CLINICAL STUDY PROTOCOL: CP-MGD007-02

22 October 2018

A Phase 1b/2, Open Label, Dose Escalation Study of MGD007, a Humanized gpA33 × CD3 DART® Protein in Combination with MGA012, an Anti-PD-1 Antibody, in Patients with Relapsed or Refractory Metastatic Colorectal Carcinoma

NCT03531632

CLINICAL STUDY PROTOCOL: CP-MGD007-02
PROTOCOL AMENDMENT 1

Study Title:	A Phase 1b/2, Open Label, Dose Escalation Study of MGD007, a Humanized gpA33 × CD3 DART® Protein in Combination with MGA012, an Anti-PD-1 Antibody, in Patients with Relapsed or Refractory Metastatic Colorectal Carcinoma
Study Number:	CP-MGD007-02
Study Phase:	Phase 1b/2
Product Numbers:	MGD007, MGA012 (also known as INCMGA00012)
IND Number:	119748
Indication:	Relapsed or Refractory Metastatic Colorectal Carcinoma
Coordinating Principal Investigator:	TBD
Sponsor:	MacroGenics, Inc. 9704 Medical Center Drive Rockville, MD 20850 301-251-5172
Sponsor's Medical Monitor:	Refer to study contact list

REVISION HISTORY

Status	Date
Original Protocol	01 March 2018
Original Protocol – Change Memo 1	19 April 2018
Protocol Amendment 1	22 October 2018

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SPONSOR SIGNATURES

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Study Number: CP-MGD007-02

This clinical study protocol has been approved by the Sponsor:

Signed: ***See Appended Electronic Signature Page*** Date: _____

[redacted]
Director, Clinical Research
MacroGenics, Inc.

Signed: ***See Appended Electronic Signature Page*** Date: _____

[redacted]
Associate Director, Biostatistics
MacroGenics, Inc.

RATIONALE FOR PROTOCOL AMENDMENT 1

The substantive changes in Amendment 1 are the removal of the Q2W cohort (every 2-week MGD007 scheduled dosing) and minor adjustment to the composition of the MGD007 drug product formulation buffer while maintaining the same buffer strength. The Q2W cohort was removed from the study to focus resources on testing of the combination using the weekly regimen of MGD007. This change impacted **Sections 2, 4, 7, 9, 14**, and appendices in which Q2W was included.

The table below outlines the substantive modifications to the body of the protocol. Corresponding changes were made to the Synopsis for consistency; those changes are not included below.

A redline version showing detailed changes to the protocol will be provided upon request.

Summary of Changes in CP-MGD007-02 Original Protocol

Section	Summary of Main Changes and Rationale
Sponsor Signatures	[redacted] as Medical Monitor for this program.
Sections 2, 4, 7, 9, and 14	Language with regards to the Q2W cohort was removed.
Section 4.1.1	The amount of treatment a patient must receive to be considered evaluable for the DLT evaluation period has been modified to 75% of both the required MGD007 doses and the required MGA012 doses.
Section 5.1	Inclusion criterion 7 was modified to include patients previously treated with MGD007 in Study Protocol CP-MGD007-01; stipulations were included.
Section 5.2	History of prior allogeneic bone marrow, stem-cell, or solid organ transplantation was added, as new Exclusion Criterion 3 and subsequent exclusion criteria were renumbered.
Section 5.5	Death had been inadvertently omitted in original protocol and has been added as this event should be included as a reason for patient discontinuation from a clinical study.
Section 6	Minor formulation adjustment in MGD007 drug product composition due to the addition of PS80 to the drug substance (DS) formulation. To maintain the same buffer strength, it required an adjustment to the sodium phosphate ratio and PS80 concentration in the DP formulation to account for the addition of PS80 in the DS buffer. In addition, there is clarification that allowable colors of MGA012 drug product solution may have a pale-yellow color. Edits were made within the subsections of this section: Sections 6.4.1, 6.4.3 and 6.4.6.
Section 7.1	Guidelines for duration of prophylactic use of budesonide was amended to include a continuation of 5 days after MGD007 infusion, to better mitigate MGD007 adverse effects on the gastrointestinal tract and limit the use of dexamethasone.
Section 8.1.1	Text was included from a protocol change memo, CP-MGD007-02 Original Protocol, Change Memo 1 (dated 19 April 2018), regarding avoidance of the concomitant use of CYP450 substrates with a narrow therapeutic index during study treatment was added, given the potential for CYP enzyme suppression due to cytokine elevation.
Section 12.2.2	AESIs requiring reporting to the Sponsor within 24 hours were specifically listed for clarity, as provided in Section 12.2.4.
Section 12.2.4	Infusion-related reactions or CRS events language was modified to include all events reported as adverse events of special interest (AESI), similar modification made in Section 7.2.
Section 14.1	Sample size was decreased from a potential total of 104 to 52 patients due to removal of the Q2W cohort.
Appendix 1	Vital signs footnote for Cycle 1 footnote was amended for clarity and accuracy.
Appendix 2	Appendices renumbered starting at Appendix 2 because of the removal of the Q2W cohort (previously Appendix 2).

LIST OF ABBREVIATIONS

%CV	unknown description
µg	microgram
ADA	anti-drug antibody
ADCC	antibody-dependent cellular cytotoxicity
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
APTT	activated partial thromboplastin time
AST	aspartate transaminase
AUC	area under the curve
BiTE	bispecific T cell engager
BiW	twice a week
BOR	best overall response
BUN	blood urine nitrogen
cCR	confirmed complete response
CDC	complement-dependent cytotoxicity
CEA	carcinoembryonic antigen
CFR	Code of Federal Regulations (U.S.)
CHO	Chinese hamster ovary
CI	confidence interval
CL	clearance
C_{max}	maximum observed serum concentration
CNS	central nervous system
cPR	confirmed partial response
CR	complete response
CRC	colorectal cancer
CRF	case report form
CRS	Cytokine Release Syndrome
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL	cytotoxic T lymphocyte
CTLA-4	cytotoxic T lymphocyte-associated protein 4
C_{trough}	trough concentration
CV	coefficient of variation
DART	Dual Affinity Re-Targeting (protein)
dL	deciliter
DLT	dose-limiting toxicity

DoR	Duration of Response
E:T	effector to target (cell ratio)
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EGFR	epidermal growth factor receptor
ELISA	Enzyme-linked immunosorbent assay
EOI	end of infusion
Fc	fragment crystallizable
FcγR	Fc gamma receptor
FcRn	neonatal Fc receptor
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Good Laboratory Practice
gpA33	glycoprotein A33
hCG	urine human chronic gonadotropin
Hgb	hemoglobin
hr	hour(s)
IB	Investigational Brochure
ICFs	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN-γ	interferon gamma
IgG	immunoglobulin G
IHC	immunohistochemistry
IL	interleukin
IND	Investigational New Drug application
irAE	immune-related adverse event
IRB	Institutional Review Board
irCR	immune-related Complete Response
IRE	immediately reportable event
irPD	immune-related disease progression
irPR	immune-related Partial Response
irRECIST	immune-related response criteria
irSD	immune-related Stable Disease
IV	intravenous(ly)
K_D	equilibrium dissociation constant
kDa	kilodalton

kg	kilogram
LID	Lead-in dose
LTFU	lost to follow up
µg	micrograms
mAb	monoclonal antibody
MAD	maximum administered dose
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean cell volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligrams
min	minute
mL	milliliter
mm	millimeter
MMR	mismatch repair
MRI	magnetic resonance imaging
MRT	mean residence time
MSI	microsatellite instability
MSS	microsatellite-stable
MTD	maximum tolerated dose
n	number
NCA	noncompartmental analysis
NCI	National Cancer Institute
ng	nanogram
NK	natural killer
nM	nanomolar
NOAEL	no-observed-adverse-effect level
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	pharmacodynamics
PFS	progression-free survival
PK	pharmacokinetics
PQC	product quality complaint
PR	Partial Response
PT	prothrombin time
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
QW	once weekly

RBC	red blood cells
RECIST	Response Evaluation Criteria in Solid Tumors
RLU	relative light unit
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous(ly)
SD	standard deviation
SEB	Staphylococcal Enterotoxin B
SOC	System Organ Class
SPR	surface plasmon resonance
$t_{1/2}$	terminal half-life
TCR	T cell receptor
TILs	tumor infiltrating lymphocytes
TNF-α	tumor necrosis factor alpha
ULN	upper limit of normal
US	United States
V_{ss}	unknown description
WBC	white blood cells

1 SYNOPSIS

Sponsor: MacroGenics, Inc.	**IND Number:** 119748
Name of Product: MGD007, MGA012 (also known as INCMGA00012)	
Study Title: A Phase 1b/2, Open Label, Dose Escalation Study of MGD007, a Humanized gpA33 × CD3 DART® Protein in Combination with MGA012, an Anti-PD-1 Antibody, in Patients with Relapsed or Refractory Metastatic Colorectal Carcinoma	
Study Number: CP-MGD007-02	
Study Phase: 1b/2	
Investigator(s)/Centers: This study will be conducted at approximately 10 sites in the United States (US).	

Dose Escalation Phase:

Primary Objective:

To characterize the safety, tolerability, dose-limiting toxicities (DLTs), and maximum tolerated dose (MTD) of MGD007 when combined with MGA012 in patients with relapsed/refractory metastatic colorectal carcinoma after at least 2 and up to 5 prior standard regimens of therapy in metastatic setting; or who did not tolerate fluoropyrimidines, oxaliplatin or irinotecan; or who are not good candidates for standard of care.

Secondary Objective:

- To characterize the pharmacokinetics (PK), pharmacodynamic activity, and immunogenicity of MGD007 and MGA012 in combination.
- To investigate the preliminary antitumor activity of MGD007 combined with MGA012 as measured by objective response rate, disease control rate, and progression-free survival (PFS) rate at 16 weeks in patients with relapsed/refractory metastatic colorectal carcinoma using both conventional Response Evaluation Criteria in Solid Tumors (RECIST 1.1), **Appendix 5**, and immune-related response criteria (irRECIST), **Appendix 6**.

Cohort Expansion Phase:

Primary Objective:

- To investigate antitumor activity of MGD007 combined with MGA012 when dosed at the MTD (or maximum administered dose [MAD] if no MTD is defined) as measured by objective response rate, disease control rate, and PFS rate at 16 weeks in patients with relapsed/refractory metastatic colorectal carcinoma using both conventional Response Evaluation Criteria in Solid Tumors (RECIST 1.1), **Appendix 5,** and immune-related response criteria (irRECIST), **Appendix 6**.

Secondary Objective:

- To further characterize the safety and tolerability, of MGD007 when combined with MGA012 in patients with relapsed/refractory metastatic colorectal carcinoma after at least 2 lines of therapy in a metastatic setting.
- To characterize the PK, pharmacodynamic activity, and immunogenicity of MGD007 and MGA012 in combination.
- To explore the impact of this combination on PFS, immune-related PFS (irPFS), and overall survival (OS) in patients with relapsed/refractory metastatic colorectal carcinoma.

Study Design:

Overview:

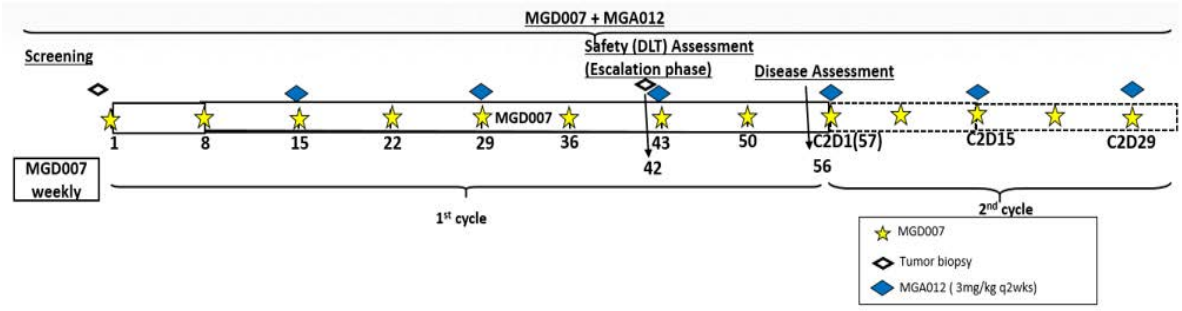
This study is an open-label, Phase 1b/2, dose escalation and cohort expansion study designed to characterize the safety, tolerability, PK, pharmacodynamics, immunogenicity, and preliminary antitumor activity of MGD007 and MGA012, administered in combination by IV infusion, in patients with histologically proven, relapsed/refractory metastatic colorectal carcinoma, irrespective of the KRAS and MMR status of their tumors. This study will enroll patients as described below.

The study will proceed in 2 distinct phases as follows: Dose Escalation Phase to determine the MTD or MAD (if no MTD is defined) of the combination, followed by a Cohort Expansion Phase to further define the safety and initial antitumor activity of the combination with the doses established in the Dose Escalation Phase.

Patients will be treated with MGD007 and MGA012 as shown in the figure below. MGD007 will be administered at the target dose for each assigned cohort as an IV infusion over 120 minutes, once weekly (QW), in 8-week treatment cycles. MGA012 will be administered at 3 mg/kg as an IV infusion over 60 minutes, once every 2 weeks (Q2W) beginning on Cycle 1 Day 15, and every 2 weeks thereafter. For each patient, administration of the first dose of MGA012 will occur 2 weeks after the first dosing of MGD007. The DLT evaluation period will last until Cycle 1 Day 42. Disease status will be evaluated on Cycle 1 Day 56 (± 3 days) using CT and/or MRI as appropriate for the sites of disease, accompanied by physical examination, and then will be evaluated every 8 weeks while on study treatment. Although response assessment will be performed according to both conventional (RECIST 1.1 **[Appendix 5]**) and irRECIST **(Appendix 6)**, patients will be managed according to irRECIST principles. This approach allows for limited treatment of patients beyond the initial radiographic documentation of disease progression, assuming the Investigator feels that the patients are tolerating therapy adequately, that patients remain otherwise clinically stable despite this initial radiographic evidence of disease progression, and that the Investigator feels the patient may still derive benefit from continuation of therapy.

Patients who achieve response status of immune-related complete response (irCR), immune-related partial response (irPR), immune-related stable disease (irSD), or unconfirmed immune-related progressive disease (irPD), per the immune-related response criteria **(Appendix 6)** at the end of the Cycle 1 radiographic disease assessment, may be eligible to receive subsequent administrations of MGD007 and MGA012 for up to 12 cycles (~ 2 years), assuming that the patients remain clinically stable and have not experienced DLTs that necessitated permanent discontinuation of study drug.

Overall Study Treatment Schema



The dose levels are shown below:

Dose Level	MGD007 Dose (QW)	MGA012 Dose (Q2W)
Dose Level 1	0.4 µg/kg	3 mg/kg
Dose Level 2	0.6 µg/kg	3 mg/kg
Dose Level 3	0.8 µg/kg	3 mg/kg

Patients who experience progressive disease, as evidenced by ≥ 20% increase in the dimensions of target lesions or the occurrence of new lesions, may continue therapy at the discretion of the Investigator, pending confirmation of progressive disease at the next planned tumor assessment and satisfaction of criteria for irPD. Subsequent cycles of therapy after an initial documentation of progressive disease should be administered only to patients who have demonstrated acceptable tolerance to treatment with study drug, who remain otherwise clinically stable, and who in the assessment of the Investigator, may derive clinical benefit from the continuation of treatment with study drug.

No dose reductions of MGA012 or MGD007 are allowed during the study, except for patients being treated at doses that are subsequently found to exceed the MTDs for this schedule.

Data regarding the KRAS and MMR mutational status (MSI or MSS) will be collected for all patients; statuses for both must be formally documented for patients in the Cohort Expansion Phase. Patients will be required to have at least 1 site of measurable disease as defined by RECIST 1.1 criteria **(Appendix 5)**. In addition, patients must have had an identified tumor tissue block (preferred) and/or tumor specimens sufficient for 20 slides that can be utilized for assay of gpA33, CD3, PD-1, and PD-L1 expression via immunohistochemical staining.

Following the last dose of study drug, all patients will be followed every 3 months for survival during a 2-year Survival Follow-up Period.

Number of Patients Enrolled:

The number of patients enrolled in the Dose Escalation Phase cannot be precisely determined in advance. There may be up to 27 patients enrolled, depending on results in the course of the trial and the number of MGD007 and MGA012 doses explored. This patient number does not take into account replacement of non-evaluable patients or enrollment to a dose cohort that is expanded in Dose Escalation Phase.

The Cohort Expansion Phase of the study will enroll approximately 25 patients. This number may be higher because at the end of the Cohort Expansion Phase, 15 tumor paired biopsies will be required, if metastases are accessible and obtained with acceptable clinical risk (see **Section 5.1**, **# 9)**. If this number is not reached, additional patients will be enrolled in the study to ensure that the 15 paired biopsies are obtained (see **Section 4.1.2**).

The number of patients does not take into account patients who may be replaced for clinical reasons. For initial planning, the maximum number of patients to be enrolled in this trial is anticipated to be approximately 52 patients.

Study Population:

The patient population to be enrolled in this study will consist of adult patients with histologically proven, relapsed/refractory metastatic colorectal carcinoma irrespective of the KRAS and MMR status of their tumors, although data regarding the KRAS and MMR mutational status will be collected for all patients.

Key Entry Criteria:

The patient population to be enrolled in this study, will consist of adult patients with histologically proven, relapsed/refractory metastatic colorectal carcinoma. In the Dose Escalation Phase, patients must have had recurrence, progression, or intolerance to standard therapy consisting after at least 2 prior standard regimens (containing a fluoropyrimidine plus a platinum analogue and/or irinotecan) for metastatic disease. During the Cohort Expansion portion of the study, patients will be allowed to participate in the study after 1 prior standard regimen. Patients who are inappropriate candidates for or have refused treatment with these regimens are also eligible. Patients should have received no more than 5 prior therapies.

Patients in the Dose Escalation Phase must have ECOG performance status of 0 or 1, radiographic evidence of measurable disease suitable for response monitoring, and no serious concurrent illnesses that would increase the risk to the patient or confound the study data.

See **Section 5** for a complete list of eligibility criteria.

Study Drugs:

- MGA012 (also known as INCMGA00012) is an anti-PD-1 monoclonal antibody (mAb) protein produced in Chinese hamster ovary (CHO) cells.
- MGD007 is a gpA33 × CD3 DART protein produced in CHO cells.

Duration of Treatment and Study Duration:

Patients will be treated with MGD007 and MGA012 administered in 8-week treatment cycles until disease progression, intolerable toxicity, or patient and investigator's decision.

The maximum amount of time an individual patient may be on study is 12 treatment cycles, or approximately 2 years.

Enrollment of the study should last approximately 18 months.

The total time for conduct of the trial is expected to be approximately 66 months (which includes 2 years of survival follow-up). These estimates of the timing for study conduct may vary from that observed in the actual conduct of the trial.

Criteria for Evaluation:

Safety Assessments:

The safety assessment will be based on the evaluation of AEs that occur from the time of initiation of administration of study drug through the End of Treatment Visit or 30 days after the last dose of study drug (whichever is later) and will be determined based on signs, symptoms, physical examination findings, and/or laboratory test results from enrolled patients, as appropriate. Progression of the underlying neoplasm resulting in hospitalization or death (e.g., patient hospitalized for or dies from progressive disease [PD] only, without any other SAE) will be documented as an antitumor activity outcome and not as an SAE.

Response Assessments:

Tumor assessments will be obtained using CT and/or MRI scans. Target and non-target lesions will be designated at screening and then evaluated at Cycle 1 Day 56 (±3 days), and subsequently every 8 weeks while on study treatment. At each tumor assessment time point, the overall response status will be determined based on assessment of target and non-target lesions as well as appearance of any new lesions. For RECIST v1.1 **(Appendix 5)**, the overall responses will be categorized as CR, PR, SD, PD, or NE. For irRECIST **(Appendix 6)**, the overall responses will be categorized as irCR, irPR, irSD, irPD, or irNE. For patient management, the response determination according to irRECIST will prevail. For patients who demonstrate acceptable tolerability of treatment with MGD007 and MGA012, and an objective response assessment of irCR, irPR, or irSD, or unconfirmed clinically stable irPD, therapy may be continued. For patients in whom progression is confirmed at the next scheduled tumor assessment, the criteria for irPD will have been met, and treatment with MGD007 and MGA012 should be discontinued. However, for individual patients who meet these criteria, but who are otherwise considered to be experiencing clinical benefit in the judgment of the Investigator, consideration may be given to continue treatment with the MGD007 and MGA012 combination, on a case-by-case basis, in consultation with the Sponsor.

Pharmacokinetic Assessments:

Serum concentrations of MGD007 and MGA012 will be measured using ELISAs. Single and multiple dose PK parameters, C_{max}, T_{max}, $AUC_{(0\text{-}T)}$, $AUC_{(TAU)}$, $AUC_{(INF)}$, C_{trough}, CL, V_{ss}, and $t_{1/2}$ will be derived from MGD007 and MGA012 serum concentration versus time data.

Pharmacodynamics/Biomarkers:

Samples collected for serum biomarkers are collected in the Dose Escalation Phase and the Cohort Expansion Phase.

Immunogenicity Assessments:

The generation of anti-drug antibodies (ADA) directed against MGD007 and MGA012 will be assayed using ELISAs.

Analysis Populations:

Two general populations will be used for the purposes of this analysis - the Safety Population and the Response Evaluable Population as defined below.

Safety Population:

All patients who received at least one dose of any study drug. This population will be used for analyses of safety, pharmacodynamics, and immunogenicity. It will also be used for summary of baseline data and analyses of PFS and OS.

Response Evaluable Population:

All patients who received at least one dose of any study drug, had baseline measurable disease, and had at least one post-baseline radiographic tumor assessment or discontinued from treatment due to clearly documented, clinically progressive disease or death. This population will be used for summary of tumor assessment data and analyses of response rates.

Statistical Methods:

A separate statistical analysis plan (SAP) and statistical programming plan (SPP) will further describe the details regarding statistical methods and will govern the analysis.

Sample Size: The study plans to treat approximately 52 patients: up to 27 in Dose Escalation Phase and approximately 25 in the Cohort Expansion Phase. At the end of the Cohort Expansion Phase, 15 paired tumor biopsies will be required; paired tumor biopsies will be mandatory if tumor lesions are accessible for biopsy with acceptable clinical risk in the judgment of the investigator and after discussion with the Sponsor. If 15 paired biopsies have not been collected in the initial 25 patients, additional patients with paired tumor biopsies will be enrolled, to ensure that the 15 paired biopsies are obtained. It is estimated that approximately 90% of the 25 patients will be MSS patients.

Safety: Treatment-emergent AEs will be summarized by SOC and PT, by relationship to study drugs, and by highest severity. For laboratory tests, number and percent of patients shifted from baseline to post-baseline maximum severity in CTCAE grade will be summarized.

Efficacy: Number and percent of patients with their best overall response will be summarized. Objective response rate will be calculated as proportion of patients in response evaluable population achieving a best response of CR or PR. Disease control rate is calculated as the proportion of patients who achieve a CR, PR, or SD. PFS rate at 16 weeks will be calculated as the probability that patients are free of disease progression and alive at 16 weeks after the first dose of MGD007 by Kaplan-Meier method, based on response evaluable population and safety population, respectively. The response rates will be determined using both RECIST 1.1 and irRECIST. Two-sided exact 95% confidence intervals will be constructed around the response rates. Kaplan-Meier methods will be used to estimate duration of response, PFS, and OS.

Pharmacokinetic Analysis: Summary statistics will be tabulated separately for serum PK parameters by MGD007 and MGA012 dose. Geometric means and percent coefficients of variation will be reported for C_{max}, $AUC_{(0-T)}$, $AUC_{(TAU)}$, $AUC_{(INF)}$, and C_{trough}; arithmetic means and standard deviations will be reported for $t_{1/2}$, CL, and V_{ss}; and medians, minimum, and maximum will be reported for T_{max}. Separate scatter plots of C_{max} and AUC will be provided versus dose to assess dose dependency. Dose proportionality may be assessed using a power model.

Immunogenicity Analysis: The proportion of patients who are negative for ADA at baseline and become positive in this assay, the proportion of patients who are negative at baseline and remain negative, and those who have positive ADA at baseline that increase or decrease in titer over the course of treatment will be summarized. Analysis will be conducted separately for MGD007 and MGA012.

2 BACKGROUND INFORMATION

2.1 Rationale for Study

Bispecific antibodies are powerful tools for the immunologic treatment of cancer. In particular, they can be leveraged to enhance tumor killing in a non-MHC-restricted manner by redirecting effector cells (e.g., T cells, NK cells, macrophages, and monocytes) to the tumor cells. The interaction of T cells and tumor cells initiates the killing process by T cells, including activation of CD3, formation of immunologic synapses, activation and proliferation of T cells, secretion of cytokines and cytotoxic granules, and lysis of tumor cells. The activated CD8+ and CD4+ T cells lyse cancer cells predominantly through perforin and granzyme B. The activated T cells secrete various cytokines such as IFN-γ, TNF, IL-2, IL-6, and IL-10.

The bispecific antibodies include notably DART proteins and bispecific T cell engagers (BiTE). Blinatumomab, as a BiTE antibody against CD19/CD3, has been approved for the treatment of relapsed/refractory B-precursor acute lymphoblastic leukemia by the U.S. Food and Drug Administration (FDA) in December 2014 **(51)**. Bispecific antibodies have had more success in hematological malignancies than in solid tumors, but there are numerous ongoing studies.

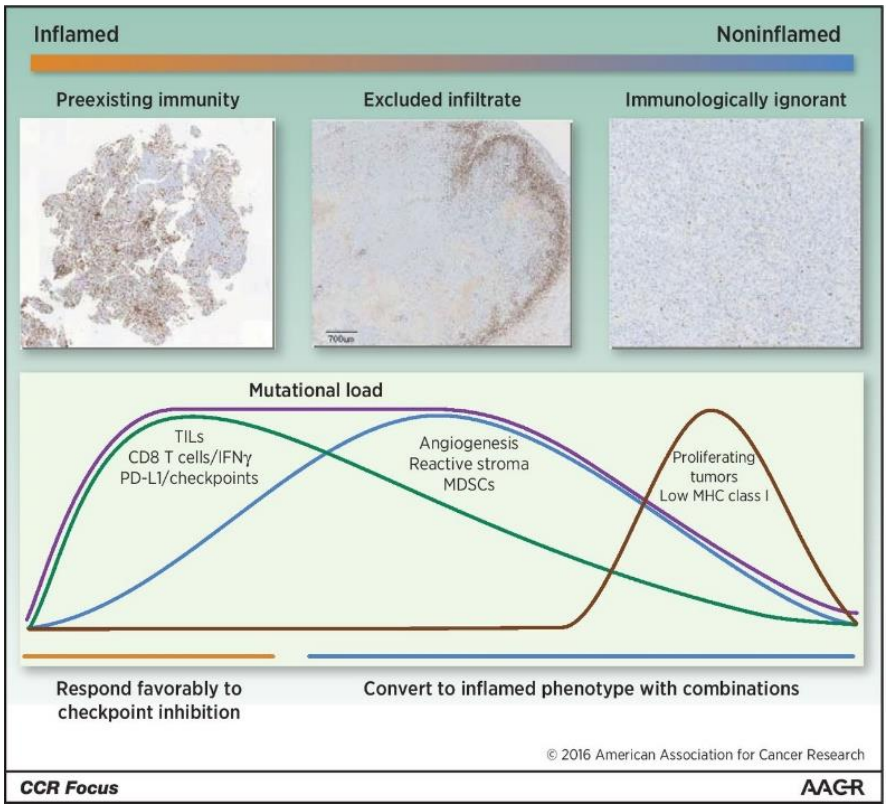
MGD007 is a glycoprotein A33 (gpA33) × CD3 DART® protein that binds 2 distinct antigens (human gpA33 and CD3) simultaneously. The gpA33 antigen is a transmembrane glycoprotein expressed almost exclusively in the intestinal epithelium and is present in > 95% of primary and metastatic human colorectal cancers (CRCs) **(14, 48)**. CD3 plays an important role in T cell receptor (TCR) signaling. Thus, MGD007 was designed to redirect the killing function of CD3-expressing effector T cells to target cells expressing gpA33.

CD3 bispecific molecules that can bring T cells to tumors could potentially introduce T cell infiltration in tumors that do not naturally possess this characteristic. In order to have an antitumor effect, these T cells should sustain cytolytic and proliferative function in the presence of inhibitory signals in the tumor microenvironment. T cells naturally undergo activation-induced upregulation of co-inhibitory pathways, which may limit the antitumor immune response. PD-1, CTLA-4, and other co-inhibitory receptors are upregulated in T cells following exposure to antigens. Additionally, tumor cells increase the expression of coinhibitory ligands such as PD-L1 following exposure to T cell secreted T helper 1 cytokines, including IFN-γ **(28, 29, 42)**.

MGA012 is an anti-PD-1 antibody that was designed to function as an immune checkpoint inhibitor and disrupt a major negative immune signaling axis in exhausted/ dysfunctional T cells which express the PD-1 receptor, and to cancer cells or APCs, which express their corresponding ligands: PD-L1 and PD-L2. MGA012 is believed to break this inhibitory axis and to overcome the suppressive mechanisms that cancer cells and some APCs (i.e., MDSCs, macrophages) employ. Indeed, in vitro studies have demonstrated MGA012 blocks PD-1/PD-L1 and PD-1/PD-L2 interactions, inhibits PD-1 signaling, and enhances T-cell responses to antigenic stimulation (see **Section 2.5**).

MGD007 redirects T-cell killing of gpA33-expressing target cells, predominantly through CD8 T cells, and activates CD4 T cells that support cell lysis; MGA012 inhibits the PD-1/PD-L1 axis. Based on the 2 molecules' mechanisms of action, the combination of MGD007 with MGA012 is hypothesized to have several antitumor advantages over current treatments by disruption of the following mechanisms: 1) Take off the breaks induced by the negative signal and functional impairment delivered to T cells by PD-1 with its ligands, PD-L1 and PD-L2 interaction and 2) blocking the frequent pre-existing PD-L1 expression in the tumor microenvironment, which inhibits CD8+ CTL proliferation and survival and promotes differentiation of CD4+ T cells into Treg cells (52). **Figure 1** shows a classification of tumors based on the location and intensity of CD8+ T cell expression.

Figure 1 **The Tumor Immunity Continuum: Images of Tumor CD8 Immunohistochemistry and Patterns of T Cells associated with Tumor Cells**



Source: Hegde, 2016 (17)

Tumors with pre-existing immunity are represented by abundance of tumor-infiltrating lymphocytes (TILs); dense functional CD8+ T cell infiltration reflected by increased IFNγ signaling; expression of checkpoint markers, including PD-L1; and high mutational burden. Colorectal cancer can be ranked in the 2 other patterns representative of non-inflamed tumors, i.e., either immunologically ignorant and poorly infiltrated by lymphocytes, or with an immunosuppressive microenvironment created to evade immune surveillance, by recruiting myeloid-derived suppressor cells or secreting factors including TGFβ, which plays a dual role

of inducing the expression of extracellular matrix genes and suppressing the expression of chemokines and cytokines required to facilitate T-cell infiltration into tumors **(17)**.

Immunologically ignorant tumors that contain very low infiltration of T cells are genomically stable with highly proliferating tumor cells **(17)**. These characteristics do not apply to a specific subset of CRCs that display a defect in the mismatch repair (MMR) pathway, resulting in microsatellite instability (MSI). MSI-high (MSI-H) CRCs represent approximately 10% to 15% of all CRCs. Germline and sporadic MSI-H tumors are similar and are often hyper- or ultra-mutated. The 85 percent of CRCs that are not MSI-high are considered microsatellite stable (MSS) **(7)**.

Several studies showed clinical benefit of immunotherapy, mainly PD-1 inhibition for immunogenic MSI-H CRCs, whereas there is no evidence to date to suggest the same in MSS CRCs **(45)**. As an example, in a Phase 2 study assessing the efficacy of pembrolizumab in MSI-H tumors, immune-related objective response rate and immune-related progression-free survival (PFS) rate at 20 weeks were 40% (4 of 10 patients) and 78% (7 of 9 patients), respectively, for MMR deficient CRCs and 0% (0 of 18 patients) and 11% (2 of 18 patients) for MMR proficient CRCs **(22)**. Likewise, nivolumab provided durable responses and disease control in pre-treated patients with MSI-H metastatic CRC **(31)**.

In the most frequent subtype of CRC, i.e. MSS, the reactive stroma and dense extracellular matrix create a barrier to the infiltration of immune cells into the tumor, which manifests as an excluded infiltrate phenotype with peritumoral or stromal T-cell localization. Tumors that exhibit high expression of gene signatures of reactive stroma or TGFβ signaling are often associated with lower expression of immune markers **(13, 32, 39)**. Clinical evidence suggests that checkpoint inhibitors largely act by reinvigorating pre-existing antitumor T-cell responses and are most effective in tumors as characterized by tumor PD-L1 positivity. Inhibition of the PD-1/PD-L1 axis with MGA012 could therefore enhance the antitumor activity of MGD007 in patients by triggering CD8 T cell immune reactivity and tumor infiltration and by preventing T cell exhaustion.

In studies that performed comparisons of local primary tumors vs metastatic deposits in the same patient, positive expression of PD-L1 was found in about 80% of metastatic colorectal carcinomas, and PD-L1 expression has been reported to be significantly more prevalent in metastatic colorectal carcinomas than in primary tumors. PD-L1 expression appears to increase during evolution of the metastatic process **(16, 47, 37)**.

In a study of 49 patients with metastatic CRC, PD-1+ expression was markedly upregulated on CD8+ T cells in tumors compared with that in peripheral blood and PD-L1 was highly expressed in tumors rather than tumor-free lymph nodes, which was closely correlated with the impairment of IFN-γ production of tumor-infiltrating PD-1+ CD8+ T cells. The authors suggested a suppressive effect of PD-1+ on CD8+ T-cell function in tumors **(52)**.

Different authors have assessed the use of Immunoscore (IS), an index based on the density of CD3+ and CD8+ TILs in the tumor center and invasive margin of tumors, as a prognostic marker for CRC. Tumor-associated macrophages (TAMs) have also been reported to have prognostic value. The density of CD3+, CD4+, CD8+, FOXP3+, CD68+, and CD163+

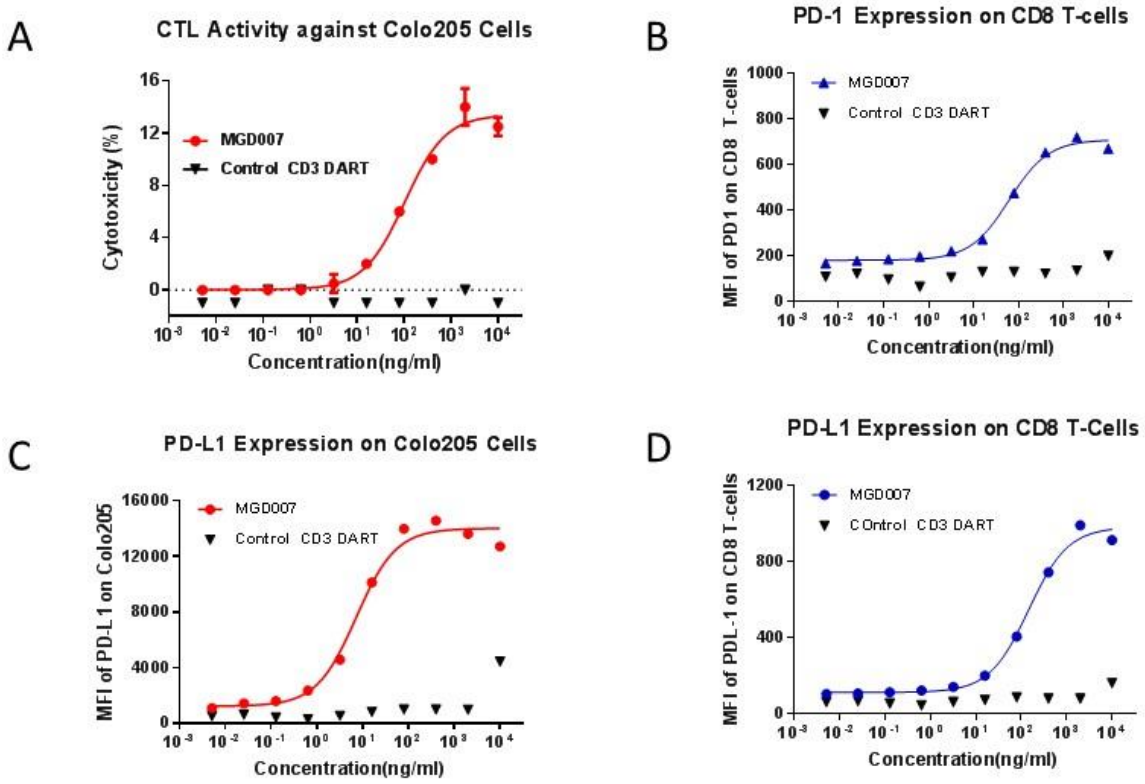
immune cells within CRC tissue was determined using immunohistochemistry (IHC) and digital image analyzer (n 196). The IS was obtained by quantifying the densities of CD3+ and CD8+ TILs. Higher IS values were significantly correlated with better prognosis (p 0.020). Multivariate analysis revealed that IS was an independent prognostic marker (p 0.012) **(4, 21)**.

The clinical relevance of PD-L1 expression by tumor cells and TILs in CRC has been investigated in 186 MSI-H and 153 MSS tumors. PD-L1 expression was evaluated in tumor cells at the center and periphery, and immune cells at the center (IC) and periphery (IP) of CRC tumors. IHC slides were stained for CD3 and CD8. Notably, in both MSI-H and MSS CRC, PD-L1 expression in the center and in the periphery were independently associated with improved prognosis ($P < 0.05$) **(23)**.

Another study, in The Cancer Genome Atlas (TCGA) cohort of 276 patients with CRC, assessed the prognostic value of PD-L1 in tumor cells and of PD-1 in TILs. Multivariate Cox regression analysis indicated that higher expressions of PD-1 and PD-L1 correlated with better prognosis of CRC patients. TILs-PD-1 was an independent prognostic factor for overall survival (OS) and disease-free survival (DFS) of CRC patients, especially for the MMR-proficient subgroup **(25)**.

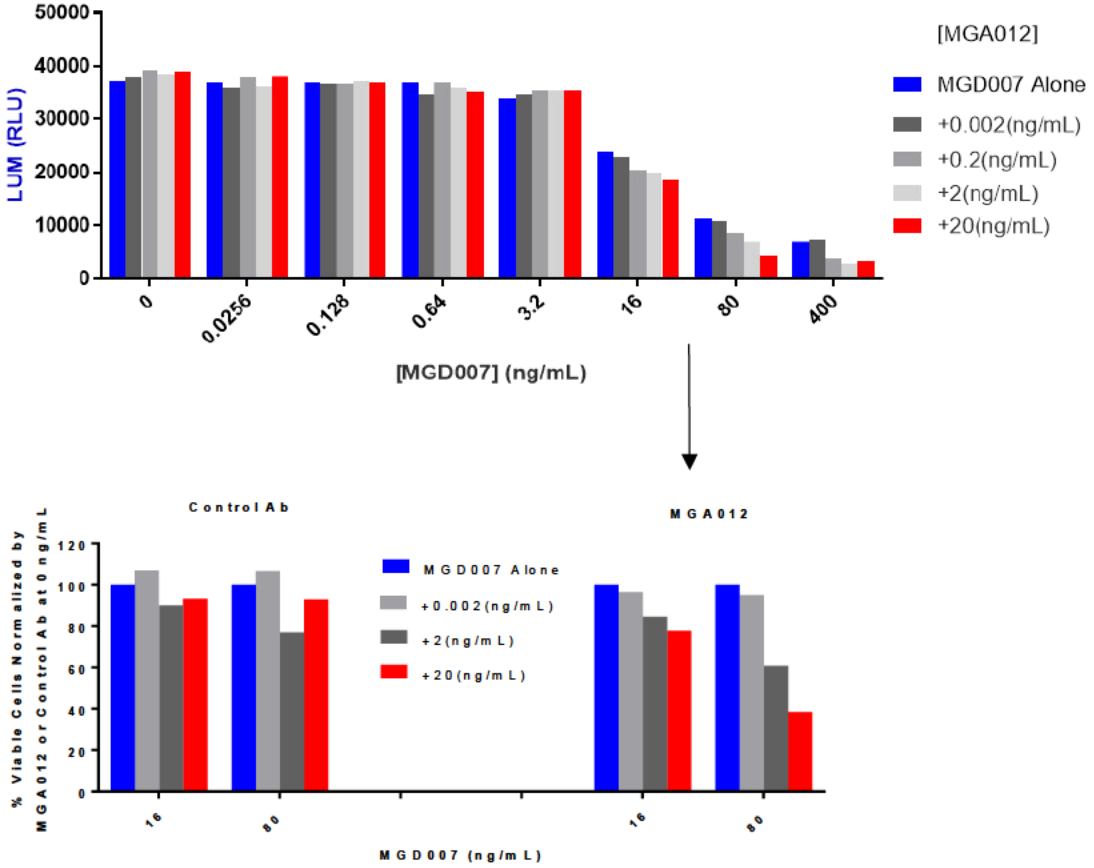
In addition to the constitutive expression of PD-1/PD-L1 in the CRC microenvironment, it is anticipated that both PD-1 and PD-L1 may be inducibly up-regulated as a consequence of the mechanism of action of MGD007, resulting in a possible further layer of checkpoint inhibition that theoretically could limit therapeutic responses to MGD007 monotherapy. Concomitant with gpA33 expressing Colo205 CRC cell lysis mediated by MGD007 (**Figure 2A**) is a parallel up-regulation of PD-L1 (**Figure 2C**) on residual target cells. Furthermore, both PD-1 (**Figure 2B**) and PD-L1 (**Figure 2D**) are also up-regulated on the effector T-cell population. Overcoming the PD-1/PD-L1 pathway axis with MGA012 could therefore enhance the antitumor activity of MGD007 in patients, a hypothesis supported by in vitro evidence of enhanced MGD007-mediated gpA33 tumor cell killing at select concentrations of MGD007 and MGA012 (representative experiment shown in **Figure 3**). Furthermore, in the presence of pre-activated T-cells (expressing PD-1 and PD-L1) and gpA33 expressing cancer cells, MGD007-mediated increases in IFNγ and TNFα can be further enhanced in the presence of MGA012 (**Figure 4**).

Figure 2 MGD007 Mediated Up-regulation of PD-1 and PD-L1



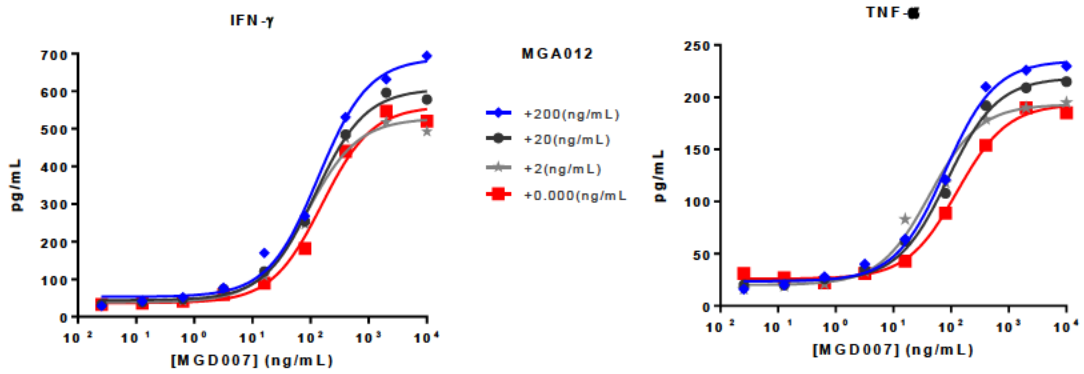
A-D: MGD007-mediated cytolysis of gpA33-expressing cells is associated with up-regulation of PD-1 and PD-L1. Colo205 colorectal cancer cells were mixed with freshly isolated human T-cells at E:T ratio = 5:1 in the presence of increasing concentrations of MGD007 or control CD3 DART. (A) The level of Colo205 target cell cytotoxicity mediated by MGD007 determined by evaluation of LDH release at 24 hrs. (B) The surface expression level of PD-1 on the effector T-cell population and the surface expression level of PD-L1 on the tumor target cells (C) and the effector T-cell population (D) were determined at 24 hrs by flow cytometry.

Figure 3 **MGA012 Enhances MGD007 Mediated Lysis of gpA33+ve COLO205**



Colo205/Luc cells (stably transfected with constitutive luciferase reporter gene) were mixed with freshly isolated human T cells or control antibody as indicated (E:T = 3:1). Cell viability was determined by evaluation of luciferase levels at 48 hrs (upper panel). The % viable cells shown observed in presence of 16 or 80 ng/ml MGD007 and increasing concentration of Control Ab or MGA012 (bottom panel).

Figure 4 **MGA012 Enhances MGD007 Mediated Cytokine Release Upon Co-engagement of T-Cells with gpA33+ve Tumor gpA33+ve Tumor Cells**



MGA012 enhances MGD007-mediated T-cell cytokine release upon co-engagement with gpA33+ve target cells. Colo205/Luc cells (stably transfected with constitutive luciferase reporter gene) were mixed with pre-activated T-cells readily expressing PD-1 and PD-L1 at 3:1 E:T ratio in the presence of MGD007 ± MGA012 at increasing concentrations as indicated. Supernatants were collected following 48-hr incubation and applied to an ELISA assay to determine levels of IFN-γ (left panel) and TNF-α (right panel). A control isotype mAb (data not shown) did not enhance MGD007-mediated T-cell cytokine release.

Such experiments provide proof-of-principle that a combination approach that blocks checkpoint inhibition of T cells with the use of the antagonistic anti PD-1 monoclonal antibody (mAb) MGA012, while recruiting cytotoxic and helper T cells to gpA33-expressing tumors with MGD007, a gpA33 × CD3 DART, may further enhance antitumor activity than can be achieved by either modality alone and provide rationale for testing this combination approach clinically.

2.2 Disease Background

Colorectal carcinoma is the fourth most commonly diagnosed cancer in the U.S., and the second-most common cause of cancer death. It is estimated that in 2013, there were 142,820 new cases of colorectal carcinoma and 50,830 deaths due to colorectal carcinoma (41). Both the incidence and number of deaths due to colorectal carcinoma have been decreasing overall in the past several decades (8, 40), perhaps as a reflection of improved screening and diagnosis of patients and improvements in therapy. There are a variety of heritable syndromes that confer increased likelihood of developing colorectal carcinoma. An increased risk for the development of colorectal carcinoma has also been observed in patients with inflammatory bowel disease. Other potential risk factors include smoking, consumption of processed meats, diabetes, alcohol use, obesity, and a family history of colorectal carcinoma. Approximately 50%-60% of patients afflicted with colorectal carcinoma have metastatic disease at diagnosis (24, 46, 55), with common sites of involvement including liver, lymph nodes, lung, peritoneum, and soft tissues.

In those patients with limited resectable metastatic tumors, surgical resection may be employed and may be curative in some instances, but most of them have unresectable disease at diagnosis. Neoadjuvant chemotherapy may be used in an attempt to achieve reduction in the tumor and render it resectable. Neoadjuvant chemotherapy may commonly consist of FOLFOX (folinic acid/5-FU, oxaliplatin) or FOLFIRINOX (folinic acid/5-FU/irinotecan/oxaliplatin)-based regimens administered +/- anti-EGFR antibody (e.g., cetuximab or bevacizumab) **(10, 30, 35, 54)**.

For patients with unresectable metastatic disease, therapy most commonly consists of combination regimens with one or more of the following agents: 5-FU/leucovorin, irinotecan, capecitabine, oxaliplatin with or without anti-VEGF agents (bevacizumab, aflibercept) or anti-EGFR antibodies (cetuximab, panitumumab), or multi-specific tyrosine-kinase inhibitors (TKI) (regorafenib). Common chemotherapy regimens include FOLFOX, FOLFIRI, FOLFIRINOX, or CapeOx administered with or without bevacizumab, panitumumab, or cetuximab, depending on KRAS status **(1, 5, 19, 26, 34, 50)**. Agents such as aflibercept are generally utilized in patients who have progressed after front-line chemotherapy.

In third-line therapy, there are a few treatments that have received U.S. FDA approval, such as Lonsurf® (trifluridine and tipiracil [TAS 102]) **(27)** and Stivarga® (regorafenib) **(15)**. The FDA approved TAS-102 in 2015. The efficacy and safety were evaluated in a randomized, double-blind, placebo-controlled study involving 800 patients with previously treated metastatic colorectal carcinoma. The median OS was 7.1 months (95% confidence interval [CI], 6.5 to 7.8) in the TAS-102 group and 5.3 months (95% CI, 4.6 to 6.0) in the placebo group. The hazard ratio (HR) for death (TAS-102 vs. placebo) was 0.68 (95% CI, 0.58 to 0.81; $P < 0.001$). The 1-year OS rates were 27% and 18%, respectively. The median PFS was 2.0 months (95% CI, 1.9 to 2.1) in the TAS-102 group and 1.7 months (95% CI, 1.7 to 1.8) in the placebo group. The HR for progression (TAS-102 vs. placebo) was 0.48 (95% CI, 0.41 to 0.57; $P < 0.001$) **(27)**. Regorafenib received FDA approval in 2012 for the treatment of patients who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, with an anti-VEGF therapy, and, if KRAS wild type, with an anti-EGFR therapy. In an international, randomized, placebo-controlled trial that enrolled 760 patients, a significant prolongation in OS was observed in patients who received regorafenib (HR 0.77 [95% CI: 0.64, 0.94]; p 0.0102). The median survival time was 6.4 months (95% CI: 5.8, 7.3) in the regorafenib group and 5.0 months (95% CI: 4.4, 5.8) in the placebo group. Median PFS was 2.0 months (95% CI: 1.9, 2.3) in the regorafenib group and 1.7 months (95% CI: 1.7, 1.8) in the placebo group **(15)**.

Even though several existing agents and combination regimens using these agents have demonstrated the ability to induce objective responses and to extend both progression-free survival and overall survival in patients with colorectal carcinoma, the prognosis of patients with metastatic colorectal carcinoma remains extremely poor overall, with 5-year survival rates estimated to be as low as 6-8%. There remains an urgent need for new approaches for the treatment of patients with colorectal carcinoma, and this has fueled intense effort to test various new approaches in this setting, including the use of immunotherapeutic agents.

The observation that local infiltration of T cells, including CD8+ T cells, and local expression of genes associated with the cytotoxic phenotype (i.e., IFN-γ, granulolysin, and granzyme B) and markers of T cell migration may associate with more favorable clinical prognosis in patients with colorectal carcinoma, suggests that immune therapeutic approaches that enable T cell mediated reactivity against colorectal carcinoma tumors could offer the prospect of clinically meaningful antitumor activity.

2.3 Background on MGD007

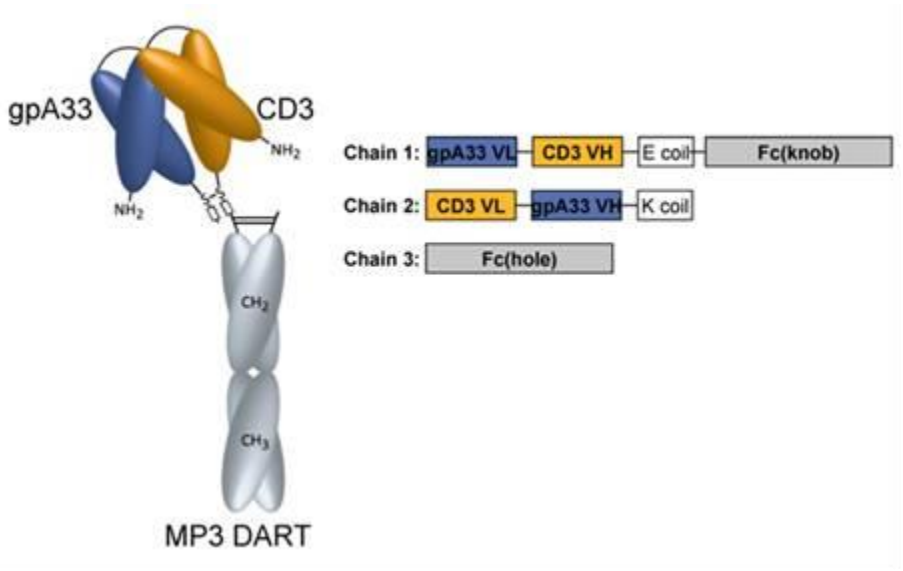
2.3.1 Background on MGD007

MGD007 is a gpA33 × CD3 DART protein produced in Chinese hamster ovary (CHO) cells. DART proteins are bispecific, antibody-based molecules that can bind 2 distinct antigens simultaneously. MGD007 is designed to target gpA33-positive cells for recognition and elimination by CD3-expressing T lymphocytes as effector cells. To prolong half-life, MGD007 also contains a human IgG1 Fc region that has been mutated to eliminate undesired binding to FcγR and complement, but that retains neonatal FcR (FcRn) binding to take advantage of the IgG salvage pathway mediated by this receptor.

The gpA33 antigen is a transmembrane protein expressed on nearly all primary and metastatic colorectal tumors. Expression of gpA33 on normal tissues is restricted to the small and large intestines. The anti-gpA33 component of MGD007 is based on a humanized version of the MacroGenics proprietary mAb, RECA47. CD3 is an invariant complex of proteins (comprising cell surface gamma, delta, epsilon, and zeta chains) that is required for expression of and signaling through the antigen-specific TCR on T cells. The anti-CD3 component of MGD007 is based on the MacroGenics proprietary mAb, hXR32. MGD007 is under development as a therapeutic candidate for the treatment of colorectal carcinoma.

A schematic of MGD007 is shown in **Figure 5**.

Figure 5 DART Protein Schematic and Assembly



MGD007 is composed of 3 chains that are covalently linked by disulfide bonds. Chains 1 and 2 form a heterodimer by a disulfide bond at the C-terminus of the chains and by virtue of oppositely charged coiled-coiled sequences (E-coil and K-coil). Chains 1 and 3 are covalently linked by 2 disulfide bonds in the Fc hinge region. To prevent homodimerization of Chains 1 and 3, the knob (T366W) and hole (T366S/L368A/Y407V) mutations have been incorporated in the respective CH_3 region of each Fc. To further assure removal of any remaining homodimers of Chain 3 during purification, the H435R mutation also has been incorporated in the CH_3 region of the Fc (this mutation ablates binding to Protein A). A double mutation (L234A/L235A) has been incorporated in the CH_2 region of the Fc to eliminate binding to FcγR and C1q.

For additional detailed description of nonclinical data regarding MGD007, please also refer to the **MGD007 Investigator's Brochure**.

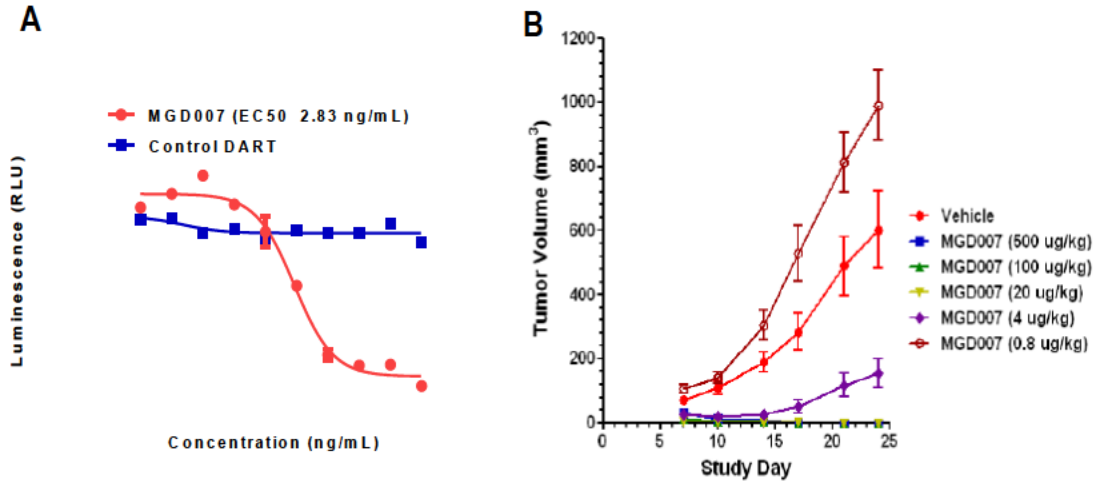
2.3.2 MGD007 Pharmacology

Bispecific binding of MGD007 to its target antigens gpA33 and CD3 has been characterized by both surface plasmon resonance (SPR) analysis and flow cytometry. SPR analysis using recombinant soluble human antigens revealed MGD007 binding affinities (K_D) of approximately 2 nM to gpA33 and 23 nM to CD3. Similar binding affinities for MGD007 were observed with cynomolgus monkey gpA33 (11 nM) and CD3 (26 nM). The approximate 10-fold greater affinity of MGD007 for gpA33 is desirable in order to favor initial binding to the gpA33-positive target cell and minimize CD3 engagement in the absence of target cells. Flow cytometry analyses confirmed the ability of MGD007 to bind natively expressed cell surface CD3 on human and cynomolgus monkey T cells and to gpA33 expressed across a panel of human CRC cell lines or to CHO cells engineered to express either human or cynomolgus monkey gpA33.

Consistent with its bispecific binding properties and designed mechanism of action, MGD007 supports potent redirected T-cell killing of multiple gpA33-expressing CRC cells in vitro in assays employing either purified human peripheral blood mononuclear cells (PBMC) or

T cells as effector cells from multiple independent human donors. In contrast, MGD007 displayed no lysis of non-gpA33-expressing cancer cells demonstrating the prerequisite for engagement of both the gpA33 and CD3 arms for MGD007-mediated activity. Using purified human T cells at an effector to target (E:T) cell ratio of 10:1, MGD007-mediated complete T-cell lysis of gpA33 expressing CRC cells (**Figure 6**). In the presence of lower E:T cell ratios (e.g., 5:1 and 1:1 T cells to target cells), MGD007 redirected T-cell killing of gpA33-expressing target cells correspondingly decreases for the same time interval as reflected by the increased EC_{50} values. CD8 T cells predominantly mediate MGD007 directed cell lysis, but CD4 T cells also support cell lysis, with activity accompanied by corresponding increases in perforin and granzyme B.

Figure 6 MGD007-mediated CTL and Antitumor Activity



(A) Viability of gpA33-expressing Colo205 cancer cells following 24-hour incubation with MGD007 in the presence of purified human T cells at an E:T cell ratio of 10:1. (B) Colo205 xenograft tumor volume following SC co-implantation with activated human T cells at a 1:1 E:T cell ratio and 4 daily intravenous doses of MGD007.

Evaluation of T-cell responses during the course of MGD007-mediated T-cell killing revealed activation of both CD4 and CD8 T cells as evidenced by increased expression of T-cell activation markers CD69 and CD25. Subsequent to activation, co-engagement of MGD007 with gpA33 cancer cells and human T cells also leads to T-cell expansion.

MGD007-mediated cytokine production in vitro was most sensitive when evaluating human PBMCs in the presence of gpA33-expressing target cells using soluble MGD007; cytokine production observed with human PBMCs alone, evaluated with soluble MGD007 as well as wet and dry coated methods, was less potent, consistent with the absence of gpA33 expression on peripheral blood cell populations. MGD007-mediated cytotoxicity against gpA33-expressing target cells in the presence of purified human T cells using an E:T cell ratio of 10:1 yields a mean EC_{20} of 2.9 to 4.5 ng/mL for target cell lysis and a mean threshold for production of the most sensitive cytokine (TNF-α) of 13.0 ng/mL; these data were used as a basis for determination of a minimum anticipated biological effect level (MABEL)-based first-in-human (FIH) starting dose. Furthermore, the Fc region incorporated into MGD007 has

been mutated to eliminate FcγR binding and silence any unwanted Fc-mediated effector functions as demonstrated by negligible antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) activity in vitro.

Antitumor activity of MGD007 has been demonstrated in murine xenograft models in which gpA33-expressing Colo205 or LS174T human CRC cells were co-implanted subcutaneously (SC) with activated human T cells at a ratio of 1:1 followed by treatment with MGD007 administered IV for 4 consecutive days **(Figure 6)**. At doses of 4 µg/kg or greater, MGD007 significantly inhibited tumor growth. Such dose levels are considerably lower than MGD007 doses and exposure levels that are well tolerated in cynomolgus monkeys **(Section 2.3.3)**.

The in vivo profile of MGD007 binding to peripheral T cells has been evaluated in cynomolgus monkeys following treatment with 4 doses of MGD007 (300 µg/kg) administered IV over 2 hours either once weekly or once every other week. Four hours following the start of infusion of the 1st MGD007 dose, bound MGD007 was detected on both CD4 and CD8 T cells at approximately 20-40% of the level of maximal MGD007 occupancy. By 48 hours after infusion, the level of detectable MGD007 was reduced to 4-17% of maximal binding while by Day 7, no bound MGD007 was detected on either CD4 or CD8 T cells. A similar profile of binding was observed in cynomolgus monkeys following subsequent MGD007 doses (except where anti-drug antibodies [ADA] apparently interfered with MGD007 binding) with no discernible difference between dosing on a weekly or every other week schedule. Taken together, these data indicate that MGD007 is not retained on circulating T cells for prolonged periods. Furthermore, evaluation of ex vivo cytotoxic T-lymphocyte (CTL) activity by PBMCs isolated from cynomolgus monkeys following treatment with 4 doses of MGD007 (300 µg/kg) revealed potent specific lysis of gpA33 target cells by MGD007 demonstrating in vivo administration of multiple MGD007 doses does not impact the ability of T cells to support CTL activity.

2.3.3 MGD007 Pharmacokinetics and Toxicology

The nonclinical toxicology program for MGD007 was performed exclusively in the cynomolgus monkey. The cynomolgus monkey was selected as a relevant species for toxicological evaluation because MGD007 binds human and cynomolgus monkey gpA33 and CD3 with similar affinities (**Section 2.3.2**). The similar affinities indicate that the epitopes bound by the antigen-binding regions of MGD007 are conserved between humans and cynomolgus monkeys. This is not surprising given the 87% identity between human and cynomolgus gpA33. Though the percent identity between human and cynomolgus monkey CD3 is lower (79%), the antigen binding region of the CD3 (i.e., hXR32)-component of MGD007, binds in the first 14 amino acids of the CD3ε chain where there is only 1 amino acid difference between the 2 species. Additional in vitro cell-based experiments supporting the relevance of the cynomolgus monkey include demonstration of comparable redirected T cell mediated lysis of gpA33-expressing CRC tumor cells by MGD007 with either human or cynomolgus monkey PBMCs and demonstration of comparable binding of MGD007 to cell surface expressed human gpA33 or cynomolgus monkey gpA33.

Moreover, a non-GLP tissue cross-reactivity study evaluating MGD007-staining of a panel of 5 tissues from both human and cynomolgus monkey (colon, liver, lung, pancreas, and small intestine) demonstrated the staining profile was the same across both species. As expected, strong, frequent staining of the epithelium in colon and small intestine was observed in both species. In addition, consistent with CD3 expression, lymphocyte staining was observed across all organs examined except pancreas. Some weak to moderate, cytoplasmic and membrane staining of lung macrophages was also observed in both species; specific staining of lung macrophages, however, was not observed in the GLP tissue cross-reactivity study of MGD007 in human tissues. Additionally, MGD007 does not bind with both CD3 and gpA33 in species such as rat and mouse (data on file), which supports the use of cynomolgus monkeys as the single relevant toxicological species.

In repeated-dose non-GLP and GLP toxicology studies, MGD007 has been administered to a total of 52 monkeys at doses ranging from 0.3 to 300 µg/kg. In 2 initial, non-GLP, exploratory studies, 4 animals received escalating doses of MGD007 starting at 0.3 or 100 µg/kg and increasing to a maximum dose of 300 µg/kg. In the remaining studies (2 non-GLP studies and 1 GLP study) a total of 48 animals received 4 repeated administrations of MGD007 at weekly intervals at doses of 30 (n 12), 100 (n 12), and 200 (n 8) µg/kg or at doses of 300 µg/kg (n 16) at weekly or every-other-week intervals. MGD007 administered as 2 to 3-hour IV infusions on a weekly schedule for up to 4 weeks was well tolerated in all animals treated with doses up to 100 µg/kg and in 7/8 animals with 200 µg/kg. In these animals, the only notable toxicological finding was emesis following the first dose of MGD007 (considered only possibly related) that occurred in up to 10/24 animals treated with doses of 30, 100, or 200 µg/kg in the GLP toxicology study. The exact frequency of emesis was uncertain because evidence of vomiting sometimes was attributed to 2 animals that were pair-housed in a cage per testing facility SOP, even though only 1 animal may have experienced the event.

The primary toxicity associated with MGD007 was on-target toxicity of the small and large intestines, primary sites of gpA33 expression, observed at doses of 300 µg/kg, the highest dose studied, and possibly in 1 animal treated at 200 µg/kg. As a result of the 1 animal treated at 200 µg/kg experiencing adverse effects that were similar, but less severe, to animals experiencing definitive on-target toxicity at the higher dose of 300 µg/kg, the no-observed-adverse-effect level (NOAEL) was conservatively set at 100 µg/kg. On-target toxicity was associated with clinical observations of emesis and/or abnormal feces (e.g., watery feces or feces with mucoid material) occurring in almost all animals after the 1st and 2nd doses primarily. In some cases, and only in animals receiving an initial dose of 300 µg/kg, these clinical observations led to moribundity and euthanasia following the first administration of MGD007 in 5/16 animals. Two animals treated at the 300 µg/kg level also had evidence of blood in fecal material. Histopathological correlates in the animals with the most severe clinical signs that had to be euthanized included moderate to severe, focal and widespread areas of epithelium necrosis throughout the small and large intestines with concurrent ulceration in some animals. Two animals also had evidence of epithelium necrosis in the stomach, but with lower severity.

Mild to moderate decreases in red-cell parameters (~ 20-30%) with intact erythrocyte response were also attributed to MGD007 at doses of 300 µg/kg. Additionally, there was

1 animal treated with 4 doses of 300 µg/kg MGD007 that was observed to have a brown, red fluid adhered to the mucosal surfaces of the stomach at gross necropsy (which occurred 5 weeks post-last dose); however, there were no associated microscopic findings in the stomach of this animal. It is noted that this animal had the most severe drops in red cell parameters, exhibited an increased mean cell volume and red cell distribution width, and a decreased mean corpuscular hemoglobin concentration in association with a more pronounced reticulocyte response. These data, together with the observations of blood in the fecal material of 2 animals, indicate that at the highest dose studied (300 µg/kg), MGD007 may be associated with some extent of gastrointestinal bleeding.

An important safety concern associated with CD3-targeting therapies, like MGD007, is the potential for cytokine release. Cytokines monitored in the MGD007 toxicology studies (supporting IND filing) included TNF-α, IFN-γ, IL-2, IL-4, IL-5, and IL-6 measured 4 hours and 24 hours post administration of MGD007. Across all studies and doses tested there were no MGD007-related changes in circulating TNF-α, IFN-γ, IL-4, or IL-5 levels, with levels of these cytokines remaining below 10 pg/mL, and generally were much lower or undetectable. IL-6 and IL-2 levels fluctuated following both vehicle and MGD007 dosing, only exceeding 100 pg/mL in a few instances. In the high dose non-GLP toxicity study, IL-6 levels were tending to be among the highest (peak measured IL-6 levels of 984 pg/mL) in the animals that were euthanized due to severe toxicity compared with IL-6 levels in animals that were not euthanized. Fluctuation in IL-2 was observed in only one study and was less pronounced than the observed changes in IL-6. Overall, observed fluctuations in cytokine levels were greatest after the 1st dose of MGD007 but frequently were not higher than fluctuations observed after vehicle infusions. These elevations in IL-6 were further confirmed in another recent pre-clinical non-GLP toxicity study that had been completed in which high dose MGD007 was administered with steroids to cynomolgus monkeys (**MGD007 Investigator's Brochure**). In this study, cytokine levels were evaluated at 2 hours, 6 hours, and 22 hours post-administration of MGD007 following both first dose and second dose. Evaluation of cytokines revealed increases at 6 hours for IL-6 and IL-10, modest increases in IFN-γ and IL-2, and little to no increase in IL-4, IL-5, and TNF-α. Elevations were observed following first dose of MGD007, which were much more modest or absent following the second dose, similar to earlier GLP toxicity studies. In general, animals that received steroids had lower levels of observed cytokines, which is consistent with expected mode of action for steroids. Across all studies, transient elevations in circulating cytokine levels, most notably IL-6 and IL-10, are observed in cynomolgus monkeys following an initial high dose of MGD007.

Anti-drug antibodies against MGD007 were detected in approximately half of the monkeys treated with MGD007 (24/47 monkeys evaluable for ADA). ADA was generally first detected after the 2nd or 3rd weekly infusion of MGD007. The frequency of ADA appeared to increase, and the emergence of first detectable ADA tended to occur earlier, with increasing dose level over the dose range evaluated (30 to 300 µg/kg). In the GLP toxicology study for which ADA titers were also evaluated, higher maximum titers (up to 1:20480) were achieved for the highest dose group (200 µg/kg) compared with the lower dose groups (maximum titers of 1:16 and 1:5120 in the 30 and 100 µg/kg dose groups, respectively). It is important to note that ADA in cynomolgus monkeys is not considered predictive of ADA in humans. Of the 24 animals that developed ADA, only 9 animals also had decreased exposure subsequent to

the emergence of the ADA. Nonclinical PK parameter estimates, however, were not affected by ADA because the PK evaluations were based primarily on serum concentrations of MGD007 measured in monkeys prior to the emergence of ADA.

MGD007 PK evaluation performed by 2-compartmental modeling using pooled data across 3 of the toxicology studies conducted in cynomolgus monkeys (n 41 evaluable animals) indicated that MGD007 PK appear linear across the 30 to 300 µg/kg dose range evaluated. Overall, dose proportional increases in maximum serum concentration (C_{max}) were also observed across the dose range evaluated in these studies. MGD007 PK was also independent of gender. The mean clearance (CL) of MGD007 was 1.0 mL/h/kg, much lower than the glomerular filtration rate (GFR) in cynomolgus monkeys (~ 125 mL/h/kg), indicating that MGD007 is not cleared renally, as would be expected for a large molecular weight protein (~ 109 kDa). The mean volume of distribution for the central compartment (V_1; 53 mL/kg) is consistent with initial distribution of MGD007 into the plasma space in cynomolgus monkeys (~ 45 mL/kg). The mean volume of distribution at steady state (V_{ss}; 134 mL/kg) indicates MGD007 distribution into a space smaller than the extracellular space in cynomolgus monkeys (~ 200 mL/kg). The mean elimination half-life for the beta phase ($t_{1/2,\beta}$) of MGD007 ranged from 86 to 162 hours (3.6 to 6.8 days) across all groups. Thus, MGD007 demonstrated the expected prolonged $t_{1/2}$ given the human IgG Fc domain in this DART protein.

Based on these findings, the safety and PK profile of MGD007 appears acceptable to permit testing in human patients with advanced colorectal carcinoma.

The nonclinical safety data generated to date for MGD007 are described in further detail in the **MGD007 Investigator's Brochure.**

2.3.4 CP-MGD007-01 Clinical Study Update

As of a data cut-off date of 10 January 2018, 75 patients have been treated in the CP-MGD007-01 study and have received at least 1 dose of MGD007 administered by 2-hour infusion either once a week (QW), twice a week (BiW), every 3 weeks (Q3W), or every other week preceded by a Lead-in Dose (LID). The MTD of MGD007 was defined as 1.0 µg/kg in either of the QW or Q3W schedules of administration, respectively. Among all patients treated to date with MGD007, across all dose levels and schedules of administration, including patients treated at doses subsequently determined to exceed the MTD, drug-related adverse events (AEs) (any grade), were observed in 96% of patients, and Grade 3 or greater AEs were observed in 65% of patients. The most common drug-related AEs occurring in >10% of treated patients in decreasing order were as follows: diarrhea, nausea, vomiting, fatigue, pyrexia, abdominal pain, chills, lymphocyte count decreased, decreased appetite, tachycardia, asymptomatic lipase increased, dehydration, hypophosphatemia, hypocalcemia, hypokalemia, and anemia. Side effects have been manageable and readily reversible using protocol supportive care measures.

Notably, based on the mechanism of action of MGD007 with engagement of redirected T-cell mediated killing of target cells that express gpA33, and the recognized distribution of gpA33 in the normal gastrointestinal epithelium, it was anticipated that gastrointestinal (GI) AEs could be the most clinically significant toxicity observed in patients treated with MGD007.

As anticipated, the most clinically significant AEs observed in patients treated with MGD007 include nausea, vomiting and diarrhea, and in particular, diarrhea. As of the data cutoff, across all doses and schedules tested, including patients treated at doses subsequent found to exceed the MTD, drug-related GI AEs, irrespective of grade, were seen in 70 patients (93%), with Grade 3 or greater AEs observed in 37 patients (49%). Drug-related diarrhea of any grade was observed in 63 patients (84%), with Grade 3 or greater diarrhea in 23 patients (31%). Drug-related nausea of any grade was observed in 54 patients (72 %) with Grade 3 or greater nausea in 10 patients (13 %). Drug-related vomiting of any grade was observed in 55 patients (73 %) with Grade 3 or greater vomiting in 21 patients (28 %). Gastrointestinal side effects have been manageable and readily reversible using protocol supportive care measures. More details regarding the clinical experience with MGD007 monotherapy are described in the **MGD007 Investigator Brochure**.

The breakdown for data regarding the occurrence of diarrhea across the respective schedules tested to date is summarized in **Table 1**. Several distinct doses and schedules have been tested to date to optimize the potential therapeutic window for MGD007, including more recent investigation of schedules using more frequent, lower dose schedules of administration (0.8 µg/kg QW and 0.5 µg/kg BIW) or step-wise intrapatient lead-in dose escalation (LID, 0.5 µg/kg to 1.0 µg/kg). In addition to conventional, supportive care measures including anti-diarrheals, IV fluids, systemic corticosteroids, the approach to supportive care for the program has evolved to include prophylactic budesonide, an oral, non absorbable steroid, and early intervention with tocilizumab, an anti-IL-6R antibody in patients who develop Grade 2 or greater GI side effects despite conventional supportive care and prophylactic budesonide. Prophylactic budesonide has been incorporated to provide local immune suppression in the GI tract, and is intended to help limit the need for use of systemic corticosteroids and the accompanying potential for systemic immune suppression. Similarly, tocilizumab has been incorporated to enable more selective inhibition of cytokine-mediated side effects in patients treated with MGD007, with less potential need for use of systemic corticosteroids.

Notably, as shown in **Table 1**, the incidence of diarrhea was noticeably reduced in the 0.8 µg/kg (QW) cohort and the 0.5 µg/kg (BiW) cohort, while modest reductions in the incidences of diarrhea are noted in the LID cohort. Treatment-related SAEs and treatment-related AEs ≥ Grade 3 are substantially reduced in the 0.8 µg/kg (QW) cohort (1 patient [10%]) **(Table 1)**. Guided by these additional improvements in the tolerability of MGD007, the QW as well as the LID dose schedule will be utilized for investigation of the combination of MGD007 and MGA012 in this study. The initial starting dose for MGD007 on the QW cohort will be 0.4 µg/kg, with subsequent planned dose levels utilizing MGD007 doses of 0.6 µg/kg and 0.8 µg/kg. On the LID cohort, the initial starting dose will be 0.5 µg/kg, followed by a step-up to target doses of 0.5, 0.8, and 1.0 µg/kg on successive dose levels. In both cohorts, the starting doses of MGD007 for the respective combination cohorts are below those that have demonstrated acceptable tolerability for MGD007 monotherapy.

Table 1 Overall Summary of Number of Patients with Adverse Events by Preferred Term of Diarrhea

Patients Reporting at Least One event of Diarrhea (PT)	QW- 0.8 µg/kg (N=10)	QW Other (0.6, 1 µg /kg) (N=11)	Q3W- 1 µg/kg (N=28)	Q3W Other (0.6, 1.5, 3 µg /kg) (N=14)	BiW (0.5 µg /kg) (N=6)	LID (0.5/1 µg /kg) (N=6)	All (N=75)
Diarrhea	7 (70.0%)	10 (90.9%)	27 (96.4%)	13 (92.9%)	2 (33.3%)	5 (83.3%)	64 (85.3%)
Treatment-Related Diarrhea [a]	7 (70.0%)	10 (90.9%)	26 (92.9%)	13 (92.9%)	2 (33.3%)	5 (83.3%)	63 (84.0%)
Diarrhea ≥ Grade 3 [a]	1 (10.0%)	2 (18.2%)	10 (35.7%)	7 (50.0%)	1 (16.7%)	2 (33.3%)	23 (30.7%)
Treatment-Related Diarrhea ≥ Grade 3 [a]	1 (10.0%)	2 (18.2%)	10 (35.7%)	7 (50.0%)	1 (16.7%)	2 (33.3%)	23 (30.7%)
Serious Diarrhea	1 (10.0%)	2 (18.2%)	10 (35.7%)	5 (35.7%)	1 (16.7%)	3 (50.0%)	22 (29.3%)
Treatment-Related Diarrhea	1 (10.0%)	2 (18.2%)	10 (35.7%)	5 (35.7%)	1 (16.7%)	3 (50.0%)	22 (29.3%)
Diarrhea that Resulted in Study Discontinuation	0	0	0	3 (21.4%)	0	0	3 (4.0%)
Diarrhea that Resulted in Drug Withdrawal	0	0	0	3 (21.4%)	0	0	3 (4.0%)
Diarrhea Adverse Events of Special Interest	0	2 (18.2%)	9 (32.1%)	6 (42.9%)	0	2 (33.3%)	19 (25.3%)

a Includes events with causality assessments of 'Possible', 'Probable' or 'Definite'.

b Based on CTCAE criteria version 4.0

Data cut on 10 January 2018

Abbreviations: BiW = twice a week; QW = once a week; Q3W = every three weeks; LID= Lead-in Dose.

Finally, among 59 response-evaluable patients, as of the cut-off date of 10 January 2018, 19 patients had stable disease (SD), 4 patients on the QW schedules, 14 patients on the Q3W schedule, and 1 patient on the LID schedule (see **Table 2**). Among these patients, 7 patients had SD for at least 12 weeks from first dose of MGD007. One patient who is now off study, who was treated at the 1.5 µg/kg dose of MGD007, a dose level that exceeds the MTD, sustained a confirmed partial response and remained on treatment for 8 months since initiation of therapy. Additionally, a patient treated at the 1.0 µg/kg dose of MGD007 sustained an unconfirmed partial response and had been on treatment for more than 4 months. In addition to the clinical evidence of antitumor activity, IHC analyses of fresh tumor biopsy samples obtained from patients following treatment at 1.0 µg/kg in the Tumor Biopsy Cohort revealed on-target binding of MGD007 to gpA33 on cancer cells.

Table 2 Summary of RECIST Response - Evaluable Population

Best Overall Response	QW- 0.8 µg/kg (N=5)	QW Other (0.6, 1 µg /kg) (N=11)	Q3W- 1 µg/kg (N=26)	Q3W Other (0.6, 1.5, 3 µg /kg) (N=11)	BiW (0.5 µg /kg) (N=2)	LID (0.5/1 µg /kg) (N=4)	All (N=59)
Partial Response [a]	0	0	1 (3.8)	1 (9.1)	0	0	2 (3.4)
Stable Disease	1 (20.0)	3 (27.3)	14 (53.8)	0	0	1 (25.0)	19 (32.2)
Progressive Disease	2 (40.0)	7 (63.6)	10 (38.5)	7 (63.6)	2 (100)	2 (50.0)	30 (50.8)
Not Evaluable	2 (40.0)	1 (9.1)	1 (3.8)	3 (27.3)	0	1 (25.0)	8 (13.6)

a Includes 1 confirmed partial response and 1 unconfirmed partial response.

The SD is based on a minimum of 6 weeks from first dose of MGD007.

Data cut-off date:10 January 2018

Note: Evaluable patients are defined as follows: all patients who received at least one dose of MGD007 and had at least one post-infusion radiographic tumor assessment or in the absence of this assessment, clear clinical evidence of disease progression.

2.4 Background on PD-1

Better understanding of the role of the immune system in tumor control has paved the way for strategies to enhance the immune response against cancer. Monoclonal antibodies against the immune checkpoints such as CTLA-4 and PD-1 and its ligand (PD-L1) have demonstrated high activity in lung, melanoma, renal and other tumors. The PD-1 receptor is an inhibitory receptor expressed by T-cells, which is engaged by ligands including PD-L1 and PD-L2, expressed by antigen-presenting cells. Interaction of PD-1 with its ligands leads to the delivery of a negative signal to the T-cell expressing PD-1 and inhibits T-cell function. This pathway helps the body maintain self-tolerance. Many tumor cells, however, have co-opted this pathway and express high levels of PD-L1 and thereby evade T cell attack. Within the tumor microenvironment, PD-1/PD-L1 interactions limit inflammation and inhibit cytotoxic T lymphocyte (CTL) activity. PD-1 activation inhibits CD8+ CTL proliferation, survival and their effector function and can also induce apoptosis of TILs and promote differentiation of CD4+ T cells into Treg cells.

Immune checkpoint blockade utilizing anti-PD-1 or anti-PD-L1 antibodies has now proven to have clinical benefit among numerous clinical indications, including both hematologic malignancies and solid tumors. Furthermore, anti-PD-1/PD-L1 directed therapeutics are now being investigated in a wide range of combination studies across various indications, including studies with other CD3-based bispecifics **(44)**.

2.5 Background on MGA012

MGA012 (also known as INCMGA00012) is a humanized, hinge-stabilized, IgG4κ mAb that recognizes human PD-1. MGA012 is derived from the murine mAb clone, MG13.78, which was generated using standard hybridoma technology from mice immunized with a His-tagged, human PD-1 extracellular domain molecule. MGA012 contains a hinge-stabilized human

IgG4 Fc domain to limit effector function, while retaining neonatal FcR (FcRn) binding to extend circulating half-life. MGA012 is produced in CHO cells. The molecular weight of the intact, glycosylated molecule is approximately 148 kDa. MGA012 is cross-reactive with human and cynomolgus monkey PD-1 proteins.

MGA012 is designed to bind to PD-1, which is expressed on T (CD4+ and CD8+), B cells, NK cells and myeloid-derived cells, and to inhibit its interactions with the ligands PD-L1 and PD-L2, and thereby disrupt the PD-1 PD-L1/L2 negative signaling pathway, particularly for T cells directed against tumors **(6, 12, 33)**.

2.5.1 MGA012 Pharmacology

In vitro pharmacology studies with MGA012 were conducted to demonstrate its biological properties, including its ability to bind to PD-1 protein and to cell surface PD-1, to inhibit ligand (PD-L1 and PD-L2) binding to cell surface PD-1, to directly inhibit the PD-1/PD-L1 inhibitory pathway, and to exhibit functional activity with human PBMCs by enhancing IFN-γ secretion following stimulation with Staphylococcal Enterotoxin B (SEB). Moreover, these biological activities of MGA012 were comparable to those observed with other anti-PD-1 mAbs, which were evaluated as reference molecules; these included replicas of pembrolizumab and nivolumab, which were generated by MacroGenics based on their published sequences. Secondary PD studies were conducted to confirm that MGA012 does not mediate ADCC or CDC activity, mitogenic activity, hemolytic activity, nor cytokine release. MGA012 cross reacts with nonhuman primate PD-1 and in vivo studies with MGA012 were conducted in cynomolgus monkeys to evaluate toxicology, PK, and the binding of MGA012 to circulating PD-1+ T cells. The combined data from these nonclinical studies with MGA012 provide support for the development of MGA012 as a therapeutic candidate for the treatment of solid tumors. Please reference the MGA012 Investigator's Brochure for more detailed descriptions.

Specific binding of MGA012 to human PD-1 has been characterized in vitro by SPR analysis and flow cytometry. SPR analysis using recombinant soluble human antigens revealed that MGA012 binds to PD-1 with a K_D value of 0.6 nM. Flow cytometry analyses confirmed the ability of MGA012 to bind to cells expressing PD-1, including human PBMCs, human T cells (both CD4+ and CD8+), NS0/PDCD1 cells (cell line stably transfected to express the human PD-1 gene) and nonhuman primate (cynomolgus and rhesus monkey) PBMCs. Experiments with the PD-1 expressing cell line demonstrated that MGA012 binding to cell surface PD-1 occurred with a comparable binding curve as that obtained with the pembrolizumab and nivolumab replica molecules (MGA012 Investigator's Brochure). MGA012 also demonstrated dose-dependent binding to human PBMCs and CD4+ and CD8+ T cells, which express PD-1 at basal levels and at enhanced levels upon stimulation. MGA012 binding to human PBMCs

and T cells was comparable to that observed with the nivolumab replica (pembrolizumab replica was not tested in this experiment).

Table 3 Comparison of in Vitro Potencies of MGA012 and Nivolumab and Pembrolizumab Replicas

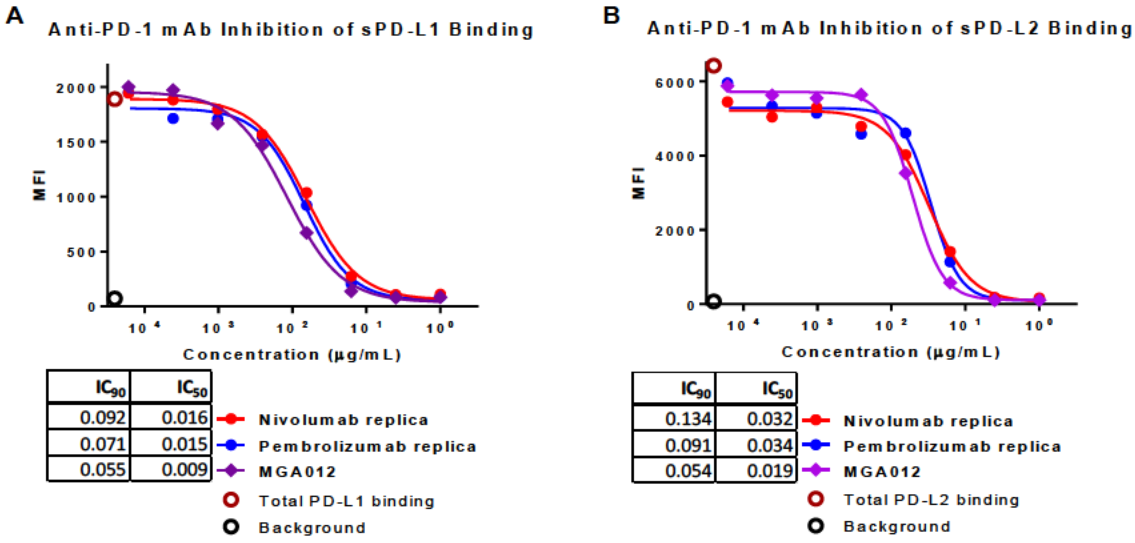
Property	EC_{50} (or IC_{50}) Values (µg/mL) [a] Mean ± SEM		
	MGA012	Nivolumab replica	Pembrolizumab replica
Binding to PD-1-expressing NS0/PDCD1 cells	0.138 ± 0.046	0.158 ± 0.058	0.140 ± 0.048
Inhibition of sPD-L1 binding to PD-1 expressing NS0/PDCD1 cells	0.010 ± 0.001	0.016 ± 0.005	0.014 ± 0.001
Inhibition of sPD-L2 binding to PD-1 expressing NS0/PDCD1 cells	0.021 ± 0.001	0.028 ± 0.004	0.028 ± 0.003
Inhibition of PD-1/PD-L1 Signaling in luciferase reporter assay	0.090 ± 0.008	0.171 ± 0.017	0.103 ± 0.016

a EC_{50}, effective concentration at 50% of maximal activity; IC_{50}, effective concentration at 50% inhibition of activity.

To support the cynomolgus monkey as a relevant species for nonclinical toxicology evaluation of MGA012, several in vitro pharmacology studies were performed to evaluate MGA012 binding to cynomolgus monkey target antigens and cells as well as its biological activity in this model system. MGA012 was shown to bind cynomolgus PD-1 though at an approximately 6-fold lower binding affinity than human PD-1 (K_D values of 3.6 and 0.6 nM for monkey and human PD-1, respectively). MGA012 also bound to both cynomolgus and rhesus monkey PBMCs induced by SEB stimulation. MGA012 did not bind to PD-1 protein from non-primate species (mouse, rat or dog).

Consistent with its specific binding properties and designed mechanism of action, MGA012 blocked the binding of the ligands PD-L1 and PD-L2 to cell surface-expressed PD-1 in a dose-dependent manner **(Figure 7)**. MGA012 blocked the PD-1/PD-L1 and PD-1/PD-L2 interactions with mean IC_{50} values of 0.010 µg/mL and 0.021 µg/mL, respectively. These IC_{50} values were comparable to those observed with the replicas of nivolumab and pembrolizumab, demonstrating that the in vitro potency of MGA012 is similar to those of the nivolumab and pembrolizumab replicas.

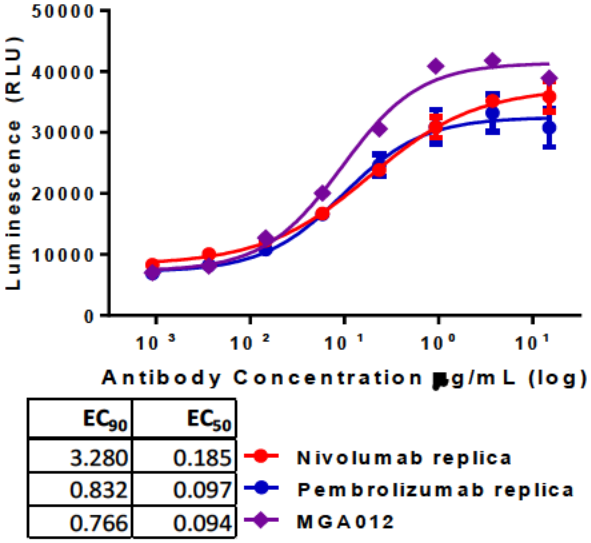
Figure 7 **MGA012-mediated Inhibition of Soluble PD-L1 or PD-L2 Binding to a PD-1-positive Cell Line (NS0/PDCD1)**



Representative dose-inhibition curves of anti-PD-1 mAbs blocking sPD-L1 (A) or sPD-L2 (B) binding to PD1-expressing NS0 cells (NS0/PDCD1). Unlabeled anti-PD-1 mAbs, including nivolumab replica (red line), pembrolizumab replica (blue line), or MGA012 (purple line), were prepared in 1:4 serial dilutions (starting at 10 µg/mL) and incubated with NS0/PDCD1 cells containing 0.1 µg of sPD-L1 or sPD-L2. Total sPD-L1 or sPD-L2 binding (open red circles) and background (open black circle) is shown as positive and negative ligand binding controls. Anti-PD-1 mAb binding was detected with a secondary-labeled goat anti-human Fc-APC conjugate. Data shown are plotted as MFI (APC) by anti-PD1 mAb concentration. Mean EC_{50} values from multiple experiments are summarized in Table 3.

MGA012 was evaluated for its ability to directly inhibit the PD-1/PD-L1 inhibitory axis through the use of a co-culture reporter assay system (9). In this system, the functional disruption of PD-1/PD-L1 mediated blockade of nuclear factor of activated T-cells signaling mediated by TCR stimulation is determined in the context of the co-culture of two cell lines: (1) NFAT-luc2/PD-1 Jurkat cells, a reporter cell line which is CD3-positive and engineered for luciferase expression controlled by an NFAT promoter triggered by TCR activation and constitutive PD-1 expression and (2) CHO-PD-L1, a stimulator cell line that stably expresses PD-L1 and a TCR activator (anti-CD3). When co-cultured, NFAT signaling (despite TCR engagement) is strongly inhibited by the PD-1/PD-L1 interaction present between the NFAT-luc2/PD-1 Jurkat cells and CHO-PD-L1 cell lines. In the presence of blocking anti-PD-1 or anti-PD-L1 mAbs, this inhibitory axis is repressed in a dose-dependent manner allowing increased NFAT signaling resulting in luciferase gene expression that is measured optically. As shown in **Figure 8**, MGA012 blocked the PD-1/PD-L1 inhibitory axis and increased luciferase expression in a dose-dependent manner. The mean EC_{50} for the increase in luciferase expression resulting from MGA012-mediated inhibition of PD-1/PD-L1 signaling was 0.090 µg/mL, a value comparable to those observed using the replicas of nivolumab and pembrolizumab.

Figure 8 **MGA012-mediated PD-1/PD-L1 Inhibitory Signaling as Measured by Luciferase Gene Expression within a Co-culture Reporter Assay System**



EC_{90}	EC_{50}
3.280	0.185
0.832	0.097
0.766	0.094

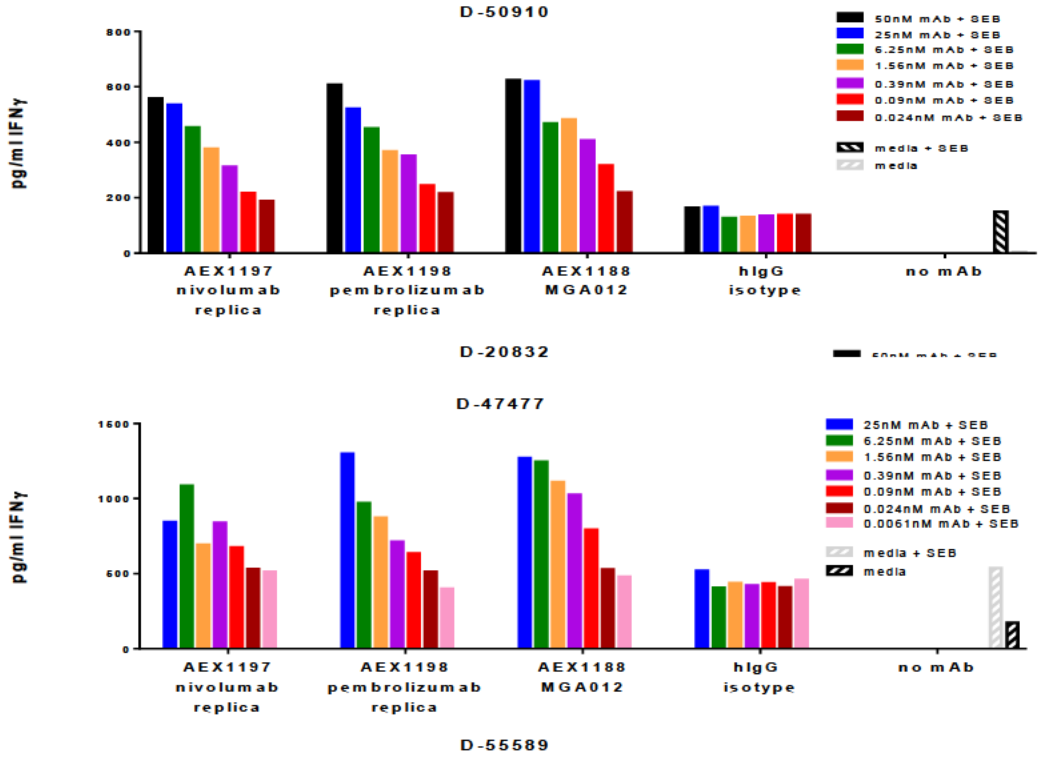
Representative evaluation of anti-PD-1 mAbs to enhance luciferase expression by releasing the inhibitory PD-1/PD-L1 axis within a co-culture reporter assay system (Promega). Unlabeled anti-PD-1 mAbs, including nivolumab replica (red line), pembrolizumab replica (blue line), or MGA012 (purple line), were prepared as 1:5 serial dilutions (starting at 20 nM) and incubated in co-culture with Jurkat reporter cells expressing PD-1 and CD3/TCR (NFAT-luc2/PD-1 Jurkat cells) and CHO stimulator cells expressing PD-L1 and a TCR activator (CHO-PD-L1 cells). Release of PD-1/PD-L1-mediated inhibition is measured by an increased luminescence under the control of TCR-mediated NFAT signaling in the presence of anti-PD-1 mAbs. The optical density of each well in duplicate is read at 450nm with luminescence relative light unit (RLU) as the readout. The data were plotted as mean RLU against concentration and fitted using a log (agonist) vs. response–variable slope (four parameter) function. Mean EC50 values from multiple experiments are summarized in Table 3.

MGA012 was evaluated functionally for its ability to enhance the secretion of cytokine IFN-γ following stimulation of human PBMCs by SEB. Human PBMCs were stimulated with SEB for 48 hours to induce/increase the expression of PD-1 on T cells, which was confirmed by flow cytometry. The majority of cells expressing PD-1 following SEB stimulation were CD3+ T cells. However, expression of PD-1 was also detected on a subset of $CD19^+$ B cells and CD56+ natural killer (NK) cells. Following the initial SEB stimulation, PBMCs were washed and re-stimulated with SEB in the presence of serially-diluted anti-PD-1 mAbs, and after 2 days, the levels of secreted IFN-γ were measured. Enhanced IFN-γ secretion was observed across all 8 human donor PBMCs evaluated; representative data with two donors are shown in **Figure 9**. All donors demonstrated enhanced IFN-γ secretion following anti-PD-1 mAb incubation compared to human IgG isotype control, and with 7 of 8 donor PBMCs, MGA012 demonstrated enhanced or comparable IFN-γ secretion to the nivolumab and pembrolizumab replicas.

In summary, the data from these in vitro pharmacology studies demonstrate that MGA012 binds to its target, PD-1, and is functional in disrupting the PD-1 PD-L1/L2 inhibitory axis.

Moreover, the biological activities of MGA012 were comparable in potency to those observed with the replicas of pembrolizumab and nivolumab, which were evaluated as reference molecules.

Figure 9 **Evaluation of MGA012 to Enhance IFN-γ Signaling Following SEB Stimulation of Human PBMCs**



Secretion of IFN-γ from SEB-stimulated human PBMCs (showing 2 representative donors of 8). Human PBMCs were stimulated for 2 days, washed twice, and restimulated with 0.5 ng/mL SEB in the presence or absence of anti-PD-1 mAbs: MGA012, nivolumab replica (AEX1197), pembrolizumab replica (AEX1198). Human PBMCs either cultured alone in media or restimulated with SEB alone or SEB incubated with human IgG isotype control served to establish basal levels of IFN-γ secretion. The secretion of IFN-γ was determined by ELISA. The optical density of each well was read at 450 nm with luminescence relative light unit (RLU) as the readout and converted by standard curve linear regression to a concentration (pg/mL).

Secondary pharmacodynamic properties of MGA012 were also evaluated, including the ability of MGA012 to mediate ADCC or CDC, to induce cellular proliferation, and to bind to/lyse red blood cells. Consistent with an IgG4-based antibody, MGA012 did not mediate ADCC activity against PD-1 expressing NS0/PDCD1 cells or activated primary human T cells. Consistent with the inability of the IgG4 Fc to bind C1q, MGA012 also did not mediate CDC activity. MGA012 treatment did not induce resting PBMCs to proliferate after 2 days of incubation, demonstrating the lack of intrinsic mutagenicity. The absence of mitogenic effect was also observed with the nivolumab or pembrolizumab replicas. Lastly, given that the planned route of administration for MGA012 in the clinic is by intravenous infusion, MGA012 was tested to ensure that it had no hemolytic properties. No hemolysis was

observed following treatment of either purified red blood cells (RBCs) or whole blood from healthy human donors with MGA012 in vitro.

MGA012-mediated cytokine production was evaluated in vitro with freshly isolated, non-stimulated PBMCs from normal human donors incubated for 24 hours with soluble MGA012 or plate-immobilized MGA012 by wet- or dry-coating. Upon exposure of PBMCs to MGA012 concentrations of 10 µg/mL and 100 µg/mL (i.e., 10-200 times higher than the positive control antibody OKT3), no cytokine production (IFN-γ, TNF-α, IL-2, IL-4, IL-6, and IL-10) was observed with all three conditions of MGA012 presentation.

2.5.2 MGA012 Pharmacokinetics and Toxicology

A summary of the nonclinical PK and toxicology data with MGA012 are provided below. Please reference the MGA012 Investigator's Brochure for more detailed descriptions.

The nonclinical toxicology program for MGA012 was performed exclusively in the cynomolgus monkey. The cynomolgus monkey was selected as the most appropriate animal model for nonclinical safety evaluation of MGA012 given the high degree of homology (96%) of the cynomolgus monkey and human PD-1 protein sequences, the ability of MGA012 to bind human and monkey PD-1 protein with similar affinity (within 6-fold), and to bind to human and monkey PBMCs following stimulation of PD-1 expression with SEB. In addition, PD-1 expression detected by the antigen binding regions in MGA012 appears to be similar in monkeys and humans as indicated by the fact that the murine mAb precursor to MGA012, which shares the same antigen specificity as MGA012, demonstrated a similar immunohistochemistry staining profile on lymphocytes in lymphoid organs from monkeys as the staining profile observed with MGA012 in lymphoid organs from humans. Non-primate species (mouse, rat, dog) were not relevant for toxicology studies due to reduced PD-1 protein sequence conservation and lack of detectable MGA012 binding to the PD-1 proteins from these species.

In a GLP tissue cross reactivity study performed on a panel of normal human tissues, MGA012 staining was observed in the membrane and cytoplasm of lymphocytes in germinal centers of lymphoid organs (lymph node, spleen, and tonsil); in medulla of thymus; in submucosal lymphoid aggregates in several human tissues including colon, esophagus, small intestine, kidney, ureter, cervix, uterus and lung; and in tissues where lymphocytes were present including kidney and prostate. This staining was expected based on literature reports of PD-1 expression on T cells in lymphocytes **(2, 20, 38, 53)**. No unexpected tissue staining was observed with MGA012.

A repeat-dose GLP toxicology study of MGA012 was conducted in which MGA012 was administered at dose levels of 0 (saline control), 10, 40 or 150 mg/kg to cynomolgus monkeys (n 5/sex/group) by 1-hour IV infusions on a once weekly schedule for a total of 4 weeks, which was followed by a 10-week recovery period.

All of the infusions were well tolerated. There were no preterm deaths nor treatment-related toxicities. There were no MGA012-related observations for the following parameters: clinical

signs, body weights, food consumption, physical examinations, ophthalmology, body temperature, blood pressure, heart rate, respiration rate, neurological examinations, electrocardiograms (ECGs), clinical chemistry, coagulation, gross pathology and organ weights.

The only findings related to MGA012 were modest decreases in lymphocytes after the first infusion and microscopic changes at the IV administration site.

Compared to pre-study values, mean absolute lymphocyte counts were moderately decreased (by 40-55%) at 23 hours after the 1st infusion in males and females treated at doses ≥ 10 mg/kg (statistically significant for males at 10 and 40 mg/kg and females at 40 and 150 mg/kg compared to controls). Lymphocyte counts returned to near pre-study levels prior to the second infusion but were mildly decreased (by 32-53%) for some individual males and females at all dose levels at 23 hours after the 2nd infusion. Lymphocyte counts increased prior to the 3rd and 4th infusions but decreased (by 45-74%) for some individual males and females at 23 hours post infusion. These modest changes in lymphocyte counts in MGA012-treated animals were mirrored by comparable fluctuations in total circulating leukocytes, T cells (both CD4+ and CD8+), B cells and NK cells, as measured by flow cytometry of peripheral blood. However, there were no changes in circulating monocytes.

Microscopic changes at the IV administration site, observed at 3 days after the last dose, consisted of minimal multifocal perivascular mononuclear cell infiltrates within the superficial dermis (males at ≥ 40 mg/kg; females at ≥ 10 mg/kg). This finding is an expected reaction to repeated injection of an exogenous protein (monoclonal antibody). No MGA012-related microscopic changes at the IV administration site were noted at 10 weeks post dosing in recovery animals.

Other microscopic changes were of uncertain relationship to MGA012 because of sporadic (non-dose-related) incidence, or because they were also noted in control animals but were noted at a higher incidence and/or severity in MGA012-treated animals. These findings included: minimal to mild perivascular mononuclear cell infiltrates present in the brain (meninges and/or choroid plexus; control and MGA012-treated), spinal cord (MGA012-treated), and urinary bladder (control and MGA012-treated); minimal mixed-cell infiltrates in adipose associated with thyroid gland (MGA012-treated), heart (control and MGA012-treated), and trachea (MGA012-treated); and minimal to mild mononuclear cell inflammation in the wall of the rectum (MGA012-treated). These diffuse patterns of immune cell infiltration were similar to those observed in the repeat-dose toxicology studies with the approved anti-PD1 antibodies, pembrolizumab at 6, 40 or 200 mg/kg and nivolumab at 1, 10, or 50 mg/kg, in cynomolgus monkeys (**FDA BLA 125514 pembrolizumab**; **FDA BLA 125554 nivolumab 2014**).

Serum cytokine levels were not evaluated in the GLP toxicology study based on the lack of MGA012-related cytokine responses in two prior non-GLP studies, with the single exception of one animal at one time point. No cytokines (IFN-γ, IL-2, IL-4, IL-5, IL-6, IL-10, and TNF-α) were induced in serum samples of cynomolgus monkeys treated with MGA012 following a single dose IV infusion of 10 mg/kg MGA012. Similarly, no cytokines were induced in serum samples of monkeys treated once weekly for 3 weeks with MGA012

administered at 1 or 100 mg/kg, except that one monkey treated at 100 mg/kg had a single significant observed elevation in IL-6 (1946 pg/mL) at 3 hours following the first infusion that resolved by 6 hours (returned to 8 pg/mL) without corresponding clinical effect. It is noted that an elevation in IL-6 of similar magnitude had been observed in a control treated animal in another monkey study.

As can be expected with a humanized protein administered to non-human primates, ADA against MGA012 were detected in several animals after repeat dosing. Evidence of decreased MGA012 serum concentrations following repeated doses of MGA012 were observed in 7/10, 4/10, and 3/10 animals in the 10, 40, and 150 mg/kg dose groups, respectively and the presence of ADA against MGA012 was confirmed in 4, 2, and 1 of the animals in these dose groups, respectively. All the animals in which ADA was not confirmed were in the terminal necropsy group during which MGA012 serum concentrations likely interfered with the ability to detect ADA. Accordingly, data from animals in which ADA appeared to affect MGA012 serum concentrations were excluded from toxicokinetic (TK) evaluations. It is noted that immunogenic responses to humanized therapeutic proteins in cynomolgus monkeys are not generally predictive of immunogenicity in humans; therefore, immunogenicity is expected to be less prevalent in humans.

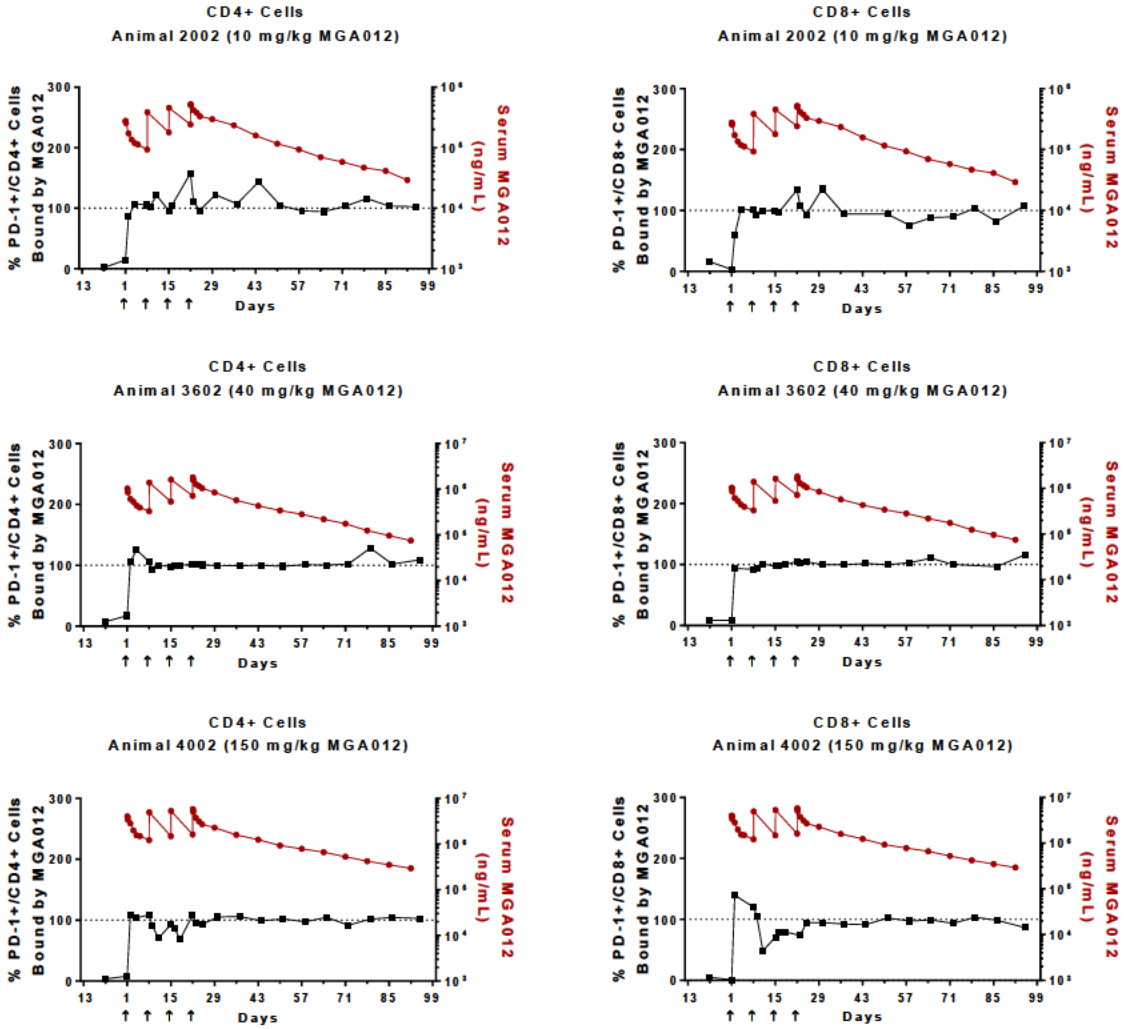
PK parameters of clearance (CL), volume of distribution at steady state (V_{ss}) and mean residence time (MRT) did not vary significantly with dose, hence the PK of MGA012 are linear across the dose range evaluated (10-150 mg/kg). Mean CL by noncompartmental analysis (NCA) ranged from 0.19-0.23 mL/h/kg across the 3 dose groups. CL by two-compartment analysis of data across all 4 cycles, after excluding data after the development of ADA, ranged from 0.21 to 0.24 mL/h/kg. Overall, CL was substantially lower than the glomerular filtration rate in cynomolgus monkeys (~ 125 mL/h/kg), indicating minimal renal clearance as would be expected for a large molecular weight protein (~ 148 kDa). Mean V_{ss} was 68 mL/kg by NCA analysis of the first dose and 72 mL/kg by two-compartment modeling of data across all cycles for the 3 dose groups. This indicates distribution into a space about 50-60% larger than the plasma space (~ 45 mL/kg), but less than the extracellular space (~ 200 mL/kg) of cynomolgus monkeys, which suggests that MGA012 extravasates from the vascular compartment into tissue extracellular space and/or binding of MGA012 to cells or tissues. For all groups combined, the mean MRT by NCA analysis of the first dose or two-compartment analysis of all cycles was 335 hours or 329 hours, respectively, or approximately 14 days. Based on the two-compartmental modeling, steady-state was predicted to be achieved in the monkeys after 5 weekly doses of MGA012 and the accumulation index was 2.4.

MGA012 binds to PD-1 on the surface of CD4+ and CD8+ T cells in cynomolgus monkeys treated with MGA012 and saturation of the binding of MGA012 to PD-1 on T cells was observed at all dose levels during the dosing phase. In animals administered MGA012 at 10, 40 or 150 mg/kg that did not develop ADA responses, serum MGA012 concentrations remained above 29 µg/mL and maximal MGA012 binding to PD-1+/CD4+ T cells and PD-1+/CD8+ T cells was maintained during the entire 10-week recovery period **(Figure 10)**. In animals that developed ADA responses, the frequency of MGA012-bound PD-1+ T cells declined to baseline levels and the declines appeared to initiate when the serum MGA012

concentrations dropped below approximately 25 μg/mL. However, it is not known if this apparent threshold relationship applies to ADA-negative animals, since the presence of ADA in ADA-positive animals may contribute to blocking the binding of MGA012 to PD-1.

In summary, administration of MGA012 via 1-hour IV once weekly for 4 weeks was clinically well tolerated in cynomolgus monkeys at levels of 10, 40, or 150 mg/kg. Observed MGA012-related effects were limited to transient decreases in circulating lymphocyte counts and minimal injection-site changes related to injection of a foreign protein. Based on these results, the NOAEL was considered to be 150 mg/kg (gender combined mean C_{max} of 3.94 mg/mL and AUC of 746 h•mg/mL). The PK parameters for MGA012 were linear across the dose range tested and the mean residence time was approximately 14 days. MGA012, at all dose levels, exhibited durable binding to PD-1-expressing T cells, which persisted for at least 10 weeks post-dosing in the monkeys that did not develop ADA responses.

Figure 10 **Frequency of PD-1+/CD4+ and PD-1+/CD8+ Cells Bound by MGA012 and MGA012 Serum Concentrations in Cynomolgus Monkeys**



The percentages of PD 1+/CD4+ and PD-1+/CD8+ cells bound by MGA012 were compared to the serum concentrations of MGA012 for cynomolgus monkeys treated with MGA012 at 10, 40, or 150 mg/kg and followed during the 10-week post-dose recovery period. Percentages of PD 1+/CD4+ cells bound by MGA012 (left panels) and percentages of PD-1+/CD8+ cells bound by MGA012 (right panels) are represented by black squares and the dashed reference lines indicate saturated (100%) binding. Serum MGA012 concentrations are represented by red circles. Data are from representative animals from each dose group that that did not develop anti-drug antibodies (ADA) during the 10-week recovery period. The days of MGA012 dosing are marked by arrows below the x-axis.

2.5.3 CP-MGA012-01 Clinical Study Update

Study CP-MGA012-01 is a Phase 1, open-label, multicenter dose-escalation study to define the toxicity profile, maximum tolerated dose (MTD), immunogenicity, pharmacokinetic (PK),

and potential anti-tumor activity of MGA012 in patients with relapsed, refractory advanced or metastatic solid tumors. The study consists of a Dose Escalation Phase and a Cohort Expansion Phase. During the Dose Escalation Phase, two schedules of administration are evaluated, once every two weeks (Q2W) and once every four weeks (Q4W), using a standard 3 + 3 design. Cohort expansion to assess further activity in specific solid tumors (endometrial carcinoma, cervical carcinoma, non-small cell lung carcinoma, and sarcoma) is ongoing.

The study completed enrollment in the Dose Escalation Phase, and the DLT evaluation period for the final patient in the top dosing cohorts (Cohorts 3a and 3b) was completed on 22 August 2017. A total of 37 patients have been treated in Dose Escalation including 3 patients in Cohort 1 (1 mg/kg Q2W), 10 patients in Cohort 2a (3 mg/kg Q2W), 10 patients in Cohort 2b (3 mg/kg Q4W), 8 patients in Cohort 3a (10 mg/kg Q2W), and 6 patients in Cohort 3b (10 mg/kg Q4W). These numbers include patients enrolled as replacements for non-evaluable patients as well as patients enrolled to gain further experience at respective dose levels.

The most common treatment-related AEs reported in 2 or more patients in the Dose Escalation Phase were: fatigue (n 9, 24.3%), nausea (n 5, 13.5%); tumor flare, pruritus (n 4 each, 10.8%); hyperthyroidism, influenza-like illness, lipase increased, rash maculo-papular (n 3 each, 8.1%); lymphopenia, diarrhea, and tumor pain (n 2 each, 5.4%). Most of the adverse events experienced by patients have been mild or moderate in severity. Four patients experienced treatment-related AEs ≥ Grade 3. Three of these were asymptomatic elevation of lipase without clinical or radiographic evidence of pancreatitis and one was a female with uterine carcinoma with recurrent Grade 3 vulvovaginal inflammation, ulceration, proctitis and oral mucositis. The mucosal inflammation was managed with steroids and the patient remains on study with an objective response to MGA012 therapy.

Only 1 SAE of 7 reported was considered related to MGA012. This was a Grade 2 expressive aphasia in a patient with melanoma with brain metastases. Inflammation of existing brain metastasis and development of new brain metastasis were considered to have caused the aphasia. This patient had experienced similar symptoms secondary to new brain metastases four months prior to initiating therapy with MGA012.

No dose-limiting toxicity has occurred in the CP-MGA012-01 study to date, and the MTD was not exceeded at any dose and schedule evaluated. Early evidence of antitumor activity has been demonstrated, as 4 patients have experienced a partial response (2 confirmed, 2 unconfirmed).

Overall, review of the cumulative safety data demonstrates an acceptable safety profile, warranting continued clinical investigation of MGA012. The dose of 3 mg/kg administered Q2W has been selected for treatment of patients in the ongoing Cohort Expansion Phase of the study.

Preliminary clinical pharmacokinetic results from this study are described in **Section 2.6.2.1**.

2.6 MGD007/MGA012 Combination Dose Selection

In this study, only the dose for MGD007 will be escalated; the dose for MGA012 will be kept constant at the dose of 3 mg/kg. The initial dose proposed for MGD007 in this study is 0.4 µg/kg QW (QW Cohort). The rationale for selection of the respective doses of MGD007 and MGA012 is described below.

MGD007 will be given QW as 120-minute infusion, with planned escalations from 0.4 to 0.8 µg/kg combined with a 3 mg/kg dose of MGA012 IV (60-minute infusion) given on a Q2W schedule. In the event that a given dose level is found to exceed the MTD, subsequent patients will be dosed at the next lowest dose level, or an intermediate dose level designated based on review of the existing data, and consultation between the study investigators and the Sponsor.

On days when both MGD007 and MGA012 will be administered, MGA012 will be administered first.

2.6.1 Dose Selection: MGD007

Based on the observed safety profile during dose escalation, from the 0.6 to 1.0 µg/kg QW and 0.6 to 3.0 µg/kg Q3W dosing cohorts, the MTD for MGD007 was determined to be 1.0 µg/kg. With CP-MGD007-01 Amendment 3, additional cohorts were implemented, specifically, QW (0.8 µg/kg) and BiW (0.5 µg/kg), as well as a step-wise LID cohort (0.5 µg/kg initially followed by 1.0 µg/kg Q2W) to further optimize the tolerability and combinability of MGD007. Based on the safety, tolerability and preliminary antitumor activity described in **Section 2.3.4**, the starting dose will be 0.4 µg/kg administered QW. The starting dose of MGD007 for the combination arm is below the dose that has demonstrated acceptable tolerability in the MGD007 monotherapy study.

2.6.1.1 MGD007 Pharmacokinetics

In the ongoing Study CP-MGD007-01, MGD007 was evaluated in the dose range of 0.6 to 1.0 µg/kg QW and 0.6 to 3.0 µg/kg Q3W IV. A preliminary PK modeling approach was used to analyze the data using the WinNonlin PK analysis program (Phoenix® 64 WinNonlin®, Version 7.0, Certara, Princeton, New Jersey). The model used was either an open 1-compartment or 2-compartment, where applicable, and a weighting factor that was uniform, reciprocal of predicted concentration or reciprocal of predicted concentration2. The model was fitted to the Cycle 1, Day 1 (C1D1) first dose data with WinNonlin generated initial estimates.

Serum PK data for the 16 patients treated prior to Amendment 2 of Protocol CP-MGD007-01 are summarized in **Table 4**. Both C_{max} and AUC increased with increasing dose. Modeling also suggested that the clearance, half-life, and volume of distribution (V_{ss}) appear to be independent of dose. Lastly, modeling demonstrated that there was minimal accumulation of MGD007 with each dose for either a QW or Q3W schedule of administration.

Table 4 Summary Statistics of First Dose (C1D1) Pharmacokinetic Parameters for MGD007 in Study CP-MGD007-01

MGD007 Dose (µg/kg)	PK Parameters				
	C_{max} (ng/mL)	$AUC_{(INF)}$ (ng•h/mL)	CL (mL/h/kg)	V_{ss} (mL/kg)	$t_{1/2}$ (h)
	GeoMean (%CV)	GeoMean (%CV)	Mean (SD)	Mean (SD)	Mean (SD)
0.6 QW (N = 4)	14.36 (44)	574.24 (47)	1.12 (0.48)	69.93 (42.11)	54.50 (42.65)
0.6 Q3W (N = 3)	13.96 (26)	871.74 (23)	0.70 (0.15)	79.55 (22.01)	89.40 (35.15)
1 QW (N = 3)	29.38 (47)	813.89 (10)	1.23 (0.12)	63.32 (9.10)	37.61 (8.04)
1 Q3W (N 4)	26.43 (83)	769.28 (21)	1.32 (0.26)	68.49 (9.95)	39.02 (7.67)
3 Q3W (N = 2)	66.30 (24)	3335.31 (13)	0.90 (0.11)	74.66 (52.54)	65.84 (48.41)
Overall (N = 16)	NR	NR	1.09 (0.34)	70.72 (21.98)	55.42 (32.95)

Abbreviations: $AUC_{(INF)}$ = area under the serum concentration time curve from time zero extrapolated to infinite time; C1D1 = Cycle 1 Day 1; C_{max} = maximum observed serum concentration; CL = total body clearance; CV = coefficient of variation; GeoMean = geometric mean; N = number of patients; NR = not reported; QW = once every week; Q3W = once every 3 weeks; SD = standard deviation; $t_{1/2}$ = serum terminal elimination half-life; V_{ss} = volume of distribution at steady-state

First dose exposure parameters for 0.5 mg/kg Q2W (Q2W Cohort) are marginally higher than steady state values, because of contribution from the LID.

Modeling and simulations of the PK data of MGD007 were performed, using model parameters from the 0.6 to 3.0 µg/kg QW or Q3W (N 16) and the predicted first dose and steady state exposure parameters (C_{max}, $AUC_{(TAU)}$, and C_{trough}) for the 0.4 µg/kg starting dose for QW dosing were derived and compared to the exposure parameters for the MTD of 1.0 µg/kg QW in Study CP-MGD007-01. The first dose and steady-state exposure parameters (C_{max}, $AUC_{(TAU)}$, and C_{trough}) for the 0.4 µg/kg QW starting dose were approximately 2.5-fold lower than the MTD dose (1.0 µg/kg QW) in Study CP-MGD007-01 **(Table 5)**.

Table 5 Predicted Exposure Parameters and Exposure Multiples for MGD007 0.4 µg/kg for QW Dosing

Interval	Exposure Parameter	Study CP-MGD007-01	Study CP-MGD007-02	Multiples of Exposure Based on Mean Values
		1 µg/kg QW (N = 16) GeoMean (%CV)	0.4 µg/kg QW (N = 16) GeoMean (%CV)	0.4 µg/kg QW
First Dose	C_{max} (ng/mL)	25.09 (54)	10.04 (54)	2.5
	$AUC_{(TAU)}$ (ng•h/mL)	862.27 (29)	344.91 (29)	2.5
	C_{trough} (ng/mL)	0.88 (80)	0.36 (80)	2.5
Steady State	C_{max} (ng/mL)	26.66 (50)	10.66 (50)	2.5
	$AUC_{(TAU)}$ (ng•h/mL)	970.53 (36)	388.21 (36)	2.5
	C_{trough} (ng/mL)	1.02 (100)	0.41 (100)	2.5

Abbreviations: $AUC_{(TAU)}$ = area under the serum concentration time curve in a dosing interval; C_{max} = maximum observed serum concentration; C_{trough} = trough serum concentration (concentration at the end of a dosing interval); CV = coefficient of variation; GeoMean = geometric mean; N = number of patients; QW = once every week.

NOTE: MTD was established at 1.0 µg/kg QW or Q3W in Study CP-MGD007-01

Evaluation of serum samples obtained from a data set of 23 patients (dose escalation) for cytokine levels following the initial dose of MGD007, revealed temporal increases of varying magnitude of IL-6, IL-10 and IL-2 in a subset of patients (data not shown). Elevated cytokine levels are consistent with MGD007 coengagement of gpA33 and CD3 T-cells and consequential T cell activation providing evidence of MGD007-mediated pharmacodynamics activity.

In Study CP-MGD007-01, the starting dose of 0.6 µg/kg was determined using a conservative approach to dose selection relying both on the NOAEL from the non-human primate GLP toxicology study as well as MABEL principles (per Protocol CP-MGD007-01). The C_{max} and AUC achieved in monkeys at the NOAEL dose of 100 µg/kg were 114- and 92-fold higher than, respectively, the corresponding values predicted in humans treated with the selected starting dose of 0.6 µg/kg, thus providing a large safety margin for first human exposure. Indeed, observed PK data for the 0.6 µg/kg dose from Study CP-MGD007-01, confirmed the large safety margins (112- and 190-fold higher for the QW schedule, respectively; and 121- and 135-fold higher for the Q3W schedule, respectively). The 0.4 µg/kg starting dose for QW dosing in the present study is lower than the NOAEL/MABEL estimated starting dose in Study CP-MGD007-01 (0.6 µg/kg) and is expected to provide at least 130-fold safety factor

based on the NOAEL of MGD007 in the GLP toxicology study performed in cynomolgus monkeys of 100 µg/kg MGD007.

2.6.2 Dose Selection: MGA012

The initial dose proposed for MGA012 in this study is based on the PK and safety profile from the ongoing Phase 1, FIH dose escalation and expansion Study CP-MGA012-01, in which dose escalation was carried out from 1 mg/kg Q2W to 10 mg/kg Q2W or Q4W. The safety profile of MGA012 based on a total of 37 patients exposed to MGA012 in Study CP-MGA012-01 demonstrated that the majority of AEs were mild or moderate (CTCAE Grade 1 or 2), with toxicities manageable by standard medical therapy. See **Section 2.5.3** for a more detailed description of the safety profile from Study CP-MGA012-01.

2.6.2.1 MGA012 Pharmacokinetics

In the ongoing Study CP-MGA012-01, MGA012 in the dose range of 1 to 10 mg/kg Q2W or Q4W IV was evaluated. A preliminary 2-stage PK modeling approach was used to analyze the data using the WinNonlin PK analysis program (Phoenix® 64 WinNonlin®, Version 7.0, Certara, Princeton, New Jersey). The model used was either an open 1-compartment or 2-compartment, where applicable, and a weighting factor of reciprocal of predicted concentration or predicted concentration^2. In the first stage, the model was fitted to the Cycle 1, Day 1 (C1D1) first dose data with WinNonlin generated initial estimates. In the second stage, the model was fitted to the first and multiple dose data together with the initial estimates from stage 1. The final modeled PK parameter values after the first dose reported were from stage 2. MGA012 PK parameters are summarized by treatment and study day in **Table 6**.

Table 6 Summary Statistics of First Dose (C1D1) Pharmacokinetic Parameters for MGA012 in Study CP-MGA012-01

MGA012 Dose (mg/kg)	PK Parameters				
	C_{max} (ng/mL)	$AUC_{(INF)}$ (ng•h/mL)	CL (mL/h/kg)	V_{ss} (mL/kg)	$t_{1/2}$ (h)
	GeoMean (%CV)	GeoMean (%CV)	Mean (SD)	Mean (SD)	Mean (SD)
1 (N = 3)	14.9 (37)	3359 (27)	0.304 (0.077)	87.2 (12.1)	216.8 (45.9)
3 (N = 18)	73.1 (36)	15352 (37)	0.200 (0.070)	84.4 (37.8)	401.5 (346.0)
10 (N = 10)	227.7 (22)	59515 (30)	0.169 (0.050)	86.4 (21.0)	422.3 (167.9)
Overall (N = 28 [a])	NR	NR	0.189 (0.072)	85.1 (30.9)	408.9 (282.6)

a For Overall, N = 28 because CL, V_{ss}, and $t_{1/2}$ appear to be comparable between the 3 and 10 mg/kg.

Abbreviations: $AUC_{(INF)}$ = area under the serum concentration time curve from time zero extrapolated to infinite time; C1D1 = Cycle 1 Day 1; C_{max} = maximum observed serum concentration; CL = total body clearance; CV = coefficient of variation; GeoMean = geometric mean; N = number of patients; NR = not reported; Q2W = once every 2 weeks; SD = standard deviation; $t_{1/2}$ = serum terminal elimination half-life; V_{ss} = volume of distribution at steady-state

NOTE: For the 3 and 10 mg/kg dose groups, data from Q2W and Q4W treated patients were combined into a single group because the PK assessment was after the first dose.

Preliminary PK data from 31 patients, including 3 patients in Cohort 1 (1 mg/kg Q2W), 10 patients in Cohort 2a (3 mg/kg Q2W), 8 patients in Cohort 2b (3 mg/kg Q4W), 6 patients in Cohort 3a (10 mg/kg Q2W), and 4 patients in Cohort 3b (10 mg/kg Q4W), suggested that first dose MGA012 C_{max} was dose proportional and $AUC_{(INF)}$ increased in a greater than dose proportional manner over the dose range of 1 to 10 mg/kg IV. Mean (SD) parameter values for CL, Vss, and t1/2 appear to be comparable between the 3 and 10 mg/kg doses. Excluding the 1 mg/kg dose, the overall (N 28) mean CL, Vss, and $t_{1/2}$ values of MGA012 were 0.189 mL/h/kg, 85.1 mL/kg, and 408.9 h (~ 17 days), respectively. The half-life of MGA012 suggests that the drug is expected to attain steady-state conditions within 85 days and predicted accumulation for the Q2W and Q4W regimens is expected to be ~ 2 and ~ 1.5, respectively. The volume of distribution indicates that MGA012 distribution is > than blood volume, but < than extracellular fluid volume.

Modeling and simulations of the PK data of MGA012 were performed, using model parameters from the 3 mg/kg Q2W (N 5) and 10 mg/kg Q2W (N 3) and the predicted first dose and steady-state exposure parameters (C_{max}, $AUC_{(TAU)}$, and C_{trough}) for the 3 mg/kg Q2W starting dose were derived and compared to the exposure parameters for the 10 mg/kg Q2W dose in Study CP-MGA012-01. The starting dose in this study (3 mg/kg Q2W) is approximately 3-fold lower than the top dose demonstrated to be safe in Study CP-MGA012-01 (10 mg/kg Q2W). Furthermore, first dose and steady-state exposure parameters (C_{max}, $AUC_{(TAU)}$, and C_{trough}) for the 3 mg/kg Q2W starting dose were approximately 3-fold lower than for the top dose investigated in Study CP-MGA012-01 (10 mg/kg Q2W) **(Table 7)**.

Table 7 Predicted Exposure Parameters and Exposure Multiples for MGA012 3 mg/kg Q2W

Interval	Exposure Parameter	Study CP-MGA012-01	Study CP-MGA012-01	Multiples of Exposure Based on Mean Values
		10 mg/kg Q2W (N = 3) GeoMean (%CV)	3 mg/kg Q2W (N = 5) GeoMean (%CV)	
First Dose	C_{max} (µg/mL)	202.7 (21)	60.9 (15)	3.3
	$AUC_{(TAU)}$ (µg•h/mL)	26192 (10)	8037 (19)	3.3
	C_{trough} (µg/mL)	41.1 (13)	11.6 (9)	3.5
Steady State	C_{max} (µg/mL)	270.4 (17)	86.6 (22)	3.1
	$AUC_{(TAU)}$ (µg•h/mL)	40816 (8)	14341 (36)	2.8
	C_{trough} (µg/mL)	66.9 (16)	23.6 (67)	2.8

Abbreviations: $AUC_{(TAU)}$ = area under the serum concentration time curve in a dosing interval; C_{max} = maximum observed serum concentration; C_{trough} = trough serum concentration (concentration at the end of a dosing interval); CV = coefficient of variation; GeoMean = geometric mean; N = number of patients; Q2W = once every 2 weeks.

3 STUDY PURPOSE AND OBJECTIVES

3.1 Dose Escalation Phase

3.1.1 Primary Objectives

To characterize the safety, tolerability, dose-limiting toxicities (DLTs), and maximum tolerated dose (MTD) of MGD007 when combined with MGA012 in patients with relapsed/refractory metastatic colorectal carcinoma after at least 2 and up to 5 prior standard regimens of therapy in metastatic setting; or who did not tolerate fluoropyrimidines, oxaliplatin or irinotecan; or who are not good candidates for standard of care.

3.1.2 Secondary Objectives

- To characterize the pharmacokinetics (PK), pharmacodynamic activity, and immunogenicity of MGD007 and MGA012 in combination.
- To investigate the preliminary antitumor activity of MGD007 combined with MGA012 as measured by objective response rate, disease control rate, and progression-free survival (PFS) rate at 16 weeks in patients with relapsed/refractory metastatic colorectal carcinoma using both conventional Response Evaluation Criteria in Solid Tumors (RECIST 1.1), **Appendix 5**, and immune-related response criteria (irRECIST), **Appendix 6**.

3.1.3 Exploratory Objectives

- To explore the relationships between PK, pharmacodynamics of MGD007/MGA012, and antitumor activity.
- To explore the impact of this combination on PFS, immune-related PFS (irPFS), and overall survival (OS) in patients with relapsed/refractory metastatic colorectal carcinoma.
- To investigate the immunoregulatory activity of MGD007 combined with MGA012 in vivo, including various measures of T cell function in peripheral blood and/or tumor biopsy specimens.
- To assess potential biomarkers predictive of efficacy including but not limited to glycoprotein A33 (gpA33), CD3, TILs, PD-1, PD-L1, and immunosuppressive myeloid/lymphoid cells via immunohistochemistry and gene expression in archival tissue.

3.2 Cohort Expansion Phase

3.2.1 Primary Objective

To investigate antitumor activity of MGD007 combined with MGA012 when dosed at the MTD (or maximum administered dose [MAD] if no MTD is defined) as measured by objective response rate, disease control rate and PFS rate at 16 weeks in patients with relapsed/refractory metastatic colorectal carcinoma using both conventional Response Evaluation Criteria in Solid Tumors (RECIST 1.1), **Appendix 5**, and immune-related response criteria (irRECIST), **Appendix 6**.

3.2.2 Secondary Objectives

- To further characterize the safety and tolerability of MGD007 when combined with MGA012 in patients with relapsed/refractory metastatic colorectal carcinoma after at least 2 lines of therapy in a metastatic setting.
- To characterize the PK, pharmacodynamic activity, and immunogenicity of MGD007 and MGA012 in combination.
- To explore the impact of this combination on PFS, immune-related PFS (irPFS), and overall survival (OS) in patients with relapsed/refractory metastatic colorectal carcinoma.

3.2.3 Exploratory Objectives

- To explore the relationships between PK and pharmacodynamics of MGD007/MGA012 and antitumor activity.
- To investigate the immunoregulatory activity of MGD007 combined with MGA012 in vivo, including various measures of T cell function in peripheral blood and/or tumor biopsy specimens.
- To assess potential biomarkers predictive of efficacy including but not limited to glycoprotein A33 (gpA33), CD3, TILs, PD-1, PD-L1, and immunosuppressive myeloid/lymphoid cells via immunohistochemistry and gene expression in archival tissue and assess the effect of the combination on tumor biomarkers, comparing initial and on treatment paired tumor biopsies.

4 STUDY DESIGN

4.1 Overall Study Design and Plan

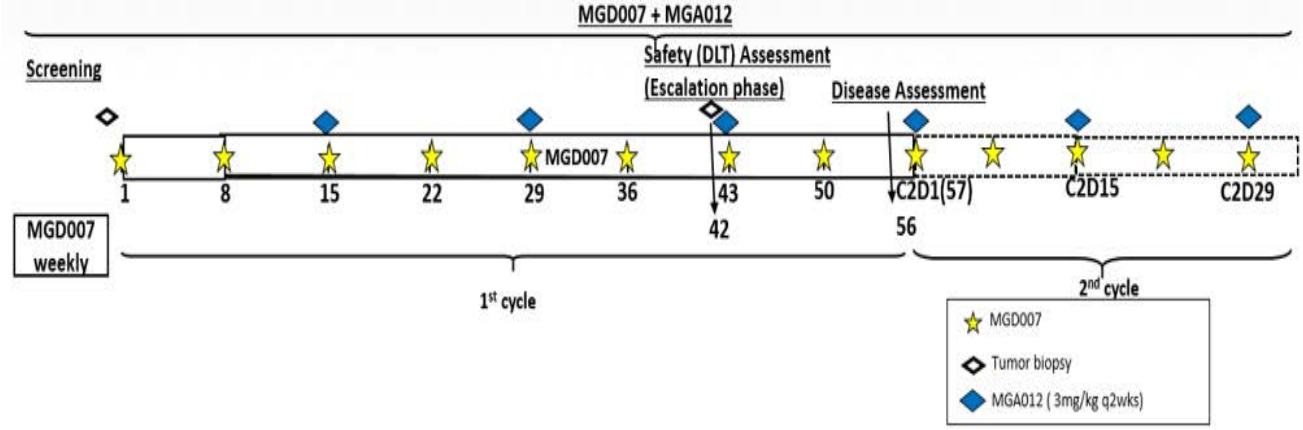
This study is an open-label, Phase 1b/2 dose escalation and cohort expansion study designed to characterize the safety, tolerability, PK, pharmacodynamics, immunogenicity, and preliminary antitumor activity of MGD007 and MGA012, administered in combination by IV infusion, in patients with histologically proven, relapsed/refractory metastatic colorectal carcinoma, irrespective of the KRAS and MMR status of their tumors. This study will enroll patients as described below.

The study will proceed in 2 distinct phases as follows: Dose Escalation Phase to determine the MTD or MAD (if no MTD is defined) of the combination, followed by a Cohort Expansion Phase to further define the safety and initial antitumor activity of the combination with the doses established in the Dose Escalation Phase.

Patients will be treated with MGD007 and MGA012 as shown in **Figure 11**. MGD007 will be administered at the target dose for each assigned cohort as an IV infusion over 120 minutes, once weekly (QW), in 8-week treatment cycles. MGA012 will be administered at 3 mg/kg as an IV infusion over 60 minutes, once every 2 weeks (Q2W) beginning on Cycle 1 Day 15, and every 2 weeks thereafter. For each patient, administration of the first dose of MGA012 will occur 2 weeks after the first dosing of MGD007. The DLT evaluation period will last until Cycle 1 Day 42. Disease status will be evaluated on Cycle 1 Day 56 (± 3 days) using CT and/or MRI as appropriate for the sites of disease, accompanied by physical examination, and will then be evaluated every 8 weeks while on study treatment. Although response assessment will be performed according to both conventional (RECIST 1.1 **[Appendix 5]**) and irRECIST **(Appendix 6)**, patients will be managed according to irRECIST principles. This approach allows for limited treatment of patients beyond the initial radiographic documentation of disease progression, assuming that the Investigator feels that the patients are tolerating therapy adequately, that patients remain otherwise clinically stable despite this initial radiographic evidence of disease progression, and that the Investigator feels the patient may still derive benefit from continuation of therapy.

Patients who achieve response status of immune-related complete response (irCR), immune-related partial response (irPR), immune-related stable disease (irSD), or unconfirmed immune-related progressive disease (irPD), per the immune-related response criteria **(Appendix 6)** at the end of Cycle 1 radiographic disease assessment may be eligible to receive subsequent administrations of MGD007 and MGA012 for up to 12 cycles (~ 2 years), assuming that the patients remain clinically stable and have not experienced DLTs that necessitated permanent discontinuation of study drug.

Figure 11 Overall Study Treatment Schema



Patients who experience progressive disease, as evidenced by ≥ 20% increase in the dimensions of target lesions or the occurrence of new lesions, may continue therapy at the discretion of the Investigator, pending confirmation of progressive disease at the next planned tumor assessment and satisfaction of criteria for irPD. Subsequent cycles of therapy after an initial documentation of progressive disease should be administered only to patients who have demonstrated acceptable tolerance to treatment with study drug, who remain otherwise clinically stable, and who in the assessment of the Investigator, may derive clinical benefit from the continuation of treatment with study drug.

No dose reductions of MGA012 or MGD007 are allowed during the study, except for patients being treated at doses that are subsequently found to exceed the MTDs for either schedule.

Data regarding the KRAS and MMR mutational status (MSI or MSS) will be collected; statuses for both must be formally documented for patients in the Cohort Expansion Phase. Patients will be required to have at least 1 site of measurable disease as defined by RECIST 1.1 criteria **(Appendix 5)**. In addition, patients must have had an identified tumor tissue block (preferred) and/or tumor specimens sufficient for 20 slides that can be utilized for assay of gpA33, CD3, PD-1, and PD-L1 expression via immunohistochemical staining.

Following the last dose of study drug, all patients will be followed every 3 months for survival during a 2-year Survival Follow-up Period.

4.1.1 Dose Escalation Phase

The goal of the Dose Escalation Phase is to initially characterize the safety and tolerability of MGD007 combined with MGA012, and to define the DLTs and MTD (or MAD if no MTD is defined) of the combination. The MTD is defined as the dose level at which < 33% of patients experience a DLT.

For the purpose of guiding decisions regarding dose escalation, the definition of DLT will be based on the occurrence of drug-related AEs that occur up to Cycle 1 Day 42 of MGD007 combined with MGA012 administration.

Dose escalation will follow a conventional 3+3+3 design: MGD007 and MGA012 will be evaluated in sequential escalating doses in cohorts of 3 to 9 patients each. Dose levels of MGD007 to be evaluated are displayed in **Table 8**.

MGA012 will be administered at an unchanged dose of 3 mg/kg Q2W, i.e., the recommended dose in combination, beginning on Cycle 1 Day 15. On days when both MGD007 and MGA012 will be administered, MGA012 should be administered first.

During the 42-day DLT evaluation period, patients who receive less than 75% of the planned doses of either MGD007 or MGA012 secondary to AEs considered unrelated to study treatment or any other cause unrelated to study treatment are considered unevaluable for safety and toxicity during the DLT evaluation period and will be replaced.

Continued dose escalation will proceed using a conventional 3+3+3 design according to the dose escalation rules outlined below. Dose escalation cohorts are presented in **Table 8**.

Table 8 MGD007 QW: Dose Escalation Cohorts

Dose Level	MGD007 Dose (QW)	MGA012 Dose (Q2W)
Dose Level 1:	0.4 µg/kg	3 mg/kg
Dose Level 2:	0.6 µg/kg	3 mg/kg
Dose Level 3:	0.8 µg/kg	3 mg/kg

The MGA012 dose remains unchanged during the escalation.

In the event of a drug-related DLT occurring in a patient, the number of patients will be expanded according to the 3+3+3 design (see **Section 4.3**).

No intra-patient dose reduction will be performed.

If the MTD is exceeded at any dose level, a dose de-escalation to an intermediate dose level will be discussed, based on review of the available safety, efficacy, and/or PK data, and will be implemented upon agreement between the Investigators and the Sponsor. Any escalation cohort, not exceeding the MTD, can be expanded to a maximum of 15 patients for further evaluation of safety and efficacy.

4.1.2 Cohort Expansion Phase

The Cohort Expansion Phase will include 25 patients; approximately 90% of these will be MSS patients and 10% MSI-H.

Paired tumor biopsies will be mandatory if tumor lesions are accessible for biopsy with acceptable clinical risk in the judgment of the investigator and after discussion with the Sponsor. Fifteen paired biopsies will be required at the end of the Cohort Expansion Phase (see **Section 5.1, # 9**). If 15 paired biopsies have not been collected in the initial 25 patients,

additional patients with paired tumor biopsies will be enrolled, to ensure that the 15 paired biopsies are obtained (see **Section 4.5.1**).

Patients who withdraw before completing the first tumor assessment for a reason other than progression of disease or death may be considered unevaluable for response. In these cases, replacement patients may be enrolled in the same dose level as required to complete the cohort.

4.2 Dose Limiting Toxicity

For the purpose of guiding dose escalation decisions, dose-limiting toxicities (DLTs) are defined by drug-related AEs that occur up to Cycle 1 Day 42. The severity of AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v 4.03 (NCI CTCAE v 4.03). Dose-limiting toxicities will be defined separately for hematologic, non-hematologic, and hepatic non-hematologic events.

In general, for patients who experience an AE that may meet the criteria for a DLT, subsequent administration of the study drugs should be held pending management and/or resolution of the event and assessment of attribution to the study drug. Criteria for subsequent continuation of therapy are outlined in are outlined below.

Dose limiting toxicities are defined separately for hematologic and non-hematologic events as described below.

4.2.1 Hematologic Dose Limiting Toxicity

Hematologic DLT is defined as follows:

- Grade 4 neutropenia lasting > 5 days
- ≥ Grade 3 febrile neutropenia lasting > 48 hours or any ≥ Grade 3 febrile neutropenia associated with hemodynamic compromise or objective evidence of infection
- Grade 4 thrombocytopenia, irrespective of duration
- Grade 3 thrombocytopenia associated with clinically significant bleeding
- ≥ Grade 3 hemolysis
- ≥ Grade 3 anemia associated with other clinically significant complications.

The following event will be specifically **excluded** from the definition of hematologic DLT:

- ≥ Grade 3 lymphopenia

4.2.2 Non-hematologic Dose-Limiting Toxicity

Non-hematologic DLT is defined as any ≥ Grade 3 non-hematologic event **with the following exceptions**:

- Grade 3 electrolyte abnormality that lasts less than 72 hours, is not otherwise associated with clinical complications, and responds to medical intervention
- Grade 3 fever that lasts < 72 hours and is not associated with hemodynamic compromise
- Grade 3 nausea or vomiting that lasts < 72 hours and responds to medical intervention
- Grade 3 or 4 amylase and/or lipase elevation that is not associated with either clinical or radiographic evidence suggestive of pancreatitis
- Grade 3 gastrointestinal AEs of diarrhea, constipation, abdominal pain, cramping, dyspepsia, or dysphagia that resolves to ≤ Grade 1 within 7 days with medical therapy
- Grade 3 fatigue that lasts < 7 days.
- Grade 3 infusion-related reaction or cytokine release syndrome that lasts < 12 hours and responds to medical intervention.
- Grade 3 or 4 endocrinopathy that is adequately controlled with hormone supplementation
- Grade 3 skin toxicity that resolves to ≤ Grade 2 within 14 days of initiation of oral corticosteroids
- Grade 3 inflammatory reaction (e.g., with associated pain, swelling) attributed to a local anti-tumor response (e.g., inflammatory reaction at sites of metastatic disease, lymph nodes, etc.) that resolves to ≤ Grade 2 within 7 days.

Note: The following Grade 2 or greater non-hematologic AE may also be considered as DLT:

- Grade 2 AEs that are prolonged inordinately, based upon the medical judgment of the Investigator, and/or lead to permanent discontinuation of MGA012 due to patient intolerance.
- Eye pain or reduction in visual acuity that does not respond to topical therapy and does not improve to Grade 1 within 14 days of the initiation of topical therapy, or that requires systemic treatment.

4.2.3 Hepatic Non-hematologic Dose Limiting Toxicity

Hepatic non-hematologic DLT will be defined as follows:

- Any elevation of one or more transaminases > 8 × the institutional upper limit of normal (ULN) irrespective of duration.
- Any Grade 3 elevation of one or more transaminases > 5.0 8.0 × the ULN that does not resolve to Grade 2 (i.e., > 3.0 5.0 × ULN) within 7 days and Grade 1 (i.e., > ULN 3.0 × ULN) within 14 days. In addition, steroids must be tapered to ≤ 10 mg of prednisone or equivalent per day, by Day 14.
- A Grade 3 elevation of total bilirubin that is > 5 × the ULN, irrespective of duration.
- Any Grade 3 elevation of total bilirubin >3.0 5.0 × ULN that does not resolve to Grade 2 (i.e., >1.5 3.0 × ULN) within 7 days and Grade 1 (i.e., >ULN 1.5 × ULN) within 14 days. In addition, steroids must be tapered to ≤ 10 mg of prednisone or equivalent per day, by Day 14.
- Any event meeting the criteria for Hy's law as follows (all 3 features):
    - Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 3 × ULN
    - Concurrent elevation of total bilirubin > 2 × ULN without initial evidence of cholestasis
    - No alternative etiology can be identified

4.3 Dose Escalation Rules

The Dose Escalation Phase of this trial will proceed using a conventional 3 + 3 + 3 approach.

If 0 of the first 3 patients treated at a given dose level experience a drug-related DLT during the DLT evaluation period, the dose will be escalated, and 3 patients will be enrolled and treated at the next higher dose level (up to the planned highest dose level).

If 1 of the first 3 patients treated at a given dose level experiences a drug-related DLT, then 3 additional patients will be enrolled at that dose level (thus making a total of 6 patients in this cohort) to further assess the safety of the combination of MGD007 and MGA012.

- If ≥ 2 of these 3 additional patients (i.e., ≥ 3 of the 6 patients enrolled in the cohort) experience a DLT, it will be concluded that the MTD has been exceeded, and 3 patients will be enrolled and treated at the next lower dose level.
- If 1 of these 3 additional patients experiences a drug-related DLT, then another 3 additional patients (for a total of 9 patients in the cohort, 3 + 3 + 3) will be enrolled and treated at that dose level to further characterize the safety of MGD007.

- If 0 of the 3 additional patients experiences a DLT, then the dose will be escalated, and 3 patients will be enrolled at the next higher dose level.

If ≥ 2 patients out of the first 3 patients treated at a given dose level, or ≥ 3 of first 6 patients treated at a given dose level, or ≥ 3 out of 9 patients treated at a given dose level experience a drug-related DLT, then it will be concluded that the MTD for MGD007 has been exceeded at that dose level, and an additional 3 patients will be added and treated at the next lower dose level.

Following these rules for dose escalation, the MTD/MAD will be the highest dose administered during the Dose Escalation Phase of the study at which the incidence of DLT is < 33%. Depending on the nature of the DLT, the dose reduction can concern both drugs or only one.

Dose escalation to the next dose level is permitted only after the patients enrolled in the current dose cohort have completed the DLT evaluation period and safety data have been reviewed by the Sponsor's Medical Monitor and Pharmacovigilance Physician as well as the Investigators participating in the study.

At the discretion of the Sponsor, dose escalation may be stopped before an MTD is reached. In this case, the MAD may be chosen based on an assessment of available PK, PD, safety, and response data. An MTD does not have to be reached to initiate the Cohort Expansion Phase of the study if the available data demonstrate that a lower dose level may provide antitumor activity while minimizing potential risk. In addition, if an MTD is established, the Sponsor may decide to open the Cohort Expansion Phase at a dose lower than the MTD, based on the totality of the PK, PD, biomarker, safety, and response data.

At the discretion of the Sponsor, any escalation cohort at a dose level not exceeding the MTD may be expanded to a maximum of 15 patients for further evaluation of safety, PK, and antitumor activity.

When an MTD or MAD is established, any patient remaining on treatment at a lower dose level will be given the option to escalate to the MTD/MAD dose.

4.4 Guidelines for Dose Modification

No dose modifications will be allowed with exception of 1) reduction of infusion rate during re-challenge for patients experiencing an infusion reaction **(Section 7.2)** or 2) reduction of dose in patients receiving MGD007 or MGA012 at a dose that is subsequently determined to exceed the MTD (**Section 4.1.1**).

4.4.1 Dose Delays in Escalation and Expansion Cohorts

Patients who experience toxicity that is potentially dose-limiting should have study drug held pending assessment, management, and resolution of the toxicity. For patients in whom the toxicity is assessed to be unrelated to study drug or for whom the toxicity does not meet the

criteria for DLT, therapy may be re-instituted at the same dose and schedule that was administered prior to the event, presuming the toxicity has resolved as per guidelines outlined in **Section 7**. Dose interruptions of up to 28 days are allowed. Reinstitution of therapy shall be conducted as follows:

- The procedures at the originally scheduled missed visit should be performed as soon as possible with treatment reinstituted as if no delay had occurred, picking up at the day where the interruption occurred, and patients should receive the planned dose and have assessments performed as outlined in the Time and Events Schedule **(Appendix 1)**.

4.5 Study Duration

Enrollment of the study should last approximately 18 months.

The maximum amount of time an individual patient may be on study is 12 treatment cycles, or approximately 2 years. The total time for conduct of the trial is expected to be approximately 66 months (which includes 2 years of survival follow-up). These estimates of the timing for study conduct may vary from that observed in the actual conduct of the trial.

4.5.1 Patient Accrual

The number of patients enrolled in the Dose Escalation Phase cannot be precisely determined in advance. There may be up to 27 patients enrolled depending on results in the course of the trial and the number of MGD007 and MGA012 doses explored. This patient number does not take into account replacement of non-evaluable patients or enrollment to a dose cohort that is expanded in Dose Escalation Phase.

The Cohort Expansion Phase of the study will enroll approximately 25 patients. This number may be higher because at the end of the Cohort Expansion Phase, 15 tumor paired biopsies will be required, if metastases are accessible and obtained with acceptable clinical risk (see **Section 5.1**, **# 9)**. If this number is not reached, additional patients will be enrolled in the study to ensure that the 15 paired biopsies are obtained (see **Section 4.1.2)**.

The number of patients does not take into account patients who may be replaced for clinical reasons. For initial planning, the number of patients to be enrolled in this trial is anticipated to be approximately 52 patients.

4.5.2 Definition of End of Study

The end of study will occur after the last patient has met off-study criteria and the data collection process is completed (time of study database lock).

End of study for each patient is defined as follows: Patient is lost to follow-up (LTFU) (**Section 5.3)** or discontinues from the study due to any reason listed in **Section 5.5**. Each patient's end of study status will be recorded in the End of Study CRF page.

4.6 Appropriateness of Measurements

Routine laboratory evaluations including hematology, chemistry, coagulation, and urinalysis will be carried out in local institutional laboratories. Additional local safety laboratory assessments may be used to supplement the protocol-prescribed assessments and may be used to elucidate certain AEs.

5 SELECTION AND WITHDRAWAL OF PATIENTS

To be eligible for study participation, patients must meet all the inclusion criteria. Patients will be excluded from the study if they meet any exclusion criteria. No exceptions to these criteria will be granted by the Sponsor.

The patient population to be enrolled in this study will consist of adult patients with histologically proven, relapsed or refractory metastatic colorectal carcinoma.

5.1 Inclusion Criteria

1. Ability to provide informed consent and documentation of informed consent prior to initiation of any study-related tests or procedures that are not part of standard-of-care for the patient's disease. Patients must also be willing and able to comply with study procedures, including the acquisition of specified research specimens.
2. Age ≥ 18 years old.
3. Histologically proven, relapsed/refractory metastatic colorectal carcinoma.
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 **(Appendix 4)**.
5. Life expectancy ≥ 12 weeks.
6. Measurable disease as per RECIST 1.1 criteria **(Appendix 5**) and documented by computed tomography and/or magnetic resonance imaging. Patients with evaluable disease only will not be enrolled on this study.

   Note: Lesions to be used as measurable disease for the purpose of response assessment must either: a) not reside in a field that has been subjected to prior radiotherapy, or b) have demonstrated clear evidence of radiographic progression since the completion of prior radiotherapy and prior to study enrollment.

7. During the dose escalation portion of the study, patients must have had recurrence, progression or intolerance to standard therapy consisting of at least 2 prior standard regimens (containing a fluoropyrimidine plus a platinum analogue and/or irinotecan) for metastatic disease. During the Cohort Expansion portion of the study, patients will be allowed to participate in the study after 1 prior standard regimen. Patients who are inappropriate candidates for or have refused treatment with these regimens are also eligible. Patients should have received no more than 5 prior therapies. Patients previously treated with MGD007 on Study Protocol CP-MGD007-01 and who did not develop antibodies to MGD007 while on the CP-MGD007-01 study, may be enrolled. Patients that were previously treated on CP-MGD007-01 will only be treated on this study once MTD/MAD has been defined.

8. In addition, patients to be enrolled in the study must have an identified formalin-fixed, paraffin embedded tumor specimen and/or tumor specimens sufficient for 20 slides to enable determination of the expression of gpA33, CD3, PD-1, and PD-L1 within tumor specimens using immunohistochemical staining. The expression of gpA33 in tumor specimens will be analyzed retrospectively and will not be used to prospectively determine protocol eligibility.
9. For the 15 patients who will have paired tumor biopsies, tumor lesions must be accessible for biopsy with acceptable clinical risk in the judgment of the investigator. Paired tumor biopsies will be mandatory if tumor lesions are accessible for biopsy with acceptable clinical risk in the judgment of the investigator and after discussion with the Sponsor. Fifteen paired biopsies will be required in each cohort at the end of the Cohort Expansion Phase. For each patient, the identified lesion to be biopsied should not have been previously irradiated and should not be the only lesion being utilized as measurable disease target lesion for objective response assessment. The lesion to be biopsied should be of sufficient size to enable acquisition of at least 2 tumor biopsy cores using a biopsy needle.
10. Acceptable laboratory parameters as follows:
    a. Platelet count $\geq 100 \times 10^3$/microliter without transfusion within 4 weeks prior to the initiation of study drug.
    b. Hemoglobin ≥ 8.0 g/dL without transfusion within 1 week prior to the initiation of study drug.
    c. White blood cell count (WBC) $\geq 2.0 \times 10^3$/microliter in the absence of any growth factor support within 4 weeks prior to the initiation of study drug.
    d. Absolute neutrophil count $\geq 1.5 \times 10^3$/microliter in the absence of any growth factor support within 4 weeks prior to the initiation of study drug.
    e. ALT/AST ≤ 3.0 times the ULN, up to 5.0 times the ULN for patients with liver metastases.
    f. Total bilirubin ≤ 1.5 times ULN, except patients with Gilbert's syndrome, who may enroll if the conjugated bilirubin is within normal limits.
    g. Creatinine < 1.5 mg/dL, or a calculated or measured creatinine clearance > 50 mL/min.
    h. Negative urine or serum pregnancy test for women of child-bearing potential.
11. Female patients of childbearing potential (not surgically sterilized and between menarche and 1-year post menopause) must have a negative urine or serum pregnancy test performed within 72 hours prior to the initiation of study drug administration. If a patient is sexually abstinent but capable of becoming pregnant, she must agree to remain abstinent from the time of consent through 120 days after discontinuation of study drug administration. Should sexual activity commence, the patient must agree to use highly effective contraceptive measures from the time of consent through 120 days after discontinuation of study drug administration.

a. Highly effective methods of contraception include hormonal contraceptives, intrauterine device or system, vasectomy, or tubal ligation. If a highly effective method is not achievable, then a "double barrier" method is an effective alternative in which the male partner must use a condom with spermicide and the female partner must use a diaphragm or cervical cap concurrently.

12. Male patients with partners of childbearing potential must use barrier contraception (i.e., condom). In addition, male patients should also have their partners use another method of contraception from the time of consent through 120 days after discontinuation of study drug administration.
13. Patients who are not pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the prescreening or screening visit through 120 days after the last dose of study drug.

5.2 Exclusion Criteria

1. Patients with symptomatic central nervous system (CNS) metastases. Patients with history of prior CNS metastasis must have been treated, must be asymptomatic, and must not have any of the following at the time of enrollment:
    a. No concurrent treatment for the CNS disease (e.g. surgery, radiation, corticosteroids ≥ 10 mg prednisone/day or equivalent)
    b. No progression of CNS metastases on MRI or CT for at least 14 days after last day of prior therapy for the CNS metastases
    c. No concurrent leptomeningeal disease or cord compression
2. Patients with any history of known or suspected autoimmune disease with the specific exceptions of vitiligo, resolved childhood atopic dermatitis, psoriasis not requiring systemic treatment (within the past 2 years), and patients with a history of Grave's disease that are now euthyroid clinically and by laboratory testing.
3. History of prior allogeneic bone marrow, stem-cell, or solid organ transplantation.
4. Criterion for excluded prior therapies:
    a. Treatment with any major surgical procedure, systemic anti-neoplastic therapy, or investigational therapy within the 4 weeks prior to the initiation of study drug administration.
    b. Treatment with radiation therapy within 2 weeks prior to the initiation of study drug administration.
    c. Treatment with systemic corticosteroids (≥ 10 mg per day prednisone or equivalent) or other immune suppressive drugs within the 14 days prior to the initiation of study drug administration.

d. Prior history of Grade 3 or greater drug-related diarrhea/colitis during treatment with checkpoint inhibitors including anti-LAG-3, anti-PD-1, anti-PD-L1, or anti-CTLA-4 antibodies.

5. Clinically significant cardiovascular disease including but not limited to:
    a. Myocardial infarction or unstable angina within the 6 months prior to the initiation of study drug.
    b. Stroke or transient ischemic attack within 6 months prior to the initiation of study drug.
    c. Clinically significant cardiac arrhythmias.
    d. Uncontrolled hypertension: systolic blood pressure (SBP) > 180 mmHg, diastolic blood pressure (DBP) > 100 mmHg.
    e. Congestive heart failure (New York Heart Association class III-IV).
    f. Pericarditis or clinically significant pericardial effusion.
    g. Myocarditis.
6. Clinically significant gastrointestinal disorders including but not limited to:
    a. Any history of gastrointestinal perforation unless the affected area has been surgically resected no less than 3 months prior to the initiation of study drug and is deemed to no longer be at risk of perforation by the investigator.
    b. History of clinically significant gastrointestinal bleeding within 6 months prior to the initiation of study drug.
    c. Chronic malabsorption syndromes.
    d. Current acute or chronic diarrhea > Grade 2 in severity.
    e. Chronic gastrointestinal infection in the 3 months prior to the initiation of study drug administration.
    f. History of *Clostridium difficile* colitis within 3 months prior to the initiation of study drug administration.
    g. History of acute pancreatitis within 3 months prior to the initiation of study drug administration or any history of chronic pancreatitis.
    h. Diverticulitis that is clinically significant in the opinion of the Investigator based on the extent or severity of known disease and/or the occurrence of clinically significant disease flares within 3 months prior to the initiation of study drug administration.
7. Clinically significant pulmonary compromise, including but not limited to pneumonia, presence of active pneumonitis or history of non-infectious pneumonitis, or a requirement for supplemental oxygen use to maintain adequate oxygenation.

8. Evidence of active viral, bacterial, or systemic fungal infection requiring parenteral treatment within 7 days prior to the initiation of study drug. Patients requiring any systemic antiviral, antifungal, or antibacterial therapy for active infection must have completed treatment no less than one week prior to the initiation of study drug.
9. Known history of positive testing for human immunodeficiency virus or history of acquired immune deficiency syndrome.
10. Known history of hepatitis B or hepatitis C infection or known positive test for hepatitis B surface antigen, hepatitis B core antigen, or hepatitis C polymerase chain reaction.
11. Second primary invasive malignancy that has not been in remission for greater than 2 years; except non-melanoma skin cancer; cervical carcinoma in situ on biopsy; or squamous intraepithelial lesion on Pap smear; localized prostate cancer (Gleason score < 6); or resected melanoma in situ.
12. History of trauma or major surgery within 4 weeks prior to the initiation of study drug administration.
13. Any serious underlying medical or psychiatric condition that would impair the ability of the patient to receive or tolerate the planned treatment at the study site.
14. Known hypersensitivity to recombinant proteins, polysorbate 80, or any excipient contained in the drug formulation or custom vehicle (**Section 6.4**).
15. Vaccination with any live virus vaccine within 4 weeks prior to the initiation of study drug administration. Inactivated annual influenza vaccination is allowed.
16. Dementia or altered mental status that would preclude understanding and rendering of informed consent.
17. Prisoners or other individuals who are involuntarily detained.
18. Any investigative site personnel directly affiliated with this study.
19. Any issue that in the opinion of the investigator would contraindicate the patient's participation in the study or confound the results of the study.

5.3 Withdrawal of Patient from the Study

Patients who withdraw before Cycle 1 Day 42 during the Dose Escalation Phase for a reason unrelated to drug toxicity or efficacy may be considered to have inadequate data to support efficacy assessment (see **Section 4.1.1**). In this case, replacement patients may be enrolled but the patients will be considered in intention to treat. These patients will be followed for safety assessments (see **Section 12.2**).

See **Section 4.5.1** for replacement criteria for those patients who were planned to have paired tumor biopsies.

Procedures for handling patients who fail to appear for study visits and criteria regarding when to consider patients lost-to-follow-up (LTFU) will be defined in the Study Procedures

Manual. A patient may be determined to be LTFU after there have been 3 documented phone contact attempts. If this fails, a certified letter should be sent to the patient. Only after these attempts have failed can a patient be determined to be LTFU.

5.4 Rules for Study Treatment Discontinuation

Patients who tolerate treatment may continue to receive treatment with the study drug(s) as specified in the protocol until any one of the following conditions are met:

- Patient meets any criteria for immune-related disease progression (irPD)
- Withdrawal of patient due to an AE or SAE
- Withdrawal of patient consent
- Completion of protocol-defined therapy
- Investigator discretion
- Pregnancy
- Occurrence of drug-related DLT
- Dose delay > 28 days due to drug-related AE
- Repeated administration of prohibited concomitant medications
- The Sponsor, Investigator, or Regulatory Agency terminates the study
- Death

For individual patients who meet these criteria, but who are otherwise considered to be experiencing compelling clinical benefit in the judgment of the Investigator, consideration may be given to continue treatment with the MGD007 and MGA012 combination, for up to maximum of total of 12 cycles, on a case-by-case basis, in consultation with the Sponsor.

For patients who experience drug-related DLTs that occurs prior to the initiation of MGA012, or for selected immune-related adverse events clearly related to the mechanism of action of MGA012, continued treatment of patients with either MGA012 or MGD007 monotherapy, respectively, may be considered selectively on a case-by-case basis, in consultation with the Sponsor.

If the Investigator decides that the patient should be withdrawn from the study or from dosing for any reason other than disease progression, the site must enter the information in the eCRFs within 24 hours (**Section 12.2.2**).

5.5 Guidelines for Discontinuation of Patient from Study

Patients who are no longer on treatment but are still followed on the study can be terminated from the study for the following reasons:

- Completion of protocol-defined follow-up period.
- Uncontrolled intercurrent illness unrelated to cancer that prevents continuing study follow-up.
- Noncompliance with protocol-required evaluations.
- The patient requests to be discontinued from the study, i.e., withdrawal of consent.
- The Sponsor, investigator, or regulatory agency terminates the study.
- Death

6 STUDY TREATMENTS

6.1 Method of Assigning Patients to Treatment Groups

Patients will be assigned sequentially to the dose escalation cohorts.

Patients in the Cohort Expansion Phase will receive the MGD007 and MGA012 dosage based upon results from the Dose Escalation Phase.

6.2 Blinding

Not applicable. This is an open-label study.

6.3 Emergency Unblinding

Not applicable. This is an open-label study.

[redacted]

[redacted]

6.4.4 Study Infusion Preparation

6.4.5 General Guidelines and Precautions

Under no circumstances is the Investigator allowed to release these clinical supplies for use by another physician not named on Form FDA 1572 or to administer study drug to a patient who is not enrolled in this study. Study drug must be dispensed at an institution specified on Form FDA 1572.

6.4.5.1 MGD007

MGD007 is administered to patients at very low doses. All doses employed in this study are described in units of micrograms/kg

A microgram (µg) is
1 millionth ($1/10^6$) of a gram (g),
1 thousandth ($1/10^3$) of a milligram (mg)

MGD007 is a CD3-targeting therapy; therefore, it is possible that MGD007 may induce severe/fatal Cytokine Release Syndrome (CRS) when administered to humans.

Errors in dilution could result in severe/fatal CRS.
Every reasonable precaution should be exercised in the preparation, verification, and administration of the MGD007 dose. Independent verification of patient weight and of the calculated dose must be carried out and documented by a second individual. Similarly, the syringe pump settings should be independently reviewed and documented by a second individual before study drug administration commences.

MGD007 should not be administered as an IV push or bolus. All doses of MGD007 will be administered as an IV infusion over 120 minutes with a commercially available syringe pump. **All syringe pumps must be calibrated prior to use for the administration of MGD007**. [redacted]

The calculated dose will be administered based on the patient's actual weight at Day 1. Significant (≥ 10%) change in body weight from baseline should prompt recalculation of dose. Patients with weight (>120 kg) should be dosed based on Ideal Body Weight (IBW) calculations based on the following formula:

Estimated ideal body weight in (kg):
Males: IBW 50 kg + 2.3 kg for each inch over 5 feet.
Females: IBW 45.5 kg + 2.3 kg for each inch over 5 feet.
Refer to the Pharmacy Manual for further instructions on allowable parameters for dose rounding of MGD007.

Infusion or allergic reactions may occur with the infusion of monoclonal antibodies and other protein-based therapeutics. Precautions for anaphylaxis should be observed during MGD007 administration. Supportive measures may include, but are not limited to, epinephrine, antihistamines, corticosteroids, IV fluids, vasopressors, oxygen, bronchodilators, diphenhydramine, and acetaminophen. Resuscitation equipment and other supplies for the emergency management of an allergic/toxic reaction must be available. Please refer to **Section 7.2** for specific guidelines regarding the management of infusion reactions. Supportive care measures consistent with optimal patient care will be provided throughout the study according to institutional standards.

6.4.5.2 MGA012

The calculated dose will be administered based on the patient's actual weight at Cycle 1 Day 1. Body weights will be measured at Screening and at every dosing visit of each cycle. Significant (≥ 10%) change in body weight from baseline should prompt recalculation of dose. Refer to the Pharmacy Manual for further instructions on allowable parameters for dose rounding of MGA012.

Patients with weight (>120 kg) should be dosed based on Ideal Body Weight (IBW) calculations based on the following formula:

Estimated ideal body weight in (kg):
Males: IBW 50 kg + 2.3 kg for each inch over 5 feet.
Females: IBW 45.5 kg + 2.3 kg for each inch over 5 feet.
Refer to the Pharmacy Manual for further instructions on allowable parameters for dose rounding of MGD007.

Infusion or allergic reactions may occur with the infusion of monoclonal antibodies and other protein-based therapeutics. Precautions for anaphylaxis should be observed during MGA012

administration. Supportive measures may include, but are not limited to, epinephrine, antihistamines, corticosteroids, IV fluids, vasopressors, oxygen, bronchodilators, diphenhydramine, and acetaminophen. Please refer to **Section 7.2** for specific guidelines regarding the management of infusion reactions. Supportive care measures consistent with optimal patient care will be provided throughout the study according to institutional standards.

6.4.6 Study Drug Preparation and Administration

Visually inspect parenteral drug products for particulate matter and discoloration prior to administration. Return the vial if solution is cloudy, there is pronounced discoloration (MGD007 drug product solution may have pale-yellow or pale brown color and MGA012 drug product solution may have a pale-yellow color), or there is foreign particulate matter.

Instructions on the preparation of MGD007 and MGA012 are detailed in the Pharmacy Manual.

- Do not mix the study drug with, or administer as an infusion with, other medicinal products.
- **On days that patient receives both MGD007 and MGA012, MGA012 must be administered prior to administration of MGD007.**

6.4.6.1 MGD007

Administration of MGD007 should begin immediately after preparation of the dosing solution but no later than 4 hours after preparation when stored in the vial at 2°to 8°C (see Pharmacy Manual). If there is a delay in administration of study drug such that it will not be administered on the day of preparation, the Medical Monitor should be notified immediately. Instructions on how to proceed will be provided.

- Administer MGD007 via syringe pump over 120 minutes through an IV line. MGD007 should not be administered as an IV push or bolus.

6.4.6.2 MGA012

Following dilution [redacted] MGA012 will be administered by IV infusion over 60 minutes.

Administration of MGA012 should begin immediately after preparation of the dosing solution but no later than 4 hours after preparation when stored at room temperature (see Pharmacy Manual). [redacted] If there is a delay in administration of study drug such that it will not be administered according to the

above parameters, the Medical Monitor should be notified immediately. Instructions on how to proceed will be provided.

[redacted]

6.5 Placebo or Active Comparator

There will be neither placebo nor active control drug for this study.

6.5.1 Combination Therapy

MGA012 should be infused ***prior to*** MGD007 when both study drugs are administered on the same day. After MGA012 infusion, the IV line should be flushed with normal saline infusion given at the same rate as the MGA012 infusion.

Do not manually push normal saline after MGA012 or MGD007 infusion.

6.6 Treatment Compliance

The study drug will be administered by healthcare professionals under the supervision of the Investigator. Records of dose calculation, administration, and dosing regimen will be accurately maintained by site staff. The monitor will review dose calculation, administration, and regimen, as well as medication accountability during study site visits and at the completion of the study.

6.7 Packaging and Labeling

Please see the MGD007 and MGA012 Pharmacy Manuals for detailed information about the packaging of the study drugs. All investigational product will be labeled with a minimum of the protocol number, directions for use, storage conditions; the statements “For clinical trial use only,” and/or “CAUTION: New Drug Limited by Federal (United States) Law to Investigational Use,” and the Sponsor's name and address.

[redacted]

6.8 Storage and Accountability

Accurate accounting of all study drug must be maintained. The Investigator agrees to keep an inventory of study drugs using the institution's drug accountability logs or logs provided by MacroGenics. Drug disposition records must be kept in compliance with applicable guidelines and regulations.

A Pharmacy Manual will be provided to the Investigator or designee. When the study is completed, copies of all study drug accountability records must be provided to the Sponsor. Original drug accountability records must be maintained with the rest of the documentation for inspection by the study monitors.

6.9 Investigational Product Disposition at End of Study

Upon completion or termination of the study, all unopened vials of study drug must be returned to MacroGenics or its representative, unless the site has received written authorization from MacroGenics to destroy study drug at the site. All drug returns to MacroGenics or its representative must be accompanied by the appropriate documentation and be clearly identified by protocol number and study site number on the outermost shipping container. If MacroGenics approves the destruction of drug at the site, the Investigator must ensure arrangements are made for proper disposal and that appropriate records of disposal are documented and maintained, and copies provided to the Sponsor.

Additional details regarding storage, handling, and accountability can be found in the Pharmacy Manual.

7 POTENTIAL ADVERSE EVENTS AND SUPPORTIVE CARE MEASURES

7.1 Premedication and Prophylaxis

Clinically significant AEs that may be anticipated based on the mechanisms of action and/or clinical experience to date with MGD007 and/or MGA012 include, but are not limited to gastrointestinal AEs (nausea, vomiting, diarrhea, etc.), infusion related reactions (including CRS), and immune-related AEs. Guidelines for management of these events are provided below in **Sections 7.2** to **7.5**. In addition, premedication and prophylactic measures described here should be implemented to ameliorate the occurrence and/or severity of gastrointestinal adverse events and infusion-related reaction/CRS.

The supportive care regimen should generally be utilized for all patients being treated with MGD007/MGA012, and will include:

- Dexamethasone (20-mg IV) should be given prior to first dose of MGD007 on Cycle 1.
- Budesonide (9 mg PO daily) starting at 48 hours prior to MGD007 infusion and continuing for 5 days after the MGD007 infusion must be given for at least the first 2 and up to 6 doses of MGD007. Further use of budesonide may be used selectively as indicated in the judgment of the investigator.
- Nonsteroidal supportive care medications will be given prior to first dose of MGD007 on Cycle 1 Day 1 and as clinically indicated post infusion. Use of these medications must be given for the first 6 doses of MGD007 infusion; further use may be given selectively as indicated in the judgment of the investigator. These medications include:
    - Acetaminophen 650 mg PO
    - Diphenhydramine 50 mg IV
    - Ranitidine 50 mg IV or equivalent H_2-antagonist
    - Ondansetron 16 mg IV or equivalent antiemetic

Post-infusion:

- IV hydration 500 to 1000cc normal saline administered over 1 to 2 hours post infusion of MGD007 should be considered.
- Monitor for at least 6 hours after each of the following infusions: Cycle 1 Days 1 and 15.
- Inpatient observation for up to 24 hours after initial dose of MGD007 is recommended and may be implemented with subsequent doses of MGD007 at the discretion of the investigator.

7.1.1 Rationale for Premedication and Prophylaxis

In addition to 20 mg dexamethasone intravenously (IV) prior to the first dose of MGD007 only, all new patients will receive prophylactic budesonide, an oral non-absorbable corticosteroid, in an attempt to limit the GI toxicities of MGD007 with less systemic immune suppression. This measure focuses on providing budesonide as local steroidal supportive medication within the intestinal tract, to mitigate and control the adverse effects of MGD007 on the GI tract and limit the use of systemic dexamethasone. Limiting systemic corticosteroid use is desirable, in that the immunosuppressive effects of high doses of systemic steroids could interfere with the mechanism of action of MGD007 and MGA012.

Based on preclinical data and the clinical experience noted to date, early management of toxicity will include tocilizumab. Specifically, if Grade 2 or greater vomiting or diarrhea occurs, early management will include tocilizumab (anti-IL6 receptor) at a dose of 8 mg/kg given intravenously. This approach is being deployed to intervene earlier and limit the progression of GI toxicity in patients treated with MGD007 with a less steroid-intensive approach. Repeat dosing of tocilizumab may occur after each MGD007 dosing if required in the judgment of the investigator. Nonetheless, if toxicities are not well controlled with prophylactic oral budesonide and early use of tocilizumab, systemic steroids and/or other measures may be employed as clinically indicated to treat toxicity. Rehydration with oral and/or IV supplemental fluids is also encouraged.

7.2 Infusion-Related Reactions Including Cytokine Release Syndrome

The predicted mechanism of action of MGD007 is the creation of an immunological synapse between the tumor target cells bearing gpA33 and immune effectors bearing the T cell specific-CD3 complex, leading to T cell activation and killing of the tumor cell. Activation of T cells can be associated with the production of various cytokines.

Infusion-related reactions including hypersensitivity/anaphylactic/anaphylactoid reactions or Cytokine Release Syndrome (CRS) may occur. Precautions for the management of these reactions should be observed during MGD007 administration.

Infusion reactions have also been observed with monoclonal antibodies, including antibodies directed against PD-1 or PD-L1. Infusion reactions (including cytokine release syndrome [CRS]) associated with administration of either MGD007 or MGA012 should be managed according to the standard practice of medicine. General guidelines for the management of such reactions are provided in this section. However, severe reactions may require more intensive interventions (e.g., steroids, anti-TNFα antibodies, and/or IL-6 inhibitors).

Patients should be monitored closely for the development of infusion-related reactions during infusions. Patients must remain in the infusion center for monitoring for at least 6 hours after the infusions on Cycle 1 Days 1 and 15. Medications and supportive measures for the

treatment of severe hypersensitivity reactions should be available for immediate use for an infusion reaction during study drug administration and may include, but are not limited to, subcutaneous (SC) epinephrine (0.3 to 0.5 mL of a 1:1000 solution), antihistamines (e.g., diphenhydramine 25 to 50 mg IV), corticosteroids (e.g., hydrocortisone 25- to 100-mg IV push or equivalent), IV fluids, vasopressors, oxygen, bronchodilators, and antipyretics. Resuscitation equipment and other supplies for the emergency management of an allergic/toxic reaction must be available. The patient should be treated according to the best available local practices and procedures. All supportive measures consistent with optimal patient care will be provided throughout the study according to institutional standards.

Should symptoms of fever or chills develop, it may be difficult to distinguish among potential causes of the symptoms including emerging infection, or infusion reaction. Patients should be evaluated carefully for the presence of infection, with the acquisition of cultures and/or implementation of empiric antibiotic therapy as appropriate based on the assessment of the Investigator. Please refer to **Section 7.2.2** for detailed guidance regarding the management of infusion reactions.

7.2.1 Grading and Management of Infusion Reactions

Infusion reactions will be categorized as follows:

- Grade 1: mild reaction; infusion interruption not indicated, intervention not indicated; Note: Although interruption in infusion is not indicated, temporary rate reduction is indicated before resuming original rate, as the patient tolerates (see **Section 7.2.2**)
- Grade 2: therapy or infusion interruption indicated but responds promptly to symptomatic treatment [e.g., antihistamines, non-steroidal anti-inflammatory drugs (NSAIDS), narcotics, IV fluids]; prophylactic medications indicated for ≤ 24 hours
- Grade 3: prolonged (e.g., not rapidly responsive to medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates);
- Grade 4: life-threatening consequences; pressor or ventilatory support indicated;
- Grade 5: death.

The above grading scale is the CTCAE v4.03 grading scale for CRS, which is nearly identical to the CTCAE v4.03 grading scale for infusion reaction and allergic reaction and is therefore considered appropriate for grading all infusion reactions in this study, irrespective of the underlying mechanism of the reaction. The Sponsor's Medical Monitor or designee should be contacted immediately if questions arise concerning the grade of the reaction.

7.2.2 Management of Observed Infusion Reactions

All infusion-related reactions should be reported as AESIs and/or SAEs, as applicable.

The following are treatment guidelines (which may be modified as needed by the Investigator according to the best practices of medicine) for infusion reactions. If symptoms of IRR develop follow the guidelines provided in **Table 11**.

Table 11 Management of Infusion-Related Reactions

IRR/CRS (NCI CTCAE v4.03)	Management	Follow-up
Grade 1 Mild transient reaction, infusion interruption not indicated, intervention not indicated	• Decrease rate of infusion by 50%. • Monitor for worsening. • Continue rate at 50% reduction and increase dose rate to the original rate by doubling the infusion rate after 30 minutes, as tolerated to the initial rate.	• Monitor closely for worsening symptoms. Educate patient to report worsening immediately. • If worsens: Treat as Grade 2 or 3/4, as appropriate. • Consideration can be given to beginning all subsequent infusions at 50% rate and increasing as tolerated. • Premedication for subsequent dose as recommended (**Section 7.1**)

Grade 2
Therapy or infusion interruption indicated but responds promptly to symptomatic treatment
	• Stop the infusion if ongoing.
	• Administer:
	  ○ Diphenhydramine 50 mg IV
	  ○ Ibuprofen 400 mg PO for fever
	  ○ Oxygen/bronchodilators/IV fluids
	• Resume the infusion at 50% of the prior rate once the infusion reaction has resolved or decreased to Grade 1.
	• Tocilizumab 8 mg/kg IV may be considered selectively in patients where the event is clearly associated with the administration of MGD007 or occurs prior to the initiation of therapy with MGA012
	• Consult Medical Monitor.
		• Monitor for worsening of symptoms
		• If worsens or persists after medical intervention: Treat as Grade 3/4 as appropriate
		• Consideration can be given to beginning all subsequent infusions at 50% rate and increasing as tolerated.
		• Premedication for subsequent dose as recommended (**Section 7.1**).

Table 11 Management of Infusion-Related Reactions

IRR/CRS (NCI CTCAE v4.03)	Management	Follow-up

Grade 3
Prolonged (not responsive to symptomatic treatment) or recurrence after initial improvement, hospitalization indicated for clinical sequelae.
	• Stop the infusion if ongoing.
	• Disconnect tubing.
	• DO NOT FLUSH the tubing.
	• Administer:
	  ○ Diphenhydramine 50 mg IV
	  ○ Dexamethasone 20 mg IV or methylprednisolone 2-4 mg/kg
	  ○ Ibuprofen 400mg PO for fever
	  ○ Oxygen/bronchodilators/IV fluids
	• Tocilizumab 8 mg/kg IV may be considered selectively in patients where the event is clearly associated with the administration of MGD007 or occurs prior to the initiation of therapy with MGA012
	• Consult Medical Monitor.
	• Report as IRE
	• Report as SAE (if appropriate)
		• Monitor for worsening of symptoms
		• If worsens: Treat as Grade 4
		• If reaction resolves within 12 hours, then MGA012 can be administered on next scheduled dose.
		• *No further doses of study drugs (MGD007 and MGA012) if a Grade 3 infusion reaction does not resolve within 12 hours despite medical management*
		• Premedication for subsequent dose as recommended **(Section 7.1)**.
		• Permanently discontinue study drugs (MGD007 and MGA012) if there is a recurrence of Grade 3 reaction at rechallenge.

Table 11 Management of Infusion-Related Reactions

IRR/CRS (NCI CTCAE v4.03)	Management	Follow-up
Grade 4 Life threatening consequences, urgent intervention indicated	• Stop the infusion if ongoing. • Disconnect tubing. • DO NOT FLUSH the tubing. • Administer: o Diphenhydramine 50 mg IV o Dexamethasone 20 mg IV OR methylprednisolone 2 mg/kg. o Tocilizumab 8 mg/kg as for Grade 3 events o Ibuprofen 400 mg PO for fever o Oxygen/bronchodilators/IV fluids. o Pressors/Ventilatory support • Consult Medical Monitor • Report as IRE & SAE	• *No further doses of study drugs (MGD007 and MGA012). Permanently discontinue study drugs (MGD007 and MGA012).*
Grade 5 Death	• Report as IRE & SAE	

7.3 Management of Diarrhea or Colitis

Based on the respective mechanisms of action, both MGD007 and MGA012 may cause GI side effects that may include diarrhea and/or colitis. Patients should be monitored closely for evidence of diarrhea or other change in bowel habits, as well as other signs and symptoms suggestive of colitis. Clinical observations have shown that MGD007 may cause very early (within 72 hours of drug administration) GI side effects that may include diarrhea, nausea and vomiting. These events can be managed successfully with careful supportive care, as well as prompt recognition and intervention with immune suppression where indicated, including anti-cytokine antibody (tocilizumab) and corticosteroids. Colitis related to checkpoint inhibition with anti PD-1 antibodies is much less common than diarrhea associated with treatment with MGD007, typically doses not arise acutely after drug treatment, and is generally treated initially with corticosteroids followed by anti-cytokine therapy (anti-TNF) in patients who fail to respond to corticosteroids. Patients on the present study should be monitored closely for evidence of diarrhea or other change in bowel habits, and patients who develop signs or symptoms including abdominal pain, bloating, nausea, vomiting, and diarrhea with blood in the stools should also be evaluated carefully for potential colitis.

For patients who develop acute GI symptoms prior to the initiation of MGA012 or within 72 hours of treatment with the combination of MGD007 and MGA012 should be treated initially according to MGD007 supportive care principles as outlined below in **Section 7.3.1.** For

patients who fail to respond to early anti-cytokine therapy within 48 to 72 hours, corticosteroids should be initiated promptly as outlined below. For patients in whom the onset of GI symptoms are over 72 hours after administration of the MGD007/MGA012 combination or in whom signs and symptoms are suggestive of colitis, supportive care should be initiated according to **Section 7.3.2**, with initial treatment with corticosteroids as outlined below.

7.3.1 Diarrhea Occurring Before Addition of MGA012 to MGD007 or Early (within 72 Hours) After Administration of the MGD007/MGA012 Combination

- Grade 1 diarrhea - Closely monitor the diarrhea until resolution
- Grade 2 diarrhea:
    - Bowel rest
    - Supplemental IV fluids when necessary with close monitoring of fluid and electrolyte status
    - Tocilizumab (anti IL6 receptor) administered as a single 8 mg/kg IV dose. Repeat dosing of tocilizumab may occur after each MGD007 dosing.
    - Monitoring of frequency of bowel movements and stool guaiac
    - For patients unresponsive to tocilizumab (which should be given first), implementation of additional immune suppression consisting of IV corticosteroids using solumedrol at a dosage of 2 mg/kg/day divided twice daily. As tolerated, patients may be converted to oral corticosteroids (i.e., prednisone 2 mg/kg/day divided twice daily) and tapered as appropriate and guided by the patients' clinical status.
- Grade 3 diarrhea (or Grade 2 diarrhea with blood)
    - Hold both MGD007 and MGA012
    - Hospitalize promptly for further evaluation and management
    - Bowel rest
    - Supplemental IV fluids with close monitoring of fluid and electrolyte status
    - Tocilizumab 8 mg/kg IV
    - Monitoring of frequency of bowel movements and stool guaiac
    - For patients unresponsive to tocilizumab (which should be given first), implementation of additional immune suppression consisting of IV corticosteroids using solumedrol at a dosage of 2 mg/kg/day divided twice daily. As tolerated, patients may be converted to oral corticosteroids (i.e., prednisone 2 mg/kg/day divided twice daily) and tapered as appropriate guided by the patients' clinical status.
    - Stool characterization tests should be performed
    - Imaging to rule out bowel obstruction or perforation

- Consideration of colonoscopy as appropriate
- For patients with severe colitis, or those who do not respond to tocilizumab or corticosteroids, additional immune suppression with anti TNF-alpha antibodies (i.e., infliximab) should be considered early in the course
- For patients with Grade 3 diarrhea that lasts less than 48 hours and responds to medical intervention, treatment may be resumed after resolution of the diarrhea to Grade 1 or less in severity within 14 days.

- Grade 4 diarrhea: discontinue MGD007 and MGA012 and treat as for Grade 3 diarrhea. MGD007 and MGA012 should be permanently discontinued.

7.3.2 Diarrhea with Onset > than 72 Hours After Administration of the Combination of MGD007/MGA012 or Clinical Manifestations Suggestive of Colitis

- Grade 1 diarrhea - Closely monitor the diarrhea until resolution.
- Grade 2 diarrhea - Increase frequency of monitoring until resolution. For management of symptoms:
  - loperamide/diphenoxylate
  - low-dose steroids if clinically indicated.
  - Consider management as per Grade 3 diarrhea with prolonged Grade 2 event lasting more than 5 to 7 days or relapsed diarrhea.
- Grade 3 diarrhea - Hold both MGD007 and MGA012. Hospitalize patient promptly for further evaluation and management including:
  - Bowel rest
  - Supplemental IV fluids with close monitoring of fluid and electrolyte status.
  - Monitor frequency of bowel movements
  - Consider imaging to rule out bowel obstruction or perforation
  - Consideration of colonoscopy as appropriate
  - Implementation of initial empiric immune suppression consisting of IV corticosteroids using methylprednisolone at a dosage of 2 mg/kg/day (or equivalent) divided twice daily. As tolerated, patients may be converted to oral corticosteroids (i.e., prednisone 2 mg/kg/day divided twice daily) and tapered as appropriate and guided by the patients' clinical status.
  - Taper corticosteroids as clinically indicated

- For patients with severe colitis, or those who do not respond to corticosteroids, additional immune suppression with anti TNF-alpha antibodies (i.e., infliximab) should be considered early in the course.
- May consider restarting MGD007 and MGA012 if it is determined that there is no colitis, or an alternative cause of diarrhea is found, **and** diarrhea resolves to ≤ Grade 1 within 14 days

- Grade 4 diarrhea-discontinue MGD007 and MGA012 and treat as for Grade 3. MGD007 and MGA012 should be permanently discontinued.

If the etiology of the diarrhea is uncertain, tocilizumab administration also can be considered, in the case of Grade 2 or greater diarrhea at the discretion of the Investigator, in consultation with the Sponsor.

7.4 Nausea/Emesis

Based on observations from nonclinical and the clinical experience to date, there is some risk that patients may experience nausea and/or vomiting in conjunction with MGD007 treatment. It is recommended that patients be treated prophylactically with antiemetics in conjunction with the first and subsequent doses of MGD007 (**Section 7.1**). For those patients who do experience nausea and/or vomiting after initial dosing, antiemetics should be given as clinically appropriate and consistent with institutional practice. Acceptable antiemetics include but are not limited to serotonin 5-HT3 receptor antagonists, neurokinin 1 receptor antagonists, prochlorperazine, and diphenhydramine. Patients with Grade 2 vomiting despite the specified pre-medication regimen should be promptly managed with a one-time dose of tocilizumab (anti-IL6 receptor) 8 mg/kg IV. Repeat dosing of tocilizumab may occur after each MGD007 dosing. If toxicities are not controlled with tocilizumab, systemic steroids and/or other measures as clinically indicated are recommended. Rehydration with oral or IV supplemental fluids should also be considered.

7.5 Immune-Related Adverse Events

Blockade of immune checkpoints (PD-1, PD-L1 and CTLA-4) has been associated with several immune mediated adverse events that develop as a result of disruption of immune tolerance in normal tissues **(18, 36, 43)**. These include but are not limited to pneumonitis, autoimmune hepatitis, glomerulonephritis, central neurotoxicity (encephalitis), peripheral neuromuscular toxicity, diarrhea or colitis (discussed in **Section 7.3**), hypophysitis, thyroiditis, or other autoimmune endocrinopathies (e.g., pancreatitis and diabetes), myocarditis, and Stevens Johnson Syndrome/Toxic Epidermal Necrolysis. These IrAEs can occur lately and require a prolonged follow up. The occurrence of any of these may dictate interruption and potentially discontinuation of study drug administration pending further evaluation and reporting them to the Sponsor as AESIs. Most low-grade immune-related AEs (irAEs) can be managed symptomatically. Persistent low-grade or moderate toxicities may require treatment with corticosteroids or in refractory cases other immune suppressing agents such as

mycophenolate or infliximab. High-grade immune-related toxicities will, in almost all cases, require treatment with high-dose corticosteroids.

Temporary interruptions of the study drugs may be required in the event of treatment-related, immune-related toxicity. General guidelines for specific toxicity regarding dosing and treatment are provided below. All toxicities will be graded according to NCI CTCAE v4.03.

Patients who receive corticosteroid therapy for ≥ 4 weeks at a dose equivalent to ≥ 20 mg of prednisone per day, consideration should be given to implementation of antibiotic prophylaxis for opportunistic infections.

7.5.1 Hepatic Toxicity

7.5.1.1 Elevations in Transaminases

Treatment management algorithm for patients experiencing hepatic toxicity are as follows:

- Grade 1 elevations - No specific therapy required.
- Grade 2 elevations - For elevations in transaminases 3 to 5 × ULN, rule out viral and other etiologies, and consider immediate oral steroids such as prednisone 60 mg/day divided twice daily, and hold MGD007 and MGA012.
    - If improvement to ≤ Grade 1 does not occur within 48 hours consider IV steroids such as methylprednisolone at 2 mg/kg/day divided twice daily or oral steroids such as prednisone 60 to 120 mg per day, divided twice daily.
    - Resume MGD007 and MGA012 at the next scheduled dose if no more than 2 doses of the combination were missed.
    - If improvement to ≤ Grade 1 does not occur within 14 days, discontinue MGD007 and MGA012.
- Grade 3 elevations - Hold MGD007 and MGA012.
    - For elevations in transaminases > 8 × ULN, permanently discontinue MGD007 and MGA012.
        - Begin immediate IV steroids, and
        - If no response to corticosteroid therapy within 3 to 5 days is observed, consider adding immune suppression therapy with mycophenolate.
        - Monitor liver function tests at least twice weekly (or more frequently as clinically appropriate in the judgment of the Investigator) until transaminases have returned to Grade 1 or baseline.
    - For elevations in transaminases > 5 but ≤ 8 × ULN:

- Begin immediate IV steroids; suggest methylprednisolone at a dosage of 2 mg/kg/day divided twice daily.
- Consider additional immune suppression as above for patients who do not respond to corticosteroid therapy within 3 to 5 days.
- Monitor liver function tests at least twice weekly (or more frequently as clinically appropriate in the judgment of the Investigator) until transaminases have returned to Grade 1 or baseline.
- If the elevation does not improve to Grade 2 within 7 days and to Grade 1 within 14 days, discontinue MGD007 and MGA012.

  - Resume MGD007 and MGA012 administration if following conditions are met:
    - Laboratory elevations downgrade to ≤ Grade 2 within 7 days and improve to ≤ Grade 1 or baseline within 14 days.
    - Steroids have been tapered to ≤ 10 mg per day of prednisone or equivalent.
    - On resuming MGD007 and MGA012, AST, ALT, and total and direct bilirubin laboratory test values will be evaluated at least once per week for 3 consecutive weeks.
  - Permanently discontinue MGD007 and MGA012 treatment in the case of a second increase of AST or ALT to ≥ Grade 3.

- Grade 4 elevations - Discontinue MGD007 and MGA012 and treat as for Grade 3 elevation. MGD007 and MGA012 should be permanently discontinued.

7.5.2 Elevations in Total Bilirubin

Management guidelines for patients experiencing elevations in total bilirubin are as follows:

- Grade 1 elevations - No specific therapy required.
- Grade 2 elevations - Hold MGD007 and MGA012 until improvement to ≤ Grade 1.
  - Consider oral steroids.
  - If improvement to ≤ Grade 1 does not occur within 14 days, discontinue MGD007 and MGA012 and begin oral steroids.
- Grade 3 elevations - Hold MGD007 and MGA012
  - For elevations in total bilirubin > 5 × ULN, permanently discontinue MGD007 and MGA012 and initiate IV steroids, suggest methylprednisolone at a dosage of 2 mg/kg/day divided twice daily, and,

- If no response to corticosteroid therapy within 3 to 5 days is observed, consider adding immune suppression therapy with mycophenolate.
- Monitor liver function testing at least twice weekly (or more frequently as clinically appropriate in the judgment of the Investigator) until total bilirubin has returned to Grade 1 or baseline.

- For elevations in total bilirubin > 3.0 but ≤ 5 × ULN:
  - Begin immediate IV steroids, suggest methylprednisolone at a dosage of 2 mg/kg/day divided twice daily. Consider additional immune suppression as above for patients who do not respond to corticosteroid therapy within 3 to 5 days.
  - Monitor liver function including total bilirubin testing at least twice weekly (or more frequently as clinically appropriate in the judgment of the Investigator) until total bilirubin has returned to Grade 1 or baseline.
  - If the elevation does not improve to Grade 2 within 7 days and to Grade 1 within 14 days, discontinue MGD007 and MGA012.
- Resume MGD007 and MGA012 administration if:
  - Laboratory elevations downgrade to ≤ Grade 2 within 7 days and improve to ≤ Grade 1 or baseline within 14 days.
  - Steroids have been tapered to ≤ 10 mg per day of prednisone or equivalent.
  - On resuming MGD007 and MGA012, AST, ALT, and total bilirubin laboratory test values will be evaluated at least once per week for 3 consecutive weeks.
- Permanently discontinue MGD007 and MGA012 in the case of a second increase of total bilirubin to ≥ Grade 3.

- Grade 4 elevations - Discontinue MGD007 and MGA012 and treat as for Grade 3 elevation. MGD007 and MGA012 should be permanently discontinued.

7.5.3 Pneumonitis

Management guidelines for patients experiencing pneumonitis are as follows:

- Grade 1 pneumonitis - No specific therapy required; close monitoring of lung function and imaging.
- Grade 2 pneumonitis - Hold MGD007 and MGA012

  - Consider corticosteroids: 1 to 2 mg/kg of oral prednisone or equivalent, per day divided twice daily.
  - Taper over 4 weeks as clinically indicated.
  - Resume MGD007 and MGA012 administration at the next scheduled dose if pneumonitis resolves to ≤ Grade 1 within 3 days with or without treatment.
- Grade 3 and 4 pneumonitis - discontinue MGD007 and MGA012.
  - Hospitalize the patient.
  - Initiate maximal supportive care including IV corticosteroids, suggest methylprednisolone at 2 to 4 mg/kg/day divided twice daily. Higher doses may be used in consultation with the Sponsor's Medical Monitor.
  - If no response to corticosteroid therapy is observed within 3 to 5 days, consider adding immune suppression therapy (i.e., infliximab, etc.).
  - MGA012 should be permanently discontinued
  - Upon resolution of the pneumonitis to Grade 1 or less in severity, resumption of MGD007 monotherapy may be considered on a case-by-case basis in consultation with the Sponsor.

7.5.4 Dermatologic Toxicity

Management guidelines for patients experiencing dermatologic toxicity are as follows:

- Grade 1 or 2 skin reactions
  - Symptomatic treatment with low-dose topical corticosteroids (betamethasone 0.1% or hydrocortisone 1%) or antihistamines (diphenhydramine).
  - Persistent Grade 1 or 2 rash should be managed with higher dose topical corticosteroids and/or oral prednisone (1 to 2 mg/kg/day) if there is not improvement with topical therapies or the rash is associated with other dermal toxicities such as pruritus.
- Grade 3 skin reactions Hold MGD007 and MGA012
  - Initiate oral corticosteroids (oral prednisone 1 to 2 mg/kg/day).
  - MGD007 and MGA012 may be restarted at the next scheduled dosing if symptoms resolve to ≤ Grade 2 within 14 days.
  - Grade 3 skin toxicity that does not resolve to ≤ Grade 2 within 14 days of initiation of oral corticosteroids requires permanent discontinuation of study drugs (MGD007 and MGA012).
- Grade 4 skin reactions - Discontinue MGA012 and MGD007

- Initiate oral corticosteroids (oral prednisone 1 to 2 mg/kg/day).
- Consideration should be given to start IV corticosteroids (methylprednisolone 1 to 2 mg/kg/day) for Grade 4 dermatologic toxicities with tapering on resolution to < Grade 2 over 30 days.
- MGD007 and MGA012 should be permanently discontinued.

7.5.5 Nephritis

Management guidelines for patients experiencing nephritis are as follows:

- Grade 1 nephritis - No specific therapy required; close monitoring of renal function.
- Grade 2 nephritis - Hold MGD007 and MGA012.
  - Consider nephrology consultation and renal biopsy to confirm interstitial nephritis.
  - Begin corticosteroids: 1 to 2 mg/kg of oral prednisone or equivalent, per day divided twice daily. Taper over 4 weeks as clinically indicated.
  - Resume MGD007 and MGA012 administration at next scheduled dose if:
    - Nephritis resolves to ≤ Grade 1 within 14 days with or without treatment.
- Grade 3 and 4 nephritis - Permanently discontinue MGD007 and MGA012.
  - Consider hospitalization, nephrology consultation, and renal biopsy to confirm interstitial nephritis.
  - Begin corticosteroids: 2 to 4 mg/kg of oral or IV prednisolone or equivalent per day divided twice daily. Taper over 4 weeks as clinically indicated.

7.5.6 Immune-mediated Hypophysitis

Management guidelines for patients experiencing hypophysitis are as follows:

- Grade 1 hypophysitis - No specific therapy required.
- Grade ≥ 2 hypophysitis - Hold MGD007 and MGA012
  - Consult endocrinologist.
  - Consider hospitalization.
  - Consider short course of high dose IV corticosteroids: e.g., methylprednisolone 2-4 mg/kg IV (or equivalent) divided twice daily.
  - Initiate hormonal replacement as indicated.

- MGD007 and MGA012 treatment may be resumed as allowed by protocol when:
  - Endocrinopathy is controlled with appropriate replacement therapy.
  - Corticosteroid dose reduced to ≤ 10 mg prednisone or equivalent per day.
- Brain MRI recommended.

- Grade 4 hypophysitis - MGD007 and MGA012 should be permanently discontinued.

7.5.7 Thyroid Toxicity

Thyroid disorders may occur at any time during treatment. Monitor patients for changes in thyroid function per protocol and as indicated based on clinical evaluation and for clinical signs and symptoms of thyroid disorders. Isolated hypothyroidism may generally be managed with replacement therapy without treatment interruption and without corticosteroids; treatment management algorithms for patients experiencing endocrinopathy, and a suggested treatment guideline for hyperthyroidism is described below:

- Grade 1 hyperthyroidism - No specific therapy required.
- Grade 2 hyperthyroidism - Hold MGD007 and MGA012.
  - Consider starting oral corticosteroid therapy.
  - Short course of corticosteroid such as methylprednisolone 1 to 2 mg/kg IV (or equivalent) divided twice daily.
  - Resume MGD007 and MGA012 if corticosteroid dose is reduced to ≤ 10 mg prednisone or equivalent per day and stable on hormone replacement therapy (if necessary).
- Grade 3 or 4 hyperthyroidism - Hold MGD007 and MGA012.
  - Consider hospitalization and consulting endocrinologist.
  - Begin IV corticosteroids such as methylprednisolone 2 to 4 mg/kg IV (or equivalent) divided twice daily.
  - Initiate hormonal replacement as necessary.
  - Consider restarting MGD007 and MGA012 with complete resolution or stable on hormone replacement therapy within 14 days and if corticosteroid dose is reduced to ≤ 10 mg prednisone or equivalent per day.

PLEASE NOTE FOR EVENTS DESCRIBED IN SECTIONS 7.2 - 7.5: For patients who experience drug-related DLT that occurs prior to the initiation of MGA012, or for selected immune-related AEs clearly related to the mechanism of action of MGA012, continued

treatment of patients with either MGA012 or MGD007 monotherapy, respectively, may be considered selectively, on a case-by-case basis, in consultation with the Sponsor.

8 CONCOMITANT THERAPY AND RESTRICTIONS

8.1 Concomitant Therapy

All concomitant medications, including prophylactic pre-infusion medications, and blood products administered during the patient's participation in the study until the end of treatment visit must be recorded in the source document and on the electronic Case Report Form (eCRF). All changes in infusions, including interruptions and their duration as well as reductions in rate and duration, must be recorded.

8.1.1 Prohibited Therapy

The following rules concerning concurrent treatment(s) will apply in this study:

- Any other anti-neoplastic therapies including but not limited to chemotherapy or other small molecules, biologics, or radiotherapy are not allowed.
    - For patients who require palliative radiotherapy (i.e., cumulative dose less than 30 Gy, limited field of distribution) for reasons other than disease progression, therapy may be interrupted for up to 4 weeks. Palliative radiotherapy may not be given concurrently with the study drug. Treatment with palliative therapy should be initiated at least 24 hours after receiving study drug, and reinitiation can begin 2 weeks after the completion of palliative radiotherapy. If palliative radiotherapy fields overlap tumor lesions that are designated target lesions, the patient may continue on study, but will no longer be evaluable for objective response from the time palliative radiotherapy is initiated.
- Patients may not receive other investigational drugs during the period of study participation.
- The use of other immunosuppressive agents is prohibited unless they are being used to treat an AE.
- Prophylactic use of granulocyte colony stimulating factor, granulocyte-macrophage colony stimulating factor, or other growth factors is prohibited.
- Patients should not receive vaccination with any live virus vaccine during the study and for 120 days following a patient's last dose of MGA012 or of MGD007. Inactivated annual influenza vaccination is allowed.
- Because both MGD007 and MGA012 employs a mechanism of action dependent upon the engagement of T lymphocytes, the use of corticosteroids should be limited to the extent possible. Chronic doses of corticosteroids in excess of 10 mg daily of prednisone or equivalent is prohibited other than for the management of drug-related adverse experiences. Steroids may be employed in the treatment of suspected MGD007- and MGA012-associated autoimmune AEs in consultation with the Sponsor. Specifically, use of budesonide is required with MGD007 dosing per schedule outlined in **Section 7.1**.

- Use of biphosphonates or RANK-L inhibitors is prohibited.
- Concomitant use of CYP450 substrates with a narrow therapeutic index should be avoided.

8.1.2 Permitted Therapies

Patients may receive the following concurrent therapy:

- Antiemetics, antidiarrheals, anticholinergics, antispasmodics, antipyretics, antihistamines, analgesics, antibiotics and other antimicrobials, histamine receptor antagonists or proton pump inhibitors, and other medications intended to treat symptoms or signs of disease.
- Transfusions such as red blood cells and platelets are permitted to treat symptoms or signs of anemia or thrombocytopenia.

8.2 Restrictions

8.2.1 Fluid and Food Intake

There are no requirements for fasting and no restrictions for fluid and food intake by the patients during the study, although it is recommended that, to the extent possible, patients have a fluid intake of ≥ 2 liters on days associated with PK sampling, and that electrocardiograms be obtained pre-meal.

8.2.2 Patient Activity Restrictions

There are no restrictions on patient activities and no requirement for patient confinement during the study.

9 STUDY PROCEDURES

This section provides a general description of the procedures and assessments associated with this study. The timing of the study procedures is presented in **Appendix 1**.

9.1 Informed Consent

The Investigator is responsible for ensuring that the patient or his/her legal representative provides informed consent prior to performing any study-related assessments, evaluations, or procedures that are not part of standard-of-care for the patient's disease. Informed consent for this study must be provided by signing an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved informed consent document (Consent for Study Participation). A copy of the relevant signed informed consent document must be provided to the patient and the original maintained according to institutional procedures. The patient's medical records will include documentation of the informed consent process.

9.2 Screening Period

Patients may receive the first dose up to 28 days from signing the informed consent. This period is defined as the screening period. At the screening visit, patients will enter the study upon signing the informed consent document. No screening activities outside of usual standard-of-care should be performed prior to obtaining informed consent from the patient. Only those patients who meet all inclusion/exclusion criteria specified in **Section 5** will be entered into this study.

9.3 Registration

Only those patients who meet all inclusion/exclusion criteria specified in **Section 5** will be entered into this study.

Once the patient has been determined to be eligible for enrollment into the study, the patient must be registered with MacroGenics. The following information should be provided during registration:

- Date of signed informed consent
- Planned date of first administration

Instructions for the registration process are provided in the Study Procedures Manual.

9.4 Medical History

A complete medical history should be obtained during the screening visit. All concurrent medical conditions in the last 60 days and any significant past medical conditions (e.g., hospitalizations, surgeries, chronic conditions, prior cancer history, etc.) should be

collected. Any untoward event that occurs prior to the first dose of study drug should be recorded as medical history and not as an AE unless it is due to a protocol-related procedure.

9.5 Prior and Concomitant Medications

All concomitant medications and blood products administered during screening and the patient's participation in the study until the End of Treatment Visit must be recorded in the source document and on the eCRF.

Prior courses of systemic cancer therapy (e.g., chemotherapy, immunotherapy, etc.) will be documented in the medical records and on the eCRF.

9.6 Physical Examination

The Investigator will perform physical examination of all patients; the examination will be conducted as specified in **Appendix 1**. Full physical examination will be performed at screening and at the End of treatment visit, and it will include height (screening only), weight, and examination of skin, HEENT (head, eyes, ears, nose, and throat), lymph nodes, heart, chest, lungs, abdomen, extremities, and neurologic system. All other physical examinations will be directed physical examinations based on patient symptoms, tumor location, and as clinically indicated.

9.6.1 Vital Signs

Vital signs include temperature, pulse, blood pressure, and respiratory rate and are obtained as specified in **Appendix 1**. It is recommended vital signs are obtained in a seated, semi-recumbent, or supine position after an appropriate rest.

9.7 ECOG Performance Status

ECOG performance status should be measured as specified in **Appendix 1** and **Appendix 4**.

9.8 Clinical Laboratory Tests

Blood and urine samples will be collected at the times specified in **Appendix 1.** Hematology, chemistry, pregnancy, urinalysis, coagulation time, and endocrine evaluation tests will be performed locally. Safety laboratory tests should be performed and reviewed before study drug administration.

9.8.1 Central Laboratory Assays

Clinical laboratory tests to be performed are presented in **Appendix 2**. There are no clinical laboratory tests (see **Appendix 2)** being analyzed at a central laboratory for this study.

Other laboratory tests (e.g., PK, anti-drug antibody [ADA] assays **[Appendix 3]**) will be analyzed at Sponsor-specified central laboratories. Additional details on collection,

processing, storage, and shipping of central laboratory samples will be provided in the Laboratory Manual.

9.8.2 Pharmacokinetics

Blood samples for MGD007 and MGA012 PK will be collected at the time points shown in **Appendix 3**. Blood samples will be collected from the arm contralateral to the site of IV infusion. If an indwelling catheter is used, the fluid in the catheter will be removed and discarded prior to the collection of blood sample for PK assessment.

Actual date and time of the start and end of infusions and PK sample collection will be recorded on the eCRFs.

9.8.3 Pharmacodynamics/Biomarkers

Procedures for the acquisition, handling, and processing of pharmacodynamic biomarker specimens will be provided in the Laboratory Manual. These tests will be collected according to **Appendix 3**. Samples are to be obtained at the time points specified in the Time and Events Schedule and the PK, immunogenicity, and pharmacodynamic biomarkers blood sample schedule for MGD007 and MGA012 **(Appendix 1** and **Appendix 3**, respectively).

9.8.4 Sample Collection, Storage, and Shipping

Details on laboratory specimen processing, storage, and shipping will be provided in the Laboratory Manual.

9.9 Radiographic, CT, or MRI Assessments

Baseline tumor imaging consists of a CT/MRI scan for all patients. The subsequent tumor assessments on treatment should use the same imaging modality as that for the baseline assessment; for subsequent imaging timepoints see **Appendix 1**.

A CT or MRI scan of the brain will be performed in cases in which it is clinically indicated (e.g., suspicion of brain metastases) and repeat brain scans will be performed only if the screening brain scan was positive, or as clinically indicated.

9.10 Electrocardiography

Twelve-lead electrocardiograms will be obtained according to the Time and Events Schedules **(Appendix 1)** in order to evaluate the potential cardiac effect, including QTc interval prolongation. There are no requirements for fasting and no restrictions for fluid and food intake by the patients during the study, although it is recommended that, to the extent possible, ECGs be obtained pre-meal.

To account for intrinsic variability, all ECGs should be obtained in triplicate (3 ECGs per time point at approximately 1-minute intervals). Central interpretation of ECGs will be used for data analysis purposes.

Actual times of the ECG assessments will be recorded on the eCRFs.

9.11 End of Treatment Visit

A list of evaluations to be performed for the EOTV is provided in **Appendix 1**; a CT or MRI Scan should be performed during the EOTV, unless a previous scan was performed < 28 days of the EOTV. Criteria for triggering the End of Treatment visit are specified in **Section 5.4**.

The End of Treatment Visit should be performed after the patient has met off-study criteria. This visit should occur no later than 30 days since the last study dose and before any subsequent anti-cancer treatment. If EOTV < 30 days since the last study dose, the site should contact the patient for safety follow-up no later than 30 days after the last study dose (see **Section 12**). It is recognized that certain patients (such as those experiencing progression of disease) may be cared for in facilities other than the participating study site, may proceed to receive other cancer therapy, and/or may elect not to return to the study site. Therefore, this visit is considered optional, but should be carried out whenever possible. All required procedures and tests should be performed if a visit is performed.

9.12 Post-treatment Follow-Up Visits

The post-treatment follow-up period includes the following:

- Survival follow-up: approximately a 2-year period for each patient following the last dose of any study drug.
- During this time, patients will be followed via telephone or other electronic contact at 3-month intervals for follow-up of OS.
- Response status: will be collected every 3 months on all patients who discontinued from study treatment due to reasons other than PD, if they have not initiated any other cancer-directed therapy.

Post-treatment follow-up is performed until the end of study for each patient.

10 ASSESSMENT OF PHARMACOKINETICS AND PHARMACODYNAMICS

10.1 Pharmacokinetics Assessments

Serum concentrations of study drug will be monitored using a quantitative sandwich enzyme-linked immunosorbent assay (ELISA) method in the Sponsor's designated central laboratory. Single and multiple dose PK parameters, maximal concentration ($C_{max)}$, time to maximal concentration (T_{max}), area under the concentration-time curve from time zero to time T ($AUC_{(0\ T)}$), area under the concentration-time curve in a dosing interval (AUC_{tau}), area under the concentration-time curve from time zero to infinite time ($AUC_{(INF)}$), trough concentration (C_{trough}), clearance (CL), volume of distribution at steady state (V_{ss}), and terminal half-life ($t_{1/2}$), will be derived from serum concentration versus time data. Population PK analyses may be conducted using data from this study alone or combined with data from other studies.

Analysis of PK data will be carried out using industry standard software. Population PK modeling may be performed, and an appropriate model and model parameters may be described. Samples will be collected for evaluation of ADA.

10.2 Pharmacodynamic/Biomarker Assessments

10.2.1 Tests Performed for Both Dose Escalation and Cohort Expansion Patients

Tests to be performed for PD/Biomarker assessments include, but are not limited to, the following:

- Characterization of alterations in serum cytokine levels to include, but not limited to, IFN-γ, IL-2, IL-6, IL-10, and TNF-α.
- MGD007 and MGA012 occupancy on PBMCs using multiparameter flow cytometry
- Characterization and comparison of the immune phenotype including PBMCs, B cells, T cells, NK cells, myeloid, and monocytes in peripheral blood and enumeration of T-cell subsets and expression of markers of T-cell activation and/or exhaustion (including, but not limited to, PD-1, CTLA-4, LAG-3, TIM-3, CD25, and markers of cytolytic activity) on PBMCs using multiparameter flow cytometry.
- Determination of immune cell infiltration (including T‑cell infiltrate and immunosuppressive myeloid/lymphoid subsets), PD‑1, PD‑L1, FoxP-3, and gpA-33 and other potential checkpoint/TAMs/regulatory expression levels in archival tumor tissue as it relates to MGD007 and MGA012 antitumor activity will be explored via immunohistochemistry (IHC) staining of archival or contemporaneous tumor biopsy specimens based on specimen availability and applicability.

10.2.1.1 Tests Performed for Cohort Expansion Patients Only

Tests to be performed for PD/Biomarker assessments include, but are not limited to, the following:

- Determination of T-cell infiltration (including but not limited to CD4+ and CD8+ T cells) into the tumor bed of paired pretreatment and on-treatment tumor biopsy specimens. Mandatory pretreatment and on-treatment tumor biopsies will be carried out only during the Cohort Expansion Phase.
- Characterization of T-cell repertoire using T-cell spectratyping on PBMCs and on immune-cellular infiltrate in the tumors done on both pre- and on-treatment tumor biopsy samples depending on tumor response and tissue availability.
- Characterization of transcript profiles in peripheral blood and/or pre- and on-treatment tumor biopsies and archival tumor specimens. Additional genomic profiling approaches and analyses, including, but not limited to, i.e.: NanoString, ctDNA, and mutational load, may be undertaken depending on tumor response and tissue availability.
- Characterization serum biomarkers may be carried out depending on observed antitumor activity.
- To evaluate MGD007 binding to gpA33 and MGA012 binding to PD-1 within tumor tissue from on-treatment biopsy specimens.

11 ASSESSMENT OF EFFICACY

11.1 Efficacy Assessments

11.1.1 Disease Response Assessments

Tumor assessments will be obtained using CT and/or MRI scans. Target and non-target lesions will be designated at screening and then evaluated at Cycle 1 Day 56 (±3 days), and then every 8 weeks while on study treatment. At each tumor assessment time point, the overall response status will be determined based on assessment of target and non-target lesions as well as appearance of any new lesions. For patients who discontinued from study treatment due to reasons other than documented, confirmed progressive disease, their treating physicians will be contacted every 3 months during post-treatment follow up period about the response status and survival of these patients.

For RECIST v1.1 **(Appendix 5)**, the overall responses will be categorized as Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD), or Not Evaluable (NE). For patients who experience an objective response of CR or PR, responses will be considered unconfirmed until the response has been documented by a subsequent confirmatory scan obtained no less than 4 weeks after the initial scan demonstrating an objective response.

For irRECIST **(Appendix 6)**, the overall responses will be categorized as immune-related Complete Response (irCR), immune-related Partial Response (irPR), immune-related Stable Disease (irSD), immune-related Progressive Disease (irPD), or immune-related Not Evaluable (irNE). For patients who experience an objective response of irCR or irPR, responses will be considered unconfirmed until the response has been documented by a subsequent confirmatory scan obtained no less than 4 weeks after the initial scan demonstrating an objective response.

For the purpose of patient management, the response determination according to irRECIST will prevail.

For patients who demonstrate acceptable tolerability of treatment with MGD007 and MGA012, and an objective response assessment of irCR, irPR, or irSD, or unconfirmed clinically stable irPD, therapy may be continued.

For patients who are otherwise clinically stable, but have met conventional criteria for PD, therapy may be continued at the discretion of the Investigator pending confirmation of progression at the next scheduled tumor assessment. This approach allows for limited treatment of patients beyond the initial radiographic documentation of disease progression, assuming that patients are tolerating therapy adequately, that patients remain otherwise clinically stable despite this initial radiographic evidence of disease progression and that the Investigator feels the patient may still derive benefit from continuation of therapy. Treatment of patients according to irRECIST principles is supported by well-documented evidence that in some patients treated with T-cell directed, immune-modulatory agents, tumors can evolve

to an objective response after an initial period, characterized by either apparent radiographic growth of target lesions or the development of new target lesions that would otherwise meet the criteria for disease progression using conventional response criteria.

For patients in whom progression is confirmed at the next scheduled tumor assessment, the criteria for irPD will have been met, and treatment with MGD007 and MGA012 should be discontinued. The patient should be removed from study participation after completion of the Post-treatment Follow-up period (see **Section 9.12**). However, for individual patients who meet these criteria, but who are otherwise considered to be experiencing clinical benefit in the judgment of the Investigator, consideration may be given to continue treatment with the MGD007 and MGA012 combination, on a case-by-case basis, in consultation with the Sponsor; see **Section 5.4**.

11.1.2 Survival Assessments

Patients who are discontinued from study treatment will be followed for survival status every 3 months for a 2-year survival follow up period following the final dose of study drug, or until they expire, withdraw consent, or are lost to follow up (see **Section 9.12**).

11.2 Immunogenicity Assessments

The generation of ADA directed against MGD007 and MGA012 will be assayed using ELISA method. Blood samples for the immunogenicity assessments will be collected at the time points shown in **Appendix 3**.

12 ADVERSE EVENT REPORTING AND ASSESSMENT OF SAFETY

The safety assessment will be based on the evaluation of AEs that occur from the time of initiation of administration of study drug through the End of Treatment Visit or 30 days after the last dose of study drug (whichever is later) and will be determined based on signs, symptoms, physical examination findings, and/or laboratory test results from enrolled patients, as appropriate.

Protocol-related AEs and SAEs will be collected from the time the patient has consented to study participation. AEs and SAEs reported between the time the patient signs the informed consent form and the administration of the first dose of study drug will be captured as medical history unless the events are attributed to protocol-specified procedures that are not part of standard of care that occur during this time period, in which case the events will be collected on the SAE Form (as appropriate) and the Adverse Event CRFs.

SAEs considered related to study drug may be reported at any time, even after the patient's final visit.

Progression of the underlying neoplasm resulting in hospitalization or death (e.g., patient hospitalized for or dies from progressive disease [PD] only, without any other SAE) will be documented as an antitumor activity outcome and not as an SAE. If an SAE occurs in a patient and it is unclear whether the event is related to PD, the SAE should be reported.

- A laboratory abnormality should be reported as an AE if it is associated with an intervention. An intervention includes, but is not limited to, discontinuation of treatment, dose reduction/delay, or concomitant therapy. In addition, any medical important laboratory abnormality may be reported as an AE at the discretion of the investigator. This includes laboratory abnormalities for which there are no interventions but the abnormal value(s) suggests a disease or organ toxicity. If clinical sequelae are associated with a laboratory abnormality, the diagnosis or medical condition should be reported (e.g., renal failure, hematuria) not the laboratory abnormality (e.g., elevated creatinine, Urine RBC increased).

12.1 Definitions

12.1.1 Adverse Event

Adverse event means any untoward medical occurrence in a patient or clinical trial patient associated with the use of a drug in humans, whether or not considered drug related. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

12.1.2 Adverse Drug Reaction

Adverse drug reaction (ADR) is a noxious and unintended response to the medicinal product related to any dose. As used herein, the phrase "response to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility.

12.1.3 Adverse Event of Special Interest

An adverse event of special interest (AESI) is an event of scientific and medical interest or concern to the Sponsor's product or program, for which ongoing monitoring and rapid communication to the Sponsor could be appropriate. It may be a serious or non-serious AE, which may require further investigation in order to characterize and understand it.

12.1.4 Attribution/Assessment of Causality

Attribution/Assessment of Causality is a determination that describes the relationship or association of the study product with an adverse event.

This assessment of causality or relationship of AEs to the study drug is provided by the investigator and is determined by 1) temporal relationship of the event to the administration of study drug; 2) whether an alternative etiology has been identified, and 3) biological plausibility. Causality must be assessed separately for each study drug.

The causality assessment categories that will be used for this study are described below.

Causality assessments that are considered **not related** to study drug:

None: The event is related to an etiology other than the study drug (the alternative etiology should be documented in the patient's medical record).

Unlikely: The event is unlikely to be related to the study drug and likely to be related to factors other than study drug. An alternative explanation is more likely (e.g., concomitant drugs, concomitant disease), or the relationship in time suggests that a causal relationship is unlikely.

If an SAE is considered "unlikely" or "unrelated" to study drug, the Investigator should offer his/her clinical opinion as to what factor(s), agent(s), or process(es) were the likely causative mechanism for the event.

Causality assessments that are considered **related** to study drug:

Possible: There is an association between the event and the administration of the study drug and there is a plausible mechanism for the event to be related to study drug; but there may

also be alternative etiology, such as characteristics of the patient's clinical status or underlying disease.

Probable: There is an association between the event and the administration of study drug; there is a plausible mechanism for the event to be related to the study drug and the event could not be reasonably explained by known characteristics of the patient's clinical status or an alternative etiology is not apparent.

Definite: There is an association between the event and the administration of study drug; there is a plausible mechanism for the event to be related to the study drug, causes other than the study drug is ruled out, and/or the event re-appeared on re-exposure to the study drug.

12.1.5 Serious Adverse Event

A SAE is any adverse event that results in any of the following outcomes:

- Death
- Life-threatening (immediate risk of death)
- Inpatient hospitalization for longer than 24 hours or prolongation of existing hospitalization (even if the event is Grade 1)
- Persistent or significant disability or incapacity
- Congenital anomaly/birth defect
- Important medical events

12.1.6 Severity Criteria

An assessment of severity grade will be made using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) (Version 4.03). The CTCAE are published standardized definitions for AEs to describe the severity of laboratory and organ toxicity for patients receiving cancer therapy. The investigator should use clinical judgment in assessing the severity of events not directly experienced by the patient (e.g. laboratory abnormalities).

For events not contained in CTCAE, the Investigator may assign intensity according to the following generic CTCAE grading scale:

- Grade 1 Mild; asymptomatic or mild symptoms, clinical, or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).

- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

12.2 Adverse Event Collection and Documentation

12.2.1 All Adverse Events

All patients who receive at least one dose of study drug will be considered evaluable for safety. AEs will be determined based on signs, symptoms, physical examination findings, and/or laboratory test results from enrolled patients as appropriate.

All adverse events whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until 30 days following the last dose of study drug or until the start of a subsequent systemic anti-cancer therapy, if earlier.

Both protocol-related AEs and SAEs will be collected from the time the patient has consented to study participation. AEs and SAEs reported between the time the patient signs the informed consent form and the administration of the first dose of study drug will be captured as concurrent medical history unless the events are attributed to protocol-specified procedures. Events attributed to protocol-specified procedures will be collected on the Adverse Event eCRFs and Serious Adverse Event form as appropriate.

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the eCRF. All records will need to capture:

- The details of the duration, severity, and seriousness of each adverse event,
- the action taken with respect to the study drug(s),
- the investigator’s attribution/causality assessment concerning the relationship of the adverse event to study therapy,
- the outcome of the event.

Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g. cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). All treatment measures that are required for adverse event management must be recorded in the source document. The intensity (severity) of adverse events will be assessed using NCI CTCAE (Version 4.03) and serious events will

be determined by the definition provided in **Section 12.1.5** above. Generally, all non-serious AEs should be entered into the eCRFs within 5 business days of the sites awareness.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The Sponsor will also report to the investigator all suspected unexpected serious adverse reactions. The investigator must report suspected unexpected serious adverse reactions to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol, unless otherwise required and documented by the IEC/IRB.

For this study, the patient must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study.

12.2.2 Immediately Reportable Events

Immediately Reportable Events (IREs) are events that must be reported immediately to MacroGenics within 24 hours of the study site's awareness of the event.

- SAEs
- Pregnancy in a study patient or partner of a study patient. [Note: If the female partner of a male patient becomes pregnant, the partner must be requested to complete a Pregnant Partner Consent Form so that pregnant partner, fetal and/or newborn information can be collected.] Upon confirmation of serum pregnancy testing, the patient will be followed for the outcome of pregnancy. All live newborns will be followed 6 months after the birth, and all necessary information will be collected to assess the effects of study drug on the newborn. If necessary, the follow-up period will be extended for the newborn.
- The following AESIs (**Section 12.2.4**):
    - ≥ Grade 3 IRRs or CRS
    - Grade 2 or greater immune-related AEs of the following: events of colitis, pneumonitis, hepatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), myocarditis, nephritis, hypophysitis, and hypo/hyper-thyroidism which are considered immune-mediated events
    - Abnormal liver enzymes that meet the criteria for potential Hy's law, which is defined as AST and/or ALT that is greater than 3 × ULN and total bilirubin that is greater than 2 × ULN and without any alternate etiology
    - Grade 2 or greater diarrhea associated with visible blood in the stool or melena
    - Any Grade 3 or greater diarrhea irrespective of evidence of GI bleeding
- Administration of a dose significantly greater (specifically, + 20% or higher) than the planned dose, and results in an event of clinical consequence.

- AEs leading to permanent discontinuation of study drug in an individual patient.
- Withdrawal of the patient from study drug administration for any reason other than disease progression.

In those cases, in which the IRE is considered related to study drug, the study drug may be discontinued, and the patient will continue participation in the study for observational safety and analysis (except for cases where the patient is withdrawn from the study by the Investigator or withdrew the consent). At any time after completion of the study, if an Investigator becomes aware of a serious adverse event that s/he suspects is related to study drug, the Investigator should report the event to MacroGenics Product Safety.

12.2.3 Serious Adverse Events

All SAEs occurring during the study must be reported to the Sponsor.

After 30 days following the last dose of study drug administration, only SAEs the Investigator believes considered related to study drug or a protocol procedure, should be reported to the Sponsor.

Information regarding SAEs will be transmitted to the Sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site and transmitted to the Sponsor within 24 hours of the site becoming aware of the serious adverse event. The initial and follow-up serious adverse reports should be scanned and emailed or transmitted by facsimile (fax) to the Sponsor.

All Grade 3 or Grade 4 SAEs considered related to study drug must be followed until recovery to baseline or Grade 1.

The Investigator must follow all SAEs until resolution and record the date of resolution. Resolution of an event is defined as the return to pre-treatment status or stabilization of the condition with the expectation that it will remain chronic.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the patient 's participation in the study, must be followed until any of the following occurs:

- The event resolves.
- The event stabilizes.
- The event returns to baseline, if a baseline value/status is available.

- The event can be attributed to etiology other than the study drug or to factors unrelated to study conduct.
- It becomes unlikely that any additional information can be obtained (patient or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a patient's participation in a study must be reported as a SAE, except hospitalizations for the following:

- A standard hospitalization for administration of study drug therapy will not be reported as a serious adverse event.
- A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling, pharmacokinetic or biomarker blood sampling).
- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care or hospice facility).
- Surgery or procedure planned before entry into the study (must be documented in the eCRF).

Disease progression should not be recorded as an AE or SAE term; events related to disease progression/worsening of underlying disease (including those with a fatal outcome) will be collected as efficacy endpoints and not documented as AEs/SAEs. These events may not qualify for expedited reporting to regulatory agencies if consistent with expected rates of progression for the underlying disease. However, if an SAE occurs in a patient and it is unclear if the event is due to progressive disease, the SAE should be reported.

12.2.4 Protocol-specific Adverse Events of Special Interest

Specific adverse events or groups of adverse events will be followed as part of standard safety monitoring activities by the Sponsor. The Sponsor will be notified of these events in a timely manner, regardless of seriousness (i.e., serious and non-serious adverse events).

- All infusion-related reactions or CRS events (Note: ≥ Grade 3 IRRs or CRS events are additionally considered immediately reportable events) (see **Section 7.2**)
- Grade 2 or greater Immune related AEs of the following: events of colitis, pneumonitis, hepatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), myocarditis, nephritis, hypophysitis, and hypo/hyper-thyroidism which are considered immune-mediated events (see **Section 7.5**)

- Abnormal liver enzymes that meet the criteria for potential Hy's law, which is defined as AST and/or ALT that is greater than 3 × ULN and total bilirubin that is greater than 2 × ULN and without any alternate etiology
- Grade 2 or greater diarrhea associated with visible blood in the stool or melena
- Any Grade 3 or greater diarrhea irrespective of evidence of GI bleeding

12.2.5 Pregnancy

All initial reports of pregnancy in female patients or partners of male patient s must be reported to the Sponsor by the study-site personnel within 24 hours of their knowledge of the event using the MacroGenics Pregnancy Exposure Form. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the Serious Adverse Event Form. Any patient who becomes pregnant during the study must discontinue further study drug administration.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male patient is included in the study will be reported by the study-site personnel within 24 hours of their knowledge of the event. If the female partner of a male patient becomes pregnant, the partner must be requested to complete a Pregnant Partner Consent Form so that pregnant partner, fetal and/or newborn information can be collected.

Upon confirmation of serum pregnancy testing, the patient will be followed for the outcome of pregnancy. All live newborns will be followed at birth and 6 months after birth, and all necessary information will be collected to assess the effects of study drug on the newborn. If necessary, the follow-up period will be extended for the newborn.

12.2.6 Reporting of Adverse Events to the Sponsor

Throughout the study, the Investigator must document all AEs on the eCRF in a timely manner. IREs, as defined in **Section 12.2.2** are events that must be reported immediately to MacroGenics within 24 hours of being identified. These IREs must be transmitted via an SAE form (if the event meets serious criteria) or be entered into the eCRFs within 24 hours of awareness; see **Table 9**.

The Investigator must immediately complete and transmit the Serious Adverse Event (SAE) Report Form, within 24 hours of identifying the serious adverse event, to MacroGenics Product Safety or designee. The SAE Report Form and Completion Guidelines, and Contact Information for Reporting SAEs, are found in the Study Procedures Manual.

For reports of pregnancy, the MacroGenics Pregnancy Exposure Form must be completed and transmitted to MacroGenics Product Safety within 24 hours of becoming aware of the pregnancy. The Investigator must attempt to follow the pregnancy to term or termination in order to report the outcome and health status of the mother and child. The Pregnancy Exposure Form is found in the Study Procedures Manual.

Please refer to the **Table 12** for reporting timeframes to MacroGenics by event type.

Table 12 CP-MGD007-02 Safety Reporting

Type of Event:	Hard Copy Form/Timeline for reporting/Where to Report	eCRF Timeline for Data Entry
Serious Adverse Event (SAE) *[a]	Serious Adverse Event Form within 24 hours of awareness Report mail to SAEReports@macrogenics.com Or fax to (301) 354-3800	Within 5 calendar days of awareness
Pregnancy [a]	Pregnancy Exposure Form/ Within 24 hours of awareness/ Email to SAEReports@macrogenics.com Or fax to (301) 354-3800	Within 5 calendar days of awareness
≥ Grade 3 IRRs or CRS [b]	Not Applicable*	Within 24 hours of awareness
Hy's law [b] (AST and/or ALT that is greater than 3 × ULN and total bilirubin that is greater than 2 × ULN, without any alternate etiology)	Not Applicable*	Within 24 hours of awareness
≥ Grade 2 immune-related AEs [b]	Not Applicable*	Within 24 hours of awareness
≥ Grade 2 diarrhea associated with visible blood in the stool or melena [b]	Not Applicable*	Within 24 hours of awareness
≥ Grade 3 diarrhea irrespective of evidence of gastrointestinal bleeding [b]	Not Applicable*	Within 24 hours of awareness
AEs leading to permanent discontinuation of study drug in a patient [b]	Not Applicable*	Within 24 hours of awareness
Withdrawal of patient from study drug administration due to toxicity (e.g. AE, SAE, AESI) or pregnancy [b]	Not Applicable*	Within 24 hours of awareness
Administration of a dose significantly greater (specifically, + 20% or higher) than the planned dose, and results in an event of clinical consequence [b]	Not Applicable*	Within 24 hours of awareness
Product quality issues with an associated clinical consequence [b]	Not Applicable*	Within 24 hours of awareness
Non-Serious Adverse Events (except for Pregnancy) [c]	Not Applicable	Within 5 calendar days of awareness

Abbreviations: AE = adverse event; AESI = adverse event of special interest; CRS = Cytokine Release Syndrome; eCRF=electronic case report form; IRR = infusion-related reaction; SAE = serious adverse event.

*If it meets SAE criteria – refer to SAE reporting instructions

a Hard Copy Form within 24 hours of awareness and eCRF data entry within 5 calendar days.

b E-CRF data entry within 24 hour of awareness.

c E-CRF data entry within 5 calendar days of awareness.

13 PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, i.e., any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patient s, investigators, and the Sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the Sponsor or its affiliates will be conducted in accordance with those procedures.

13.1 Procedures

All initial clinical PQCs must be reported to the Sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a SAE, the study-site personnel must report the PQC to the Sponsor according to the SAE reporting timelines (refer to **Section 12.2.3**, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the Sponsor.

13.2 Contacting Sponsor Regarding Product Quality

Report any product quality issue via e-mail to the following:
Quality.complaints@macrogenics.com.

14 STATISTICAL ANALYSIS

This section outlines the statistical methodology and principles which will be used for data analysis in this study. A separate statistical analysis plan (SAP) and statistical programming plan (SPP) will further describe the details regarding statistical methods and will govern the analysis.

14.1 Determination of Sample Size

The study plans to treat approximately 52 patients: up to 27 in Dose Escalation Phase and approximately 25 in the Cohort Expansion Phase.

The sample size of up to 27 patients for each cohort in the Dose Escalation Phase is based on 3+3+3 design with planned 3 dose cohorts. Additional patients may be enrolled for nonevaluable patients or if the enrollment to a dose cohort is expanded (up to 15 patients) or intermediate dose levels are evaluated in Dose Escalation Phase.

The Cohort Expansion Phase plans to treat approximately 25 patients in relapsed/refractory metastatic colorectal carcinoma, approximately 90% of them are MSS patients, e.g., 22 MSS and 3 MSI-H patients. At the end of the Cohort Expansion Phase, 15 paired tumor biopsies will be required, if tumor lesions are accessible with acceptable clinical risk (see **Section 5.1, # 9)**. If 15 paired biopsies have not been collected in the initial 25 patients, additional patients with paired tumor biopsies will be enrolled, to ensure that the 15 paired biopsies are obtained.

The sample size in the Cohort Expansion Phase is primarily based on providing preliminary estimation of objective response rate and disease control rate. **Table 13** provides the 2-sided 95% confidence interval (CI) for a number of potential responses among the 25 patients.

Table 13 Response Rates and 95% Confidence Intervals

Sample Size	Number of Responses	Response Rate (%)	95% Confidence Interval (%)
25	2	8	1.0, 26.0
25	3	12	2.5, 31.2
25	4	16	4.5, 36.1
25	5	20	6.8, 40.7
25	6	24	9.4, 45.1
25	7	28	12.1, 49.4

During the Cohort Expansion Phase, patients who withdraw before completing the first tumor assessment for a reason other than clinically confirmed progressive disease or death may be considered unevaluable for response. In these cases, replacement patients may be enrolled in the same dose level.

14.2 Analysis Populations

The study analyses will be performed on the following populations:

- Safety Population: All patients who received at least one dose of any study drug. This population will be used for analyses of safety, PD, and immunogenicity. It will also be used for summary of baseline data and analyses of PFS and OS.
- Response Evaluable Population: All patients who received at least one dose of any study drug, had baseline measurable disease, and had at least one post-baseline radiographic tumor assessment or discontinued treatment due to clearly documented, clinically progressive disease or death. This population will be used for summary of tumor assessment data and analyses of response rates.

14.3 Demographics and Baseline Characteristics

Patient disposition, demographics, baseline characteristics, disease history, medical history, and prior cancer treatment will be summarized using descriptive statistics.

14.4 Study Drug Exposures and Concomitant Medications

Study drug exposures and concomitant medications will be summarized by descriptive statistics. The summary of study drug exposure will include descriptive statistics as well as frequency counts for the number of doses or cycles received, the total dose actually administrated as well as the total dose intended, and the dose intensity which is calculated as percentage of total dose actually administrated divided by total dose intended during whole treatment period. Dose intensity by cycle will be summarized.

14.5 PK/PD Analysis

14.5.1 Pharmacokinetic Analysis

Summary statistics will be tabulated separately for serum PK parameters by MGD007 and MGA012 dose. Geometric means and percent coefficients of variation will be reported for C_{max}, $AUC_{(0\ T)}$, $AUC_{(TAU)}$, $AUC_{(INF)}$, and C_{trough}; arithmetic means and standard deviations will be reported for $t_{1/2}$, CL, and V_{ss}; and medians, minimum, and maximum will be reported for T_{max}. Separate scatter plots of C_{max} and AUC will be provided versus dose to assess dose dependency. Dose proportionality may be assessed using a power model. Population PK analyses may be conducted using data from this study alone or combined with data from other studies.

14.5.2 Immunogenicity Analysis

The proportion of patients who are negative for ADA at baseline and become positive in this assay, the proportion of patients who are negative at baseline and remain negative, and those who have positive ADA at baseline that increases or decreases in titer over the course of treatment will be summarized. Analysis will be conducted separately for MGD007 and MGA012.

14.5.3 Pharmacodynamic Analysis

Summary statistics for pharmacodynamic parameters, such as, but not limited to, those listed under in **Section 10.2** and corresponding changes from baseline, will be summarized and/or may also be presented graphically as will possible associations between changes in pharmacodynamic measures of interest and MGD007 in combination with MGA012 dose and exposure may be explored.

14.6 Efficacy and Endpoint Analyses

14.6.1 Response Endpoints and Analyses

For RECIST v1.1, the best overall response (BOR) will be categorized as CR, PR, SD, PD, or NE. To be qualified as BOR, CR and PR require confirmation at least 4 weeks after initial observation of such response, and SD requires to be observed at least once after 8 weeks (minus 3 days) from the start of MGD007 treatment.

For irRECIST, the best overall response (BOR) will be categorized as irCR, irPR, irSD, irPD, or irNE. To be qualified as BOR, irCR, irPR, and irPD require confirmation at least 4 weeks after initial observation of such response, and irSD requires to be observed at least once after 8 weeks (minus 3 days) from the start of MGD007 treatment.

The objective response rate (ORR) per RECIST v1.1 is estimated as the proportion of patients in response evaluable population who achieve BOR of CR or PR. Disease control rate is calculated as the proportion of patients who achieve a CR, PR, or SD. Progression-free

survival rate at 16 weeks will be calculated as the probability that patients are free of disease progression and alive at 16 weeks after the first dose of MGD007 by Kaplan-Meier method described below, based on response evaluable population and safety population, respectively. The 2-sided 95% exact binomial CI of the response rates will be calculated. The response rates per irRECIST will be estimated similarly. Subgroup analyses of these response rates by KRAS gene type (wild and mutant) and by MMR status (MSS and MSI-H) will be performed.

14.6.2 Analysis of Tumor Size Change Over Time

The tumor size is defined as the sum of diameters of the target lesions. The tumor size change from baseline over time will be summarized and may be presented by spider plot. The best tumor size percent change from baseline will be presented by waterfall plot.

14.6.3 Time-to-event Endpoints and Analyses

Progression-free survival will be defined as the time from the first dose date of MGD007 to the date of first documented progression or death from any cause, whichever occurs first. The documented progression is determined by objective assessment of disease per RECIST v1.1 and irRECIST, respectively. For patients who are not known to be dead or progressed at the time of data cut-off for PFS analysis, the PFS will be censored at the date of the last tumor assessment. Specifically, the following censoring rules will be applied as primary analysis of PFS. Sensitivity analyses may be performed to assess the robustness of the primary PFS analysis and will be described in the SAP.

Table 14 Censoring Rules for Primary Analysis of PFS

Situation	Date	Outcome
No baseline tumor assessments	First dose date	Censored
Death prior to first scheduled tumor assessment	Date of death	Progressed
No post-baseline tumor assessments in absence of death prior to first scheduled tumor assessment	First dose date	Censored
Documented progression	Date of progression	Progressed
Initiation of alternative anti-cancer treatments in absence of documented progression	Date of last tumor assessment prior to initiation of such treatment	Censored
Death or documented progression immediately after missing two or more consecutive scheduled tumor assessments	Date of last tumor assessment prior to missed assessments	Censored

Duration of Response (DoR) is defined as the time from the date of initial response (CR or PR) to the date of first documented progression or death from any cause, whichever occurs first. The DoR is calculated only for the responders. For responders who are not known to be

dead or progressed at the time of data cut-off for DoR analysis, the DoR will be censored at the date of the last tumor assessment. Specifically, the last three situations described in **Table 14** will be applied. The DoR analyses will be performed only if there are enough responders to render the analyses meaningful.

Overall survival (OS) is defined as the time from the first dose date of MGD007 to the date of death from any cause. For patients who are not known to be dead at the time of data cut-off for OS analysis, the OS will be censored at the time they are last known to be alive.

The Kaplan-Meier method will be applied to estimate PFS, DoR, and OS curves; their median times; PFS rates at 4 (corresponding to 16 weeks), 6, and 12 months; and OS rates at 6, 12, and 24 months, respectively. The method of Brookmeyer and Crowley **(3)** will be used to construct 95% CI for median time of each time-to-event endpoint. The 95% CIs for PFS and OS rates at each time point of interests will be calculated by normal approximation after log(-log) transformation. PFS and OS will be analyzed by MMR status and by KRAS gene type when sample size warrants.

The above PFS and DoR analyses will be performed with the documented progression determined by RECIST v1.1 and irRECIST, respectively.

14.7 Safety Endpoints and Analyses

14.7.1 Adverse Events

Only treatment-emergent AEs will be summarized in tables. The following AEs will be provided in summary tables as well as displayed in listings:

- All AEs
- AEs with CTCAE severity grade ≥ 3
- Study drug related AEs
- Study drug related AEs with CTCAE severity grade ≥ 3
- SAEs
- Study drug related SAEs
- AEs that result in discontinuation of study treatment
- AEs that led to interruption or withdrawal of individual study drug
- Fatal AEs
- Immediately reportable AEs (if applicable)
- AEs of special interest (if applicable)

All of these tables will display the number and percent of patients that experience the given event and will display events by MedDRA System Organ Class (SOC) and Preferred Term (PT). Events will be displayed alphabetically for SOC and in descending order of overall PT incidence. An overall summary of AEs will display the number and percent of patients who experience at least one event of each of the above types.

14.7.2 Laboratory Values

Summaries of laboratory values will display descriptive statistics for numerically quantified labs. Summaries will be grouped by laboratory panel (hematology, blood chemistry, and urinalysis) and will be displayed by visit for each laboratory parameter. Number and percent of patients shifted from baseline to post-baseline maximum severity in CTCAE grade will be summarized.

14.7.3 Other Safety Endpoints

ECGs will be collected and analyzed for evidence of cardiac toxicity, especially prolongation of QT interval. Vital signs will be summarized with descriptive statistics at each visit and time point where they are collected. Shift tables may be performed.

14.8 Other Assessments or Analyses

Additional analyses, if any, will be described in the statistical analysis plan.

15 QUALITY CONTROL AND ASSURANCE

Quality review activities will be undertaken to ensure accurate, complete, and reliable data. MacroGenics and/or its representatives will do the following:

- Provide instructional material to the study sites, as appropriate.
- Sponsor a start-up training session (Investigator Meeting or Study Initiation Visit) to instruct the Investigators and study coordinators. This session will give instruction on the protocol, the completion of the eCRFs, and study procedures.
- Make periodic visits to the study site to monitor protocol compliance and general Good Clinical Practice GCP compliance.
- Be available for consultation and stay in contact with the study site personnel by mail, e-mail, telephone, and/or fax.
- Review and evaluate eCRF data and use standard computer checks to detect and query errors in data collection.
- Conduct a quality review of the database.

15.1 Monitoring, Auditing and Inspections

To ensure the safety of patients in the study, compliance with applicable regulations, and ensure accurate, complete, and reliable data, the Investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as source documents for the study.

MacroGenics or its designee will monitor the study on a regular basis throughout the study period according to the study Monitoring Plan. The Investigator will allocate adequate time for such monitoring activities. The study monitor periodically will conduct a cross-check of the patient data recorded on eCRFs against source documents at the study site. The Investigator will also ensure that the monitor is given access to all the above noted study-related documents, source documents (regardless of media) and study-related facilities (e.g., investigational pharmacy, etc.), and has adequate space to conduct the monitoring visit. Queries may be raised if any datum is unclear or contradictory. The Investigator and study site personnel must address all queries in a timely manner.

Participation as an Investigator in this study implies acceptance of the potential for inspection by the study Sponsor/Representatives, US or non-US government regulatory authorities, IRB/IEC and applicable compliance and quality assurance offices. The Investigator will permit study-related audits and inspections and will provide access to all study-related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.). The Investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

15.2 Data Collection and Management

The Investigator is responsible for maintaining accurate, complete, and up-to-date records for each patient. The Investigator is also responsible for maintaining any source documentation related to the study, including any films, tracings, or other media containing data pertaining to this protocol.

The anonymity of participating patients must be maintained. For data collection, and management purposes, patients are to be identified by a patient number only. Documents that identify the patient beyond patient number (e.g., patient initials) will not be submitted to the Sponsor (e.g., the signed informed consent document) and must be maintained in strict confidence by the Investigator, except to the extent to allow auditing by the regulatory authorities, study monitor, or Sponsor representatives.

Site personnel record all data for each patient through electronic case report forms (eCRFs) using the Medidata RAVE™ an Electronic Data Capture (EDC) system provided and approved by the Sponsor. Refer to the Study Procedures Manual for additional information regarding eCRFs, if any that will be used as source documentation. Study sites must complete eCRFs for each patient in a timely manner shortly after each patient visit. As the person ultimately responsible for the accuracy of all eCRF data, the Investigator must sign the Investigator's Statement in each patients eCRF.

The EDC system automatically generates queries resulting from the computer checks embedded into the system to ensure data accuracy, quality, consistency, and completeness. Manual queries resulting from review by monitors, medical coders, and Data Management staff are also generated from within the EDC system, where they are tracked. Study sites resolve the queries and correct the entered data accordingly. Every change to data is captured in the EDC system audit trail. Adverse events are coded using MedDRA, whereas concomitant medications are coded using the WHO Drug Dictionary. Upon completion of the study, or after reaching a pre-specified point in the study, Data Management will lock the database and generate the SAS datasets necessary for analysis and reporting. Upon completion of the study, each study site will be provided with the eCRFs for each of their patients.

16 ADMINISTRATIVE CONSIDERATIONS

16.1 Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Approval

The Investigator should provide the Sponsor with a statement of compliance from the IRB/IEC indicating compliance with the applicable regulations in the region and ICH. Any documents that the IRB/IEC may need to fulfill its responsibilities, such as the protocol and any amendments, IB, and information concerning patient recruitment, payment or compensation procedures, or information from the Sponsor will be submitted to the IRB/IEC. The IRB/IEC's written approval of the study protocol and the informed consent forms (ICFs) will be in the possession of the Investigator and the Sponsor before the study drug is initiated at the Investigator's site. The Investigator will transmit the IRB/IEC's approval statement to the Sponsor. This approval must include the date of review and refer to the study by protocol title and/or study number and version number and refer to the ICFs by version number or date. If the IRB/IEC or institution uses its own unique number for the protocol instead of the Sponsor's number, that unique number should be noted on the approval statement. If approval of the ICFs is stamped on the forms (instead of documented in the IRB/IEC approval statement) the date of approval and/or expiration must be included.

Protocol modifications or changes may not be initiated without approval from the Sponsor and prior written IRB/IEC approval (when required), except when necessary to eliminate immediate hazards to the patients. Such modifications will be submitted to the IRB/IEC; and written verification that the modification was submitted should be obtained.

The Investigator must, where required by local regulations, submit to the IRB/IEC:

- The protocol and the Investigator's Brochure (IB) and any amendments or updates.
- The informed consent form(s) and any amendments or changes.
- Any documents given to patients or potential patients (e.g., recruitment materials, diary cards) and the plan for distribution/use.
- Revisions of other documents originally submitted for review or for notification.
- Serious and/or unexpected AEs occurring during the study.
- New information that may adversely affect the safety of patients or conduct of the study.
- At minimum, an annual update and/or request for re-approval of study, unless otherwise specified by IRB/IEC.
- Protocol deviations.
- Notification when the study has been completed.
- Proof of indemnity/liability insurance.
- Other documents required by the IRB/IEC.

16.2 Ethical Conduct of the Study

The investigational study will be conducted according to the Protection of Human Patients (21 CFR [Code of Federal Regulations] 50), Institutional Review Boards (21 CFR 56), Obligations of Clinical Investigators (21 CFR 312.60 312.69), the current ICH Guideline for Good Clinical Practice (ICH E6), and all other applicable regulations.

16.3 Patient Information and Consent

It is the responsibility of the Investigator to obtain and document written informed consent from the patient. Informed consent in compliance with the principles of informed consent in ICH E6 and all applicable local regulations should be obtained before any protocol-specified procedures or interventions are conducted. The Sponsor reserves the right to delay initiation of the study at a site where ICFs do not meet the standards of applicable local regulations or ICH E6.

Information should be given to the patient in both oral and written form, and patients must be given ample opportunity to inquire about details of the study.

The consent form generated by the Investigator must be approved by the IRB/IEC. The Investigator will provide the Sponsor with a copy of the IRB/IEC-approved consent forms and a copy of the IRB/IEC's written approval before the start of the study.

Consent forms must be written (and appropriately translated in the patient's native language or language in which the patient has fluency) so as to be understood by the prospective patient. Informed consent will be documented by the use of a written consent form approved by the IRB/IEC. The form must be signed and dated by the patient, and by the person who conducted the discussion of the informed consent.

All versions of each patient's signed ICF must be kept on file by the Investigator for possible inspection by regulatory authorities and/or authorized MacroGenics monitoring and regulatory compliance persons. The patient should receive a copy of the signed and dated written ICF and any other written information provided to the patients.

16.4 Patient Confidentiality

To maintain confidentiality of patients, all laboratory specimens, evaluation forms, reports, and other records will be identified by a coded number. Clinical information will not be released without written permission of the patient, or an individual with legal decision making authority for the patient or the patient's interests, except as necessary for monitoring by the relevant regulatory authorities, the Sponsor of the clinical study, or the Sponsor's representative. The Investigator must also comply with all local applicable privacy regulations [e.g., US Health Insurance Portability and Accountability Act of 1996 (HIPAA)], on protection of individuals with regard to personal data.

16.5 Case Report Forms and Study Records

Source data in a clinical study are the original records or certified copies where clinical observations are first recorded, which may include, but are not limited to, the patient's medical file, original laboratory reports, histology, and pathology reports (as applicable). The Investigator is responsible for maintaining adequate and accurate medical records from which accurate information will be entered into the eCRFs designed to capture data pertinent to the clinical investigation. Data should be recorded on paper source documents or electronic in an electronic medical records system. Electronic CRFs should be completely in their entirety by the Investigator or his/her designee. Prior to eCRF database lock, the Investigator will verify the completeness and accuracy of the data and indicate that he/she has done so by providing an electronic signature on the appropriate eCRF. The Investigator will retain a copy of all source documents.

16.6 Access to Source Documentation

The Investigator and study center will permit the Sponsor, its representatives, IRB/IEC, and all relevant regulatory agencies access to all original source data and documents regardless of media, for study monitoring audits and inspections.

16.7 Retention of Data

Per ICH guidelines, all essential documents, including eCRFs, source documents (regardless of media), signed ICFs, and laboratory test results, should be retained by the Investigator for at least 2 years after last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. There may be other circumstances for which MacroGenics is required to maintain study records for longer periods; therefore, MacroGenics should be contacted before study records are removed from the control of the study site for any reason. The Investigator must obtain written permission from MacroGenics prior to destruction of study documents.

16.8 Sample Retention and Further Testing

Samples acquired for protocol-specified assays will be retained for at least 1 year following the end of the study and may be retained up to 2 years after last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. If patients consent, or an individual with legal decision making authority for the patient or the patient's interests consent, to the use of their study samples for non-study research purposes, these samples may also be used for exploratory testing (including assay development/ optimization) and may be retained up to 15 years from the end of study.

16.9 Financial Disclosure

The Investigator and Sub-Investigators will be required to disclose any applicable financial arrangement as defined in US regulation (i.e., 21 CFR 54).

The following information will be collected about the investigators, their spouse and each dependent child: any significant payments of other sorts from MacroGenics, Inc., or any alliance partner, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in the study drug; and any significant equity interest in MacroGenics, Inc., as defined in 21 CFR 54. Investigators are obliged to update the Sponsor with any changes in reported information up to 1 year following the end of the study.

In addition, Investigators and Sub-Investigators will be required to disclose if they are an employee of MacroGenics, or an immediate family member of a MacroGenics employee, officer, or director. This is in order to assist MacroGenics with its compliance with Securities and Exchange Commission rules requiring disclosure of certain transactions with related persons as defined in 17 CFR 229.404. “Immediate family member of a MacroGenics employee” means a child, stepchild, parent, stepparent, spouse, sibling, mother-in-law, father-in-law, son-in-law, brother-in-law, or sister-in-law of any MacroGenics employee, officer, or director or any person sharing the household of such MacroGenics employee, officer, or director.

In consideration of participation in the study, MacroGenics, will pay the Investigator or nominated payee the sums set out in the payment schedule attached to the Investigator agreement.

Financial disclosure information will be documented in writing and signed and dated by the Investigator. This information will be collected prior to that investigator taking part in the research.

16.10 Publication and Disclosure Policy

Data collected in this clinical study belong to the study Sponsor. The publication terms regarding use of the study data will be noted in the Clinical Trial Agreement. This includes authorship: scheduling and prioritizing analyses for reports, publications, and presentations; and developing a review and approval process.

16.11 Discontinuation of the Study or Study Sites

16.11.1 Discontinuation of Study Sites

Site participation may be discontinued if MacroGenics, the Investigator, a regulatory authority, or the IRB/IEC of the study sites deems it necessary for any reason.

16.11.2 Discontinuation of the Study

The study may be discontinued by a regulatory authority or at the discretion of the Sponsor.

The Investigator maintains the right to discontinue his/her participation in the study should his/her clinical judgment so dictate. The Investigator will notify the IRB/IEC of any study discontinuation. Study records must be retained as noted above.

16.12 Identification of the Coordinating Principal Investigator

A Coordinating Principal Investigator will be appointed by the Sponsor Medical Monitor prior to the end of the study.

As part of his or her responsibilities, the Coordinating Principal Investigator will review the final clinical study report (CSR). Agreement with the final CSR will be documented by the dated signature of the Coordinating Principal Investigator.

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Appendix 1 Time and Events Schedules: QW Cohort

QW Cohort																	
		Cycle 1								Cycle 2 and Subsequent Cycles							
EVALUATION/ PROCEDURE	**Screening [1]**	**Day 1**	**Day 2 [4]**	**Day 8 (± 1day)**	**Day 15, 29, 43 (± 1day)**	**Day 16,17, 19 [4]**	**Day 22, 36, 50 (± 1day)**	**Day 42 (± 5 days)**	**Day 56 (± 3 days)**	**Day 1 (± 1day)**	**Day 2 [4]**	**Day 8 (± 1day)**	**Day 15, 29, 43 (± 1day)**	**Day 22, 36, 50 (± 1day)**	**Day 56 (± 3 days)**	**EOTV [2]**	**Post-treatment Follow up [3]**
STUDY DRUG ADMINISTRATION (patients may switch to MGA012 monotherapy after receiving 2 full cycles of MGD007 and MGA012 treatment)																	
Administer MGA012					X					X			X				
Administer MGD007		X		X	X		X			X		X	X	X			
ELIGIBILITY																	
Informed Consent	X																
Baseline Tumor Imaging	X																
Designate Target/ Non-Target Lesions	X																
See **Appendix 5**.																	
Medical History/Cancer Disease History	X																
Medical history/Cancer Disease History: History will be collected during Screening, up through the first dose of study drug.																	
Weight	X	X		X	X		X			X		X	X	X		X	
Physical Exam	X	X								X						X	
Physical Exam: Height (screening only) and examination of skin, head, eyes, ears, nose, throat, lymph nodes, heart, chest, lungs, abdomen, extremities, and neurologic systems.																	
Directed History/Physical				X	X		X					X	X	X			
Directed Physical Exam: To be guided based on review of systems and patient history																	
Archival Tumor Specimen	X																
All patients to be enrolled in the study must have an identified formalin-fixed, paraffin embedded tumor specimen and/or tumor specimens sufficient for 20 slides. The specimens will be analyzed retrospectively and will not be used to determine patient eligibility.																	
Premedication and prophylaxis	Required pre-meds and prophylaxis include: Oral budesonide, IV dexamethasone and nonsteroidal supportive care medications. All pre-med and prophylaxis requirements are detailed in **Section 7.1**.																
Concomitant Medications	---Continuous---																
ECOG PS	X									X						X	
ECG	X	X			X					X			X			X	
Electrocardiogram: To be performed in triplicate (approximately 1 minute apart). **Screening**: ECG will be taken at one timepoint. Cycle 1 Day 1: pre-infusion (before the start of infusion on visit day), end of infusion (± 10 min of the EOI). **Cycle 1 Day 15 and subsequent doses of MGD007 and MGA012 combined:** pre-infusion of MGA012 (before the start of infusion on visit day), end of infusion of MGD007 (± 10 min of the EOI);																	

QW Cohort																	
		Cycle 1								Cycle 2 and Subsequent Cycles							
EVALUATION/ PROCEDURE	**Screening [1]**	**Day 1**	**Day 2 [4]**	**Day 8 (± 1day)**	**Day 15, 29, 43 (± 1day)**	**Day 16,17, 19 [4]**	**Day 22, 36, 50 (± 1day)**	**Day 42 (± 5 days)**	**Day 56 (± 3 days)**	**Day 1 (± 1day)**	**Day 2 [4]**	**Day 8 (± 1day)**	**Day 15, 29, 43 (± 1day)**	**Day 22, 36, 50 (± 1day)**	**Day 56 (± 3 days)**	**EOTV [2]**	**Post-treatment Follow up [3]**
at End of Treatment Visit ECG will be taken at one timepoint.																	
Pregnancy Test	X	X								X						X	
Pregnancy test: Serum or urine human chorionic gonadotropin (hCG) for women of childbearing potential should be performed at Screening visit and on Day 1 pre-infusion. Test results must be reviewed before the study drug infusion on Day 1 of Cycle 1 and all subsequent cycles. Testing should also be performed at the End of Treatment visit. If screening test is performed within 72 hours of 1st infusion, repeat of the test on Day 1 may be deferred.																	
Eligibility Checklist & Register Patient	X																
SAFETY/PK/MECHANISTIC STUDIES																	
Assess for Protocol Procedure Related AEs/SAEs	X																
Assess for Adverse Events		-----Continuous----															
The safety assessment will be based on the evaluation of AEs that occur from the time of initiation of administration of study drug through the End of Treatment Visit or 30 days after the last dose of study drug (whichever is later).																	
Vital Signs	X	X		X	X		X			X		X	X	X		X	
Vital Signs: Temperature, heart rate, blood pressure, and respiratory rate. **Screening**: Vital signs will be taken once. **Cycle 1 Days 1, 8, 22, 36, and 50 (MGD007 alone):** Vital signs will be taken immediately before the infusion (up to 10 minutes before the infusion); at 15 (± 5 min), 30 (± 5 min), and 60 minutes (± 10 min) after the start of the infusion; at the end of infusion (± 10 min); and at 1- and 4-hours after completion of the infusion (±10 min). The 4-hour post infusion vital signs may be deferred based on the judgment of the investigator for all days except Cycle 1 Day 1 **Cycle 1 Days 15, 29, 43 (MGA012 and MGD007 combined)**: Vital signs will be taken immediately before MGA012 infusion (up to 10 minutes before the infusion) and at the end of MGA012 infusion (±10 min); at 15 (± 5 min), 30 (± 5 min), and 60 minutes (± 10 min) after the start of MGD007 infusion; at the end of MGD007 infusion (± 10 min); and at 1- and 4-hours after completion of MGD007 infusion (±10 min). The 4-hour post infusion vital signs may be deferred based on the judgment of the investigator for all days except Cycle 1 Day 15. **Cycle 2 and Beyond (MGA012 and MGD007 combined):** Vital signs will be taken immediately before MGA012 infusion (up to 10 minutes before the infusion) and at end of MGA012 infusion (±10 min); at the end of the MGD007 infusion (± 10 min); and at 1 hour after completion of the infusion (±10 min). **Cycle 2 and Beyond (MGD007 alone):** Vital signs will be taken immediately before MGD007 infusion (up to 10 minutes before the infusion); at the end of the MGD007 infusion (± 10 min); and at 1 hour after completion of the infusion (±10 min). **At End of Treatment:** Visit vital signs will be taken once.																	
Hematology	X	X		X	X		X			X		X	X	X		X	
See **Appendix 2** for list of hematology assessments; To be taken pre-infusion. Labs can be taken up to 3 days before infusion.																	
Serum Chemistry	X	X		X	X		X			X		X	X	X		X	
See **Appendix 2** for list of chemistries; To be taken pre-infusion. Labs can be taken up to 3 days before infusion.																	
Coagulation	X	X		X	X		X			X		X	X	X		X	
See **Appendix 2** for list of coagulation assessments; To be taken pre-infusion. Labs can be taken up to 3 days before infusion.																	
Endocrine tests	X									X						X	

QW Cohort																	
		Cycle 1								Cycle 2 and Subsequent Cycles							
EVALUATION/ PROCEDURE	**Screening [1]**	**Day 1**	**Day 2 [4]**	**Day 8 (± 1day)**	**Day 15, 29, 43 (± 1day)**	**Day 16,17, 19 [4]**	**Day 22, 36, 50 (± 1day)**	**Day 42 (± 5 days)**	**Day 56 (± 3 days)**	**Day 1 (± 1day)**	**Day 2 [4]**	**Day 8 (± 1day)**	**Day 15, 29, 43 (± 1day)**	**Day 22, 36, 50 (± 1day)**	**Day 56 (± 3 days)**	**EOTV [2]**	**Post-treatment Follow up [3]**
See **Appendix 2** for list of endocrine tests; To be taken pre-infusion. Labs can be taken up to 3 days before infusion.																	
CEA	X									X						X	
CEA: At screening; Cycle 2, Day 1 pre-dose; Day 1 of every other cycle thereafter - predose																	
Urinalysis	X	X								X						X	
See **Appendix 2** for list of urinalysis test; To be taken pre-infusion. Labs can be taken up to 3 days before infusion.																	
Pharmacokinetic, Immunogenicity, and Pharmacodynamic Biomarkers	Sampling to be performed according to **Appendix 3**.																
Tumor biopsies on study (Cohort Expansion subjects only)	X							X									
On treatment tumor biopsy: Fresh tumor biopsy pre-treatment (after enrollment and prior to the Cycle 1 Day 1 dose) and at Cycle 1 Day 42 ± 5 days. Paired tumor biopsies will be mandatory if tumor lesions are accessible for biopsy with acceptable clinical risk in the judgment of the investigator and after discussion with the sponsor.																	
Tumor Assessment (CT/MRI)									X						X	X	
Tumor Assessment (CT/MRI): Radiographic disease assessments will occur on Cycle 1 Day 56 (±3 days) and then every 8 weeks. Assessment will also be done at End of Treatment Visit.																	
KRAS and MMR	X																
Formal documentation required for all patients in the Cohort Expansion Phase. Should be captured as part of cancer disease history. If unavailable during screening, this can be collected while on study.																	
Follow-up by phone or electronic contact	Overall Survival Follow-up: Documentation of overall survival follow-up described in protocol **Section 9.12.**																X

1 The Screening visit should occur within 28 days prior to Day 1.

2 The End of Treatment Visit should be performed after the patient has met off-treatment criteria and occur no later than 30 days since the last study dose and before any subsequent anti-cancer treatment; see **Section 9.11**.

3 Post-treatment follow-up collected every 3 months by phone or other electronic contact; response status, if available, will be collected every 3 months in patients who discontinued from study treatment due to reasons other than progressive disease, if they have not initiated any other cancer-directed therapy. See **Section 9.12**.

4 See **Appendix 3** for samples to be collected at visit.

Abbreviations: CEA = carcinoembryonic antigen; D = day; ECG = Electrocardiogram; EOI = end of infusion; EOTV = end of treatment visit;

Appendix 2 Clinical Laboratory Tests

Pregnancy test: Blood or Urine Human chorionic gonadotropin (hCG) **Hematology:** Hemoglobin Platelet count White blood cell count Absolute neutrophils, lymphocytes, and eosinophils **Serum chemistry:** Albumin Alkaline phosphatase Alanine aminotransferase Amylase Aspartate aminotransferase Bicarbonate Bilirubin (Total and Direct) Blood urea nitrogen Calcium Chloride Creatinine Glucose Lipase Magnesium Phosphate Potassium Sodium Urate	**Coagulation:** Prothrombin time (PT) Activated Partial Thromboplastin Time (aPTT) INR Fibrinogen **Endocrine tests:** Free thyroxine Thyroid-stimulating hormone **Urinalysis:** Protein Occult blood

Appendix 3 Pharmacokinetics, Immunogenicity, and Pharmacodynamic Biomarkers Blood Sampling Schedule for MGD007 & MGA012

Blood samples for MGD007 and MGA012 PK, ADA, and PD biomarkers will be collected per **Table 15**.

Table 15 Pharmacokinetic, Immunogenicity, and Pharmacodynamic Biomarkers Blood Sampling Schedule for MGD007 & MGA012 [1]

Cycle	Day	MGD007 & MGA012 PK Sampling Time [2]	MGD007 & MGA012 ADA Sampling Time	Cytokines [2]	Flow Cytometry Occupancy	Flow Cytometry Subsets	Serum Bio-markers [3]	T-cell repertoire [3]	ctDNA analysis [3]	Transcript profile [3]
1	1	Pre MGD007 infusion	Pre MGD007 infusion	Pre MGD007 infusion	Pre MGD007 infusion	Pre MGD007 infusion	Pre MGD007 infusion	Pre MGD007 infusion	Pre MGD007 infusion	Pre MGD007 infusion
	1	End of MGD007 infusion								
	1	2 hours after end of MGD007 infusion		2 hours after end of MGD007 infusion	2 hours after end of MGD007 infusion	2 hours after end of MGD007 infusion				
	1	6 hours after end of MGD007 infusion		6 hours after end of MGD007 infusion						
1	2			Day 2	Day 2	Day 2				
1	8	Pre MGD007 infusion			Pre MGD007 infusion	Pre MGD007 infusion	Pre MGD007 infusion			
	8	End of MGD007 infusion								
	8				2 hours after end of MGD007 infusion	2 hours after end of MGD007 infusion				
1	15	Pre MGA012 infusion	Pre MGA012 infusion	Pre MGA012 infusion	Pre MGA012 infusion	Pre MGA012 infusion	Pre MGA012 infusion			

Table 15 Pharmacokinetic, Immunogenicity, and Pharmacodynamic Biomarkers Blood Sampling Schedule for MGD007 & MGA012 [1]

Cycle	Day	MGD007 & MGA012 PK Sampling Time [2]	MGD007 & MGA012 ADA Sampling Time	Cytokines [2]	Flow Cytometry Occupancy	Flow Cytometry Subsets	Serum Bio-markers [3]	T-cell repertoire [3]	ctDNA analysis [3]	Transcript profile [3]
1	15	End of MGA012 infusion								
	15	End of MGD007 infusion								
	15				2 hours after end of MGD007 infusion	2 hours after end of MGD007 infusion				
	15	1 hour after end of MGD007 infusion								
	15	2 hours after end of MGD007 infusion								
	15	4 hours after end of MGD007 infusion								
	15			6 hours after end of MGD007 infusion						
1	16	Day 16		Day 16	Day 16	Day 16				
1	17	Day 17								
1	19	Day 19								

Table 15 Pharmacokinetic, Immunogenicity, and Pharmacodynamic Biomarkers Blood Sampling Schedule for MGD007 & MGA012 [1]

Cycle	Day	MGD007 & MGA012 PK Sampling Time [2]	MGD007 & MGA012 ADA Sampling Time	Cytokines [2]	Flow Cytometry Occupancy	Flow Cytometry Subsets	Serum Bio-markers [3]	T-cell repertoire [3]	ctDNA analysis [3]	Transcript profile [3]
1	22	Pre MGD007 infusion				Pre MGD007 infusion				
	22	End of MGD007 infusion				End of MGD007 infusion				
1	29	Pre MGA012 infusion	Pre MGA012 infusion	Pre MGA012 infusion	Pre MGA012 infusion	Pre MGA012 infusion	Pre MGA012 infusion			
	29	End of MGA012 infusion								
	29	End of MGD007 infusion			End of MGD007 infusion	End of MGD007 infusion				
	29			2 hours after end of MGD007 infusion						
1	42							Pre Biopsy	Pre Biopsy	Pre Biopsy
1	43	Pre MGA012 infusion								
	43	End of MGA012 infusion								
	43	End of MGD007 infusion								

Table 15 Pharmacokinetic, Immunogenicity, and Pharmacodynamic Biomarkers Blood Sampling Schedule for MGD007 & MGA012 [1]

Cycle	Day	MGD007 & MGA012 PK Sampling Time [2]	MGD007 & MGA012 ADA Sampling Time	Cytokines [2]	Flow Cytometry Occupancy	Flow Cytometry Subsets	Serum Bio-markers [3]	T-cell repertoire [3]	ctDNA analysis [3]	Transcript profile [3]
2	1	Pre MGA012 infusion	Pre MGA012 infusion	Pre MGA012 infusion	Pre MGA012 infusion	Pre MGA012 infusion	Pre MGA012 infusion	Pre MGA012 infusion	Pre MGA012 infusion	
	1	End of MGA012 infusion								
	1	End of MGD007 infusion			End of MGD007 infusion					
	1			2 hours after end of MGD007 infusion						
2	2			Day 2						
2	15	Pre MGA012 infusion								
	15	End of MGA012 infusion								
	15	End of MGD007 infusion								
2	29				Pre MGA012 infusion	Pre MGA012 infusion				
	29				End of MGD007 infusion					

Table 15 Pharmacokinetic, Immunogenicity, and Pharmacodynamic Biomarkers Blood Sampling Schedule for MGD007 & MGA012 [1]

Cycle	Day	MGD007 & MGA012 PK Sampling Time [2]	MGD007 & MGA012 ADA Sampling Time	Cytokines [2]	Flow Cytometry Occupancy	Flow Cytometry Subsets	Serum Bio-markers [3]	T-cell repertoire [3]	ctDNA analysis [3]	Transcript profile [3]
3	1	Pre MGA012 infusion	Pre MGA012 infusion			Pre MGA012 infusion	Pre MGA012 infusion	Pre MGA012 infusion	Pre MGA012 infusion	
	1	End of MGA012 infusion								
	1	End of MGD007 infusion								
3	29					Pre MGA012 infusion				
4	1	Pre MGA012 infusion	Pre MGA012 infusion			Pre MGA012 infusion	Pre MGA012 infusion			
	1	End of MGA012 infusion								
	1	End of MGD007 infusion								
4	29					Pre MGA012 infusion				
5 and Subsequent Cycles	1	Pre MGA012 infusion	Pre MGA012 infusion							

Table 15 Pharmacokinetic, Immunogenicity, and Pharmacodynamic Biomarkers Blood Sampling Schedule for MGD007 & MGA012 [1]

Cycle	Day	MGD007 & MGA012 PK Sampling Time [2]	MGD007 & MGA012 ADA Sampling Time	Cytokines [2]	Flow Cytometry Occupancy	Flow Cytometry Subsets	Serum Bio-markers [3]	T-cell repertoire [3]	ctDNA analysis [3]	Transcript profile [3]
5 and Subsequent Cycles	1	End of MGA012 infusion								
	1	End of MGD007 infusion								
EOT Visit		EOT	EOT		EOT	EOT				
		IRR/CRS		IRR/CRS						

Note: Do not collect PK samples from infusion port; samples will be collected from the contralateral arm. When collecting multiple samples, collect the PK sample first. Actual start and end of infusion times and all sample collection times will be recorded on the CRFs. All sample time points are hours (h) after EOI, unless otherwise specified.

Note: Duration of infusion for MGA012 = 60 minutes and for MGD007 = 120 minutes

1 Window times for samples required at EOI or after EOI are as follows: up to -10 minutes before the infusion is complete; ± 10 min for samples to be collected at 1, 2, 4, 6 hours after EOI.

2 Additional samples may be obtained selectively at additional time points in patients who experience signs and symptoms of cytokine release.

3 Cohort Expansion Subjects only. Samples on Cycle 1 Day 42 are for subjects having biopsies only.

Abbreviations: ADA = Anti-drug antibody; EOI = End of infusion; EOT = End of treatment; PK = Pharmacokinetic; QW = Once a week; Trt = Treatment

Appendix 4 Eastern Cooperative Oncology Group (ECOG)Performance Status

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

Appendix 5 RECIST 1.1 Guidelines

Adapted from Eisenhauer 2009 (11).

All patients with be required to have at least 1 measurable lesion to be considered as having measureable disease at baseline for the determination of eligibility for this study. Measurable lesions are defined below.

1 Measurability of Tumor at Baseline

1.1 Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

1.1.1 Measurable

Tumor lesions: Must be accurately measured in at least one dimension (*longest* diameter in the plane of measurement is to be recorded) with a *minimum* size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as nonmeasurable).
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in *short* axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the *short* axis will be measured and followed. See also notes below on 'Baseline documentation of target and nontarget lesions' for information on lymph node measurement.

1.1.2 Nonmeasurable

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly nonmeasureable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

1.1.3 Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, *with identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the *soft tissue component* meets the definition of measurability described above.
- Blastic bone lesions are nonmeasurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other locoregional therapy, are not considered measurable unless there has been demonstrated progression in the lesion prior to study enrollment.

1.2 Specifications by methods of measurements

1.2.1 Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

1.2.2 Method of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should

always be done rather than clinical examination unless the lesions(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised.

Tumor markers: Tumor markers *alone* cannot be used to assess *objective* tumor response.

2 Tumor Response Evaluation

2.1 Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the *overall tumor burden at baseline* and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included. Measurable disease is defined by the presence of at least one measurable lesion (as detailed above).

2.1.1 Baseline Documentation of 'Target' and 'non-target' Lesions

Where more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as *target lesions* and will be recorded and measured at baseline. For example, in instances where patients have only one or two organ sites involved, a maximum of two and four lesions respectively will be recorded). Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesions which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. As noted above, pathological nodes which are defined as measurable and may be identified as target lesions must meet criterion of a short axis of ≥ 15 mm by CT scan. Only the *short* axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A *sum of the diameters* (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the *baseline sum diameters.* If lymph nodes are to be included in the sum, then as noted above, only the *short* axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as *non-target lesions* and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

2.2 Response Criteria

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

2.2.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): at least a 20% increase in the sum of diameters of target lesions, taking as reference the *smallest sum on study* (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (*Note:* the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

2.2.2 Special Notes on the Assessment of Target Lesions

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. In order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs, it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (*Note:* It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. However, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesions. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2.2.3 Evaluation of Nontarget Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measureable, they need not be measured and instead should be assessed only *qualitatively* at the time points specified in the protocol.

Complete Response (CR): Disappearance of all nontarget lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of one or more nontarget lesions(s).

Progressive Disease (PD): *Unequivocal progression* (see comments below) of existing non-target lesions. (*Note:* the appearance of one or more new lesions is also considered progression).

2.2.4 Special Notes on Assessment of Progression of Nontarget Disease

The concept of progression of nontarget disease requires additional explanation as follows:

When a patient also has measurable disease. In this setting, to achieve 'unequivocal progression; on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression *solely* on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease. The same general concepts apply here as noted above, *however*, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had

overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

2.2.5 New Lesions

The appearance of new malignant lesions denotes disease progression. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was *not* scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

2.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

2.3.1 Time Point Response

It is assumed that at each protocol specified time point, a response assessment occurs. **Table A-1** on the next page provides a summary of the overall response status calculation at each time point for patients who have measureable disease at baseline.

2.3.2 Missing Assessments and Inevaluable Designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements is made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up

only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

2.3.3 Best Overall Response: All Time Points

The *best overall response* is determined once all the data for the patient is known.

Table A-1 Time point response: patients with target (+/- non-target) disease

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Best response determination in trials where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the objective response is confirmed on a follow-up scan obtained no less than 4 weeks after the initial scan demonstrating an objective response. In this circumstance, the best overall response can be interpreted as in **Table A-2**.

Table A-2 Best overall response when confirmation of CR and PR required

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR [a]
CR	SD	SD
CR	PD	SD
CR	NE	SD
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration". Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is *not* a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in **Table A-1** and **Table A-2**.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

2.4 Confirmation/Duration of response

2.4.1 Confirmation

Objective responses should be confirmed by CT and/or MRI scans obtained no less than 4 weeks after the original scan.

2.4.2 Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study). The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

2.4.3 Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the *smallest sum on study* (if the baseline sum is the smallest, this is the reference for calculation of PD).

Appendix 6 Immune-Related RECIST Guidelines

The immune-related RECIST (irRECIST) are adapted from Wolchok 2009 **(49)**.

All patients will be required to have at least 1 measurable lesion to be considered as having measureable disease at baseline for the determination of eligibility for this study. Measurable lesions are defined below.

1 Measurability of Tumor at Baseline

1.1 DEFINITIONS

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

1.1.1 Measurable

Tumor lesions: Must be accurately measured in at least one dimension (*longest* diameter in the plane of measurement is to be recorded) with a *minimum* size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measureable).
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measureable, a lymph node must be ≥ 15 mm in *short* axis when assessed by CT scan (CT scan slice thickness no greater than 5 mm). At baseline and in follow-up, only the *short* axis will be measured and followed. See also notes below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

1.1.2 Non-measurable

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measureable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measureable by reproducible imaging techniques.

1.1.3 Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measureable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered measurable unless there has been demonstrated progression in the lesion prior to study enrollment.

1.2 Specifications by Methods of Measurements

1.2.1 Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

1.2.2 Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesions(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised.

Tumor markers: Tumor markers will not be used to assess *objective* tumor response.

2 Tumor Response Evaluation

2.1 Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the *overall tumor burden at baseline* and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included. Measurable disease is defined by the presence of at least one measurable lesion (as detailed above).

2.2 Baseline Documentation of 'Target' And 'Non-Target' Lesions

Where more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as *target lesions* and will be recorded and measured at baseline. For example, in instances where patients have only one or two organ sites involved, a maximum of two and four lesions respectively will be recorded). Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesions which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. As noted previously, pathological nodes which are defined as measurable and may be identified as target lesions must meet criterion of a short axis of ≥ 15 mm by CT scan. Only the *short* axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A *sum of the diameters* (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the *baseline sum diameters.* If lymph nodes are to be included in the sum, then as noted above, only the *short* axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as *non-target lesions* and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression'. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

2.3 Response Criteria

This section provides the definitions of the criteria used to determine objective tumor response for target lesions by immune-related response criteria (i.e., irRECIST).

2.3.1 Evaluation of Target Lesions

Immune-Related Complete Response (irCR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Immune-Related Partial Response (irPR): at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Immune-related Progressive Disease (irPD): at least a 20% increase in the sum of diameters of target lesions, taking as reference the *smallest sum on study* (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Unlike conventional RECIST criteria, the appearance of new measurable lesions does not automatically denote disease progression under immune-related response criteria. Rather the dimensions of new measurable lesions are added to overall sum of tumor diameters for determination of objective response status. Patients will not be considered as having progression unless the new overall sum of diameters has increased by $\geq$ 20% from the smallest sum of tumor diameters achieved while on study.

Immune-Related Stable Disease (irSD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

2.3.2 Special Notes on the Assessment of Target Lesions

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. In order to qualify for irCR, each node must achieve a short axis < 10 mm. For irPR, irSD and irPD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs, it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (*Note:* It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be

present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. However, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesions. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2.3.3 Evaluation of Non-target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measureable, they need not be measured and instead should be assessed only *qualitatively* at the time points specified in the protocol.

Immune-Related Complete Response (irCR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesions(s)

Immune-Related Progressive Disease (irPD): Unlike conventional RECIST 1.1, new measurable lesions or increases in the size of non-target lesions do not define PD in isolation in the immune-related response criteria. Rather, immune-related PD is established if the sum of diameters is $\geq$ 20% of the nadir of the sum of diameters for a given patient.

2.3.4 New Lesions

The appearance of new malignant lesions alone does not denote disease progression. Instead, the diameter of new lesions is added to the sum of diameters for target and non-target lesions.

2.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. The patient's best overall response assignment will depend on the findings of both target and non-target disease.

2.4.1 Time Point Response

It is assumed that at each protocol specified time point, a response assessment occurs. For patients experiencing irCR or irPR, a confirmatory scan obtained no less than 4 weeks after the

original scan is required to confirm the objective response. For patients experiencing irPD, but who demonstrate acceptable tolerability of treatment as evaluated by the Investigator, a confirmatory scan obtained no less than 4 weeks after the original scan is required for the confirmation of irPD.

Immune-related response determination per irRECIST

Target Lesions	Non-Target Lesions	%Change Tumor Burden	Immune-Related Response Status
CR	CR	-100%	irCR
PR	Any	≤-30%	irPR
PR	Any	≥-30% to <+20%	irSD
PR	Any	≥+20%	irPD
SD	Any	≥-30% to <+20%	irSD
SD	Any	≥+20%	irPD
PD	Any	≥+20%	irPD

No new lesions allowed to achieve irCR status. Otherwise, presence or absence of new measurable or new non-measurable lesions does not affect response status in isolation. New measurable lesions added to cumulative tumor burden to calculate % change tumor burden for the determination of immune-related response status.

Immune-Related Complete Response (irCR): Complete disappearance of all target and non-target lesions and no new lesions. The short axis of all lymph nodes must be ≤ 10 mm.

Immune-Related Partial Response (irPR): The sum of diameters has decreased ≥ 30% from the baseline but does not meet the criteria for irCR.

Immune-Related Stable Disease (irSD): The patient does not meet criteria for irCR, irPR or irPD.

Immune-Related Progressive Disease (irPD): The sum of diameters for target lesions and new measureable lesions has increased by ≥ 20% from the nadir sum of diameters.

2.4.2 Missing Assessments and Inevaluable Designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements is made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response.

2.4.3 Best Overall Response: All Time Points

The *best overall response* is determined once all the data for the patient is known.

Complete or partial responses may be claimed only if the objective response is confirmed on a follow-up scan obtained no less than 4 weeks after the initial scan demonstrating an objective response. Absent this subsequent radiographic confirmation, irCR or irPR designations will be considered as unconfirmed responses.

2.4.4 Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with irCR may not have a total sum of 'zero' on the case report form (CRF).

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration". Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is *not* a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Table 1.

2.5 Confirmation/Duration of Response

2.5.1 Confirmation

Objective responses should be confirmed by CT and/or MRI scans obtained no less than 4 weeks after the original scan.

2.5.2 Duration of Overall Response

The duration of overall response is measure from the time measurement criteria are first met for irCR/irPR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study). The duration of overall complete response is measured from the time measurement criteria are first met for irCR until the first date that recurrent disease is objectively documented.

2.5.3 Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the *smallest sum on study* (if the baseline sum is the smallest, this is the reference for calculation of irPD).

Appendix 7 Principal Investigator's Agreement

Study Title: A Phase 1b/2, Open Label, Dose Escalation Study of MGD007, a Humanized gpA33 × CD3 DART® Protein in Combination with MGA012, an Anti-PD-1 Antibody, in Patients with Relapsed or Refractory Metastatic Colorectal Carcinoma

Study Number: CP-MGD007-02

I have read the protocol described above.

I have fully discussed the objectives of this study and the contents of this protocol with the Sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution of the ethical review of the study, without written authorization from MacroGenics, Inc. It is, however, permissible to provide information to a patient in order to obtain consent.

I agree to conduct this trial according to this protocol and to comply with its requirements, patient to ethical and safety considerations and guidelines, and to conduct the study in accordance with ICH guidelines on GCP and with the applicable regulatory requirements.

I understand that the Sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the Sponsor.

Signed: _____

Date: _____

Name (printed): _____

Title: _____

Affiliation: _____

Address: _____

Phone Number: _____

CP-MGD007-02 Protocol Amendment 1 (22-Oct-2018)
This is the electronic signature page for the above referenced document.

User Task: eSignatories Approval	[redacted]Data Management/Statistics Approval (Intended or Designee) 23-Oct-2018 20:06:10 GMT+0000

User Task: eSignatories Approval	[redacted]search Approval (Intended or Designee) 23-Oct-2018 20:40:42 GMT+0000