, and up to 12 months of follow up for analysis. Reporting on the primary outcome would occur after all patients have been dosed for up to 6 months or come off treatment in that time period. Secondary outcomes would be reported approximately 30 months after study initiation.

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	1	+	2	=	3
Not Hispanic or Latino	7	+	12	=	19
Ethnic Category: Total of all subjects	(8)	+	(14)	=	(22)
Racial Category					
American Indian or Alaskan Native	0	+	0	=	
Asian	0	+	0	=	
Black or African American	1	+	1	=	
Native Hawaiian or other Pacific Islander	0	+	0	=	
White	7	+	13	=	
Racial Category: Total of all subjects	(8)	+	(14)	=	(22)

13.3. Stratification Factors

We will plan to report outcomes according to whether patients received prior HMA (azacitidine or decitabine) or not, as well as whether patients received prior agents targeting the TGFB pathway (e.g. luspatercept, sotatercept); we will not have prespecified enrollment targets for these subpopulations, however, and these categories will be only used for data reporting.

13.4. Interim Monitoring Plan

Please refer to 13.1 regarding a plan for early evaluation for futility using a simon 2-stage design, as well as toxicity monitoring during a DLT period for the first 6 patients enrolled.

13.5. Analysis of Primary Endpoints

Please refer to section 13.1

13.6. Analysis of Secondary Endpoints

Secondary endpoints include the rates and severity of adverse events, 1-year overall survival (OS), progression free survival (PFS), time to disease progression, and duration of response to therapy with MBG453. Descriptive statistics will be used for patient and treatment characteristics and for correlative studies. We will estimate OS, PFS, and duration of response using the method of Kaplan and Meier. Toxicities will be presented using descriptive statistics and evaluated according to the NCI criteria.

Planned exploratory correlative studies will seek to characterize changes in immune and myeloid populations during treatment with MBG453, as well as any associations between mutation profiles and patient responses. These will be analyzed using descriptive statistics.

13.7. Reporting and Exclusions

All patients who receive at least one (1) dose of study treatment will be considered evaluable for analysis. Patients who are enrolled but never start protocol therapy will be considered non-evaluable and may be replaced in the study. Such events will be noted in reporting of the study outcomes.

13.7.1. Evaluation of Toxicity

All participants will be evaluable for treatment-related toxicities from the time of their first dose of MBG453.

13.7.2. Evaluation of the Primary Efficacy Endpoint

All eligible participants will be assessed for response and outcome to therapy if they meet the above criteria.

14. PUBLICATION PLAN

The results should be made public within 18 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and

Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B INFORMATION ON POSSIBLE DRUG INTERACTIONS

Information on Possible Interactions with Other Agents for Patients and Their Caregivers and Non-Study Healthcare Team

The participant _____ is enrolled on a clinical trial using the experimental agent **MBG453**. This clinical trial is sponsored by Novartis. This form is addressed to the participant, but includes important information for others who care for this participant.

MBG453 is an antibody therapy that interacts with the immune system. It is not know to directly interact with other drugs but may have effects including autoimmune or inflammatory responses that may need to be monitored or treated. Because of this, it is very important to tell your study doctors about all of your medicine before you start this study. It is also very important to tell them if you stop taking any regular medicine, or if you start taking a new medicine while you take part in this study. When you talk about your medicine with your study doctor, include medicine you buy without a prescription at the drug store (over-the-counter remedy), or herbal supplements such as St. John's wort. **It is important to inform the study doctor if you are prescribed any medication that may suppress the immune system, including steroids (such as the drug prednisone).**

Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants or nurse practitioners) that you are taking part in a clinical trial. **Bring this paper with you and keep the attached information card in your wallet**

Other medicines can be a problem with your study drugs.

- You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

- Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you. Your study doctor's name is

_____

and he or she can be contacted at

_____

INFORMATION ON POSSIBLE DRUG INTERACTIONS You are enrolled on a clinical trial using the experimental agent **MBG453.** Because of this, it is very important to: ➢ Tell your doctors if you stop taking regular medicine or if you start taking a new medicine. ➢ Tell all of your prescribers (doctor, physicians' assistant, nurse practitioner, and pharmacist) that you are taking part in a clinical trial. ➢ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.	➢ Your study doctor's name is _____ and can be contacted at _____.