CLINICAL TRIAL PROTOCOL: CP-MGA271-03
PROTOCOL AMENDMENT 6

Study Title:	A Phase 1, Open-Label, Dose Escalation Study of MGA271 in Combination with Pembrolizumab and in Combination with MGA012 in Patients with Melanoma, Squamous Cell Cancer of the Head and Neck, Non-Small Cell Lung Cancer, Urothelial Cancer, and Other Cancers
Study Number:	CP-MGA271-03
Study Phase:	Phase 1
Product Name:	MGA271 in combination with pembrolizumab (KEYTRUDA®) and MGA271 in combination with MGA012 (also known as INCMGA00012)
Product Numbers:	MGA271 and MGA012
IND Number:	
EudraCT Number	2017-001293-42
Indication:	Melanoma, squamous cell cancer of the head and neck, non-small cell lung cancer, mesothelioma, urothelial cancer, clear cell renal cell carcinoma, ovarian cancer, thyroid cancer, triple-negative breast cancer, pancreatic cancer, colon cancer, soft tissue sarcoma, and prostate cancer
Coordinating Principal Investigator:	
Sponsor:	MacroGenics, Inc. 9704 Medical Center Drive Rockville, MD 20850 301-251-5172
Sponsor's Medical Monitor:	Refer to Study Contact List

Confidentiality Statement

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

SPONSOR SIGNATURES

Study Title:	A Phase 1, Open-Label, Dose Escalation Study of MGA271 in Combination with Pembrolizumab and in Combination with MGA012 in Patients with Melanoma, Squamous Cell Cancer of the Head and Neck, or Non-Small Cell Lung Cancer, Urothelial Cancer, and Other Cancers
Study Number:	CP-MGA271-03 Amendment 6

This clinical study protocol has been approved by the Sponsor:

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

MacroGenics, Inc.

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

MacroGenics, Inc.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	Anti-drug antibodies
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALB	Albumin
ALK	Anaplastic lymphoma kinase
ALK-P	Alkaline phosphatase
ALT	Alanine aminotransferase (SGPT)
Anti-CTLA-4	Cytotoxic T lymphocyte antigen 4 antibody
Anti-PD-1	Programmed cell death protein 1 antibody
Anti-PD-L1	Programmed death ligand 1antibody
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the curve
B7-H3	B7 homolog 3
BUN	Blood urea nitrogen
°C	Degrees Celsius
Ca	Calcium
CBC	Complete blood count
CFR	Code of Federal Regulations
Cl	Chloride
CI	Confidence interval
CL	Plasma clearance
CNS	Central nervous system
cCR	Confirmed complete response
CR	Complete response

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 antigen 4
DBP	Diastolic blood pressure
DC	Dendritic cell
dL	Deciliter
DLT	Dose limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
ELISA	Enzyme-linked immunosorbent assay
EOI	End of Infusion
E:T	Effector cell:target cell ratio
FcγR	Fc gamma receptor
FDA	Food and Drug Administration
F/F	Phenylalanine/phenylalanine
FFPE	Formalin-fixed paraffin-embedded
FIH	First-in-human
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
hCG	Human chorionic gonadotropin
Hct	Hematocrit
HEENT	Head, eyes, ears, neck, throat
Hgb	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HPV	Human papilloma virus

IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IL	Interleukin
IgG	Immunoglobulin G
irAE	Immune-related adverse event
irCR	Immune-related complete response
irPD	Immune-related progressive disease
irPR	Immune-related partial response
irPFS	Immune-related progression free survival
irRC	Immune-related response criteria = Immune-related RECIST criteria
irRECIST	Immune-related RECIST criteria
IRB	Institutional Review Board
IRE	Immediately Reportable Event
IUD	Intrauterine device
IV	Intravenous
K	Potassium
Kg	Kilogram
LAG-3	Lymphocyte-activating gene 3
LDH	Lactate dehydrogenase
MAD	Maximum administered dose
mcg or µg	Microgram
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
MHC	Major histocompatibility class

mIg	Membrane-bound immunoglobulin
mL	Milliliter
Mm	Millimeter
Msec	Millisecond
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
Na	Sodium
NCI	National Cancer Institute
NK	Natural Killer
NOAEL	No observed adverse effect level
NSAID	Non-steroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall Survival
Pap	Papanicolaou
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed death ligand 1
PFS	Progression free survival
PK	Pharmacokinetics
PR	Partial response
PT	Prothrombin time
Q	Inter-compartment clearance
Q3W	Every 3 weeks
QW	Every week
RANK-L	Receptor-activator of nuclear factor kappa B ligand

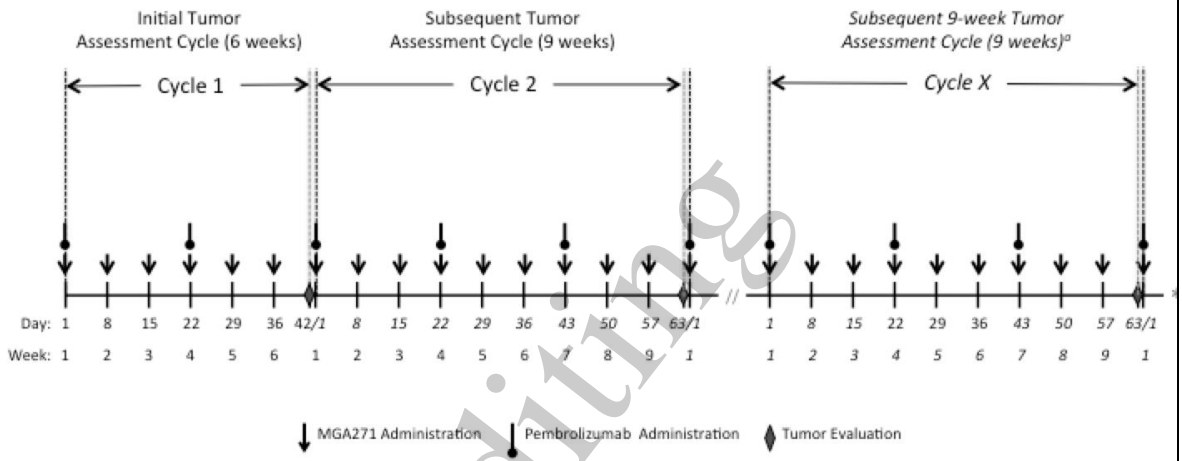
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RES242	MGA271 with wild-type Fc
SAE	Serious adverse event
SBP	Systolic blood pressure
SC	Subcutaneous
SCCHN	Squamous cell cancer of the head and neck
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SJS	Stevens-Johnson syndrome
SOC	System Organ Class
$T_{1/2\alpha}$	Distribution half-life
$T_{1/2\beta}$	Terminal half-life
T4	Thyroxine
TcR	T-cell antigen receptor
TEAE	Treatment-emergent adverse event
TEN	Toxic Epidermal Necrolysis
TKI	Tyrosine-kinase inhibitor
Tregs	Regulatory T-cells
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
US	United States
USP	United States Pharmacopeia
V_c	Central volume
V_1	Volume of distribution of the central compartment
V_p	Peripheral volume
V_{SS}	Volume of distribution at steady state
V/V	Valine/valine
WBC	White blood cell

1 SYNOPSIS

Sponsor: MacroGenics, Inc.	**IND Number:**
Name of Finished Product: MGA271	
Study Title: A Phase 1, Open-Label, Dose Escalation Study of MGA271 in Combination with Pembrolizumab and in Combination with MGA012 in Patients with Melanoma, Squamous Cell Cancer of the Head and Neck, Non-Small Cell Lung Cancer, Urothelial Cancer, and Other Cancers	
Study Number: CP-MGA271-03	
Investigator(s)/Centers: This study will be executed at approximately 30-40 institutions in the United States (US) and, potentially, Canada, Europe (EU), Asia Pacific, and Australia experienced in cancer immunotherapy and/or the conduct of Phase 1 studies in patients with melanoma, squamous cell cancer of the head and neck (SCCHN), non-small cell lung cancer (NSCLC), urothelial cancer, and other cancers.	
Study Phase: 1	
Primary Objective(s): The primary objectives of this study are: • To characterize the safety, tolerability, dose-limiting toxicities (DLT), and maximum tolerated dose (MTD) or maximum administered dose (MAD) (if no MTD is defined) of MGA271 when administered intravenously (IV) weekly in combination with 2 mg/kg pembrolizumab administered IV every 3 weeks (Q3W) to patients with unresectable locally advanced or metastatic melanoma, SCCHN, NSCLC, urothelial cancer, and other cancers. • To characterize the safety, tolerability, and DLT of 15 mg/kg MGA271 when administered IV Q3W in combination with a flat-dose of 375 mg of MGA012 (anti-PD-1 antibody) administered IV Q3W to patients with unresectable locally advanced or metastatic melanoma, SCCHN, NSCLC, urothelial cancer, and other cancers.	
Secondary Objective(s): Secondary objectives of this study are: • To characterize the pharmacokinetics (PK) and immunogenicity of MGA271 administered IV weekly in combination with IV pembrolizumab Q3W, and of MGA271 in combination with MGA012, both administered IV every 3 weeks. • To characterize the pharmacodynamic (PD) activity of MGA271 when administered IV weekly in combination with pembrolizumab Q3W, and of MGA271 in combination with MGA012, both administered IV Q3W. • To investigate the preliminary antitumor activity of MGA271 when administered IV weekly in combination with IV pembrolizumab Q3W, and of MGA271 in combination with MGA012, both administered IV Q3W using both conventional Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (**Appendix 5**) and immune-related response criteria (irRC) (i.e., irRECIST as defined in **Appendix 6**).	
Study Design: *General Study Design* This study is a Phase 1, open-label, dose escalation and cohort expansion study designed to characterize the safety, tolerability, PK, PD, immunogenicity, and preliminary antitumor activity of MGA271 administered IV weekly in combination with pembrolizumab administered IV every 3 weeks (Q3W). Beginning with Amendment 5, this study will also characterize the safety and tolerability of MGA271 in combination with	

MGA012 (anti-PD-1 antibody), both administered by IV, Q3W, through the addition of a new cohort, Cohort 4.

The study consists of a **Dose Escalation Phase** to determine the MTD or MAD (if no MTD is defined) of MGA271 administered in combination with 2 mg/kg pembrolizumab to patients with mesothelioma, urothelial cancer, NSCLC, SCCHN, clear cell renal cell carcinoma (ccRCC), ovarian cancer, melanoma, thyroid cancer, triple-negative breast cancer (TNBC), pancreatic cancer, colon cancer, soft tissue sarcoma, or prostate cancer, followed by a **Cohort Expansion Phase** in patients with melanoma, NSCLC, SCCHN, and urothelial cancer to further define the safety and initial efficacy of the combination with the MGA271 dose established in the first phase. The study treatment schema is presented in the following figure.



a Patients may receive up to 5 subsequent 9-week treatment cycles of MGA271 + pembrolizumab depending on response to study treatments.

* All patients will enter an Efficacy Follow-up Period after receipt of the last dose of study treatment to be followed for up to 24 weeks for survival.

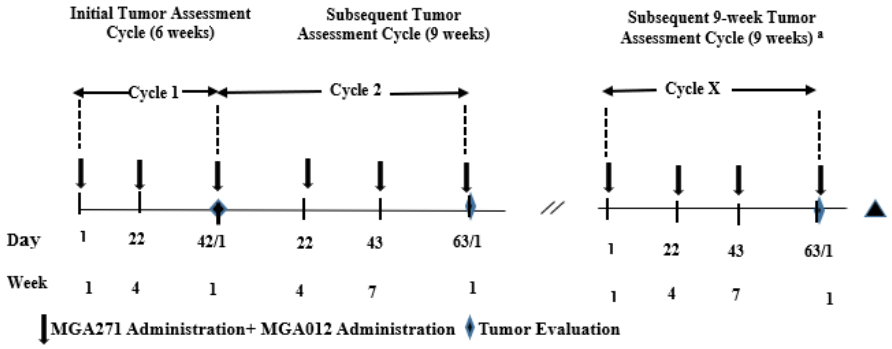
MGA271 will be administered as an IV infusion over 120 minutes on a once-weekly schedule. Pembrolizumab will be administered at 2 mg/kg as an IV infusion over 30 minutes every 3 weeks. On the days that both agents are administered, pembrolizumab will be administered first, followed by MGA271.

For both the Dose Escalation and Cohort Expansion phases, patients' first tumor assessment will be obtained on Cycle 1 Study Day 42 of the **Initial Tumor Assessment Cycle**.

Patients who remain clinically stable and do not experience unacceptable toxicity that necessitates permanent discontinuation of the study drugs at the completion of the Initial (6-week) Tumor Assessment Cycle will be eligible to receive additional treatment with pembrolizumab and MGA271. Assuming that the patient remains clinically stable, maintains a response status of stable disease (SD) or better, and does not experience unacceptable toxicity that necessitates permanent discontinuation of the study drugs, patients may receive up to 5 additional 9-week treatment cycles during **Subsequent Tumor Assessment Cycles**, for a maximum total of 51 doses of MGA271 and 17 doses of pembrolizumab.

Beginning with Amendment 5, in Cohort 4, 15 mg/kg MGA271 will be administered as an IV infusion over 120 minutes Q3W in combination with 375 mg MGA012 administered as an IV infusion over 60 to 75 minutes Q3W. On dosing days, MGA012 will be administered first, followed by MGA271. The study treatment schema is presented in the figure below.

Figure 3 MGA271 + MGA012 Treatment Schema: Cohort 4



a Patients may receive up to 5 subsequent 9-week treatment cycles of MGA271 + MGA012 depending on response to study treatments

▲ All patients will enter an Efficacy Follow-up Period after receipt of the last dose of study treatment to be followed for up to 96 weeks for survival.

Patients who remain clinically stable and do not experience unacceptable toxicity that necessitates permanent discontinuation of the study drugs, at the completion of the Initial (6 week) Tumor Assessment Cycle will be eligible to receive additional treatment with MGA271+MGA012. Assuming that the patient remains clinically stable, maintains a response status of SD or better, and does not experience unacceptable toxicity that necessitates permanent discontinuation of the study drugs, patients may receive up to 5 additional 9-week treatment cycles during Subsequent Tumor Assessment Cycles, for a maximum total of 17 doses of MGA271 and 17 doses of MGA012.

All subsequent tumor assessments will occur on Study Day 63 of each **Tumor Assessment Cycle** thereafter. Following the last dose of study drug, all patients will be followed for survival during a 6-month (24-week) **Efficacy Follow-up Period**.

Dose Escalation Phase:

The goal of the Dose Escalation Phase is to initially characterize the safety and tolerability of MGA271 and pembrolizumab administered in combination, and more specifically to describe the DLTs for each dose level studied and to define the MTD or MAD (if no MTD is defined) based on the frequency of occurrence of DLTs in each cohort.

For the purposes of guiding decisions regarding dose escalation, the DLT Evaluation Period is defined as the time following administration of the first dose of pembrolizumab to the day of the third planned administration of pembrolizumab (i.e., Cycle 1/Initial Tumor Assessment Cycle).

The Dose Escalation Phase of the study will enroll patients with unresectable, locally advanced or metastatic mesothelioma, urothelial cancer, NSCLC, SCCHN, ccRCC, ovarian cancer, melanoma, thyroid cancer, TNBC, pancreatic cancer, colon cancer, soft tissue sarcoma, or prostate cancer. Dose escalation will follow a conventional 3+3+3 design: MGA271 will be evaluated in sequential escalating doses ranging from 3 mg/kg to 15 mg/kg in combination with 2 mg/kg pembrolizumab in cohorts of 3 to 9 patients each. Dose levels of MGA271 to be evaluated include 3 mg/kg (starting dose), 10 mg/kg, and 15 mg/kg. If it is determined that the MTD is exceeded in the first dose cohort, a dose de-escalation cohort to evaluate a lower dose of MGA271 (1 mg/kg) in combination with 2 mg/kg pembrolizumab will be enrolled.

The dose escalation schema is outlined below:

Cohort	MGA271 Dose	Pembrolizumab Dose	MGA012
Cohort 1 [a]	1 mg/kg	2 mg/kg	N/A
Cohort 1	3 mg/kg (starting dose)	2 mg/kg	N/A
Cohort 2	10 mg/kg	2 mg/kg	N/A
Cohort 3	15 mg/kg	2 mg/kg	N/A
Cohort 4	15 mg/kg	N/A	375 mg

a To be evaluated only if the starting dose is determined to exceed the MTD.

An intermediate dose of MGA271 may be explored selectively during the dose escalation portion of the study, based on review of the cumulative safety, efficacy, and/or PK data on the respective arms and based upon agreement between the investigators and the Sponsor as follows:

- If Cohort 2 exceeds the MTD the following dose levels may be evaluated:
  - Cohort 1a: 7 mg/kg MGA271 + 2 mg/kg pembrolizumab (n=3-9 patients)
- If Cohort 3 exceeds the MTD the following dose levels may be evaluated:
  - Cohort 2a: 12 mg/kg MGA271 + 2 mg/kg pembrolizumab (n=3-9 patients)

Any escalation cohort, not exceeding the MTD, can be expanded to a maximum of 15 patients for further evaluation of safety and efficacy.

The MTD for MGA271 will be defined as the dose level at which < 33% of patients experience a drug-related DLT during the DLT evaluation period. If no MTD is defined for the combination of MGA271 and pembrolizumab after escalation to the maximum protocol-specified dose, that dose level will be designated as the MAD. DLTs are defined, and Dose Escalation Rules described below.

Beginning with Amendment 5, a new cohort, Cohort 4, will be added to explore safety and tolerability of MGA271+MGA012 administered in combination. Since MTD was not reached for the MGA271 and pembrolizumab cohorts, 15 mg/kg was determined as the maximum administered dose (MAD) for MGA271. Patients will receive 15 mg/kg MGA271 (MAD) in combination with a flat-dose of 375 mg MGA012, with both study drugs administered on a Q3W schedule (see Table above) .

For the purposes of guiding decisions regarding dose escalation, the DLT Evaluation Period is defined as the time following administration of the first dose of MGA271 plus MGA012 to the day of the third planned administration of MGA012 (i.e., Cycle 1/Initial Tumor Assessment Cycle).

Enrollment in Cohort 4 will follow a conventional 3+3+3 design, with decision rules as outlined in **Section 4.3**. If the 15 mg/kg MGA271 +375 mg MGA012 combination dose is deemed tolerable, additional patients will be added for up to a total of 15 dose evaluable patients in the cohort. No higher doses of the combination are planned. If the 15 mg/kg MGA271+375 mg MGA012 combination dose level is found to exceed the MTD, de-escalation to 10 mg/kg MGA271 + 375 mg MGA012 may be explored and if that dose level were to exceed the MTD, a further de-escalation to 3 mg/kg MGA271 + 375 mg MGA012 may be explored following the same conventional 3+3+3 design. Any of these dose levels, not exceeding the MTD, can be expanded up to a maximum of 15 patients for further evaluation of safety and efficacy.

Cohort Expansion Phase:

During the Cohort Expansion Phase, additional cohorts of patients with unresectable, locally advanced or metastatic melanoma (up to n=16), 2 cohorts of NSCLC (n= up to 20 in each cohort), 2 cohorts of SCCHN (up to n=20 in each cohort) or urothelial cancer (up to n=16) will be enrolled to receive MGA271 in combination with pembrolizumab at the MTD (or MAD) established from the Dose Escalation Phase of the study. The goals for this portion of the study will be to:

1. Further characterize the safety of MGA271 in combination with pembrolizumab at the MTD (or MAD);
2. Further evaluate the PK, PD, and immunogenicity of MGA271 in combination with pembrolizumab; and
3. Provide a preliminary assessment of the antitumor activity of MGA271 in combination with pembrolizumab in patients with advanced melanoma, NSCLC, SCCHN, or urothelial cancer.

Efficacy Follow-up Period:

The Efficacy Follow-up Period consists of the 6-month (24-week) period following the final dose of study drug (pembrolizumab or MGA271 or MGA012, whichever is last). During this time, patients will be followed via telephone or other electronic contact at 12-week intervals for follow-up of overall survival.

Dose Limiting Toxicity:

For the purposes of safety management and defining DLTs, the combination of MGA271 and pembrolizumab, or the combination of MGA271+ MGA012 will be treated as one entity. If a DLT is considered related to study drug, no distinction will be made as to which agent is the causative agent and administration of both agents will be stopped. One exception to this rule will be in the circumstance in which a DLT occurs during or immediately following the first pembrolizumab infusion or MGA012 infusion and before the first MGA271 administration. In this case, the toxicity will be attributed to pembrolizumab or MGA012 alone and will not count as a DLT of the combination of study drugs; in this case the patient will be replaced by another patient in the dose cohort.

In general, for patients who experience an adverse event (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 drugs. Criteria for subsequent continuation of therapy are outlined below. No dose reductions of either MGA271 or pembrolizumab or MGA012 are allowed during the study; however, for patients being treated at a dose level subsequently determined to exceed the MTD, the dose of MGA271 will be reduced to the next lower dose level.

Dose limiting toxicities will be based on treatment-emergent, drug-related AEs (or laboratory abnormalities) occurring following administration of the first dose of pembrolizumab to the day of the third planned administration of pembrolizumab (i.e., the DLT Evaluation Period). 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 are defined separately for hematologic and non-hematologic events as follows.

Hematologic Dose Limiting Toxicity

Hematologic DLT will be 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

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

- ≥ Grade 3 lymphopenia
- Grade 3 anemia that is not associated with other clinically significant complications

Non-Hematologic Dose Limiting Toxicity

Non-hematologic DLT will be 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 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 14 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 antitumor 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 MGA271 due to patient intolerance
- Any hepatic laboratory abnormalities meeting all three Hy's law criteria (described within hepatic non-hematologic DLTs)
- Any Grade 2 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.

Hepatic Non-Hematologic Dose Limiting Toxicity

- AST or ALT > 5 x ULN or total bilirubin > 3 x ULN

  For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases ≥ 50%, relative to baseline and lasts for at least 1 week.

  Please see **Section 6.5.2.2** for further management guidelines.

- Any event meeting the criteria for Hy's law as follows (all three 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

Dose Escalation Rules

The Dose Escalation Phase of this trial will proceed using a conventional 3 + 3 + 3 approach, and will begin with enrollment of 3 patients at the initial dose level of 2 mg/kg of pembrolizumab administered as an IV infusion once every three weeks and 3 mg/kg of MGA271 administered as an IV infusion once weekly. Successive dose escalation cohorts will be enrolled as outlined below. The MTD or MAD will be determined based on the assessment of DLTs during the DLT evaluation period. Cohort 4 will begin enrollment of 3 patients at 15 mg/kg MGA271 and 375 mg MGA012; with no higher dose escalation cohorts to be explored.

Patients who do not experience a DLT but are not evaluable for safety for the full DLT evaluation period will be replaced in the same dose-level cohort.

- 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 of 15 mg/kg of MGA271).
- 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 MGA271 with pembrolizumab.
- 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 the combination. 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 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 MGA271 in combination with pembrolizumab or in combination with MGA012 has been exceeded at that dose level, and all subsequent patients will be treated at the next lower dose level.
- If 2 or more patients out of the first 6 patients treated at a given dose level experience **the same** drug-related DLT, then the enrollment in that cohort will stop, and it will be concluded that the MTD for MGA271/pembrolizumab or MGA271/MGA012 has been exceeded and all subsequent patients will be treated at the next lower dose level.
- Note that in the circumstance in which a DLT occurs during or immediately following the first pembrolizumab or first MGA012 infusion and before the first MGA271 administration, the toxicity will be attributed to pembrolizumab or first MGA012 alone and will not count as a DLT of the combination of study drugs at the dose level under study. In this case the patient will be replaced by another patient in the dose cohort.

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%.

Dose escalation to the next dose level is permitted only after the patients enrolled in the current dose cohort have competed the DLT evaluation period and all safety data have been reviewed by the Sponsor Medical Monitor and the Investigators participating in the study.

For patients being treated at a dose level subsequently determined to exceed the MTD, the dose of MGA271 will be immediately reduced to the next lower MGA271 dose level.

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 PK, PD, biomarker, safety, and response data. An MTD does not have to be reached to expand a dose cohort if the available data demonstrate that a lower dose level may provide antitumor activity while minimizing potential risk.

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 and efficacy. For the MGA271 and MGA012 (cohort 4), the cohort may be expanded up to a total of 15 patients.

Rules for Continuation of Study Therapy:

Patients who tolerate treatment with pembrolizumab and MGA271, or who tolerate treatment with MGA271+MGA012, may continue to receive additional treatment with the study drugs as specified above until any one of the following conditions are met:

- After documentation of a confirmed complete response (cCR), MGA271 and pembrolizumab, or MGA271+MGA012, are continued for one more Tumor Assessment Cycle
- Patient meets criteria for immune-related disease progression (irPD) (**Appendix 6**)
- Occurrence of drug-related DLT as defined for the DLT Evaluation Period
- The Sponsor, Investigator, or Regulatory Agency terminates the study
- Withdrawal of patient due to an AE or serious adverse event (SAE)
- Withdrawal of patient consent
- Completion of protocol defined therapy
- Investigator discretion
- Pregnancy
- Death

Note: For individual patients who meet these criteria, but are otherwise considered to be experiencing clinical benefit by the investigator, consideration may be given to extension of therapy on a case-by-case basis in consultation with the Sponsor. If a patient completes 6 cycles of therapy and is experiencing clinical benefit as determined by the investigator, consideration may be given to extension of therapy for an unrestricted number of additional 9 week treatment cycles of MGA271 and pembrolizumab or MGA271+MGA012 on a case-by-case basis in consultation with the Sponsor. Such unrestricted treatment may continue until the patient either 1) meets the criteria for permanent discontinuation (see **Section 5.3.1**), or 2) a rollover protocol becomes available.

Study Population:

The patient population to be enrolled in the Dose Escalation Phase of this study will consist of adult patients with histologically–proven, unresectable locally advanced or metastatic melanoma, NSCLC, SCCHN, mesothelioma, urothelial cancer, ccRCC, ovarian cancer, thyroid cancer, TNBC, pancreatic cancer, colon cancer, soft tissue sarcoma, or prostate cancer.

The number of patients enrolled in the Dose Escalation Phase cannot be precisely determined in advance, and could range from 9 to 45 or more patients depending on results in the course of the trial and the number of MG271 doses explored. This patient number does not take into account patient replacement for non-evaluable patients or the possibility of expanding an individual escalation cohort to 15 patients to allow for further evaluation of safety, PK and antitumor activity of the combination of MGA271 and pembrolizumab at the dose level in that cohort.

The Cohort Expansion Phase of the trial will enroll 112 patients, with a target of 16 to 20 patients into each of 6 cohorts: two cohorts of patients with NSCLC (up to 20 patients in each cohort), two cohorts of patients with SCCHN (up to 20 patients in each cohort), one cohort of patients with melanoma (up to 16 patients), and one cohort of patients with urothelial cancer (up to 16 patients). This number of patients does not take into account patients who may be replaced. During the Expansion Portion of the study, patients who withdraw before completing the first tumor assessment for a reason other than progression of disease 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. For planning, the maximum number of patients to be enrolled on this trial is anticipated to be approximately157 patients.

Inclusion/Exclusion Criteria:

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.

Inclusion Criteria

General

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. Dose Escalation Phase including Cohort 4: Histologically-proven unresectable locally advanced or metastatic.

    a. Mesothelioma that has progressed during or following at least 1 and up to 3 prior systemic treatments for unresectable locally advanced or metastatic disease. The prior systemic chemotherapy must have included a pemetrexed (anti-folate)-based regimen in combination with platinum agent. For patients in whom pemetrexed was contraindicated or not tolerated or not an approved therapy (e.g., peritoneal mesothelioma), prior therapy with a first-line platinum-based regimen is required.

    b. Urothelial cancer arising in the bladder, renal pelvis, ureter, or urethra that has progressed during or following at least 1 and up to 5 prior systemic treatments for unresectable locally advanced or metastatic disease (includes anti-PD-L1, anti-PD-1, but excludes other experimental therapies). Patients must have received at least one platinum-containing regimen (e.g., gemcitabine/cisplatin [GC], dose-dense methotrexate/vinblastine/doxorubicin/cisplatin [DDMVAC], or carboplatinum/gemcitabine). No more than 5 prior systemic regimens allowed.

    c. Thyroid cancer that has progressed during or following at least 1 and up to 5 prior chemotherapy regimen(s). Prior therapy excludes experimental therapies given in Phase 1 trials.

    d. Pancreatic cancer that has progressed during or following at least 1 and up to 3 prior chemotherapy regimens. Prior therapy excludes experimental therapies given in Phase 1 trials.

e. Ovarian cancer that has progressed during or following at least 2 and up to 4 prior therapeutic regimens (e.g., 2 prior platinum containing regimens or if platinum resistant, a liposomal doxorubicin or topotecan containing regimen). Prior therapy excludes experimental therapies given in Phase 1 trials.

f. Colon cancer that has progressed during or following at least 2 and up to 4 prior therapeutic regimens (e.g., fluoropyrimidine and/or irinotecan and/or oxaliplatin and/or anti-EGFR antibody containing regimens). Prior therapy excludes experimental therapies given in Phase 1 trials.

g. Prostate cancer that has progressed during or following at least 1 and up to 5 prior therapeutic regimens (e.g., abiraterone, enzalutamide, docetaxel). Prior therapy excludes experimental therapies given in Phase 1 trials.

h. Soft tissue sarcoma that has progressed during or following at least 1 and up to 5 prior therapeutic regimens. Prior therapy excludes experimental therapies given in Phase 1 trials.

i. TNBC that has progressed during or following at least 1 and up to 5 prior therapeutic regimens. Prior therapy excludes experimental therapies given in Phase 1 trials.

j. ccRCC that has progressed during or following at least 1 and up to 5 prior therapeutic regimens. Prior therapy excludes experimental therapies given in Phase 1 trials.

k. Melanoma that has progressed during or following at least 1 and up to 5 prior systemic treatments for unresectable locally advanced or metastatic disease. No more than 5 prior systemic regimens (excludes experimental therapies) allowed. Patients who are intolerant of, or have refused treatment with standard cancer therapy, will be allowed to enroll.

l. SCCHN that has progressed during or following at least 1 and up to 5 prior systemic treatments for metastatic or recurrent disease deemed to be incurable by the investigator (patients who refuse radical resection for recurrent disease are eligible). No more than 5 prior systemic regimens (excludes experimental therapies) allowed. Patients who are intolerant of, or have refused treatment with standard cancer therapy, will be allowed to enroll. Patients with upper esophageal or salivary gland tumors will not be considered as SCCHN.

m. NSCLC that has progressed during or following at least 1 and up to 5 prior systemic therapies for unresectable locally advanced or metastatic disease. Patients who are intolerant of, or have refused treatment with standard cancer therapy, will be allowed to enroll. Patients must not have had more than 5 prior systemic regimens (excludes experimental therapies) for unresectable locally advanced or metastatic disease.

    i. For patients with squamous cell carcinoma, or adenocarcinoma without known activating mutation: the prior systemic therapy is at least one platinum analogue based therapy with or without a docetaxel or pemetrexed containing regimen.

    ii. For patients with adenocarcinoma having a previously known activating driver mutation such as an epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) fusion: the prior systemic therapy is at least one TKI directed against the driver mutation.

    iii. Maintenance therapy following first-line therapy will not be considered a separate regimen of therapy.

    iv. Prior neoadjuvant chemotherapy for operable disease, adjuvant chemotherapy for completely resected disease or definitive chemoradiation therapy given for locally advanced disease will not be considered a separate regimen of therapy.

Cohort Expansion Phase: Histologically-proven unresectable locally advanced or metastatic:

- Melanoma that has progressed on or after at least one anti-PD-L1 or anti-PD-1 containing therapy. Patients in this cohort can have their PD-L1 tumor expression levels determined before or after enrollment.
- SCCHN, consisting of metastatic or recurrent disease (patients who refuse radical resection for recurrent disease are eligible); evaluated in 2 distinct cohorts, of up to 20 patients each where patients have progressed during or following:

  SCCHN Cohort 1: a first line, platinum-based systemic therapy without receiving prior anti-PD-1 or anti-PD-L1 containing therapy or

  SCCHN Cohort 2: a first-line, platinum-based systemic therapy and an anti-PD-1 or anti-PD-L1 containing therapy.

  In each of the 2 cohorts, at least 10 of the enrolled patients will be human papilloma virus (HPV) positive (HPV positivity is determined as per local institutional standards, e.g., p16 detection by immunohistochemistry [IHC], or HPV *in-situ* hybridization [ISH]). Patients in both SCCHN cohorts can have their PD-L1 tumor expression levels determined before or after enrollment.

- NSCLC consisting of patients with unresectable locally advanced or metastatic disease that will be evaluated in 2 distinct cohorts of up to 20 patients each where patients have progressed during or following:
  - NSCLC Cohort 1: a first-line systemic therapy as outlined below (i-iv, based on tumor histology) without receiving prior anti-PD-1 or anti-PD-L1 containing therapy. These patients must have PD-L1 tumor expression determined by IHC analysis at levels accepted by the Sponsor prior to enrollment (< 1% tumor positivity score [TPS]).
  - NSCLC Cohort 2: a first line systemic therapy as outlined below (i-iv, based on tumor histology) and an anti-PD-1 or anti-PD-L1 containing therapy. Patients in this cohort can have the PD-L1 tumor expression levels determined before or after enrollment.

  i. For patients with squamous cell carcinoma, or adenocarcinoma without known activating mutation: the prior systemic therapy is a platinum analogue based therapy with or without a docetaxel or pemetrexed containing regimen.

  ii. For patients with adenocarcinoma having a previously known activating driver mutation such as an epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) fusion: the prior systemic therapy is a TKI directed against the driver mutation.

  iii. Maintenance therapy following first-line therapy will not be considered a separate regimen of therapy.

  iv. Prior neoadjuvant chemotherapy for operable disease, adjuvant chemotherapy for completely resected disease or definitive chemoradiation therapy given for locally advanced disease will not be considered a separate regimen of therapy.

- Urothelial cancer consisting of transitional cell or mixed transitional/nontransitional (predominantly transitional) cell cancer of the renal pelvis, ureter, bladder, or urethra, in a cohort of up to 16 patients. Patients must have received at least one platinum-containing regimen, either as neo-adjuvant, adjuvant, or for metastatic disease, and progressed on an anti-PD-L1 or anti-PD-1 containing therapy. Patients in this cohort can have the PD-L1 tumor expression levels determined before or after enrollment.

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 (CT) and/or magnetic resonance imaging (MRI). Patients must have measurable disease to 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, b) have demonstrated clear evidence of radiographic progression since the completion of prior radiotherapy and prior to study enrollment.

7. Prospective determination of B7-H3 expression is not required to define eligibility for this study; however, tumor expression of B7-H3 will still be evaluated for all patients enrolled on the study, so patients must have sufficient tissue/slides for B7-H3 testing identified in order to be eligible. Patients should have a formalin-fixed, paraffin embedded (FFPE) tumor specimen or unstained slides identified for analysis, to enable determination of the expression of B7-H3 within tumor specimens using IHC staining. If an archived tumor specimen is not available, patients who undergo a fresh tumor biopsy (**Section 7.11.4.3**) can have B7-H3 expression evaluated from a FFPE sample obtained from the fresh tumor biopsy. In this case, the biopsy should be obtained prior to initiating study therapy. In cases in which an archived sample and fresh tumor sample are both available, B7-H3 expression can be confirmed with either FFPE sample.

8. All patients in the Expansion Phase will have the PD-L1 tumor expression levels assessed using an IHC method deemed acceptable by the Sponsor and based either on archival or new tissue biopsy samples, submitted as formalin-fixed paraffin-embedded tissue samples.

    a) Note: Patients in the NSCLC cohort who have not received prior anti-PD-1 or anti-PD-L1 therapy will need to have the PD-L1 IHC expression levels determined **prior to enrollment to determine eligibility**. All other patients can have PD-L1 tumor expressions determined prior to or after enrollment.

9. Patients enrolling in the study without prior documented PD-L1 tumor expression levels (determined by a Sponsor-approved method) should have a formalin-fixed, paraffin-embedded tumor specimen or unstained slides identified and available for analysis, to assess PD-L1 tumor expression levels, determined by a method selected by the Sponsor.

Laboratory Features

10. Acceptable laboratory parameters as follows:

    a. Platelet count ≥ $100 \times 10^3/\mu L$ without transfusion within 28 days prior to the initiation of study drug.

    b. Absolute neutrophil count ≥ $1.5 \times 10^3/\ \mu L$ in the absence of any growth factor support within 28 days prior to the initiation of study drug.

    c. ALT/ AST ≤ 3.0 × ULN; for patients with hepatic metastases, ALT and AST ≤ 5 × ULN.

    d. Total bilirubin ≤ 1.5 × ULN, except patients with Gilbert's syndrome, who may enroll if the conjugated bilirubin is within normal limits.

    e. Creatinine < 2 mg/dL, or a calculated or measured creatinine clearance > 50 mL/min.

Reproductive Features

11. Female patients of childbearing potential (not surgically sterilized and between menarche and 1 year postmenopause) must have a negative urine pregnancy test performed within 72 hours prior to the initiation of study drug administration. Further, female patients of childbearing potential must agree to either remain abstinent or use acceptable contraceptive measures from the time of consent through 120 days after discontinuation of study drug administration. For female patients, two forms of contraception must be utilized and may include oral, transdermal, injectable or implantable contraceptives, intrauterine device (IUD), female condom, diaphragm with spermicide, cervical cap, use of a condom by the sexual partner or a sterile sexual partner. Periodic abstinence (e.g., calendar,

ovulation, symptothermal and post-ovulation methods) and withdrawal are not considered acceptable forms of contraception in this study.

12. Male patients with partners of childbearing potential must use barrier contraception. 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. Female patients must not be breastfeeding.

Tumor Biopsy

14. Patients in the Cohort Expansion Phase who have one lesion considered to be potentially amenable to biopsy have the option of providing consent for paired pre-treatment and on-treatment biopsy samples. Tumor lesions used for biopsy should not be lesions used as RECIST target lesions, unless there are no other lesions suitable for biopsy. If a RECIST target lesion is used for biopsy, the lesion must be ≥ 2 cm in longest diameter. Tumor biopsies should be obtained only from lesions that are felt to be accessible with acceptable clinical risk, in the judgment of the investigator.

Previous Checkpoint Inhibitor Therapy

15. Patients who have previously received an immune checkpoint inhibitor (e.g., programmed-death ligand 1 antibody [anti-PD-L1], programmed cell death protein 1 antibody [anti-PD-1], cytotoxic T-lymphocyte-associated protein 4 antibody [anti-CTLA-4]) prior to enrollment must have toxicities related to the checkpoint inhibitor resolved to ≤ Grade 1 or baseline (prior to the checkpoint inhibitor) to be eligible for enrollment.

    This excludes patients who experienced the following immune checkpoint inhibitor-related AEs (i.e., the following AEs make the patient ineligible despite the AE resolving to ≤ Grade 1 or baseline):

    a. ≥ Grade 3 ocular AE.
    b. Changes in liver function tests that met the criteria for Hy's Law (> 3 × ULN of either ALT/AST with concurrent > 2 × ULN of total bilirubin and without alternate etiology).
    c. ≥ Grade 3 neurologic toxicity.
    d. ≥ Grade 3 colitis.

Exclusion Criteria:

1. Patients with symptomatic central nervous system (CNS) metastases must have been treated, be asymptomatic, and meet 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. Treatment with any systemic anti-neoplastic therapy, or investigational therapy within the 4 weeks prior to the initiation of study drug administration.

5. Treatment with radiation therapy within 2 weeks prior to the initiation of study drug administration.

6. Treatment with 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. Steroids for topical, ophthalmic, inhaled or nasal administration are allowed.

7. History of clinically significant cardiovascular disease including but not limited to:

   a. Myocardial infarction or unstable angina within the 12 weeks prior to the initiation of study drug.

   b. Uncontrolled hypertension: systolic blood pressure (SBP) >180 mmHg, diastolic blood pressure (DBP) >100 mmHg.

   c. QTcB prolongation > 480 msec.

   d. Congestive heart failure (New York Heart Association [NYHA] class III-IV).

8. Clinically-significant gastrointestinal disorders including:

   a. Any history of gastrointestinal perforation unless the affected area has been deemed by the investigator to no longer be a risk for perforation.

   b. History of clinically significant gastrointestinal bleeding within 4 weeks prior to the initiation of study drug.

   c. History of acute pancreatitis within 4 weeks prior to the initiation of study drug

   d. 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 4 weeks prior to the initiation of study drug administration.

9. 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.

10. Known positive testing for human immunodeficiency virus or history of acquired immune deficiency syndrome.

11. 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 (PCR).

12. Second primary invasive malignancy that has not been in remission for greater than 2 years. Exceptions that do not require a 2-year remission include: related 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.

13. History of trauma or major surgery within 4 weeks prior to the initiation of study drug administration.

14. Any serious underlying medical or psychiatric condition that would impair the ability of the patient to receive or tolerate the planned treatment at the investigational site.

15. Known hypersensitivity to recombinant proteins, or any excipient contained in the drug or vehicle formulation for MGA271, pembrolizumab, or MGA012 (**Section 6.1**).

16. Vaccination with any live virus vaccine within 4 weeks prior to the initiation of study drug administration. Inactivated annual influenza vaccination is allowed.

17. Dementia or altered mental status that would preclude understanding and rendering of informed consent.

18. Employees of MacroGenics, Inc.

19. Prisoners or other individuals who are involuntarily detained.

20. 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.

Study Drugs:
MGA271:

MGA271 will be administered by IV infusion over 120 minutes.

Pembrolizumab: Pembrolizumab is supplied in two configurations: a "pembrolizumab for injection" configuration that is a single-use vial containing 50 mg lyophilized powder for reconstitution with 2.3 mL sterile water for injection resulting in a 25mg/mL solution (see **Section 6.2.3**) or "pembrolizumab injection" configuration that is a single-use vial containing pembrolizumab solution at a concentration of 100 mg/4mL (i.e., 25 mg/mL).

Pembrolizumab for injection is a sterile, preservative-free, white to off-white lyophilized powder in single-use vials. Each vial is reconstituted and diluted for intravenous infusion. Each 2 mL of reconstituted solution contains 50 mg of pembrolizumab and is formulated in L-histidine (3.1 mg), polysorbate 80 (0.4 mg), and sucrose (140 mg). May contain hydrochloric acid/sodium hydroxide to adjust pH to 5.5.

Pembrolizumab injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for IV infusion. Each vial contains 100 mg of pembrolizumab in 4 mL of solution. Each 1 mL of the 100 mg/4mL solution contains 25 mg of pembrolizumab and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, USP. Pembrolizumab will be administered by IV infusion over 30 minutes through an IV line containing a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter by IV infusion.

MGA012:

Duration of Treatment and Study Duration:
MGA271 will be administered on a once weekly schedule for up to 51 doses and pembrolizumab administered once every 3 weeks for a total of up to 17 doses (i.e., up to 6 cycles). With Amendment 5, in

Cohort 4, MGA271 will be administered on a Q3W schedule for up to 17 doses of MGA271 and MGA012 administered once every 3 weeks for a total of up to 17 doses (i.e., up to 6 cycles). As per Rules for Continuation of Study Therapy, an unrestricted number of additional cycles may be permitted on a case-by-case basis in consultation with the Sponsor.

It is expected that enrollment of the dose escalation portion of the study will occur over approximately 12 months, and that enrollment of the cohort expansion portion of the study will take approximately 9 – 12 months.

The total time for conduct of the trial is expected to be approximately 72 months (which includes 24 weeks of efficacy follow-up). These estimates of the timing for study conduct may vary from that observed in the actual conduct of the trial.

Treatment Schedule (Procedure):

See Time and Events (**Appendix 1**)

Criteria for Evaluation:

Safety Assessments:

- The safety assessment will be based on the evaluation of treatment-emergent AEs that occur from the time of initiation of administration of either study drug through the End of Treatment Visit or 28 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
- AEs and SAEs will be collected from the time the patient receives the first dose of study drug until the End of Treatment Visit or 28 days after the last dose of study drug (whichever is later). Protocol-related AEs and SAEs will be collected from the time the patient has consented to study participation.
- AEs reported between the time the patient signed the informed consent and the administration of the first dose of study drug will be captured as medical history.
- 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.
- The reporting of laboratory/vital signs abnormalities as both laboratory findings and AEs should be avoided. They should not be reported as AEs unless any one of the following are met:

  Any criterion for an SAE is fulfilled

  The laboratory/vital signs abnormality causes the patient to discontinue from the study treatment

  The laboratory/vital signs abnormality causes the patient to interrupt the study treatment

  The laboratory/vital signs abnormality causes the patient to modify the dose of study treatment

  The laboratory/vital signs abnormality requires intervention

Efficacy Assessments:

Tumor assessments will be obtained at screening using CT and/or MRI scans at time intervals as specified in the **Appendix 1** (Time and Events Table). The study is divided into 6 Tumor Assessment Cycles; the first is

a 6-week cycle called the Initial Tumor Assessment Cycle, and Cycles 2 through 6 are 9-week cycles. The tumor assessment takes place at the end of each cycle. Treatment will continue until patients have completed study therapy and required follow-up, experienced disease progression, or have been withdrawn from the study. At each optional on-treatment tumor assessment time point, the objective response status will be determined.

Efficacy Assessments:

Objective Response and Response Duration

Target and non-target lesions will be designated and evaluated using both conventional RECIST 1.1 criteria (**Appendix 5**) and immune-related response criteria (**Appendix 6**) for the purposes of statistical analysis. Objective responses will be categorized as Complete Response (CR), Partial Response (PR), Stable Disease (SD), or Progressive Disease (PD) for conventional RECIST 1.1 criteria and immune-related (ir) CR, irPR, irSD, and irPD for the immune-related response criteria. Determination of the objective response rate will be calculated based on the proportion of response evaluable patients achieving CR or PR using the respective criteria, when such responses are confirmed by a subsequent scan obtained at least 28 days after the initial documentation of objective response. Response evaluable patients will include those patients who have measurable disease and have had a baseline tumor assessment and at least 1 optional on-treatment tumor assessment (see **Appendix 1**). Objective responses that are not subsequently documented with a confirmatory CT or MRI scan (e.g. unconfirmed responses) will not be included as an objective response for the purpose of calculating overall objective response rates. Response duration will be calculated from the time of initial response (CR or PR) documentation (in patients who have a subsequent confirmation of objective response) to the time of progressive disease or death, whichever occurs first. A patient's response duration will be censored if at the time of last antitumor assessment response is ongoing. Patients who discontinue study treatment for a reason other than progressive disease may be followed for efficacy until 1 of the following occurs: the patient progresses, withdraws consent for follow up, or initiates other anti-cancer therapy, or the overall trial is closed.

Progression-free survival (PFS)

PFS will be calculated as the time from the first dose of study drug until documented disease progression or death from any cause, whichever occurs first (**Appendix 3**). A patient's PFS will be censored if at the time of last assessment for progression, the patient remains progression free. PFS will be determined using both conventional RECIST 1.1 and immune-related response criteria.

Overall survival (OS)

OS will be calculated as the time from the first dose of study drug until death due to any cause or last observation or contact, whichever occurs first. A patient's OS will be censored if at the time of last contact, the patient remains alive. In addition, landmark 6-month OS rate will be determined.

Pharmacokinetic Assessments:

Serum concentrations of MGA271 and MGA012 will be monitored using a quantitative sandwich enzyme-linked immunosorbent assays (ELISA). Single and multiple dose PK parameters for MGA271 and MGA012, C_{max}, T_{max}, AUC_{tau}, C_{trough}, CL, V_{ss}, and $t_{1/2}$ will be derived from MGA271 and MGA012 serum concentration versus time data. Population PK analyses may be conducted using data from this study alone or combined with data from other studies.

Immunogenicity Assessments:

The generation of anti-drug antibodies (ADA) directed against MGA271 and MGA012 will be assayed using ELISA or Electrochemiluminescence method.

Pharmacodynamics/Biomarkers:

Tests Performed for both Dose Escalation and Cohort Expansion Patients:

- Characterization of alterations in serum cytokine levels including, but not limited to, IL-2, IL-6, IL-10, and TNF-α
- Enumeration of lymphocyte subsets, NK cells and activation status over time via multi-parameter flow cytometry on whole blood; evaluation of the regulatory T cell population over time
- Determination of B7-H3 and PD-L1 expression as well as immune cell infiltration into the tumor (e.g. CD8+ and CD4+ T cell infiltration) will be explored via IHC staining or other method of archival tumor biopsy specimens (unless fresh tumor sample submitted and used to determine B7-H3 expression and no archived sample obtained)
- Soluble B7-H3 over time analyzed by ELISA; in addition to other potential circulating serum biomarkers indicative of potential tumor response

Tests Performed for Cohort Expansion Patients:

- Determination of B7-H3 tumor cell and tumor vasculature expression, PD-L1 tumor cell membranous expression, and immune cell infiltration into the tumor bed via IHC staining (or other method for immune cell infiltration) of archival tissue and/or of optional paired pre- and on-treatment tumor biopsy specimens when available. The optional pre-treatment and on-treatment tumor biopsies will be carried out for cohort expansion patients who elect to undergo pre- and on-treatment biopsy.
- Characterization of T cell repertoire using T cell receptor (TCR) spectratyping of PBMCs on selected samples may be carried out depending on observed anti-tumor activity.
- An assessment of the ability of patient's PBMCs to support MGA271-mediated antibody dependent cellular cytotoxicity (ADCC) activity in pre- and on-treatment samples using a non-isotopic assay with the patient's PBMCs as effector cells and B7-H3 expressing tumor cell lines as target cells may be carried out depending on observed anti-tumor activity.

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 **either** MGA271 or pembrolizumab or MGA012. Safety Population will be used to summarize baseline data, safety data and for assessment of OS and PFS. Patients who receive at least one dose of MGA271 or MGA012 will be included in PK, PD, and immunogenicity analyses.
- **Response Evaluable Population:** All patients who received both MGA271 and pembrolizumab or MGA271 +MGA012 and had at least 1 post-infusion radiographic tumor assessments. Patients who meet these criteria will be eligible for the determination of best overall response and will be included in the response evaluable population used for the calculation of ORRs using both conventional RECIST 1.1 (**Appendix 5**) and irRC (i.e., irRECIST as defined in **Appendix 6**) criteria.

Statistical Methods:

Summary statistics will consist of absolute and relative frequencies of each category of discrete variables, and of means, standard deviations, medians, minimum, and maximum values of continuous variables. Safety and antitumor activity summaries will be provided for each dose level cohort in the dose escalation portion of the study, and for all dose level cohorts combined. Response rates may be calculated for specific disease sub-groups, if appropriate.

Response duration will be calculated for responders as the time from initial response (CR or PR) to the time of PD or death, whichever occurs first. Response rates will be determined using both conventional criteria using RECIST 1.1 (**Appendix 5**) as well as by irRC (i.e., irRECIST as defined in **Appendix 6**. Two-sided exact confidence intervals (CIs) will be constructed around the objective response rates.

Kaplan-Meier methods will be used to estimate response duration over time and the median response duration. Responders who complete the study without documented PD will be censored at the date of their last tumor assessment. PFS and irPFS will be calculated as the time from the initial infusion of pembrolizumab or MGA271 until documented disease progression, death from any cause, whichever occurs first. Patients with no PFS event (disease progression or death from any cause) will be censored at the date of their last tumor assessment. In addition, PFS and irPFS rates will be calculated at 3 months and 6-month time points from the first dose of study drug. Kaplan-Meier methods will be used to estimate PFS over time and the median duration of PFS. The method of Brookmeyer and Crowley (**9**) will be used to construct 95% CIs around PFS estimates of the median and other quartiles for each expansion cohort.

Overall survival is defined as the time from the initial infusion of pembrolizumab or MGA271 to death from any cause. Kaplan-Meier methods will be used to estimate the overall survival function. Patients who do not die will be censored at the date that the patient was last known to be alive. In addition, OS rate will be calculated at 6 months from the first dose of study drug.

2 BACKGROUND INFORMATION

2.1 Disease Background

In this clinical trial, patients with locally advanced unresectable or metastatic, melanoma, squamous cell cancer of the head and neck (SCCHN), non-small cell lung cancer (NSCLC), urothelial cancer and other cancers (i.e., mesothelioma, clear cell renal cell carcinoma (ccRCC), ovarian cancer, thyroid cancer, triple-negative breast cancer (TNBC), pancreatic cancer, colon cancer, soft tissue sarcoma, or prostate cancer) will be enrolled in the Dose Escalation Phase. The Cohort Expansion Phase will enroll patients with melanoma, SCCHN, NSCLC, and urothelial cancer. The rationale for selecting these distinct types of cancer is based on 3 factors: 1) the high level of unmet medical need for patients with these advanced diseases, 2) the relatively high level of B7 homolog 3 (B7-H3) expression observed in clinical specimens from these cancers, and 3) the rapidly accumulating evidence (conclusive for melanoma) that immune modulation with checkpoint inhibitors can have substantial antitumor activity in these tumors.

Melanoma: In 2014, it is estimated that approximately 76,100 patients will be diagnosed with melanoma, with an estimated 9,710 deaths due to melanoma in the United States (US) **(3)**. Melanoma is the most serious and deadly form of skin cancer, affecting adults of all ages. Even though melanoma accounts for approximately less than 2% of all skin cancers, it causes over 80% of skin cancer-related deaths. There have been significant inroads towards the treatment of advanced melanoma that have occurred over the past 5 years with the approval of immune checkpoint inhibitors directed against cytotoxic T lymphocyte-associated protein 4 (CTLA-4) or programmed cell death protein 1 (PD-1) (ipilimumab [2011], pembrolizumab [2014] and nivolumab [2014]), cytokines (peginterferon alfa-2b [2011], and tyrosine kinase inhibitors (TKIs) including B-RAF enzyme inhibitors (vemurafenib [2011] and dabrafenib [2013]), and MEK1 and MEK2 inhibitors (dabrafenib [2013]) in the US. Despite the new anticancer therapies, the vast majority of patients with advanced melanoma will have disease progression that requires further therapy. Even with the recent advancements in treatment, the median progression-free survival (PFS) for patients with advanced melanoma on pembrolizumab was approximately 5.5 months (median overall survival [OS] not reached at 12 months) **(45)**, and with ipilimumab treatment, the median OS and median PFS are approximately 10 months and 2.9 months, respectively **(28)**. Thus although current treatment options such as ipilimumab monotherapy have provided a survival benefit in advanced disease, there remains a medical need for continued improved treatment in advanced cases.

Melanoma serves as the index cancer for immune modulation as 5 immune modulators, including the PD-1 checkpoint inhibitors nivolumab and pembrolizumab, have now been approved in the US for the treatment for patients with advanced melanoma (high dose interleukin 2 is also approved to treat melanoma in addition to those listed above). In addition, the combination of CTLA-4 blockade (with ipilimumab) and blockade of the B7 family checkpoint inhibitor PD-1 (with nivolumab) demonstrated a 42% objective response rate (ORR) in patients with advanced melanoma **(58)**. An objective response rate of 42% with the ipilimumab/nivolumab combination is greater than that reported with either agent alone, approximately 11% and 28% respectively **(28;61)**. Therefore, continued efforts to

utilize the immune system against melanoma with new checkpoint inhibitor targets or combinations of agents are attractive and may well continue to yield improved results over single agent approaches.

In addition to the above, a high percentage of melanoma tumors demonstrate membranous surface expression of B7-H3, where nevi have either no or low levels of membranous expression **(Investigator's Brochure)** **(59;65)**. In addition, the level of B7-H3 expression on melanoma is associated with stage and prognosis, with higher levels associated with higher tumor stage and shorter survival than in patients having tumors with lower intensity staining **(59;65)**.

Squamous Cell Cancer of the Head and Neck: It is estimated that in 2014, approximately 55,070 patients in the US will be diagnosed with cancer of the head and neck with an estimated 12,000 deaths from this cancer **(3)**. Cancers of the head and neck constitute a collection of tumors that begin in the squamous cells lining the mucosal surfaces of the head and neck, referred to as SCCHN, and are categorized by the area of the head or neck in which they begin: Oral cavity, pharynx (includes nasopharynx, oropharynx, and hypopharynx), paranasal sinuses, and nasal cavity, and salivary glands.

Although cancers originating in the salivary glands are usually classified as part of head and neck cancers, salivary gland cancers can arise from multiple types of cells within a gland and therefore have a heterogeneous histological pathology compared to the other head and neck cancers arising from a squamous cell lining. Therefore, patients with salivary gland cancers will not be evaluated in this study.

Infection with **human papillomavirus** (HPV), specifically the cancer causing type, HPV-16, is now considered a risk factor for certain head and neck cancers, particularly oropharyngeal cancers involving the tonsils or the base of the tongue **(12;25)**. In the US the incidence of oropharyngeal cancers caused by HPV infection is increasing, while the incidence of oropharyngeal cancers related to other causes is falling **(12)**.

When SCCHN is detected in its earliest stages and treated, it is curable with excellent long term OS, however, locally recurrent and metastatic disease remains very poorly treatable with a median OS of 178 days **(64)**. Thus there remains a tremendous medical need for improved treatment in advanced cases.

Monoclonal antibodies targeting the T-cell immune checkpoint inhibitors PD-1 and PD-L1 have recently demonstrated antitumor activity in patients with advanced SCCHN. Pembrolizumab was evaluated in a cohort of 60 patients with both HPV-positive and HPV-negative SCCHN **(52)**. Of the 56 evaluable patients, 51% had a reduction in tumor volume, with 19.6% having either a partial response (PR) or complete response (CR) that was equally distributed between the HPV-positive and negative -patients. In addition, MEDI4736, a humanized monoclonal antibody targeting PD-L1, demonstrated a 32% objective response rate in a cohort of 22 patients with advanced SCCHN **(51)**.

B7-H3 has also been found to be expressed on a high percentage of SCCHN tumors **(Investigator's Brochure)** (31;42). In addition to the high percentage of tumors expressing

membranous B7-H3 in SCCHN tumors, the level of B7-H3 expression as determined by immunohistochemistry (IHC) staining on the tumor was inversely correlated with the number of tumor infiltrating CD8 + T-cells and directly proportional to the development of distal metastases and decreased survival (**31**).

Non-Small Cell Lung Cancer: In the US, it is estimated that in 2014 approximately 224,210 patients will be diagnosed with lung cancer and 80 to 85% of these cases will be one of the NSCLC histologies (**3**). The diagnosis of NSCLC is most often made when the disease is advanced or metastatic (Stage IIIB/IV), beyond the time when it can be controlled with localized therapies, leaving only systemic treatment options. The current first-line systemic treatment options for Stage IIIB/IV NSCLC patients are limited, with cisplatin-based doublet chemotherapy being the basis for most first-line treatment, with TKIs used for tumors with identified driver mutations. Despite these approaches, therapy for patients with advanced disease remains largely non-curative. The OS rate in Stage IIIB/IV disease remains poor with 1 year survival rates of 30-40% and 5 year survival rate < 5% despite maximal conventional therapy (**41**). Given the continued poor prognosis of patients with NSCLC, and substantial unmet medical need, new therapeutic approaches are required.

NSCLC, like melanoma, is a tumor where multiple immune checkpoint inhibitors have demonstrated antitumor activity including the PD-1 inhibitors nivolumab and pembrolizumab (**23**;**24**), demonstrating overall ORRs (regardless of PD-L1 status) of approximately 20% and 30% respectively. In addition, the PD-L1 inhibitor MEDI4736 (**8**) demonstrated an ORR of approximately 13%, regardless of PD-L1 status.

Like melanoma and SCCHN, membranous B7-H3 is expressed on a high percentage of NSCLC tumors with a trend towards a higher percentage of squamous carcinomas than adenocarcinoma expressing B7-H3 **(Investigator's Brochure)** (**6**). In addition, the number of tumor infiltrating T-cells in tumor tissue was found to be substantially lower in B7-H3 expressing tumors than in those tumors not expressing B7-H3, and higher expression of B7-H3 on the primary tumor was associated with a higher likelihood of metastatic disease (**57**).

Urothelial Cancer: In the U.S., it is estimated that in 2016 approximately 143,190 patients will be diagnosed with cancer of the urinary system, of which 76,960 will arise from the urinary bladder and 3,530 from the ureter and other urinary organs (American Cancer Society. Cancer Facts & Figures. American Cancer Society pamphlet 2016). Prognosis and treatment varies depending on the category at diagnosis: non-muscle-invasive, muscle-invasive, and metastatic (NCCN Guidelines Version 2.2015 Bladder Cancer). Approximately 70% of patients have non-muscle-invasive disease at the time of diagnosis, but about 31 to 78% will experience recurrence or new tumors within 5 years. One of the first immunotherapies -- bacillus Calmette-Guerin (BCG) -- has been used extensively as prophylactic or adjuvant therapy for bladder cancer post-surgery; however, the duration of maintenance is typically 3 years, with significant local and systemic toxicity. Chemotherapy with cisplatin, taxanes, and gemcitabine is recommended as first-line treatment for advanced disease; however, the benefit is limited for poor-risk patients and toxicity can be significant. Five-year overall survival has been demonstrated as 13% with gemcitabine and cisplatin (GC) and 15.3% with dose dense methotrexate, vinblastine, doxorubicin and cisplatin

(ddMVAC). There remains a significant unmet need for better, and less toxic, treatment options for patients with advanced disease.

Recent advances with new immunotherapies have occurred with the development of PD-1/PD-L1 inhibitors. Pembrolizumab demonstrated antitumor activity in a Phase 1b study of patients with recurrent or metastatic PD-L1-positive urothelial cancer **(43)**. In 28 patients with measurable disease, the ORR was 25% (11% CR and 14% PR) with a 12-month PFS rate of 19%. The ORR in patients with PD-L1-positive tumors was 38%.

Advanced melanoma, NSCLC, SCCHN, and urothelial cancer are good candidates to evaluate with a combination of pembrolizumab and MGA271. All four tumor types have been shown to express membranous B7-H3 in a high percentage of cases and all four have demonstrated susceptibility to immune modulation with monotherapy checkpoint inhibitors. Finally, despite recent advances in the treatment of each disease, there remains a tremendous unmet need for better therapy in patients with these advanced diseases.

2.2 Background on B7-H3 and PD-1

2.2.1 B7-H3

The B7 family of cell surface molecules consists of structurally related protein ligands that bind to receptors on lymphocytes and regulate immune responses. Activation of T and B lymphocytes is initiated by engagement of antigen-specific receptors, T cell antigen receptor (TcR) and membrane-bound immunoglobulin (mIg) respectively, but additional signals delivered simultaneously to members of the CD28 family of receptors by B7 ligands determine the ultimate immune response (**17**). B7 homolog 3 (B7-H3) is a novel member of the B7 family. B7-H3 has been implicated in the delivery of both co-stimulatory and co-inhibitory signals (**29**). The apparent contrasting activities of B7-H3 may be attributed to multiple factors. While the murine B7-H3 molecule exists as a 2-Ig form, the human counterpart has undergone gene duplication and exists primarily as a 4-Ig molecule (**54**). Further, as with other members of the B7 family, B7-H3 may bind, on different cells, to multiple receptors that remain to be identified.

B7-H3 is an attractive target for tumor immunotherapy without regard to its immunological properties. Tissue expression studies have demonstrated that B7-H3 protein is not expressed in most normal tissues, rather its expression is inducible on certain antigen presenting cells (**11**;**55**) and vasculature, exists on certain endocrine tissues (most notably in the cytoplasm of epithelial cells of the adrenal cortex), and is over-expressed in a wide range of cancers (including cultured cancer stem-like cells). B7-H3 is broadly over-expressed on many malignant neoplasms, including SCCHN (MacroGenics unpublished observation); bladder cancer (MacroGenics unpublished observation) (**7**); prostate cancer (**13**;**48**;**60**;**71**), where expression of B7-H3 is associated with metastatic behavior and poor outcome; renal cell carcinoma (**18**), where B7-H3 is broadly expressed in tumor vasculature; ovarian cancer (**66**); colorectal cancer (**56**); gastric cancer (**70**); non-small cell lung cancer (**57**) (MacroGenics unpublished observation); glioblastoma (**39**); melanoma (MacroGenics unpublished observation); and certain small round blue cell tumors of childhood including neuroblastoma and rhabdomyosarcoma (**10**;**26**).

2.2.2 PD-1

PD-1 is an immune-modulatory receptor expressed on activated T-cells. The physiological role of PD-1 is to limit the inflammatory response to infection and prevent autoimmunity by limiting the activity of T cells in the periphery (5;21;32).

The basis for this physiology is that the ligands for PD-1, namely PD-L1 (B7-H1) and PD-L2 (B7-DC), are up-regulated on many cell types — hematopoietic, endothelial and epithelial — in response to pro-inflammatory cytokines, notably interferon gamma. In addition, B7-DC/PD-L2 is up-regulated on dendritic cells and macrophages in response to different pro-inflammatory cytokines such as IL-4 (53;67).

Cancer cells, to avoid antitumor response, co-opt the normal physiology of the PD-1 pathway used to prevent collateral normal tissue damage that would occur in an unchecked inflammatory immune response. Expression of B7-H1/ PD-L1 as an adaptive response to antitumor immunity likely occurs because this ligand is induced on most epithelial cancers in response to interferon-gamma, similarly to epithelial and stromal cells in normal tissues (61).

In addition, PD-1 is highly expressed on induced regulatory T-cells (T-regs), and PD-1: PD-L1 interactions appear to promote the induction, conversion and maintenance of T-regs, suggesting an additional mechanism for immunosuppression in a tumor microenvironment rich in PD-1 ligands (2;20).

2.3 Study Agent Background

2.3.1 MGA271

MGA271 is a humanized monoclonal antibody that binds the B7-H3 immunoligand with high affinity (35). The antibody has been engineered to have enhanced binding to the activating FcγR, CD16A, and especially the low affinity allele of CD16A, CD16A-158F. Since most patients carry the low-affinity allele of CD16A, the enhanced binding of the Fc-optimized version is expected to impart binding improvement that benefits the whole patient population, not just those patients who are homozygous for the high-binding allele of CD16A (valine/valine (V/V) genotype, approximately 15% of the population). MGA271 also exhibits reduced binding to the low-affinity inhibitory receptor, CD32B.

Antibody dependent cellular cytotoxicity (ADCC) has been shown to be an important mechanism of action for several monoclonal antibodies including rituximab (**16**;**66**) and trastuzumab (**16**;**40**) and is likely an important mechanism of action for MGA271.

The ability of MGA271 (or RES242 [MGA271 with a wild-type Fc]) to mediate ADCC activity was evaluated across multiple cancer types expressing varying levels of B7-H3 as determined by flow cytometry. The cancer types tested included: melanoma (A375, UACC-62), lung cancer (SK-MES-1, A549), prostate cancer (LnCAP), breast cancer (JIMT-1, MDA-MB-468), bladder cancer (SW780, HT-1197), and renal cancer (ACHN) cell lines.

MGA271-mediated ADCC activity against all tumor lines that express B7-H3 at detectable levels. Furthermore, MGA271 showed enhanced ADCC potency compared to the related version of the antibody with wild type Fc domains, chBRCA84D or RES240, against all the tumor cell lines examined (see **Figure 1**). Consistent with the studies described above, the greatest enhancement in ADCC activity against the B7-H3 expressing prostate cancer cell line LnCAP was observed with effector populations obtained from individuals homozygous for the weak binding allele of CD16A (phenylalanine/phenylalanine [F/F]). In contrast, MGA271 did not mediate ADCC against Raji B-cell lymphoma cells, which do not express detectable cell surface B7-H3.

2.3.1.1 Safety

2.3.1.1.1 Nonclinical Data

2.3.1.1.2 Clinical Trial Experience

MGA271 is currently being evaluated in patients with cancer in 4 ongoing, Phase 1, MacroGenics-sponsored clinical studies. Clinical trial experience is presented for MGA271+pembrolizumab combination therapy for the current study (CP-MGA271-03) and MGA271 monotherapy for Study CP-MGA271-01. Data from remaining 2 studies are not included, 1 explores MGA271 treatment in a pediatric population and the other explores combination MGA271 and ipilimumab treatment.

Safety

As of the cutoff date of 13 April 2019, safety data are available for 133 patients exposed to MGA271+Pembrolizumab in Study CP-MGA271-03 and for 179 patients exposed to MGA271 in Study CP-MGA271-01. A discussion of safety for each study is presented below.

Study CP-MGA271-03

Adverse events considered related to MGA271+pembrolizumab treatment were reported in 116 patients (87.2%). The most common treatment-related adverse events (TRAEs) reported in ≥ 5% of patients exposed to MGA271+pembrolizumab in decreasing order of frequency were as follows: infusion-related reaction (54.1%); fatigue (27.8%); nausea (9.8%); pyrexia (9.0%); lipase increased (8.3%); arthralgia (7.5%); events of diarrhea, rash maculo-papular, and decreased appetite (6.8%, each); events of hypothyroidism and pneumonitis (6.0%, each); events of chills, anemia, lymphocyte count decreased, and pruritus (5.3% each). Greater than or equal to Grade 3 TRAEs were reported in 38 patients (28.6%). Of these, the most commonly reported in ≥ 5% of patients was infusion-related reaction (6.8%) and lipase increased (6.0%).

Forty-eight patients (36.1%) experienced at least 1 serious adverse event (SAE). The most common SAEs, reported in ≥ 2% of patients in decreasing order of frequency were: infusion-related reaction (6.8%), pneumonitis (4.5%), and dyspnea (2.3%). Twenty-three patients (17.3%) experienced SAEs considered related to MGA271+pembrolizumab; the majority of these events were ≤ Grade 3 in severity (20/23 patients [87%]). The most common SAEs considered related were infusion-related reaction (6.8%) and pneumonitis (4.5%). Fourteen patients (10.5%) experienced at least 1 ≥ Grade 3 SAE that was considered related to MGA271+pembrolizumab; with the exception of infusion-related reaction (6 patients [4.5%]) and pneumonitis (3 patients [2.3%]), the events were singularly reported.

Study CP-MGA271-01

Adverse events considered related to MGA271 monotherapy treatment have been reported in 146 patients (81.6%). The most common related AEs reported in ≥ 5% of patients exposed to MGA271 in decreasing order of frequency were as follows: infusion-related reaction (39.7%), fatigue (31.8%), nausea (19.6%), chills (14.0%), vomiting (12.8%), pyrexia (9.5%), diarrhea (8.4%), decreased appetite (7.3%), pruritus (6.1%), influenza-like illness (5.6%), and headache (5.0%). These events were generally mild (Grade 1) or moderate (Grade 2) in severity, but thirteen patients (7.3%) reported ≥ Grade 3 AEs considered related to MGA271 treatment.

Eleven patients (6.1%) experienced SAEs considered related to MGA271 treatment. The most common SAEs considered related were infusion-related reaction (3.4%) and pyrexia (1.1%]). The SAEs considered related to MGA271 treatment were generally mild (Grade 1) or moderate (Grade 2) in severity; few patients (5 patients [2.8%]) experienced at least 1 ≥ Grade 3 SAE considered to be related, with the most commonly reported as infusion-related reaction (1.7%).

Overall, MGA271 administration as a monotherapy has been generally well-tolerated, with infusion-related reactions, typically mild or moderate, being the primary safety concern. Previously implemented premedication guidelines have been continued to help mitigate the occurrence of these events. Observed infusion-related reactions have been manageable, resolving without sequelae. Patients who experienced Grade 3 infusion-related reactions have fully recovered following brief interruption in dosing and after receiving treatment based

upon symptomatology. Other AEs expected with administration of MGA271 include nausea, vomiting, and pyrexia.

2.3.1.1.2.1 Summary

In conclusion, the data from the clinical studies CP-MGA271-03 and CP-MGA271-01 as of 13 April 2019 suggest that MGA271 at doses up to 15 mg/kg combined with 2 mg/kg Pembrolizumab weekly by IV and MGA271 monotherapy at doses up to 15 mg/kg administered weekly by IV, is generally well tolerated with toxicities manageable by standard medical therapy for patients with advanced cancer.

Efficacy:

As of 12 October 2018 (1), 133 patients have been treated in this study. Combination MGA271 and pembrolizumab dose escalation and expansion cohorts are closed to further enrollment; patients enrolled in these cohorts have completed combination treatment; no MTD was defined. The MGA271 + pembrolizumab combination treatment demonstrated an acceptable safety profile. In the anti-PD-1/PD-L1 naïve patients treated with MGA271 + pembrolizumab, the objective response rates benchmarked favorably with historical experience with anti-PD-1 monotherapy: SCCHN (post-platinum chemotherapy) was 33.3% and NSCLC (PD-L1 < 1%) was 35.7%; see **Table 1**.

Table 1 Enoblituzumab (MGA271) + Pembrolizumab Combination Benchmarks Favorably

SCCHN	Study Results			
Agent (Study)	Enoblituzumab +Pembrolizumab	Nivolumab (CM-141)[a]	Pembrolizumab (KN-012)[b]	Pembrolizumab (KN-040)[c]
N	18	240	174	247
ORR	33.3%	13%	16%	15%

NSCLC	Study Results			
Agent (Study)	Enoblituzumab +Pembrolizumab	Nivolumab (CM-057)[d]	Nivolumab (CM-017)[e]	Pembrolizumab (KN-001)[f]
Histology	Both	Non-Squamous	Squamous	Both
N	14	108	54	87
ORR	35.7%	9%	17%	8%

(a) Ferris, et al., 2016, N Eng J Med; (b) Keytruda® package insert; (c) Cohen, et al., 2017, ESMO LBA45; (d) Borghaei, et al., 2015, NEJM; (e) Brahmer, et al., 2015, NEJM; (f) Garon, et al., 2015, NEJM

2.3.2 Pembrolizumab

Pembrolizumab (KEYTRUDA®) is a humanized IgG4 kappa monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2 (38). Pembrolizumab

is produced in recombinant Chinese hamster ovary cells (CHO). Pembrolizumab was initially approved by the US Food and Drug Administration (FDA) in 2014. Pembrolizumab (KEYTRUDA®) currently has approval (as of February 2019) for the following indications:

Melanoma:

- For the treatment of patients with unresectable or metastatic melanoma
- For the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection.

Non-Small Cell Lung Cancer:

- In combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations.
- In combination with carboplatin and either paclitaxel or nabpaclitaxel as first-line treatment of patients with metastatic squamous NSCLC.
- As a single agent for the first-line treatment of patients with metastatic NSCLC whose tumors have high PD-L1 expression (Tumor Proportion Score [TPS] ≥ 50%) as determined by an FDA approved test, with no EGFR or ALK genomic tumor aberrations.
- As a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA.

Head and Neck Squamous Cell Cancer (HNSCC):

- For the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.

Urothelial Carcinoma:

- For the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (Combined Positive Score [CPS] ≥10) as determined by an FDA-approved test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.
- For the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

The recommended dosage for these indications is 200 mg IV over 30 minutes every 3 weeks.

2.3.2.1 Safety

Pembrolizumab (KEYTRUDA®) can cause immune-mediated toxicities, some of which can be life-threatening and possibly lead to death.

- **Immune-Mediated Pneumonitis:** Pneumonitis occurred in 94 (3.4%) of 2799 patients receiving KEYTRUDA, including Grade 1 (0.8%), Grade 2 (1.3%), Grade 3 (0.9%), Grade 4 (0.3%), and Grade 5 (0.1%) pneumonitis. The median time to onset was 3.3 months (range: 2 days to 19.3 months), and the median duration was 1.5 months (range: 1 day to 17.2+ months). Sixty-three (67%) of the 94 patients received systemic corticosteroids, with 50 of the 63 receiving high-dose corticosteroids for a median duration of 8 days (range: 1 day to 10.1 months) followed by a corticosteroid taper. Pneumonitis occurred more frequently in patients with a history of prior thoracic radiation (6.9%) than in patients who did not receive prior thoracic radiation (2.9%). Pneumonitis led to discontinuation of KEYTRUDA in 36 (1.3%) patients. Pneumonitis resolved in 55 (59%) of the 94 patients.
- **Immune-Mediated Colitis:** Colitis occurred in 48 (1.7%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.4%), Grade 3 (1.1%), and Grade 4 (<0.1%) colitis. The median time to onset was 3.5 months (range: 10 days to 16.2 months), and the median duration was 1.3 months (range: 1 day to 8.7+ months). Thirty-three (69%) of the 48 patients received systemic corticosteroids, with 27 of the 33 requiring high-dose corticosteroids for a median duration of 7 days (range: 1 day to 5.3 months) followed by a corticosteroid taper. Colitis led to discontinuation of KEYTRUDA in 15 (0.5%) patients. Colitis resolved in 41 (85%) of the 48 patients.
- **Renal Failure and Immune-Mediated Nephritis**: Nephritis occurred in 9 (0.3%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.1%), Grade 3 (0.1%), and Grade 4 (<0.1%) nephritis. The median time to onset was 5.1 months (range: 12 days to 12.8 months), and the median duration was 3.3 months (range: 12 days to 8.9+ months). Eight (89%) of the 9 patients received systemic corticosteroids, with 7 of the 8 receiving high-dose corticosteroids for a median duration of 15 days (range: 3 days to 4.0 months) followed by a corticosteroid taper. Nephritis led to discontinuation of KEYTRUDA in 3 (0.1%) patients. Nephritis resolved in 5 (56%) of the 9 patients. Nephritis occurred in 1.7% of 405 patients receiving KEYTRUDA in combination with pemetrexed and 11 platinum in the KEYNOTE-189 study, including Grade 3 (1%) and Grade 4 (0.5%) nephritis. The median time to onset was 3.2 months (range: 16 days to 11.1 months) and the duration ranged from 1.6 to 16.8+ months. Six (86%) of the 7 patients received systemic corticosteroids, with all 6 receiving high-dose corticosteroids for a median duration of 3 days (range: 1 to 17 days) followed by a corticosteroid taper. Nephritis led to discontinuation of KEYTRUDA in 5 (1.2%) patients. Nephritis resolved in 2 (29%) of the 7 patients.

- **Immune-Mediated Hepatitis:** Hepatitis occurred in 19 (0.7%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.1%), Grade 3 (0.4%), and Grade 4 (<0.1%) hepatitis. The median time to onset was 1.3 months (range: 8 days to 21.4 months), and the median duration was 1.8 months (range: 8 days to 20.9+ months). Thirteen (68%) of the 19 patients received systemic corticosteroids, with 12 of the 13 receiving high-dose corticosteroids for a median duration of 5 days (range: 1 to 26 days) followed by a corticosteroid taper. Hepatitis led to discontinuation of KEYTRUDA in 6 (0.2%) patients. Hepatitis resolved in 15 (79%) of the 19 patients.
- **Immune-Mediated Endocrinopathies:**

  Hypophysitis

  Hypophysitis occurred in 17 (0.6%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.2%), Grade 3 (0.3%), and Grade 4 (<0.1%) hypophysitis. The median time to onset was 3.7 months (range: 1 day to 11.9 months), and the median duration was 4.7 months (range: 8+ days to 12.7+ months). Sixteen (94%) of the 17 patients received systemic corticosteroids, with 6 of the 16 receiving high-dose corticosteroids. Hypophysitis led to discontinuation of KEYTRUDA in 4 (0.1%) patients. Hypophysitis resolved in 7 (41%) of the 17 patients.

  Thyroid Disorders:

  Hyperthyroidism occurred in 96 (3.4%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.8%) and Grade 3 (0.1%) hyperthyroidism. The median time to onset was 1.4 months (range: 1 day to 21.9 months), and the median duration was 2.1 months (range: 3 days to 15.0+ months). Hyperthyroidism led to discontinuation of KEYTRUDA in 2 (<0.1%) patients. Hyperthyroidism resolved in 71 (74%) of the 96 patients.

  Hypothyroidism occurred in 237 (8.5%) of 2799 patients receiving KEYTRUDA, including Grade 2 (6.2%) and Grade 3 (0.1%) hypothyroidism. The median time to onset was 3.5 months (range: 1 day to 18.9 months), and the median duration was not reached (range: 2 days to 27.7+ months). Hypothyroidism led to discontinuation of KEYTRUDA in 1 (<0.1%) patient. Hypothyroidism resolved in 48 (20%) of the 237 patients. The incidence of new or worsening hypothyroidism was higher in patients with HNSCC occurring in 28 (15%) of 192 patients receiving KEYTRUDA, including Grade 3 (0.5%) hypothyroidism. Of these 28 patients, 15 had no prior history of hypothyroidism.

  Thyroiditis occurred in 16 (0.6%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.3%) thyroiditis. The median time of onset was 1.2 months (range: 0.5 to 3.5 months).

- **Type 1 Diabetes mellitus:** KEYTRUDA can cause type 1 diabetes mellitus, including diabetic ketoacidosis, which have been reported in 6 (0.2%) of 2799 patients receiving KEYTRUDA.

- **Immune-Mediated Skin Adverse Reactions:** Immune-mediated rashes, including Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN) (some cases with fatal outcome), exfoliative dermatitis, and bullous pemphigoid, can occur. Monitor patients for suspected severe skin reactions and exclude other causes.

The following clinically significant, immune-mediated adverse reactions occurred in less than 1% of 2799 patients treated with KEYTRUDA: arthritis (1.5%), uveitis, myositis, Guillain-Barre syndrome, myasthenia gravis, vasculitis, pancreatitis, hemolytic anemia, sarcoidosis, and encephalitis. In addition, myelitis and myocarditis were reported in other trials and post-marketing use.

The most common adverse reactions reported in ≥ 20% of patients were:

- KEYTRUDA as a single agent: fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, constipation, pain and abdominal pain.
- KEYTRUDA in combination with chemotherapy: fatigue/asthenia, nausea, constipation, diarrhea, decreased appetite, rash, vomiting, cough, dyspnea, pyrexia, alopecia, and peripheral neuropathy.

A high level of awareness for the possibility that an AE may be an immune-related AE (irAE) is necessary in the management of patients receiving pembrolizumab because the presentations of an irAE can be subtle, and other causes must be ruled out. An irAE can occur at any point during treatment with pembrolizumab. It is imperative to establish the correct diagnosis promptly, determining severity based on Common Terminology Criteria for Adverse Events (CTCAE) grading and initiating treatment with steroids, if necessary, and holding further pembrolizumab treatment is essential (**38**). Refer to **Section 6.5** for a detailed description of toxicity management. See also current KEYTRUDA® Prescribing Information.

2.3.3 MGA012

MGA012 (also known as INCMGA00012) is a humanized, hinge-stabilized, IgG4κ monoclonal antibody (mAb) that recognizes human PD-1.

2.3.3.1 Safety

2.3.3.1.1 MGA012 Nonclinical Experience

2.3.3.1.2 MGA012 Clinical Experience

Phase 1 dose-finding results in participants with advanced cancer (N = 37) have been presented **(34)**. MGA012 demonstrated acceptable tolerability with no dose-limiting toxicity observed at doses ranging from 1 to 10 mg/kg every 2 weeks (Q2W), Q4W administration was also studied. A maximum tolerated dose was not reached. T½ (β) was approximately 17 days, and steady state was achieved in approximately 85 days. Full and sustained receptor occupancy of MGA012 on both CD4+ and CD8+ T cells along with complete loss of competing fluorescently labeled anti–PD-1 staining (eJBio105 clone) were observed at all dose levels. A dose of 3 mg/kg Q2W was selected for further expansion in non small-cell lung carcinoma (NSCLC), endometrial cancer, cervical cancer, and sarcoma cohorts, with subsequent evaluation of flat dosing in tumor-agnostic and microsatellite instability (MSI) high uterine cancer cohorts.

Interim results for the expansion cohorts have recently been presented **(37)**. A total of 132 patients were enrolled into the disease-specific expansion cohorts and another 30 in the tumor agnostic flat dosing cohorts at 500 and 750 mg Q4W. Patients were predominantly Caucasian and female; the median age ranged from 44 for the sarcoma cohort to 64 for the endometrial cancer cohort. The most frequently reported treatment-emergent adverse events (TEAEs) (> 10%) in patients receiving body-weight based dosing were fatigue, diarrhea, and dyspnea. The most frequently reported TEAEs (≥ 20%) in patients receiving the fixed dose of 500 mg Q4W were fatigue, blood alkaline phosphatase increased, and blood bilirubin increased. These AEs were generally low-grade. Overall, 23/199 (12%) patients exposed to MGA012 in the study have experienced immune-related adverse events (irAEs). Most irAEs were transient, except for endocrine-related irAEs. Non endocrine irAEs that did not resolve were lipase increased, stomatitis, proctitis, diarrhea, ALT increased, and blood bilirubin increased (all 1 participant each). There were no fatal irAEs.

Confirmed RECIST responses were observed in all the expansion cohorts, none of which had been enriched by a predictive biomarker (e.g., MSI or PD-L1 status). Specifically, 5/27 (19%) evaluable NSCLC patients had confirmed RECIST responses, as did 4/29 (14%)

cervical cancer patients, 4/23 (17%) endometrial cancer patient, and 1 sarcoma patient. ORR and median duration of responses have not yet been established.

MGA012 is currently being developed for the treatment of metastatic Merkel-cell carcinoma and squamous cell carcinoma of the anal canal and as both a monotherapy and in combination with other potentially immunomodulatory agents (including chemotherapy) for a broad spectrum of solid tumors.

2.4 Rationale for Combining MGA271 and Pembrolizumab

Despite current treatment options for patients with melanoma, NSCLC, SCCHN, or urothelial cancer, substantial unmet medical need remains for patients with advanced disease. This study evaluates a novel combination of immunotherapies in patients with advanced cancer and is designed to investigate whether combined administration of MGA271 and pembrolizumab to coordinately block two distinct B7 pathways can further potentiate the potentially promising antitumor activity observed with pembrolizumab alone.

The blockade of individual immune checkpoints has demonstrated antitumor activity in a variety of cancers and has been validated in melanoma with ipilimumab and pembrolizumab. Nonetheless, the vast majority of tumors eventually progress, escaping immune detection and destruction. Therefore, strategies that combine immune checkpoint blockade through non-redundant immune checkpoints, and/or other mechanisms are being actively investigated and are beginning to demonstrate even greater potential antitumor activity than monotherapy based treatments (**58**).

The simultaneous blockade of B7-H3 with MGA271 and PD-1 with pembrolizumab represents an opportunity to potentially enhance and focus the immune system against cancer cells to mediate antitumor effects more pronounced than either single agent alone. Aside from coordinately targeting the distinct functions mediated by B7-H3 and PD-1/PD-L1 with combined administration of MGA271 and pembrolizumab, several additional lines of evidence suggest that these agents may be combined to more effectively enhance the antitumor response compared to either agent alone, including the following:

Pembrolizumab and MGA271 may enhance the immune response against tumors though reduction of T regulatory cell (T-regs) immunosuppression.

Both PD-1 and B7-H3 are reported to have roles in amplifying the impact of T-regs in the tumor bed, and these mechanisms could play a substantial role in the ability of each pathway to mediate immune suppression that allows tumors to escape immune mediated destruction. Therefore, a coordinated blockade of PD-1 and B7-H3 may have a substantial impact on reducing the effects of T-regs in the tumor bed and sharply reduce immune suppression. Below is a brief synopsis of the role that each receptor has in potentiating the effects of regulatory T cells.

PD-1

PD-1 is highly expressed on induced regulatory T cells and activation of the PD-1/ PD-L1 axis promotes the induction, conversion and maintenance of T-regs (**20**). Native CD4 T-helper cells were induced to become T-regs on exposure to PD-L1 coated beads in-vitro, and PD-L1 enhanced and sustained Foxp3 expression. The induced T-regs were shown to have immune suppressive function both in in-vitro and in-vivo murine models (**20**). In another set of experiments it was demonstrated that the induction of T-regs by PD-L1 could be abolished by blocking PD-1 on the T-helper cells (**2**) These experiments suggest that the interaction of PD-1 and PD-L1 could provide an additional mechanism for immunosuppression through de novo generation of T-regs in a tumor microenvironment rich in PD-1 ligands.

B7-H3

Expression of B7-H3 on antigen presenting dendritic cells (DC) in the tumor bed has been linked to an enhanced suppressive function of T-regs cells in murine models and in human lung cancer (**36;49;50**). In a study evaluating NSCLC tumor specimens for expression of B7 checkpoint inhibitors on tumor infiltrating lymphocytes, B7-H3 expression was significantly up-regulated on tumor infiltrating DC whereas the expression of other B7 molecules, B7-DC (PD-L2), B7-1, B7-2, B7-H1 (PD-L2), remained unchanged compared to DC derived from healthy lung tissue (**49**). T-regs and B7-H3 expressing DC work together in a feedback loop as T-regs induce further B7-H3 expression on DC and B7-H3 expressing DC further induce T-regs in the tumor bed. Thus, B7-H3 expressing dendritic cells, have an overall immunosuppressive effect by increasing the number of T-regs in the tumor. In addition, DC that express B7-H3 have decreased T-effector cell simulative effects compared to non-B7-H3 expressing DC. Therefore, blockade of B7-H3 signaling by MGA271on DC may indirectly reduce the immune-suppressive function of T-regs in the tumor bed and the combined inhibition on the effects of T-regs immunosuppression by adding pembrolizumab may synergize to substantially degrade T-reg-mediated immunosuppression.

Coordinate engagement of both innate and adaptive immunity by combining agents that potentiate ADCC with agents that modulate T-cell function may yield synergistic antitumor activity.

In addition to its potential T-cell regulatory properties, MGA271 is an Fc-enhanced monoclonal antibody modified to increase its Fc stimulatory activity and thus enhance potential ADCC immune attack on B7-H3 expressing tumor cells. The immune response is considered to be a major determinant of monoclonal antibody antitumor directed ADCC activity (**33**). Combining the 2 distinct mechanisms of action of ADCC and release of the PD-1 checkpoint inhibition against T-effector cells may synergize for increased ant-tumor activity than observed with MGA271 or pembrolizumab, alone.

The limited B7-H3 expression on normal cells may potentiate immune targeting of tumor cells while limiting self-immune reactivity.

Coordinate engagement of multiple immune-stimulatory mechanisms directed against tumors with an improved safety profile based on limited expression of B7-H3 in normal tissue,

reduces the potential for breaking tolerance against normal organs and immune-related AEs with the MGA271/pembrolizumab combination compared to combinations consisting of anti-CTLA-4 (i.e., ipilimumab or tremilimumab) and anti-PD-1 (i.e., pembrolizumab or nivolumab) antibodies.

Combinatorial immune checkpoint blockade may provide antitumor activity where either one or both agents has limited activity on its own in certain tumors.

In some cases, with immune checkpoints, blockade of a single checkpoint may demonstrate little to no antitumor activity in certain tumor types, but when a second immune checkpoint is blocked in combination with the first, substantial activity is observed. Lymphocyte-activation gene 3 (LAG-3) is a ligand expressed on T-cells that is substantially expressed on tumor infiltrating T cells, including T-effector and T-regs. The ligand for LAG-3 is major histocompatibility complex class II (MHC II) expressed on antigen presenting cells (**27**). In a murine model of established fibrosarcoma or colon cancer xenografts, murine anti-PD-1 and anti- LAG-3 antibodies had a limited to moderate effect on the growth of the tumors, respectively. Of the mice treated with anti-LAG-3, 10% and 0% were tumor free at Day 50 in the fibrosarcoma and colon cancer inoculated mice, respectively. Similarly, for the anti-PD-1 treated mice, 20% and 40% were tumor free at Day 50. In striking contrast, 70% and 80% of the mice inoculated with fibrosarcoma and colon cancer cells, respectively, were tumor-free after 50 days following combinatorial anti-LAG-3 plus anti-PD-1 immunotherapy (**69**).

2.5 Rationale for Combining MGA271 and MGA012

Beginning with Amendment 5, a new cohort (Cohort 4) will be enrolled to explore the safety and tolerability of MGA271+MGA012 treatment. The properties of MGA012 are comparable to those observed with replicas of the approved anti-PD-1 mAbs, nivolumab and pembrolizumab (**Table 2**). MGA012 also blocks the PD-1/PD-L1 inhibitory axis (measured with a luciferase reporter assay system) in a dose-dependent manner that is comparable to those observed with the nivolumab and pembrolizumab replicas (**Table 2**).

Table 2 Comparison of in vitro Potencies of MGA012 and Nivolumab and Pembrolizumab Replicas

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

1 EC50, effective concentration at 50% of maximal activity; IC50 =effective concentration at 50% inhibition of activity.

The safety, tolerability and preliminary efficacy of MGA012 has been explored in a Phase 1 study, CP-MGA012-01, as described in **Section 2.3.1.1.2.**

2.6 Rationale for Dose Selection

2.6.1 Dose Escalation Phase

2.6.1.1 Pembrolizumab

The dose of pembrolizumab administered during the study will be 2 mg/kg given once every 3 weeks via 30-minute IV infusion. This is the FDA-approved dose and schedule that was found to have clinical benefit in patients with advanced melanoma. In addition, the 2 mg/kg dose has also demonstrated antitumor activity in NSCLC (**23**;**46**) and pembrolizumab has received accelerated approval for NSCLC by the US FDA.

2.6.1.2 MGA271

The dose for MGA271 in the escalation phase will begin at 3 mg/kg IV (120-minute infusion), with proposed escalations to 10 mg/kg and then 15 mg/kg, given on a once weekly schedule. There will be a dose de-escalation to 1 mg/kg of MGA271 if the starting dose of 3 mg/kg in combination with pembrolizumab is found to exceed the maximum tolerated dose (MTD). In addition, MGA271 dose de-escalations of 7 mg/kg and 12 mg/kg may be evaluated depending on the toxicity profile of the MGA271/pembrolizumab combination observed with MGA271 doses of 10 and 15 mg/kg, respectively.

The initial dose proposed for MGA271 in the Dose Escalation Phase, 3 mg/kg, is based on the pharmacokinetic and safety profile of MGA271 from the ongoing CP-MGA271-01 Phase 1 study. In the CP-MGA271-01 study, dose escalation was carried out from

0.01 mg/kg to 15 mg/kg without a DLT observed at any dose level. As 15 mg/kg was the highest protocol specified dose, 15 mg/kg was determined as the maximum administered dose (MAD), and that dose carried into the expansion phase of that study. The safety profile of MGA271 based on a total of 51 patients exposed to MGA271 demonstrated that the majority of AEs were mild (CTCAE Grade 1 or 2), with toxicities manageable by standard medical therapy. One patient has discontinued MGA271 for a drug related toxicity that was considered to be a drug-related SAE. See **Section 2.3.1** for a more detailed description of the safety profile from Study CP-MGA271-01.

Preliminary population PK modeling of data from 78 adult subjects from Study CP-MGA271-01 and 9 pediatric subjects from Study CP-MGA271-04 who received weekly MGA271 IV infusion of 0.15, 0.5, 1.5, 5, 10, or 15 mg/kg delivered over a period of 120 minutes indicated that MGA271 PK in adult and pediatric patients can be well described by the quasi-steady-state approximation of the 2-compartment target-mediated drug disposition model. The model parameters were in agreement with the values expected for the monoclonal antibodies. Due to the small sample size of the study, no covariates except of weight were included in the final model. For a typical 75 kg subject, clearance, central volume, inter-compartment clearance, and peripheral volume were estimated as CL=0.157 L/day, V_1=3.33 L, Q=0.779 L/day, and V_2= 3.33 L, respectively. The terminal half-life and distribution half-life of the linear part of elimination (that is dominant at high concentrations) was estimated at $t_{1/2}^{term}$= 30.96 days and $t_{1/2}^{dist}$ = 1.41 days, respectively. QSS constant K_{SS} was estimated at K_{SS}=566 ng/mL. Maximum elimination rate via the target mediated pathway (equal to K_{SYN}=BASE*K_{DEG}) was estimated at 3.46 mg/L/day.

Although the 15 mg/kg dose of MGA271 demonstrates a mild toxicity profile, and is now used as the dose in the CP-MGA271-01 monotherapy expansion cohorts, a 5-fold lower dose, 3 mg/kg, will be used as the starting dose in the Dose Escalation Phase in the current study. Even though the proposed 3 mg/kg starting dose does not likely saturate the B7-H3 receptors, as suggested by the target-mediated drug disposition in the PK modeling, this 5-fold lower starting dose allows for adequate safety margin for initial testing of the combination.

Beginning with Amendment 5, MGA271 will be dosed at 15 mg/kg every 3 weeks, Q3W. Based on population PK modeling and simulation of MGA271, at 15 mg/kg dose, the estimated average C_{min_SS} was 787.6 µg/ml (276.8-1548.1 µg/ml) when the doses were administered weekly (QW) and 160.5 µg/ml (26.9-412.2 µg/ml) when the doses would be administered Q3W. As expected, the decrease in dosing frequency would decrease the average C_{min_SS} in subjects;

(**see Section 2.3.1**).

2.6.1.3 MGA012

The dose for MGA012 will be administered as a flat-dose of 375 mg, Q3W. MGA012 is administered in Study INCMGA00012-101 as both a weight-based dose (ranging from 1 mg/kg to 10 mg/kg) and at fixed doses of 500 mg and 750 mg. Treatment has been well tolerated over the entire dosing range and a maximum tolerated dose has not been reached (**34**).

The monotherapy recommended Phase 2 dose of 500 mg Q4W is based on clinical data from the ongoing first-in-human monotherapy study (INCMGA00012-101; NCT03059823). This dose-escalation study of MGA012 was performed and evaluated 37 patients at the following doses: 1 mg/kg Q2W, 3 mg/kg Q2W, 3 mg/kg Q4W, 10 mg/kg/Q2W, and 10 mg/kg Q4W. While supra dose proportionality was observed for AUC and C_{max} for the first dose from 1 mg/kg to 10 mg/kg, linear PK was shown from 3 mg/kg to 10 mg/kg.

A population PK (PPK) analysis was performed on patients in the INCMGA00012-101 study to characterize the effect of body weight on the PK of MGA012. The plasma concentrations of MGA012 can be adequately described by a 2-compartment model with first-order elimination. Higher clearance of MGA012 was estimated for the 1 mg/kg dose than for other dose groups. Body weight dependence of clearance was characterized by a power relationship with an exponent of 0.911.

A simulation was conducted to investigate the use of weight-based dosing and flat dosing for MGA012, with the aim of targeting a steady-state trough concentration of approximately 21 mcg/mL, the median trough concentration for pembrolizumab (**22**) providing flexibility for combinations with different schedules. The median MGA012 exposure and its distribution around the median at 500 mg Q4W were similar to 7 mg/kg Q4W in the simulated population, which justified clinical exploration in an expansion cohort of the study. The median steady-state concentration at 500 mg Q4W is 24.8 mcg/mL, and 58% of participants have trough concentrations greater than the target concentration. The median steady-state concentration at 350 mg every 3 weeks (Q3W) is 27.6 mcg/mL. Though not simulated, the 375 mg Q3W dose was selected to maintain dose-linearity in clinical trials.

Pharmacokinetic data were obtained from 15 patients who received MGA012 at 500 mg Q4W in the Cohort Expansion Phase of Study INCMGA00012-101. The observed $AUC_{0-\infty}$ for 500 mg Q4W is close to the steady-state AUC_{0-t} based on the PPK analysis of weight based dosing, as is the estimated clearance. The estimated $t_{1/2}$ (333 hours) is slightly shorter than that from the previous estimate of 409 hours. The mean trough plasma concentration on Cycle 2 was 17.1 mcg/mL, and the mean projected minimum plasma concentration at steady state is 23.1 mcg/mL (which meets or slightly exceeds the targeted concentration based on pembrolizumab data) with mean accumulation index of 1.50. Overall, the 500 mg Q4W dose had very similar PK properties to the 3 mg/kg Q2W dosing and has approximately a 77% probability for steady-state trough plasma concentration ≥ 10 mcg/mL, which is associated with maximum target engagement and greatest probability of efficacy. Based on these

observations, 500 mg Q4W was selected as the recommended Phase 2 dose for monotherapy. Fifteen patients are enrolled in an additional expansion cohort of Study INCMGA00012-101 that will test the 375 mg Q3W regimen. Preliminary safety experience with this dosing regimen is also favorable (Incyte Corporation, data on file). Based on these observations, a flat dose regimen of MGA012 375 mg Q3W is considered an acceptable alternative where flexibility in dosing is needed.

The Q3W recommended dose of MGA012 is 375 mg, based on a demonstration of clinical safety and favorable pharmacology in the dose-finding 0012-101 study (**37**, **14**,**15**)

2.6.2 Expansion Phase

The doses used in the Expansion Phase will be the MTD or MAD for the combination of MGA271 and pembrolizumab determined during the Dose Escalation Phase.

3 STUDY PURPOSE AND OBJECTIVES

This study is an open-label, dose escalation, Phase 1 study designed to characterize the safety, tolerability, PK, pharmacodynamics (PD), immunogenicity, and preliminary antitumor activity of IV MGA271 administered IV weekly in combination with 2 mg/kg pembrolizumab administered IV every 3 weeks in patients with unresectable locally advanced or metastatic melanoma, NSCLC, SCCHN, urothelial cancer, and other cancers. With Amendment 5, a new cohort (Cohort 4) will be initiated to explore the safety, tolerability, PK, PD, and immunogenicity of MGA271 + MGA012, both administered Q3W, in patients with unresectable locally advanced or metastatic melanoma, NSCLC, SCCHN, urothelial cancer, and other cancers, as stipulated in **Section 5.1**, Inclusion Criteria.

3.1 Primary Objective

The primary objectives of this study are:

- To characterize the safety, tolerability, DLT, and MTD, or MAD (if no MTD is defined) of MGA271 when administered IV weekly in combination with 2 mg/kg pembrolizumab administered IV every 3 weeks (Q3W) to patients with unresectable locally advanced or metastatic melanoma, SCCHN, NSCLC, urothelial cancer, and other cancers.
- To characterize the safety, tolerability, and DLT of 15 mg/kg MGA271 when administered IV Q3W in combination with a flat-dose of 375 mg of MGA012 (anti-PD-1 antibody) administered IV Q3W to patients with unresectable locally advanced or metastatic melanoma, SCCHN, NSCLC, urothelial cancer, and other cancers as stipulated in inclusion criteria.

3.2 Secondary Objective(s)

Secondary objectives of this study are:

- To characterize the PK and immunogenicity of MGA271 administered IV weekly in combination with IV pembrolizumab Q3W, and of MGA271 in combination with MGA012, both administered IV every 3 weeks.
- To characterize the PD activity of MGA271 when administered IV weekly in combination with pembrolizumab Q3W, and of MGA271 in combination with MGA012, both administered IV Q3W.
- To investigate the preliminary antitumor activity of MGA271 when administered IV weekly in combination with IV pembrolizumab Q3W, and of MGA271 in combination with MGA012, both administered IV Q3W using both conventional Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 **(Appendix 5)** and immune-related response criteria (irRC) (i.e., irRECIST as defined in **Appendix 6**).

3.3 Exploratory Objectives

- To explore the relationships between PK, PD, patient safety and antitumor activity of MGA271 when administered in combination with pembrolizumab.
- To investigate the immune-regulatory activity of MGA271 in combination with pembrolizumab and of MGA271 in combination with MGA012 in vivo, including various measures of T cell activation in peripheral blood and/or tumor biopsy specimens.
- To determine the relationships between membranous expression of B7-H3 and PD-L1 on tumor cells, immune cell infiltration within biopsy specimens (including but not limited to CD4+ and CD8+ T cells), B7-H3 and PD-L1 expression on the immune cell infiltrate, and clinical response via IHC staining of optional paired pre- and on-treatment tumor biopsy specimens.

4 TRIAL DESIGN

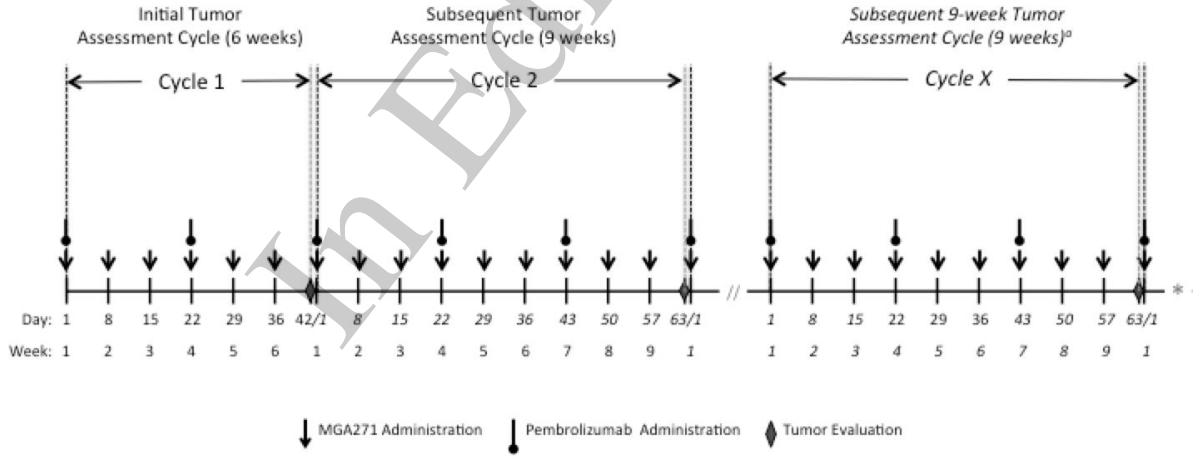
4.1 Overall Study Design and Plan

4.1.1 General Study Design

This study is a Phase 1, open-label, dose escalation and cohort expansion study designed to characterize the safety, tolerability, PK, PD, immunogenicity, and preliminary antitumor activity of MGA271 administered IV weekly in combination with pembrolizumab administered IV every 3 weeks (Q3W). Beginning with Amendment 5, this study will also characterize the safety and tolerability of MGA271 in combination with MGA012 (anti–PD-1 antibody), both administered by IV, Q3W, through the addition of a new cohort, Cohort 4.

The study consists of a **Dose Escalation Phase** to determine the MTD or MAD (if no MTD is determined) of MGA271 administered in combination with 2 mg/kg pembrolizumab, followed by a **Cohort Expansion Phase** to further define the safety and initial efficacy of the combination with the MGA271 dose established in the first phase. The study treatment schema is presented in **Figure 2**.

Figure 2 MGA271 + Pembrolizumab Treatment Schema



a Patients may receive up to 5 subsequent 9-week treatment cycles of MGA271 + pembrolizumab depending on response to study treatments

*All patients will enter an Efficacy Follow-up Period after receipt of the last dose of study treatment to be followed for up to 24 weeks for survival.

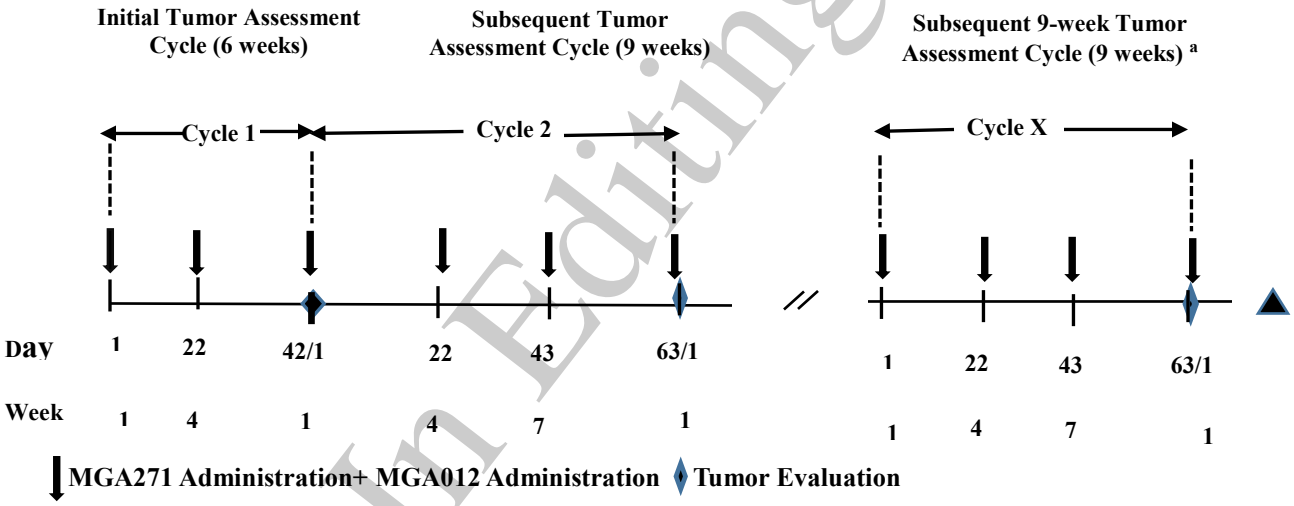
MGA271 will be administered as an IV infusion over 120 minutes on a once-weekly schedule. Pembrolizumab will be administered at 2 mg/kg as an IV infusion over 30 minutes every 3 weeks. On the days that both agents are administered, pembrolizumab will be administered first, followed by MGA271.

For both the Dose Escalation and Cohort Expansion phases, patients' first tumor assessment will be obtained on Cycle 1 Study Day 42 of the **Initial Tumor Assessment Cycle**.

Patients who remain clinically stable and do not experience unacceptable toxicity that necessitates permanent discontinuation of the study drugs, at the completion of the Initial (6-week) Tumor Assessment Cycle will be eligible to receive additional treatment with pembrolizumab and MGA271. Assuming that the patient remains clinically stable, maintains a response status of SD or better, and does not experience unacceptable toxicity that necessitates permanent discontinuation of the study drugs, patients may receive up to 5 additional 9-week treatment cycles during **Subsequent Tumor Assessment Cycles**, for a maximum total of 51 doses of MGA271 and 17 doses of pembrolizumab.

Beginning with Amendment 5, in Cohort 4: 15 mg/kg MGA271 will be administered as an IV infusion over 120 minutes Q3W in combination with 375 mg MGA012 administered as an IV infusion over 60 to 75 minutes Q3W. On dosing days, MGA012 will be administered first, followed by MGA271. The study treatment schema is presented in **Figure 3**.

Figure 3 MGA271 + MGA012 Treatment Schema: Cohort 4



a Patients may receive up to 5 subsequent 9-week treatment cycles of MGA271 + MGA012 depending on response to study treatments

▲ All patients will enter an Efficacy Follow-up Period after receipt of the last dose of study treatment to be followed for up to 24 weeks for survival.

Patients who remain clinically stable and do not experience unacceptable toxicity that necessitates permanent discontinuation of the study drugs, at the completion of the Initial (6-week) Tumor Assessment Cycle, will be eligible to receive additional treatment with MGA271+MGA012. Assuming that the patient remains clinically stable, maintains a response status of SD or better, and does not experience unacceptable toxicity that necessitates permanent discontinuation of the study drugs, patients may receive up to 5 additional 9-week treatment cycles during **Subsequent Tumor Assessment Cycles**, for a maximum total of 17 doses of MGA271 and 17 doses of MGA012.

All tumor assessments performed following the Initial Tumor Assessment Cycle will occur on Study Day 63 of each Subsequent Tumor Assessment Cycle thereafter. Following the last dose of study drug, all patients will be followed for survival during a 6-month (24-week) **Efficacy Follow-up Period**. Patients who discontinue study treatment for a reason other than progressive disease may be followed for efficacy and survival beyond the 6-month (24-week) period until 1 of the following occurs: the patient progresses, withdraws consent for follow up, or initiates other anti-cancer therapy, or the overall trial is closed.

4.1.2 Dose Escalation Phase

The goal of the **Dose Escalation Phase** is to initially characterize the safety and tolerability of MGA271 and pembrolizumab administered in combination, and more specifically to describe the DLTs for each dose level studied and to define the MTD or MAD (if no MTD is defined) based on the frequency of occurrence of DLTs in each cohort. Patients with mesothelioma, urothelial cancer, NSCLC, SCCHN, ccRCC, ovarian cancer, melanoma, thyroid cancer, TNBC, pancreatic cancer, colon cancer, soft tissue sarcoma, or prostate cancer will be enrolled in the Dose Escalation Phase.

For the purposes of guiding decisions regarding dose escalation, the **DLT Evaluation Period** is defined as the time following administration of the first dose of pembrolizumab to the day of the third planned administration of pembrolizumab (i.e., Cycle 1/Initial Tumor Assessment Cycle).

Dose escalation will follow a conventional 3+3+3 design: MGA271 will be evaluated in sequential escalating doses ranging from 3 mg/kg to 15 mg/kg in combination with 2 mg/kg pembrolizumab in cohorts of 3 to 9 patients each. Dose levels of MGA271 to be evaluated include 3 mg/kg (starting dose), 10 mg/kg, and 15 mg/kg. If it is determined that the MTD is exceeded in the first dose cohort, a dose de-escalation cohort to evaluate a lower dose of MGA271 (1 mg/kg) in combination with 2 mg/kg pembrolizumab will be enrolled.

Table 3 MGA271 Dose Escalation Cohorts

Cohort	MGA271 Dose	Pembrolizumab Dose	MGA012
Cohort 1[a]	1 mg/kg	2 mg/kg	N/A
Cohort 1	3 mg/kg (starting dose)	2 mg/kg	N/A
Cohort 2	10 mg/kg	2 mg/kg	N/A
Cohort 3	15 mg/kg	2 mg/kg	N/A
Cohort 4	15 mg/kg	N/A	375 mg

a To be evaluated only if the starting dose is determined to exceed the MTD.

An intermediate dose of MGA271 may be explored selectively during the dose escalation portion of the study, based on review of the cumulative safety, efficacy, and/or PK data on the respective arms and based upon agreement between the investigators and the Sponsor as follows:

- If Cohort 2 exceeds the MTD the following dose level may be evaluated:

- Cohort 1a: 7 mg/kg MGA271 + 2 mg/kg pembrolizumab (n=3-9 patients)

- If Cohort 3 exceeds the MTD the following dose levels may be evaluated:
  - Cohort 2a: 12 mg/kg MGA271 + 2 mg/kg pembrolizumab (n=3-9 patients)

Any escalation cohort, not exceeding the MTD, can be expanded to a maximum of 15 patients for further evaluation of safety and efficacy.

The MTD for MGA271 will be defined as the dose level at which < 33% of patients experience a drug-related DLT during the DLT evaluation period. If no MTD is defined for the combination of MGA271 and pembrolizumab after escalation to the maximum protocol-specified dose, that dose level will be designated as the MAD. Dose limiting toxicities are defined in **Section 4.2** and Dose Escalation Rules described in **Section 4.3**.

Beginning with Amendment 5, a new cohort, Cohort 4, will be added to explore safety and tolerability of MGA271+MGA012 administered in combination. Since MTD was not reached for the MGA271+pembrolizumab cohorts, 15 mg/kg was determined as the maximum administered dose (MAD) for MGA271. Patients will receive 15 mg/kg MGA271 (MAD) in combination with a flat-dose of 375 mg MGA012, with both study drugs administered on a Q3W schedule (see **Table 3**).

For the purposes of guiding decisions regarding dose escalation, the **DLT Evaluation Period** is defined as the time following administration of the first dose of MGA271 plus MGA012 to the day of the third planned administration of MGA012 (i.e., Cycle 1 /Initial Tumor Assessment Cycle).

Enrollment in Cohort 4 will follow a conventional 3+3+3 design with decision rules as outlined in **Section 4.3**. If the 15 mg/kg MGA271 + 375 mg MGA012 combination dose is deemed tolerable, additional patients may be added for up to a total of 15 dose evaluable patients in the cohort. No higher doses of the combination are planned. If the 15 mg/kg MGA271 +375 mg MGA012 combination dose level is found to exceed the MTD, de-escalation to 10 mg/kg MGA271+375 mg MGA012 may be explored and if that dose level were to exceed the MTD, a further de-escalation to 3 mg/kg MGA271+375 mg MGA012 may be explored following the same conventional 3+3+3 design. Any of these dose levels, not exceeding the MTD, can be expanded up to a maximum of 15 patients for further evaluation of safety and efficacy.

4.1.3 Cohort Expansion Phase

During the Cohort Expansion Phase, additional cohorts of patients with unresectable, locally advanced or metastatic melanoma (up to n=16), 2 cohorts of NSCLC (up to n=20 in each cohort), 2 cohorts of SCCHN (up to n=20 in each cohort) or urothelial cancer (up to n=16) will be enrolled to receive MGA271 in combination with pembrolizumab at the MTD (or MAD) established from the Dose Escalation Phase of the study. The goals for this portion of the study will be to:

1. Further characterize the safety MGA271 in combination with pembrolizumab at the MTD (or MAD);
2. Further evaluate the PK, PD, and immunogenicity of MGA271 in combination with pembrolizumab; and
3. Provide a preliminary assessment of the antitumor activity of MGA271 in combination with pembrolizumab in patients with advanced melanoma, NSCLC, SCCHN, or urothelial cancer.

4.1.4 Efficacy Follow-up Period

The **Efficacy Follow-up Period** consists of the 6-month (24-week) period following the final dose of study drug (pembrolizumab or MGA271 or MGA012, whichever is last) where patients will be followed for survival via telephone or other electronic contact at 12-week intervals from the start of the period. Patients who discontinue study treatment for a reason other than progressive disease may be followed for efficacy and survival until 1 of the following occurs: the patient progresses, withdraws consent for follow up, or initiates other anti-cancer therapy, or the overall trial is closed.

4.2 Dose Limiting Toxicity

For the purposes of safety management and defining DLTs, the combination of MGA271 and pembrolizumab, or the combination of MGA271+MGA012 will be treated as one entity. If a DLT is considered related to study drug, no distinction will be made as to which agent is the causative agent and administration of both agents will be stopped. One exception to this rule will be in the circumstance in which a DLT occurs during or immediately following the first pembrolizumab infusion or MGA012 infusion and before the first MGA271 administration. In this case, the toxicity will be attributed to pembrolizumab or MGA012 alone and will not count as a DLT of the combination of study drugs; in this case the patient will be replaced by another patient in the dose cohort.

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 drugs. Criteria for subsequent continuation of therapy are outlined below. No dose reductions of either MGA271 or pembrolizumab or MGA012 are allowed during the study.

Dose limiting toxicities will be based on treatment-emergent drug-related AEs (or laboratory abnormalities) occurring during the DLT Evaluation Period (defined as the time following administration of the first dose of pembrolizumab to the day of the third planned administration of pembrolizumab [i.e., Cycle 1/Initial Tumor Assessment Cycle.]) The severity of AEs will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

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

4.2.1 Hematologic Dose Limiting Toxicity

Hematologic DLT will be 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

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

- ≥ Grade 3 lymphopenia
- Grade 3 anemia that is not associated with other clinically significant complications

4.2.2 Non-Hematologic Dose Limiting Toxicity

Non-hematologic DLT will be 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 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 14 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 antitumor 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 MGA271 due to patient intolerance.
- Any hepatic laboratory abnormalities meeting all three Hy's law criteria (described within **Section 4.2.3** below).
- Any Grade 2 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

- AST or ALT > 5 × ULN or total bilirubin > 3 × ULN
  - For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if the AST or ALT increases by ≥50%, relative to baseline and lasts for at least 1 week.
  - Please see **Section 6.5.2.2** for further management guidelines.
- Any event meeting the criteria for Hy's law as follows (all three 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, and will begin with enrollment of 3 patients at the initial dose level of 2 mg/kg of pembrolizumab administered as an IV infusion once every three weeks and 3 mg/kg of MGA271 administered as an IV infusion once weekly. Successive dose escalation cohorts will be enrolled as outlined below. The MTD or MAD will be determined based on the assessment of DLTs during the DLT evaluation period. Cohort 4 will begin enrollment of 3 patients at 15 mg/kg MGA271 and 375 mg MGA012; with no higher dose escalation cohorts to be explored.

Patients who do not experience a DLT but are not evaluable for safety for the full DLT evaluation period will be replaced in the same dose-level cohort.

- 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 of 15 mg/kg of MGA271).
- 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 MGA271 with pembrolizumab.
- 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 the combination. 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 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 MGA271 in combination with pembrolizumab or in combination with MGA012 has been exceeded at that dose level, and all subsequent patients will be treated at the next lower dose level.
- If 2 or more patients out of the first 6 patients treated at a given dose level experience **the same** drug-related DLT, then the enrollment in that cohort will stop, and it will be concluded that the MTD for MGA271 / pembrolizumab or MGA271/MGA012 has been exceeded and all subsequent patients will be treated at the next lower dose level.
- Note that in the circumstance in which a DLT occurs during or immediately following the first pembrolizumab or first MGA012 infusion and before the first MGA271 administration, the toxicity will be attributed to pembrolizumab or

MGA012 alone and will not count as a DLT of the combination of study drugs at the dose level under study. In this case the patient will be replaced by another patient in the dose cohort.

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%.

Dose escalation to the next dose level is permitted only after the patients enrolled in the current dose cohort have competed the DLT evaluation period and all safety data have been reviewed by the Sponsor Medical Monitor and the Investigators participating in the study.

For patients being treated at a dose level subsequently determined to exceed the MTD, the dose of MGA271 will be immediately reduced to the next lower MGA271 dose level.

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 PK, PD, biomarker, safety, and response data. An MTD does not have to be reached to expand a dose cohort if the available data demonstrate that a lower dose level may provide antitumor activity while minimizing potential risk.

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 and efficacy. For the MGA271 + MGA012(Cohort 4), the cohort may be expanded up to a total of 15 patients.

4.4 Rules for Continuation of Study Therapy

Patients who tolerate treatment with pembrolizumab and MGA271, or who tolerate treatment with MGA271+MGA012, may continue to receive additional treatment with the study drugs as specified in the protocol (see **Section 4.1.1**), until any one of the following conditions are met:

- After documentation of a confirmed complete response (cCR), MGA271 and pembrolizumab, or MGA271+MGA012, are continued for one more Tumor Assessment Cycle
- Patient meets criteria for immune-related disease progression (irPD) (**Appendix 6**)
- Occurrence of drug-related DLT as defined for the DLT Evaluation Period
- The Sponsor, Investigator, or Regulatory Agency terminates the study
- Withdrawal of patient due to an AE or SAE
- Withdrawal of patient consent
- Completion of protocol defined therapy

- Investigator discretion
- Pregnancy
- Death

Note: For individual patients who meet these criteria, but are otherwise considered to be experiencing clinical benefit by the investigator, consideration may be given to extension of therapy on a case-by-case basis in consultation with the Sponsor. If a patient completes 6 cycles of therapy and is experiencing clinical benefit as determined by the investigator, consideration may be given to extension of therapy for an unrestricted number of additional 9-week treatment cycles of MGA271 and pembrolizumab or MGA271+MGA012 on a case-by-case basis in consultation with the Sponsor. Assessments and procedures for Cycles 7 and beyond will be done according to those for Cycle 6 (see **Appendix 1**). Such unrestricted treatment may continue until the patient either 1) meets the criteria for permanent discontinuation (see **Section 5.3.1**), or 2) a rollover protocol becomes available.

4.5 Guidelines for Dose Modification

No intra-patient dose escalation will be allowed. No dose reductions will be allowed with exception of 1) reduction of infusion rate during re-challenge for patients experiencing an infusion reaction **(Section 6.5.1**) or 2) reduction of dose in patients receiving MGA271 at a dose that is subsequently determined to exceed the MTD **(Section 4.3**). For patients who experience DLT that is considered related to either study drug, no further pembrolizumab or MGA271 or MGA012 will be administered.

4.5.1 Dose Delays

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 to ≤ Grade 1 in severity. Reinstitution of therapy shall be conducted as follows:

For patients in whom the toxicity is assessed to be related to study drug, dose interruptions of up to 14 days are allowed for drug related toxicity. This may include up to one missed dose of pembrolizumab and up to 2 consecutively missed doses of MGA271. For the MGA271+MGA012 combination, Cohort 4, this would allow for a maximum of one dose each of MGA271 and MGA012. The procedures at the original 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 receive the full complement of pembrolizumab and MGA271 or MGA271+MGA012 or as outlined in The Time and Event Schedule (**Appendix 1**). Patients with infusion delays > 14 days due to drug related toxicity will discontinue both study drugs, complete the End of Treatment visit, and then enter the Efficacy Follow-up Period.

4.6 Rationale for Study Design

As described in **Sections 2.4 and 2.5**, there is a strong rationale to evaluate the antitumor activity of the MGA271 and pembrolizumab/MGA012 combination in advanced melanoma, NSCLC, SCCHN, and urothelial cancer. The study is designed to determine the MTD or MAD of the combination in the Dose Escalation Phase of the study in multiple tumor types. In Cohort 4, the combination of MGA271+MGA012 will be explored in patients with the same tumor types explored in the MGA271+pembrolizumab dose escalation cohorts, i.e., mesothelioma, urothelial cancer, NSCLC, SCCHN, ccRCC, ovarian cancer, melanoma, thyroid cancer, TNBC, pancreatic cancer, colon cancer, soft tissue sarcoma, or prostate cancer; justification provided in **Section 2.5**. The DLT Evaluation period occurs within the first Tumor Assessment Cycle; patients who do not experience a DLT or other unacceptable toxicity will then be allowed to continue receiving MGA271 and pembrolizumab or MGA271+MGA012 for up to 5 additional 9-week Tumor Assessment Cycles. Once an MAD or MTD is defined, patients will be enrolled into an Expansion Phase.

4.7 Study Duration

MGA271 will be administered on a once weekly schedule for up to 51 doses and pembrolizumab administered once every 3 weeks for a total of up to 17 doses (i.e., up to 6 cycles). Beginning with Amendment 5, MGA271 will be administered on a Q3W schedule for up to 17 doses of MGA271 and MGA012 administered once every 3 weeks for a total of up to 17 doses (i.e., up to 6 cycles). As per Rules for Continuation of Study Therapy (**Section 4.4**), an unrestricted number of additional cycles may be permitted on a case-by-case basis in consultation with the Sponsor.

It is expected that enrollment of the dose escalation portion of the study will occur over approximately 12 months, and that enrollment of the cohort expansion portion of the study will take approximately 9 - 12 months.

The total time for conduct of the trial is expected to be approximately 72 months (which includes 24 weeks of efficacy follow-up). These estimates of the timing for study conduct may vary from that observed in the actual conduct of the trial.

4.7.1 Patient Accrual

The number of patients enrolled in the Dose Escalation Phase cannot be precisely determined in advance, and could range from 9 to 45 or more patients depending on results in the course of the trial and the number of MG271 doses explored. This patient number does not take into account patient replacement for non-evaluable patients or the possibility of expanding an individual escalation cohort to 15 patients to allow for further evaluation of safety, PK and antitumor activity of the combination of MGA271 and pembrolizumab at the dose level in that cohort.

The Cohort Expansion Phase of the trial will enroll 112 patients, with a target of 16 to 20 patients into each of 6 cohorts: two cohorts of patients with NSCLC (up to 20 patients in each cohort), two cohorts of patients with SCCHN (up to 20 patients in each cohort), one

cohort of patients with melanoma (up to 16 patients), and one cohort of patients with urothelial cancer (up to 16 patients). This number of patients does not take into account patients who may be replaced. During the Expansion Portion of the study, patients who withdraw before completing the first tumor assessment for a reason other than progression of disease 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.

For planning, the maximum number of patients to be enrolled on this trial is anticipated to be approximately 157 patients.

4.7.2 Definition of End of Trial

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

5 SELECTION AND WITHDRAWAL OF PATIENTS

Inclusion and exclusion criteria are designed to properly define the target population for study participation and to identify those patients who may not be appropriate candidates for study participation based on specific co-morbidities or other clinicopathologic features of their disease. 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, unresectable locally advanced or metastatic melanoma, NSCLC, SCCHN tumors, urothelial cancer, or other cancers.

5.1 Inclusion Criteria

General:

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. Dose Escalation Phase including Cohort 4: Histologically-proven unresectable locally advanced or metastatic:
    a. Mesothelioma that has progressed during or following at least 1 and up to 3 prior systemic treatments for unresectable locally advanced or metastatic disease. The prior systemic chemotherapy must have included a pemetrexed (anti-folate)-based regimen in combination with platinum agent. For patients in whom pemetrexed was contraindicated or not tolerated or not an approved therapy (e.g., peritoneal mesothelioma), prior therapy with a first-line platinum-based regimen is required.
    b. Urothelial cancer arising in the bladder, renal pelvis, ureter, or urethra that has progressed during or following at least 1 and up to 5 prior systemic treatments for unresectable locally advanced or metastatic disease (includes anti-PD-L1, anti-PD-1, but excludes other experimental therapies). Patients must have received at least one platinum-containing regimen (e.g., gemcitabine/cisplatin [GC], dose-dense methotrexate/vinblastine/doxorubicin/cisplatin [DDMVAC], or carboplatinum/gemcitabine). No more than 5 prior systemic regimens allowed.
    c. Thyroid cancer that has progressed during or following at least 1 and up to 5 prior chemotherapy regimen(s). Prior therapy excludes experimental therapies given in Phase 1 trials.

d. Pancreatic cancer that has progressed during or following at least 1 and up to 3 prior chemotherapy regimens. Prior therapy excludes experimental therapies given in Phase 1 trials.

e. Ovarian cancer that has progressed during or following at least 2 and up to 4 prior therapeutic regimens (e.g., 2 prior platinum containing regimens or if platinum resistant, a liposomal doxorubicin or topotecan containing regimen). Prior therapy excludes experimental therapies given in Phase 1 trials.

f. Colon cancer that has progressed during or following at least 2 and up to 4 prior therapeutic regimens (e.g., fluoropyrimidine and/or irinotecan and/or oxaliplatin and/or anti-EGFR antibody containing regimens). Prior therapy excludes experimental therapies given in Phase 1 trials.

g. Prostate cancer that has progressed during or following at least 1 and up to 5 prior therapeutic regimens (e.g., abiraterone, enzalutamide, docetaxel). Prior therapy excludes experimental therapies given in Phase 1 trials.

h. Soft tissue sarcoma that has progressed during or following at least 1 and up to 5 prior therapeutic regimens. Prior therapy excludes experimental therapies given in Phase 1 trials.

i. TNBC that has progressed during or following at least 1 and up to 5 prior therapeutic regimens. Prior therapy excludes experimental therapies given in Phase 1 trials.

j. ccRCC that has progressed during or following at least 1 and up to 5 prior therapeutic regimens. Prior therapy excludes experimental therapies given in Phase 1 trials.

k. Melanoma that has progressed during or following 1 or up to 5 prior systemic treatments for unresectable locally advanced or metastatic disease, with no more than 5 prior systemic regimens (excludes experimental therapies) allowed. Patients who are intolerant of, or have refused treatment with standard cancer therapy, will be allowed to enroll.

l. SCCHN that has progressed during or following 1 or up to 5 prior systemic treatments for metastatic or recurrent disease deemed to be incurable by the investigator (patients who refuse radical resection for recurrent disease are eligible) with no more than 5 prior systemic regimens (excludes experimental therapies) allowed. Patients who are intolerant of, or have refused treatment with standard cancer therapy, will be allowed to enroll. Patients with upper esophageal or salivary gland tumors will not be considered as SCCHN.

m. NSCLC that has progressed during or following 1 or up to 5 prior systemic therapies for unresectable locally advanced or metastatic

disease. Patients who are intolerant of, or have refused treatment with standard cancer therapy, will be allowed to enroll. Patients must not have had more than 5 prior systemic regimens (excludes experimental therapies) for unresectable locally advanced or metastatic disease.

i. For patients with squamous cell carcinoma, or adenocarcinoma without known activating mutation: the prior systemic therapy is at least one platinum analogue based therapy with or without a docetaxel or pemetrexed containing regimen.

ii. For patients with adenocarcinoma having a previously known activating driver mutation such as an epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) fusion: the prior systemic therapy is at least one TKI directed against the driver mutation.

iii. Maintenance therapy following first-line therapy will not be considered a separate regimen of therapy.

iv. Prior neoadjuvant chemotherapy for operable disease, adjuvant chemotherapy for completely resected disease or definitive chemoradiation therapy given for locally advanced disease will not be considered a separate regimen of therapy.

Cohort Expansion Phase: Histologically-proven unresectable locally advanced or metastatic:

- Melanoma that has progressed on or after at least one anti-PD-L1 or anti-PD-1 containing therapy. Patients in this cohort can have their PD-L1 tumor expression levels determined before or after enrollment.
- SCCHN, consisting of metastatic or recurrent disease (patients who refuse radical resection for recurrent disease are eligible); evaluated in 2 distinct cohorts, of up to 20 patients each where patients have progressed during or following:

  SCCHN Cohort 1: a first line, platinum-based systemic therapy without receiving prior anti-PD-1 or anti-PD-L1 containing therapy or

  SCCHN Cohort 2: a first-line, platinum-based systemic therapy and an anti-PD-1 or anti-PD-L1 containing therapy.

  In each of the 2 cohorts, at least 10 of the enrolled patients will be human papilloma virus (HPV) positive (HPV positivity is determined as per local institutional standards, e.g., p16 detection by immunohistochemistry [IHC], or HPV *in-situ* hybridization [ISH]). Patients in both SCCHN cohorts can have their PD-L1 tumor expression levels determined before or after enrollment.

- NSCLC consisting of patients with unresectable locally advanced or metastatic disease that will be evaluated in 2 distinct cohorts of up to 20 patients each where patients have progressed during or following:
    - NSCLC Cohort 1: a first-line systemic therapy as outlined below (i-iv, based on tumor histology) without receiving prior anti-PD-1 or anti-PD-L1 containing therapy. These patients must have PD-L1 tumor expression determined by IHC analysis at levels accepted by the Sponsor prior to enrollment (< 1% tumor positivity score [TPS]).
    - NSCLC Cohort 2: a first line systemic therapy as outlined below (i-iv, based on tumor histology) and an anti-PD-1 or anti-PD-L1 containing therapy. Patients in this cohort can have the PD-L1 tumor expression levels determined before or after enrollment.
        i. For patients with squamous cell carcinoma, or adenocarcinoma without known activating mutation: the prior systemic therapy is a platinum analogue based therapy with or without a docetaxel or pemetrexed containing regimen.
        ii. For patients with adenocarcinoma having a previously known activating driver mutation such as an epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) fusion: the prior systemic therapy is a TKI directed against the driver mutation.
        iii. Maintenance therapy following first-line therapy will not be considered a separate regimen of therapy.
        iv. Prior neoadjuvant chemotherapy for operable disease, adjuvant chemotherapy for completely resected disease or definitive chemoradiation therapy given for locally advanced disease will not be considered a separate regimen of therapy.
- Urothelial cancer consisting of transitional cell or mixed transitional/nontransitional (predominantly transitional) cell cancer of the renal pelvis, ureter, bladder, or urethra, in a cohort of up to 16 patients. Patients must have received at least one platinum-containing regimen, either as neo-adjuvant, adjuvant, or for metastatic disease, and progressed on an anti-PD-L1 or anti-PD-1 containing therapy. Patients in this cohort can have the PD-L1 tumor expression levels determined before or after enrollment.

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 (CT) and/or magnetic resonance imaging (MRI). Patients must have measurable disease to 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, b) have demonstrated clear evidence of radiographic progression since the completion of prior radiotherapy and prior to study enrollment.
7. Prospective determination of B7-H3 expression is not required to define eligibility for this study; however, tumor expression of B7-H3 will still be evaluated for all patients enrolled on the study, so patients must have sufficient tissue/slides for B7-H3 testing identified in order to be eligible. Patients should have a FFPE tumor specimen or unstained slides identified for analysis, to enable determination of the expression of B7-H3 within tumor specimens using IHC staining. If an archived tumor specimen is not available, patients who undergo a fresh tumor biopsy (**Section 7.11.4.3**) can have B7-H3 expression evaluated from an FFPE sample obtained from the tumor biopsy. In this case, the biopsy should be obtained prior to initiating study therapy. In cases in which an archived sample and fresh tumor sample are both available, B7-H3 expression can be confirmed with either FFPE sample.
8. All patients in the Expansion Phase will have the PD-L1 tumor expression levels assessed using an IHC method deemed acceptable by the Sponsor and based either on archival or new tissue biopsy samples, submitted as FFPE tissue samples.
    a. Note: Patients in the NSCLC cohort who have not received prior anti-PD-1 or anti-PD-L1 therapy will need to have the PD-L1 IHC expression levels determined **prior to enrollment to determine eligibility**. All other patients can have PD-L1 tumor expressions determined prior to or after enrollment.
9. Patients enrolling in the study without prior documented PD-L1 tumor expression levels (determined by a Sponsor-approved method) should have a formalin-fixed, paraffin-embedded tumor specimen or unstained slides identified and available for analysis, to assess PD-L1 tumor expression levels, determined by a method selected by the Sponsor.

Laboratory Features:

10. Acceptable laboratory parameters as follows:
    a. Platelet count ≥ $100 \times 10^3/\mu L$ without transfusion within 28 days prior to the initiation of study drug.
    b. Absolute neutrophil count ≥ $1.5 \times 10^3/\ \mu L$ in the absence of any growth factor support within 28 days prior to the initiation of study drug.
    c. ALT/AST ≤ 3.0 × ULN; for patients with hepatic metastases, ALT and AST ≤ 5 × ULN.

d. Total bilirubin ≤ 1.5 × ULN, except patients with Gilbert's syndrome, who may enroll if the conjugated bilirubin is within normal limits.

e. Creatinine < 2 mg/dL, or a calculated or measured creatinine clearance > 50 mL/min.

Reproductive Features:

11. Female patients of childbearing potential (not surgically sterilized and between menarche and 1 year postmenopause) must have a negative urine pregnancy test performed within 72 hours prior to the initiation of study drug administration. Further, female patients of childbearing potential must agree to either remain abstinent or use acceptable contraceptive measures from the time of consent through 120 days after discontinuation of study drug administration. For female patients, two forms of contraception must be utilized and may include oral, transdermal, injectable or implantable contraceptives, intrauterine device (IUD), female condom, diaphragm with spermicide, cervical cap, use of a condom by the sexual partner or a sterile sexual partner. Periodic abstinence (e.g., calendar, ovulation, symptothermal and postovulation methods) and withdrawal are not considered acceptable forms of contraception in this study.
12. Male patients with partners of childbearing potential must use barrier contraception. 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. Female patients must not be breast-feeding.

Tumor Biopsy

14. Patients in the Cohort Expansion Phase who have one lesion considered to be potentially amenable to biopsy have the option of providing consent for paired pre-treatment and on-treatment biopsy samples. Tumor lesions used for biopsy should not be lesions used as RECIST target lesions, unless there are no other lesions suitable for biopsy. If a RECIST target lesion is used for biopsy, the lesion must be ≥ 2 cm in longest diameter. Tumor biopsies should be obtained only from lesions that are felt to be accessible with acceptable clinical risk, in the judgment of the investigator.

Previous Checkpoint Inhibitor Therapy

15. Patients who have previously received an immune checkpoint inhibitor (e.g., anti-PD-L1, anti-PD-1 anti-CTLA-4) prior to enrollment must have toxicities related to the checkpoint inhibitor resolved to ≤ Grade 1 or baseline (prior to the checkpoint inhibitor) to be eligible for enrollment.

    This excludes patients who experienced the following immune checkpoint inhibitor-related AEs (i.e., the following AEs make the patient ineligible despite the AE resolving to ≤ Grade 1 or baseline):

a. ≥ Grade 3 ocular AE.
b. Changes in liver function tests that met the criteria for Hy's Law (> 3 × ULN of either ALT/AST with concurrent >2 × ULN of total bilirubin and without alternate etiology).
c. ≥ Grade 3 neurologic toxicity.
d. ≥ Grade 3 colitis.

5.2 Exclusion Criteria

1. Patients with symptomatic central nervous system (CNS) metastases must have been treated, be asymptomatic, and meet 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. Treatment with any systemic anti-neoplastic therapy, or investigational therapy within the 4 weeks prior to the initiation of study drug administration.
5. Treatment with radiation therapy within 2 weeks prior to the initiation of study drug administration.
6. Treatment with 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. Steroids for topical, ophthalmic, inhaled or nasal administration are allowed.
7. History of clinically significant cardiovascular disease including but not limited to:
    a. Myocardial infarction or unstable angina within the 12 weeks prior to the initiation of study drug.
    b. Uncontrolled hypertension: systolic blood pressure (SBP) >180 mmHg, diastolic blood pressure (DBP) >100 mmHg.
    c. QTcB prolongation > 480 msec.
    d. Congestive heart failure (New York Heart Association [NYHA] class III-IV)

8. Clinically-significant gastrointestinal disorders including:
    a. Any history of gastrointestinal perforation unless the affected area has been deemed by the investigator to no longer be a risk for perforation by the investigator.
    b. History of clinically significant gastrointestinal bleeding within 4 weeks prior to the initiation of study drug.
    c. History of acute pancreatitis within 4 weeks prior to the initiation of study drug
    d. 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 4 weeks prior to the initiation of study drug administration.
9. 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.
10. Known positive testing for human immunodeficiency virus or history of acquired immune deficiency syndrome.
11. 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 (PCR).
12. Second primary invasive malignancy that has not been in remission for greater than 2 years. Exceptions that do not require a 2 year remission include: related 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.
13. History of trauma or major surgery within 4 weeks prior to the initiation of study drug administration.
14. Any serious underlying medical or psychiatric condition that would impair the ability of the patient to receive or tolerate the planned treatment at the investigational site.
15. Known hypersensitivity to recombinant proteins, any excipient contained in the drug or vehicle formulation for MGA271, pembrolizumab or MGA012 **(Section 6.1)**.
16. Vaccination with any live virus vaccine within 4 weeks prior to the initiation of study drug administration. Inactivated annual influenza vaccination is allowed.
17. Dementia or altered mental status that would preclude understanding and rendering of informed consent.
18. Employees of MacroGenics, Inc.

19. Prisoners or other individuals who are involuntarily detained.
20. 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 Trial or Study Drug

5.3.1 Guidelines for Permanent Discontinuation

Patients who meet the following criteria should be permanently withdrawn from study therapy. Patients will continue to be followed as appropriate and consistent with protocol guidelines, but should receive no further study therapy with MGA271 or pembrolizumab or MGA012.

- The patient experiences adverse events that necessitate discontinuation of either study drug.
- The Investigator assesses that the patient's safety is adversely impacted by continuing study therapy.
- Uncontrolled intercurrent illness unrelated to cancer that renders continuing study treatment unsafe or regular study visits impossible.
- The Sponsor, Investigator, or Regulatory Agency terminates the study.
- The patient requests to be discontinued from the study, i.e. withdraws consent.
- Noncompliance with study medication or protocol-required evaluations.
- The patient exhibits progression of disease [according to irRC (i.e., irRECIST)].
- If the patient becomes pregnant during the study, the patient must discontinue study treatment immediately. Reports of pregnancy will be requested until delivery or termination in order to monitor the pregnancy outcome.
- A violation of enrollment criteria or other significant protocol violation is discovered after a patient has been enrolled and treated such that continued treatment would not be in the best interests of the patient.

If the Investigator decides that the patient should be withdrawn from the study or from dosing for any reason other than disease progression, the Sponsor or its designee must be alerted within 24 hours via an Immediately Reportable Event form (**Section 7.9**).

Patients who withdraw before Study Day 42 for a reason unrelated to drug toxicity may be considered to have inadequate data to support dose escalation. In this case, replacement patients may be enrolled in the same dose level.

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

6 STUDY TREATMENTS

6.1 Description of Treatments and Study Drug and Supplies

Study drugs will be administered as an open-label IV solution, followed by observation.

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.

Requests to MacroGenics, Inc. for additional study drug should be made at least 2 weeks in advance.

6.1.1 MGA271

The MGA271 drug product is a

MGA271 is supplied as a

. MGA271 must not be administered as an IV push or bolus.

6.1.2 Pembrolizumab

Pembrolizumab (marketed as KEYTRUDA by Merck & Co., Inc., Whitehouse Station, NJ 08889 U.S. License No. 1713) is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is an IgG4 kappa immunoglobulin with an approximate molecular weight of 149 kDa.

Pembrolizumab is supplied in two configurations: a “pembrolizumab for injection” configuration that is a single-use vial containing 50 mg lyophilized powder for reconstitution with 2.3 mL sterile water for injection resulting in a 25mg/mL solution (see **Section 6.2.3**) or “pembrolizumab injection” configuration that is a single-use vial containing pembrolizumab solution at a concentration of 100 mg/4mL (i.e., 25 mg/mL).

Pembrolizumab for injection is a sterile, preservative-free, white to off-white lyophilized powder in single-use vials. Each vial is reconstituted and diluted for intravenous infusion. Each 2 mL of reconstituted solution contains 50 mg of pembrolizumab and is formulated in

L-histidine (3.1 mg), polysorbate 80 (0.4 mg), and sucrose (140 mg). May contain hydrochloric acid/sodium hydroxide to adjust pH to 5.5.

Pembrolizumab injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for IV infusion. Each vial contains 100 mg of pembrolizumab in 4 mL of solution. Each 1 mL of the 100 mg/4mL solution contains 25 mg of pembrolizumab and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, USP. Pembrolizumab will be administered by IV infusion over 30 minutes through an IV line containing a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter by IV infusion.

6.1.3 MGA012

MGA012 is

6.2 Drug Preparation

6.2.1 General Guidelines and Precautions

The calculated dose for MGA271 and pembrolizumab 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. Refer to the Pharmacy Manual for further instructions on allowable parameters for dose rounding of MGA271 and pembrolizumab.

For patients with weight > 120 kg, MGA271 dose calculations will be based on Ideal Body Weight (IBW) rather than actual weight using 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.

Infusion or allergic reactions may occur with the infusion of monoclonal antibodies and other protein-based therapeutics. Precautions for anaphylaxis should be observed during both MGA271 and pembrolizumab and 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 6.5.1** 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.

When both study drugs are administered on the same day, separate infusion bags must be used for each infusion. Pembrolizumab or MGA012 is to be administered first.

An effort should be made to begin the MGA271 infusion between 30 minutes to 120 minutes after the completion of the pembrolizumab or MGA012 infusion. It is understood that this window may not always be attainable, but is the preferred window of time to administer MGA271.

6.2.2 MGA271

- Inspect parenteral drug products visually for particulate matter and discoloration prior to administration. Some visible, proteinaceous MGA271 particles may be present. Discard vial if solution is cloudy, there is pronounced discoloration ( ), or there is foreign particulate matter.
- The desired amount of MGA271 should be withdrawn from the vial(s) and diluted to the appropriate final concentration with 0.9% Sodium Chloride Injection USP, according to the instructions provided in the Pharmacy Manual.
- The infusion bag containing MGA271 should be gently inverted to mix the solution. THE BAG MUST NOT BE SHAKEN; excessive agitation may cause aggregate formation. DO NOT FREEZE.
- Discard partially used vials of MGA271.
- Administration of study drug should begin immediately after preparation but , to allow dose solution to reach room temperature. Precautions should be taken to minimize the time between dose preparation and IV infusion administration. 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.

6.2.3 Pembrolizumab

Reconstitution instructions for pembrolizumab for injection lyophilized powder:

- Add 2.3 mL of Sterile Water for Injection, USP by injecting the water along the walls of the vial and not directly on the lyophilized powder (resulting concentration 25 mg/mL).
- Slowly swirl the vial. Allow up to 5 minutes for the bubbles to clear. Do not shake the vial.

Preparation for intravenous infusion:

- Visually inspect the reconstituted solution for particulate matter and discoloration prior to administration. The solution is clear to slightly opalescent, colorless to slightly yellow solution. Discard the vial of visible particulates are observed.
- Dilute pembrolizumab injection (solution) or reconstituted lyophilized powder prior to intravenous administration.
- Withdraw the required volume from the vial(s) of pembrolizumab and transfer into an IV bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Mix diluted solution by gentle inversion. The final concentration of the diluted solution should be between 1 mg/mL to 10 mg/mL.
- Discard any unused portion left in the vial.

The product does not contain a preservative.

Store the reconstituted and diluted solutions from the pembrolizumab 50 mg vial either:

- At room temperature for no more than 6 hours from the time of reconstitution. This includes room temperature storage of reconstituted vials, storage of the infusion solution in the IV bag, and the duration of infusion.

Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of reconstitution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

Do not freeze.

Store the diluted solution from the pembrolizumab 100 mg/4 mL vial either:

- At room temperature for no more than 6 hours from the time of reconstitution. This includes room temperature storage of the infusion solution in the IV bag, and the duration of infusion.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.
- Do not freeze.

6.2.4 MGA012

- Visual inspection of drug product vials for solution clarity, foreign particulate matter and discoloration is required prior to use. If solution cloudiness or foreign particulate matter or pronounced discoloration is observed (solution may have the drug product should not be used for dose preparation.

- .

to allow dose solution to reach room temperature. Precautions should be taken to minimize the time between dose preparation and IV infusion administration.

- Instructions on the preparation of each study drug are detailed in the 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.

6.2.5 Placebo or Control

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

6.3 Study Drug Administration

6.3.1 MGA271

- Do not mix MGA271 with, or administer as an infusion with, other medicinal products.
- Administer the diluted solution over 120 minutes through an intravenous line using an infusion pump.
-
- Do NOT use non-polyolefin IV infusion bags.
- For cohorts with weekly MGA271 administration, an interval of at least 6 days should occur since the previous administration.
- For Cohort 4, MGA271 is administered Q3W ± 3 days. An interval of at least 18 days should occur since the previous administration.
- MGA271 must not be administer as an IV push or bolus.

6.3.2 Pembrolizumab

- Administer infusion solution intravenously over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter using an infusion pump.
- Do not co-administer other drugs through the same infusion line.
- Dose rounding within 10% of the originally calculated dose is allowed

6.3.3 MGA012

- MGA012 will be administered at a fixed dose of 375 mg, regardless of body weight or body surface area.
- All doses of MGA012 must be diluted in a 100-mL or 250-mL infusion bag containing 0.9% Sodium Chloride Injection, USP (normal saline), prior to dose administration. . The dose solution should be administered over 60 to 75 minutes through an IV administration set with a commercially available infusion pump.
- Do not mix MGA012 with, or administer as an infusion with, other medicinal products. All IV infusions of MGA012 must be administered separately. Do not infuse MGA012 as an IV push or bolus.
- Study treatments are administered Q3W ± 3 days. An interval of at least 18 days should occur since the previous administration.

6.4 Selection and Timing of Dose for Each Patient

Patients will be assigned to successive dose cohorts as described in **Section 4.1.2** and **Section 4.1.3**.

6.5 Potential Adverse Events and Supportive Care Measures

6.5.1 Infusion Related Reactions Including Cytokine Release Syndrome

MGA271, pembrolizumab, and MGA012 are immune modulating agents that may lead to T-cell activation and killing of the tumor cell. Activation of T cells is associated with the production of various cytokines.

Infusion reactions (including cytokine release syndrome [CRS]) associated with either MGA271, pembrolizumab, or MGA012 administration 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 the pembrolizumab and MGA271 and MGA271+MGA012 infusions. 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 50-100 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 6.5.1.3** for guidance regarding the management of infusion reactions.

If a patient has a Grade 1 or 2 infusion reaction with pembrolizumab or with MGA012 and the investigator considers it unsafe for the patient to receive MGA271 at the scheduled infusion time, the MGA271 dose may be administered on the following day (the day after the pembrolizumab infusion). For Grade 3 infusion reactions with pembrolizumab or with MGA012 that resolve completely or to Grade 1 within 12 hours, the scheduled dose of MGA271 may be administered the following day with premedications as listed below.

6.5.1.1 Grading 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 indicated before resuming original rate, as patient tolerates (see **Section 6.5.1.3**);
- 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 v 4.03 grading scale for CRS, which is nearly identical to the CTCAE v 4.03 grading scale for infusion reaction and allergic reaction, and 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.

6.5.1.2 Premedications and Prophylaxis

No specific prophylactic pre-infusion regimen is recommended for pembrolizumab unless a patient has an infusion reaction with pembrolizumab or MGA271 infusion (see below). For MGA271, the following suggested guidelines (which may be modified by the investigator) are measures to be followed to avoid potential infusion reactions.

Prior to first infusion (guidelines to be followed):

- Acetaminophen 650 mg
- Diphenhydramine 50 mg or appropriate dose of equivalent H1 antagonist
- Ranitidine 300 mg or appropriate dose of equivalent H2 antagonist at the discretion of the investigator
- Hydrocortisone 50 to 100 mg suggested or doses up to 10-20 mg dexamethasone may be administered (dose selected at the discretion of the Investigator)

Prior to subsequent MGA271 infusion, investigators may use the following premedications as considered indicated (suggested guidelines):

- Acetaminophen 650 mg
- Diphenhydramine 50 mg or appropriate dose of equivalent H1 antagonist
- Ranitidine 300 mg or appropriate dose of equivalent H2 antagonist
- Optional hydrocortisone not typically needed after first dose. However, for patients who had infusion reactions not adequately or only moderately controlled with acetaminophen, diphenhydramine, or ranitidine, subsequent doses may be tapered at the discretion of the Investigator.

6.5.1.3 Management of Observed Infusion Reactions

The following are treatment guidelines (which may be modified as needed by the Investigator according to the best practices of medicine) for infusion reactions. Note that these apply to MGA271, pembrolizumab, and MGA012:

Grade 1

- Slow the infusion rate by 50%.
- Monitor the patient for worsening of condition.
- 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. Consideration can be given to beginning all subsequent infusions at 50% rate and increasing as tolerated.

- On days when both pembrolizumab and MGA271 or MGA271 and MGA012 are given on the same day and a patient has an infusion reaction with pembrolizumab or MGA012, the MGA271 infusion can be given (without prophylactic medications) on the same day if the infusion reaction resolves within 3 hours. For scheduling purposes, the MGA271 infusion may be given the next day if the reaction lasts greater than 3 hours.
- If a patient has an infusion reaction with pembrolizumab or MGA012, prophylactic preinfusion medications should be given prior to all subsequent pembrolizumab or MGA012 infusions as written below for Grade 1 infusion reactions.
- If a patient has an infusion reaction with MGA271 on either day when it is administered after pembrolizumab, or after MGA012, or given alone, prophylactic preinfusion medications should be given prior to all subsequent MGA271 infusions as written below.
- The following prophylactic preinfusion medications are recommended prior to future infusions of MGA271 and/or pembrolizumab, and/or MGA012 for patients who experience Grade 1 infusion reactions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 650 mg at least 30 minutes before additional study drug administrations.

Grade 2

- Stop the infusion.
- Administer diphenhydramine hydrochloride 25-50 mg IV, acetaminophen 650 mg orally for fever, and oxygen and bronchodilators for mild bronchospasm.
- Resume the infusion at 50% of the prior rate once the infusion reaction has resolved or decreased to Grade 1. The rate may then be escalated to the original rate after 30 minutes, as tolerated. Consideration can be given to beginning all subsequent infusions at 50% rate and increasing as tolerated.
- Monitor for worsening condition. If symptoms recur, discontinue the infusion; no further study drug will be administered at that visit.
- When both pembrolizumab and MGA271 or MGA012 and MGA271 are given on the same day and a patient has an infusion reaction with pembrolizumab or with MGA012:
- The MGA271 infusion can be administered on the same day if the infusion reaction resolves within 3 hours. The MGA271 infusion may be given the next day if the infusion reaction last longer than 3 hours.
- Premedication of diphenhydramine hydrochloride 25-50 mg IV and acetaminophen 650 mg orally should be administered 30 minutes prior to the MGA271 dose. If no corticosteroids where given for the pembrolizumab or

MGA012 infusion reaction, hydrocortisone 50-100 mg IV or equivalent may be considered prior to MGA271 administration.

- Prophylactic pre-infusion medications should be given prior to all subsequent pembrolizumab or MGA012 infusions. Patients who experience Grade 2 infusion reaction should be pre-medicated with diphenhydramine hydrochloride 25-50 mg IV and acetaminophen 650 mg orally for subsequent doses of pembrolizumab.
- If a patient has an infusion reaction with MGA271 on any of the days that it is administered after pembrolizumab or after MGA012, or given alone, prophylactic preinfusion medications should be given prior to all subsequent MGA271 infusions.
- For patients with Grade 2 infusion reactions despite premedication with diphenhydramine and acetaminophen, corticosteroids (hydrocortisone 50-100 mg IV or equivalent) should be considered for acute management of the event and should be added to the premedication regimen for subsequent dosing of pembrolizumab and/or MGA271 or subsequent dosing of MGA012 and/or MGA271.

Grade 3

- STOP THE INFUSION AND DISCONNECT THE INFUSION TUBING FROM THE PATIENT.
- TO AVOID EXACERBATION OF INFUSION REACTION OR CRS: DO NOT FLUSH THE TUBING – ASPIRATE RESIDUAL DRUG FROM THE PORT LUMEN.
- Administer diphenhydramine hydrochloride 25-50 mg IV, hydrocortisone 25-100 mg IV (or equivalent), and other medications/treatment as medically indicated. Higher doses of corticosteroids (i.e. methylprednisolone 2 -4 mg/kg IV) may also be considered for acute management.
- IV fluids, supplemental oxygen and bronchodilators should be considered as appropriate.
- **Grade 3 infusion reaction with MGA271:** If symptoms have resolved to baseline within 12 hours, a re-challenge may be considered at the next scheduled dose, with a 50% reduction of infusion rate. In addition, patients should be pre-medicated for this re-challenge and for any subsequent doses of MGA271 with the following: diphenhydramine hydrochloride 25-50 mg IV, oral acetaminophen 625 mg and hydrocortisone 25-100 mg IV. Patients who have a Grade 3 infusion reaction that does not resolve within 12 hours despite medical management should not receive further MGA271, pembrolizumab, or MGA012 treatment.
- **Grade 3 infusion reaction with pembrolizumab or MGA012:** If the grade 3 infusion reaction occurs with pembrolizumab or with MGA012, both MGA271 and pembrolizumab or MGA271 and MGA012 will be discontinued for that day's dose. If symptoms have resolved to baseline within 12 hours, a pembrolizumab or

MGA012 re-challenge at the next scheduled infusion day may be considered, with a 50% reduction of infusion rate. In addition, patients should be pre-medicated for this re-challenge and for any subsequent doses of pembrolizumab or MGA012 with the following: diphenhydramine hydrochloride 25-50 mg IV, oral acetaminophen 625 mg and hydrocortisone 25-100 mg IV. MGA271 dosing can be resumed with at the next scheduled infusion day if the pembrolizumab or MGA012 grade 3 infusion reaction resolved to grade 1 within 12 hours. Patients who have a Grade 3 infusion reaction that does not resolve within 12 hours despite medical management should not receive further MGA271, pembrolizumab, or MGA012 treatment.

- Patients who experience a second Grade 3 infusion reaction at the time of re-challenge of MGA271 or pembrolizumab or MGA012 (irrespective of duration of first Grade 3 reaction), will permanently discontinue MGA271, and pembrolizumab and MGA012.
- Report as an Immediately Reportable Event (IRE) within 24 hours.
- Report the event as a SAE, if appropriate.

Grade 4

- STOP THE INFUSION AND DISCONNECT THE INFUSION TUBING FROM THE PATIENT.
- TO AVOID EXACERBATION OF INFUSION REACTION OR CRS: DO NOT FLUSH THE TUBING.
- Administer diphenhydramine hydrochloride 50 mg IV, methylprednisolone 2-4 mg/kg IV (or more as considered appropriate), and other medications/treatment as medically indicated (e.g., an IL-6 receptor inhibitor or IL-6 inhibitor, an IL-2 receptor inhibitor, and/or an anti-TNFα antibody).
- Give epinephrine or bronchodilators as indicated.
- Support ventilation and blood pressure as indicated.
- Report as an IRE within 24 hours.
- Report the event as an SAE.
- Patients who have a Grade 4 infusion reaction will not receive further MGA271 or pembrolizumab or MGA012.

Grade 5

- Report as an IRE within 24 hours.
- Report the event as an SAE.

All changes in the infusion of either MGA271 or pembrolizumab or MGA012, including interruption of the infusion and its duration as well as reductions in infusion rate and duration must be recorded.

6.5.2 Immune-Related Adverse Events

Immune checkpoint blockade has been associated with several syndromes resulting from the breaking of immunological tolerance in normal tissues (**28;47;62**). These syndromes include but are not limited to: pneumonitis, colitis, autoimmune hepatitis, arthritis, glomerulonephritis, dermatological toxicities including toxic epidermal necrolysis (TEN) and Stevens-Johnson Syndrome (SJS), myocarditis and cardiomyopathy, hypophysitis, thyroiditis, or other autoimmune endocrinopathies. The occurrence of any of these syndromes dictates interruption, and potentially discontinuation of study drug administration pending further evaluation and reporting them to the Sponsor as adverse events of special interest (AESIs). Most low grade 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 corticosteroids.

For the purposes of the safety management, no distinction should be made as to which drug is the causative agent and both agents stopped (temporarily held or discontinued). Signs or symptoms of inflammation should be considered drug related and immune mediated, unless an alternate etiology is identified.

Temporary interruptions of MGA271, pembrolizumab, or MGA012 may be required in the event of treatment-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.

6.5.2.1 Diarrhea or Colitis

Diarrhea that develops in patients while receiving pembrolizumab may reflect immune reactivity against normal colonic epithelium and careful monitoring for potential immune-related colitis should be instituted; see **Section 2.3.2.1** for summary of pembrolizumab safety profile.

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. Patients who develop signs or symptoms including abdominal pain, bloating, nausea, vomiting, diarrhea or blood in the stools should be evaluated carefully for potential colitis.

Grade 1 diarrhea

- Closely monitor the diarrhea until resolution.

Grade 2 diarrhea

- Increase frequency of monitoring until resolution

- Consider holding the next dose of pembrolizumab or MGA012, and/or MGA271.
- Symptomatic management
- Loperamide/diphenoxylate
- Consider budesonide 9 mg once per day or divided three times per day.
- Consider management as per Grade 3 diarrhea with prolonged event > 5 to7 days or relapsed diarrhea.

Grade 3 diarrhea

- Hospitalize patient promptly for further evaluation and management including:
- Hold pembrolizumab or MGA012, and/or MGA271
- Bowel rest
- Supplemental IV fluids with close monitoring of fluid and electrolyte status.
- Monitoring of 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 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. Taper corticosteroids as clinically indicated.
- For patients with severe colitis, or those who do not respond to corticosteroids, additional immune suppression with anti-TNF-α antibodies (i.e., infliximab) should be considered early in the course.
- Consider restarting pembrolizumab or MGA012, and MGA271, if:
- It is determined there is no colitis and an alternative cause of diarrhea is found
- Diarrhea resolves to ≤ CTCAE Grade 1 within 14 days

Grade 4 diarrhea

- Discontinue pembrolizumab or MGA012, and MGA271
- Treat as for Grade 3

6.5.2.2 Hepatic Toxicity

6.5.2.2.1 Elevations in Transaminases

Section 2.3.2.1 provides a summary of the pembrolizumab safety profile. Management guidelines 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 (Grade 2), rule out viral and other etiologies, consider immediate oral steroids such as prednisone 60 mg /day divided twice daily, and hold MGA271 and pembrolizumab or MGA012.
- If improvement to ≤ Grade 1 does not occur within 48 hours with oral steroids, 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 pembrolizumab or MGA012, and/or MGA271, at next scheduled dose if:
- No more than one dose of pembrolizumab or MGA012 was missed and no more than 2 doses of MGA271 were missed
- If improvement to ≤ Grade 1does not occur within 14 days discontinue pembrolizumab or MGA012, and MGA271

Grade 3 elevations

- Permanently discontinue MGA271 and pembrolizumab or MGA012, for AST or ALT greater than 5 times ULN unless patient has liver metastasis and began treatment with Grade 2 AST or ALT
- For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, permanently discontinue if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week
- Initiate IV steroids; suggest methylprednisolone at a dosage of 2 mg/kg/day divided twice daily.
- If no response to corticosteroid therapy within 3 to 5 days is observed, consider adding immune suppression therapy with mycophenolate. Infliximab is not recommended because of a potential for autoimmune hepatitis **(30)**.
- Monitor liver function testing 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.

Grade 4 elevations

- Discontinue pembrolizumab or MGA012, and MGA271
- Treat as for Grade 3 elevation

6.5.2.2.2 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 MGA271 and pembrolizumab or MGA012, until improvement to ≤ Grade 1
- Consider oral steroids
- If improvement to ≤ Grade 1 does not occur within 14 days, discontinue MGA271 and pembrolizumab or MGA012, and begin oral steroids

Grade 3 elevations

- For elevations in total bilirubin > 3× ULN, permanently discontinue MGA271 and pembrolizumab or MGA012, and
- Initiate IV steroids; suggest methylprednisolone at a dosage of 2 mg/kg/day divided twice daily.
- If no response to corticosteroid therapy within 3 to 5 days is observed, consider adding immune suppression therapy with mycophenolate. Infliximab is not recommended because of a potential for autoimmune hepatitis **(30)**.
- Monitor liver function testing 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.

Grade 4 elevations

- Discontinue pembrolizumab or MGA012, and MGA271
- Treat as for Grade 3 elevation

6.5.2.3 Pneumonitis

Section 2.3.2.1 provides a summary of pembrolizumab safety profile. 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 MGA271 and pembrolizumab or MGA012
- 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 MGA271 and pembrolizumab or MGA012 administration at next scheduled dose, if:
- Pneumonitis resolves to ≤ Grade 1 within 3 days with or without treatment

Grade 3 and 4 pneumonitis

- Hospitalize
- Permanently discontinue MGA271 and pembrolizumab or MGA012
- Initiation of maximal supportive care including IV corticosteroids, suggest methylprednisolone at 2- 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 3-5 days, consider adding immune suppression therapy (i.e., infliximab, etc.)

6.5.2.4 Dermatologic Toxicity

Section 2.3.2.1 provides a summary of pembrolizumab safety profile. Management guidelines for patients experiencing dermal toxicities are as follows:

In general, Grade 1 or 2 skin reactions can be treated symptomatically with low-dose topical corticosteroids (betamethasone 0.1% or hydrocortisone 1%) or with antihistamines, such as diphenhydramine. Persistent Grade 1 or 2 rash should be managed with higher dose topical corticosteroids and/or oral prednisone (1-2 mg/kg/day) if there is no improvement with topical therapies or the rash is associated with other dermal toxicities such as pruritus. Grade 3 or 4 rashes require initiation of oral corticosteroids (oral prednisone 1 – 2 mg/kg/day) and temporary holding of study drugs with Grade 3 toxicity and permanent discontinuation for Grade 4 toxicity. Grade 3 skin toxicity that does not resolve to ≤ CTCAE Grade 2 within 14 days of initiation of oral corticosteroids requires permanent discontinuation of study therapy. Strong consideration should be given to start IV corticosteroids (methylprednisolone 1-2 mg/kg/day) for Grade 4 dermatologic toxicities with tapering on resolution to < Grade 2 over 30 days.

6.5.2.5 Nephritis/Renal Failure

Section 2.3.2.1 provides a summary of pembrolizumab safety profile. Management guidelines for patients experiencing nephritis/renal failure are as follows:

Grade 1 nephritis

- No specific therapy required, close monitoring of renal function

Grade 2 nephritis

- Hold MGA271 and pembrolizumab or 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 MGA271 and pembrolizumab or MGA012 administration at next scheduled dose, if:
  - Nephritis resolves to ≤ Grade 1 within 14 days with or without treatment

Grade 3 and 4 nephritis

- Consider hospitalization, nephrology consultation and renal biopsy to confirm interstitial nephritis
- Begin corticosteroids: 2 to 4 mg/kg of oral or IV prednisone or equivalent, per day divided twice daily
  - Taper over 4 weeks as clinically indicated
- Permanently discontinue MGA271, pembrolizumab, or MGA012 for Grade 3/4 nephritis.

6.5.2.6 Immune-Mediated Endocrinopathies

Section 2.3.2.1 provides a summary of pembrolizumab safety profile. Management guidelines for patients experiencing endocrinopathies are as follows:

6.5.2.6.1 Hypophysitis

In cases of symptomatic (Grade 2 or 3) hypophysitis documented on MRI:

- Hold pembrolizumab or MGA012 and MGA271
- Consult endocrinologist
- Consider hospitalization
- Begin 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
- Pembrolizumab or MGA012 and/or MGA271 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

- Repeat brain MRI as clinically indicated

Discontinue MGA271 and pembrolizumab or MGA012 for Grade 4 hypophysitis

6.5.2.6.2 Thyroid Toxicity

Hyperthyroidism/Hypothyroidism:

There have been no reported cases of endocrine toxicities in the Phase 1 dose escalation and expansion trial of MGA271.

Thyroid disorders can occur at any time during treatment with pembrolizumab. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, 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 and a suggested treatment guideline for hyperthyroidism is described below:

Grade 1 hyperthyroidism

- No specific therapy required

Grade 2 hyperthyroidism

- Hold pembrolizumab or MGA012 and MGA271
- Resume pembrolizumab or MGA012 and/or MGA271 if stable on hormone replacement therapy (if necessary)

Grade 3 or 4 hyperthyroidism

- Hold pembrolizumab or MGA012 and/or MGA271
- Consider hospitalization and consulting endocrinologist
- Initiate hormonal replacement as necessary

May consider restarting pembrolizumab or MGA012 and MGA271 with complete resolution or stable on hormone replacement therapy

6.6 Method of Assigning Patients to Treatment Groups

Patients will be assigned sequentially to the dose escalation cohorts and cohort expansion portions of the study.

6.7 Blinding

This is an open-label study and no blinding will be employed.

6.8 Concomitant Therapy

MGA271, pembrolizumab, and MGA012 are the only cancer drugs to be administered routinely in this study. No concomitant anti-cancer therapy will be given.

All concomitant medications and blood products administered during the patient's participation in the study until the post treatment follow-up 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.

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 3000 rads, limited field of distribution) for reasons other than disease progression, therapy with MGA271 and pembrolizumab may be interrupted for up to 4 weeks. Palliative radiotherapy may not be given concurrently with either MGA271 or pembrolizumab or MGA012. Treatment with palliative therapy should be initiated at least 24 hours after receiving either MGA271 or pembrolizumab or MGA012, and re-initiation of MGA271 or pembrolizumab or MGA012 can begin one day after the completion of palliative radiotherapy if there were no complications associated with the radiotherapy. Palliative radiotherapy fields also should not overlap tumor lesions that have previously been designated as target lesions. In the event that this is medically necessary for palliative purposes, 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.
- Because MGA271, pembrolizumab, and MGA012 have 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 MGA271- or pembrolizumab- or MGA012-associated immune-inflammatory or autoimmune AEs in consultation with the Sponsor.
- The use of other immuno-suppressive agents is prohibited, unless they are being used to treat an adverse event.
- Use of granulocyte colony stimulating factor, granulocyte-macrophage colony stimulating factor or other growth factors is prohibited.

- Live vaccines within 4 weeks prior to the first dose of MGA012 and while participating in the study are prohibited. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally recombinant vaccines and are allowed any time after the DLT period is completed. However, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed. Similarly, Shingrix® vaccine for shingles is permitted after the DLT period, but Zostavax® is prohibited.

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 and should be documented on the concomitant medication form.
- Use of bisphosphonates or receptor activator of nuclear factor kappa-B ligand (RANK-L) inhibitors is allowed

6.9 Restrictions

6.9.1 Prior Therapy

Prior therapy restrictions are described in the inclusion/exclusion criteria specified in **Section 5**.

6.9.2 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 will be obtained pre-meal.

6.9.3 Patient Activity Restrictions

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

6.10 Treatment Compliance

MGA271 and pembrolizumab will be administered by healthcare professionals under the supervision of the Investigators. Records of MGA271 and pembrolizumab 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 investigational site visits and at the completion of the study.

6.11 Packaging and Labeling

6.11.1 MGA271

MGA271 will be supplied in open-label, single-dose vials. All investigational product will be labelled with a minimum of the protocol number, directions for use, storage conditions, expiry date (if applicable), batch number, 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. Please see the Pharmacy Manual for detailed information about the packaging and labeling of the study drug.

6.11.2 Pembrolizumab

Pembrolizumab will be obtained by the site from commercial supply for patients with melanoma. Pembrolizumab will be provided in the commercial packaging. Please see the Pharmacy Manual for detailed information about the packaging and labeling of pembrolizumab.

6.11.3 MGA012

MGA012 will be supplied

Please see the Pharmacy Manual for detailed information about the packaging and labeling of the study drug.

6.12 Storage and Accountability

6.12.1 MGA271

The vials containing study drug should be and must not be frozen or shaken. Protect from sunlight. To ensure compliance with storage conditions, temperature logs will be maintained.

The Investigator or his/her designee is required to maintain accurate drug accountability records. A binder containing instructions and the required accountability documentation will be provided to the Investigator or his designee. When the study is completed, copies of study drug accountability records must be sent to the Sponsor. The original drug accountability

records must be maintained with the rest of the documentation in accordance with **Section 10.1** of the protocol.

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

6.12.2 Pembrolizumab

Pembrolizumab is marketed as KEYTRUDA by Merck & Co., Inc., Whitehouse Station, NJ 08889.

Pembrolizumab is supplied in the following configurations:

- KEYTRUDA (pembrolizumab) injection (lyophilized powder): carton containing one 50 mg single-use vial (NDC 0006-3029-02).
- KEYTRUDA (pembrolizumab) injection (solution): carton containing one 100 mg/4 mL (25 mg/mL), single-use vial (NDC 0006-3026-02)

Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not shake.

6.12.3 MGA012

Vials containing MGA012 should be stored upright
in an appropriate, locked room accessible only to pharmacy personnel, the Investigator, or duly designated personnel. To ensure compliance with storage conditions, temperature logs will be maintained. Vials should be protected from light during storage and should not be shaken or frozen. Standard laboratory practices should be used for avoidance of contact.

6.12.4 Accounting for the Materials

Accurate accounting of all study medication 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. Additional details regarding storage, handling, and accountability can be found in the Pharmacy Manual.

6.13 Investigational Product Disposition at End of Study

Upon completion or termination of the study, all unopened vials of study medication 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.

7 STUDY PROCEDURES

This section provides a general description of the procedures and assessments associated with this study. Time and Events Schedule (**Appendix 1**) details the schedule of assessments by study day.

Note: On days where multiple procedures are required at the same time point, the PK sample should be collected first.

7.1 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. 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. Informed consent will be obtained prior to any study screening procedures being performed.

7.2 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 medical conditions (e.g., hospitalizations, surgeries, prior cancer history) should be collected. During the screening period (prior to first dose of pembrolizumab, MGA012, or MGA271), any untoward event that occurs should be recorded as medical history and not as an adverse event, unless it is due to a protocol-related procedure. Thereafter (i.e., after the time of study drug administration), any untoward event should be collected as an AE.

7.3 Prior and Concomitant Medications

All concomitant 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 eCRF.

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

7.4 Physical Examination

The Investigator will perform physical examination of all patients. Physical examination 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 as specified in **Appendix 1**.

Weight will be measured during screening, Day 1, and then before each dose of pembrolizumab, MGA012, or MGA271.

7.5 Vital Signs

Vital signs include temperature, pulse, blood pressure, and respiratory rate and are obtained as specified in **Table 8** for MGA271 and pembrolizumab or **Table 9** for MGA271 and MGA012.

7.6 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 labs should be performed and reviewed before study drug administration.

Please consult the Laboratory Manual for specific directions on collection and processing samples.

7.6.1 Laboratory Parameters

Clinical laboratory tests to be performed locally will include the following:

Table 4 Clinical Laboratory Tests

Pregnancy test: Urine Human chorionic gonadotropin (hCG) **Hematology:** Hematocrit (Hct) Hemoglobin (Hgb) Mean corpuscular hemoglobin (MCH) Mean corpuscular hemoglobin concentration (MCHC) Mean corpuscular volume (MCV) Platelet count Red blood cell (RBC) count White blood cell (WBC) count with differential counts **Serum Chemistry:** Albumin (ALB) Alkaline phosphatase (ALK-P) Alanine aminotransferase (ALT; SGPT) Aspartate aminotransferase (AST; SGOT) Bicarbonate Blood urea nitrogen (BUN) Calcium (Ca) Chloride (Cl) Creatinine Glucose Magnesium Phosphorus Potassium (K) Sodium (Na) Total protein Uric acid	**Special Chemistry:** Amylase Lipase Bilirubin (Total and Direct) **Coagulation:** Prothrombin time (PT) Activated Partial Thromboplastin Time (APTT) **Endocrine tests:** Free thyroxine (T4) Thyroid-stimulating hormone (TSH) **Urinalysis:** Appearance Bilirubin Color Glucose Ketones Microscopic examination of sediment Nitrite Occult blood pH Protein Specific gravity

Other tests (PK, anti-drug antibody [ADA], cytokines, determination of leukocyte subsets, evaluation of T cell activation status, expression of markers of T cells, determination of T cell infiltration, and tumor B7-H3 expression) will be carried out at Sponsor-specified central laboratories (refer to the Laboratory Manual).

7.6.2 Sample Collection, Storage, and Shipping

Clinical laboratory testing described in **Section 7.6.1** will be performed locally. Details on local and central laboratory specimen collection, storage, and shipping will be provided in the Laboratory Manual.

7.7 Electrocardiography

Twelve-lead electrocardiograms (ECGs) (in triplicate, approximately 1 minute apart) will be obtained according to the (**Appendix 1**) in order to evaluate the potential cardiac effects of the combination of MGA271 and pembrolizumab and of MGA271+MGA012, including QT interval. 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 at approximately the same time of the day to minimize diurnal variations. However, this may not be possible because of infusion times and clinic logistics.

To account for intrinsic variability, all ECGs should be obtained in triplicate (3 ECGs per time point at approximately 1-minute intervals). Central interpretation will be used for data analysis purposes; note for Cohort 4 only, ECGs will be read locally. ECGs are to be obtained as specified in **Table 8** for MGA271 and pembrolizumab and in **Table 9** for MGA271 and MGA012.

7.8 Safety Assessments

7.8.1 Criteria for Evaluation

- The safety assessment will be based on the evaluation of treatment-emergent AEs that occur from the time of initiation of administration of either study drug through the End of Treatment Visit or 28 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.
- AEs and SAEs will be collected from the time the patient receives the first dose of study drug until the End of Treatment visit or 28 days after the last dose of study drug (whichever is later). Protocol-related AEs and SAEs will be collected from the time the patient has consented to study participation.
- AEs reported between the time the patient signed the informed consent and the administration of the first dose of study drug will be captured as medical history.
- 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.
- The reporting of laboratory/vital signs abnormalities as both laboratory findings and AEs should be avoided. They should not be reported as AEs unless any one of the following are met:
    - Any criterion for an SAE is fulfilled

- The laboratory/vital signs abnormality causes the patient to discontinue from the study treatment
- The laboratory/vital signs abnormality causes the patient to interrupt the study treatment
- The laboratory/vital signs abnormality causes the patient to modify the dose of study treatment
- The laboratory/vital signs abnormality requires intervention

7.8.2 Adverse Event: Definitions

7.8.2.1 Adverse Event

An adverse event is any untoward medical occurrence in a subject or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An adverse event will also be considered to be any untoward effect of a study-related procedure, which is conducted after signed informed consent and prior to study drug administration.

7.8.2.2 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 (i.e., the relationship cannot be ruled out).

7.8.2.3 Adverse Event of Special Interest

An 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.

7.8.2.4 Treatment Emergent Adverse Event

An event that is temporally associated with administration of study product is defined as a treatment-emergent adverse event (TEAE). Events meeting this definition will be those occurring during or after administration of the first dose of study drug. Events that existed before the first administration of study product and then increased in severity during or after the first administration of study product will also be considered treatment emergent. Such

events will be captured on the eCRF as new events, with the onset date as the date of the increase in severity.

7.8.2.5 Serious Adverse Events

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

- Death
- Life-threatening (immediate risk of death)
- Inpatient hospitalization 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 that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization or the development of drug dependency or drug abuse.

7.8.2.6 Immediately Reportable Event

IREs are events that must be reported immediately to MacroGenics Product Safety within 24 hours of being identified. IREs include but are not limited to:

- SAEs
- AEs leading to permanent discontinuation of study drug in an individual patient.
- 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.]
- The following AESIs (**Section 7.8.3**):
  - Grade 3 infusion-related reactions or CRS (see **Section 6.5.1**)
  - irAE (see **Section 6.5.2**)
- Administration of a dose significantly greater than the planned dose of either MGA271, pembrolizumab, or MGA012 resulting in an event of clinical consequence.

- Withdrawal of the patient from study drug administration for any reason other than disease progression.
- 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 without any alternate etiology

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). 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, Inc. Product Safety.

7.8.3 Adverse Events of Special Interest

AESI will include the following:

- Infusion reactions including cytokine release syndrome
- Immune-related AE of Grade 3 or greater suggestive of an autoimmune process, including but not limited to: pneumonitis, colitis, autoimmune hepatitis, arthritis, glomerulonephritis, myocarditis and cardiomyopathy, hypophysitis, thyroiditis, myositis, uveitis, neurotoxicity, or other autoimmune endocrinopathies, pericarditis, or dermatologic toxicity.

7.8.4 Product Quality Issue with Clinical Consequences

If a product quality issue results in an event of clinical consequences, from the use of study product, it must be immediately reported to the Sponsor/designee as an IRE. The Sponsor will collect the information and evaluate accordingly to protect the safety of the study patients.

7.8.5 Performing Adverse Event Assessments

A physician's assessment of the event is expected to be completed in conjunction with reporting an IRE to the MacroGenics Product Safety/designee.

Medical evaluation and classification of the adverse event must be performed by the Investigator who is qualified to review AE information. The determination of seriousness, severity and causality must be made according to the following criteria:

Assessment of Seriousness: Event *seriousness* will be determined according to the definition of an SAE in **Section 7.8.2**. Seriousness serves as a guide for defining regulatory reporting obligations for AEs.

Assessment of Severity: Event *severity* will be assigned according to the Investigator's assessment using the CTCAE Version 4.03 (for described events and syndromes). For events not contained in CTCAE, the Investigator may assign severity according to the following scale:

- Grade 1= Mild
- Grade 2 = Moderate AE
- Grade 3 = Severe AE
- Grade 4 = Life-threatening or disabling AE
- Grade 5 = Death related to AE

Any event or laboratory value judged as Grade 4 severity should be separately evaluated to determine whether it also meets the serious criterion of "immediately life threatening."

Note: Severity is not synonymous with seriousness. The term "severe" is often used to describe the intensity (severity) of a specific event. The event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning.

Assessment of Causality: The Investigator is required to provide an assessment of causality or relationship of AEs to the study drug based on 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 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.

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, 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; a plausible mechanism for the event to be related to the study drug and causes other than the study drug has been ruled out and/or the event re-appeared on re-exposure to the study drug.

Assessment of Expectedness: As part of the regulatory reporting requirements, the Sponsor must perform an assessment of expectedness (expected/unexpected from the perspective of previously observed, not on the basis of what might be anticipated from the pharmacological properties of a medicinal product) for AEs. Adverse reactions will be considered unexpected if the nature, seriousness, severity or outcome of the reaction(s) is not consistent with the reference information (e.g., the Adverse Drug Reaction section of the Investigator's Brochure) for the study product.

7.8.6 Reporting of Adverse Events to the Sponsor

Adverse events will be collected and followed from the time the patient provides informed consent for the study until the End of Treatment visit or 28 days after the last dose of study drug. If a patient experiences an AE after the informed consent document is signed and prior to treatment with study drug, it should be captured as medical history; however, if the Investigator believes the AE may have been caused by a protocol-related procedure it will be recorded as an AE and entered onto the eCRF.

Adverse events occurring after the patient undergoes early termination or completes the trial (completes the End of Treatment visit), need not be reported unless the event is serious and the Investigator believes that the event may have been caused by the study drug or a protocol procedure.

To identify the occurrence of any new medical complaints or worsening of previous complaints, non-leading questioning should be posed to the patient.

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.

If a patient reports signs and symptoms that represent a single medical syndrome, diagnosis, or concept, the syndrome/diagnosis/concept should be documented (e.g., cough, runny nose, fever = Upper Respiratory Tract Infection) in the eCRF.

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.

Adverse events occurring after the patient completes the trial or after early termination need not be reported unless the event is serious and the Investigator believes that the event may have been caused by the study drug or a protocol procedure.

Clinical Laboratory Changes: Safety laboratory assessments will be carried out locally and evaluated by the Investigator to ensure patient safety. The Investigator is responsible for reviewing the results of all laboratory tests as they become available. Laboratory tests will be graded according to CTCAE v 4.03. Laboratory values that fall outside of a clinically accepted reference range or values that differ significantly from previous values must be evaluated by the Investigator for clinical significance. The Investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. If the Investigator determines the laboratory value is an abnormal change from baseline and is of clinical significance for that patient, it is considered an AE. Generally, Grade 1 laboratory findings need not be reported as AEs unless clinically significant. The Investigator will evaluate laboratory findings of ≥ Grade 2 or higher classification to determine their clinical significance and if an AE has occurred. Consistent with the CTCAE designation of Grade 3 events as severe or medically significant and Grade 4 events as life-threatening, Grade 3 and Grade 4 laboratory findings should be reported as AEs or SAEs, as appropriate. Grade 2 laboratory findings may be reported as AEs if, in the opinion of the Investigator, the event exhibits clinical significance. If clinically relevant abnormal laboratory values are associated with clinical symptom(s), or consistent with a diagnosis, the diagnosis should be reported as the AE (e.g., hemoglobin 9 g/dL in an adult female = anemia). If these clinically relevant abnormal laboratory values do not result in a diagnosis, the test result or finding should be reported as the AE assuming that it does not represent a laboratory error. Repeat testing may be indicated. Such laboratory values should generally be recorded as “increased” or “decreased” (e.g., change from baseline hemoglobin of 13 g/dL to 11g/dL = hemoglobin decreased).

7.9 Notification to the Sponsor of Events Requiring Immediate Reporting

Throughout the study, the Investigator must document all AEs on the eCRF in a timely manner. IREs, as defined in **Section 7.8.2**, are events that must be reported immediately to MacroGenics Product Safety or designee within 24 hours of being identified.

The Investigator must immediately complete and fax/email the *Immediately Reportable Event (IRE)* Report Form within 24 hours of identifying the event to MacroGenics Product Safety/designee. The IRE Report Form and IRE Report Form Completion Guidelines are found in the Study Procedures Manual.

For pregnancy, the MacroGenics Pregnancy Exposure Form must also be completed and faxed/emailed. The Investigator must attempt to follow the pregnancy to term or termination

in order to report on outcome and health status of mother and child. The Pregnancy Exposure Form is found in the Study Procedures Manual.

7.10 Emergency Unblinding

Not applicable. This is an open-label study.

7.11 Efficacy and/or Pharmacokinetic and Pharmacodynamic Assessments

7.11.1 Efficacy Assessments

7.11.1.1 Treatment of Patients According to Principles of Immune-Related Response Criteria

Tumor assessments will be obtained at screening using CT and/or MRI scans at time intervals as specified in the **Appendix 1** (Time and Events Table). The study is divided into 6 Tumor Assessment Cycles; the first is a 6-week cycle called the Initial Tumor Assessment Cycle and Cycles 2 through 6 are 9-week cycles. The tumor assessment takes place at the end of each cycle. Treatment will continue until patients have completed study therapy and required follow-up, experienced disease progression, or have been withdrawn from the study (see **Section 4.4** and **Section 5.3**). At each on-treatment tumor assessment time point, the objective response status will be determined. In the context of the statistical analysis for this trial, objective response determination and the assessment of best overall response (BOR) will be defined using both conventional RECIST1.1 criteria (**Appendix 5**) as well as an adaptation of these criteria, designated as immune-related response criteria (irRC) (i.e., irRECIST as defined in **Appendix 6**). Patient management decisions, however, will be made solely based on the immune-related response criteria (**Appendix 6**).

For patients who demonstrate acceptable tolerability of treatment with MGA271, and an objective response assessment of irCR, irPR or irSD, or unconfirmed clinically-stable irPD, therapy may be continued (see **Section 4.4** and **Section 5.3**).

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 irRC (i.e., irRECIST) principles is supported by well-documented evidence that in some patients treated with T cell directed, immune-modulatory agents, their 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 (**67**)

For patients in whom progression is confirmed at the next scheduled tumor assessment, the criteria for immune-related PD (irPD) will have been met, and treatment with MGA271, pembrolizumab, or MGA012 should be discontinued. The patient should be removed from study participation after completion of protocol specified follow-up (see **Section 8.3** and **Appendix 1**). For patients who experience an objective response of immune-related complete response (irCR) or immune-related partial response (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.

7.11.1.2 Objective Response and Response Duration

Target and non-target lesions will be designated and evaluated using both conventional RECIST 1.1 criteria (**Appendix 5**) and immune-related response criteria (**Appendix 6**) as noted above for the purposes of statistical analysis. Objective responses will be categorized as CR, PR, SD, or PD for conventional RECIST 1.1 criteria and irCR, irPR, irSD, and irPD for the immune-related response criteria. Determination of the objective response rate will be calculated based on the proportion of response evaluable patients achieving CR or PR using the respective criteria, when such responses are confirmed by a subsequent scan obtained at least 28 days after the initial documentation of objective response. Response-evaluable patients will include those patients who have measurable disease and have had a baseline tumor assessment and at least 1 on-treatment tumor assessments (see **Appendix 1**). Objective responses that are not subsequently documented with a confirmatory CT or MRI scan (e.g., unconfirmed responses) will not be included as an objective response for the purpose of calculating overall objective response rates. Response duration will be calculated from the time of initial response (CR or PR) documentation (in patients who have a subsequent confirmation of objective response) to the time of progressive disease or death, whichever occurs first.

A patient's response duration will be censored if at the time of last antitumor assessment response is ongoing. Patients who discontinue study treatment for a reason other than progressive disease may be followed for efficacy until 1 of the following occurs: the patient progresses, withdraws consent for follow up, or initiates other anti-cancer therapy, or the overall trial is closed.

7.11.1.3 Progression-free Survival (PFS)

PFS will be calculated as the time from the date of the first dose of study drug until the date of any documented PD; the date of death from any cause, or date of last assessment for tumor progression, whichever occurs first (**Appendix 3**). A patient's PFS will be censored if at the time of last assessment for progression, the patient remains progression free. PFS will be determined using both conventional RECIST 1.1 and irRC (i.e., irRECIST) criteria.

7.11.1.4 Overall Survival (OS)

OS will be calculated as the time from the first dose of study drug until death due to any cause or last observation or contact. A patient's OS will be censored if at the time of last

contact, the patient was alive. In addition, landmark 6-month OS rate will be determined. OS will be monitored as described in the Study Manual.

7.11.2 Immunogenicity

For patients receiving MGA271 and pembrolizumab, blood samples for MGA271 immunogenicity assessments (i.e., ADA) will be collected at the time points in **Table 5**; Electrochemiluminescence will be used for MGA271 ADA assay.

For patients receiving MGA271 and MGA012 (Cohort 4), MGA271 and MGA012 ADA blood samples will be collected per **Appendix 2**; ELISA method will be used for the MGA012 ADA assay.

Table 5 Immunogenicity Blood Sampling Schedule for Patients Receiving MGA271 and Pembrolizumab

Tumor Assessment Cycle	Study Day	Treatment Day of Cycle	Dose Number [a,b] MGA271 (Pembrolizumab)	ADA Sampling Time (h)	ADA Sample Collection for MGA271
Initial (1st)	1	1	1 (1)	0 (Predose) [c]	X
	22	22	4 (2)	0 (Predose) [d]	X
2nd	43	1	7 (3)	0 (Predose) [d]	X
3rd	106	1	16 (6)	0 (Predose) [d]	X
4th	169	1	25 (9)	0 (Predose) [d]	X
5th	232	1	34 (12)	0 (Predose) [d]	X
6th	337	43	49 (17)	0 (Predose) [d]	X
NA [e]	NA	NA	28 Days After the Last Dose of MGA271	NA	X

a Pembrolizumab dose and MGA271 dose administered as 0.5 hour (30 min) and 2 hours (120 min) infusions, respectively.

b On days when MGA271 is administered after pembrolizumab, MGA271 may be administered the next day for safety reasons or scheduling purposes.

c Predose ADA sample on Study Day 1 (Treatment Day 1 of Initial [1st] Cycle) will be collected prior to pembrolizumab infusion.

d All other ADA samples will be collected prior pembrolizumab and prior to the MGA271 infusion when MGA271 is given alone; the start of infusion is designated as time = 0 hour.

e Not applicable; however, ADA sample will be collected simultaneously with PK sample.

NOTE: Both planned and actual start and end of infusion times and ADA sample collection times will be recorded on the eCRFs. The window of time for obtaining ADA samples is provided in the Study Procedures Manual.

7.11.3 Pharmacokinetics

Serum concentrations of MGA271 and MGA012 will be monitored using a quantitative sandwich ELISA. Single and multiple dose PK parameters for MGA271 and MGA012, C_{max}, T_{max}, AUC_{tau}, C_{trough}, CL, V_{ss}, and $t_{1/2}$ will be derived from MGGA271 and MGA012 serum concentration versus time data.

7.11.3.1 MGA271 and MGA012 PK

For patients receiving MGA271 and pembrolizumab, blood samples for MGA271 PK will be collected at the following time points given in **Table 6** and for patients receiving MGA271 and MGA012 blood samples for MGA271 and MGA012 per **Appendix 2**. 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 ADA or PK assessment.

Table 6 Pharmacokinetics Blood Sampling Schedule for Patients Receiving MGA271 and Pembrolizumab

Tumor Assessment Cycle	Study Day	Treatment Day of Cycle	MGA271 (Pembrolizumab) Dose Number [a,b]	PK Sampling Time After the Start of Infusion (h)	PK Sample Collection for MGA271
Initial (1st)	1	1	1 (1)	0 (Predose) [c]	X
				2 (EOI) [d]	X
				3	X
				5	X
				8 (optional) [g]	X
	2	2		24	X
	3	3		48	X
	8	8	2	0 (Predose) [e]	X
				2 (EOI) [d]	X
	22	22	4 (2)	0 (Predose) [e]	X
				2 (EOI) [d]	X
2nd	43	1	7 (3)	0 (Predose) [e]	X
				2 (EOI) [d]	X
				3	X
				5	X
				8 (optional) [g]	X
	44	2		24	X
	45	3		48	X
	50	8	8	0 (Predose) [e]	X
3rd	106	1	16 (6)	0 (Predose) [e]	X
4th	169	1	25 (9)	0 (Predose) [e]	X
5th	232	1	34 (12)	0 (Predose) [e]	X
6th	337	43	49 (17)	0 (Predose) [e]	X
NA [f]	NA	NA	28 days after the last dose of study drug	NA	X

a Pembrolizumab dose and MGA271 dose administered as 0.5 hour (30 min) and 2 hour (120 min) infusions, respectively.

b On days when MGA271 is administered after pembrolizumab, MGA271 may be administered the next day for safety reasons or scheduling purposes.

c Predose PK sample on Study Day 1 (Treatment Day 1 of Initial [1st] Cycle) will be collected prior to pembrolizumab infusion; the start of infusion is designated as time = 0 hour; ADA sample will be collected simultaneously with PK sample.

d EOI= end of MGA271 infusion; sample will be collected within 5 min prior to the end of infusion.

e All predose PK samples will be collected prior to pembrolizumab on days when MGA271 is given after pembrolizumab, and prior to MGA271 infusion on days when MGA271 is given alone; the start of MGA271 infusion is designated as time = 0 hour; ADA sample will be collected simultaneously with PK sample.

f Not applicable; however, PK sample will be collected simultaneously with ADA sample.

g 8 hour PK is optional in cases where obtaining this sample is logistically not feasible for the patient

NOTE: Both planned and actual start and end of infusion times and PK sample collection times will be recorded on the CRFs. The window for PK sample collection time is provided in the Study Procedures Manual.

If MGA271 infusion is interrupted, PK time points for 120 minutes (EOI), 3, 5, 8, 24 and 48 hours after the start of infusion will be recalculated as per the actual EOI and 1, 3, 6, 22 and 46 hours post end of MGA271 infusion.

7.11.4 Pharmacodynamics/Biomarkers

Procedures for the acquisition, handling and processing of pharmacodynamic biomarker specimens will be provided in the Laboratory Manual.

7.11.4.1 Tests Performed for Both Dose Escalation and Cohort Expansion Patients:

- Characterization of alterations in serum cytokine levels to include, but not limited to, IL-2, IL-6, IL-10 and TNF-α
- Enumeration of lymphocyte subsets, NK cells and activation status over time via multi-parameter flow cytometry on whole blood; evaluation of the regulatory T cell population over time
- Determination of B7-H3 and PD-L1 expression as well as immune cell infiltration into the tumor (e.g., CD4+ and CD8+ T cell infiltration) will be explored via IHC staining or other method of archival tumor biopsy specimens (unless fresh tumor sample submitted and used to determine B7-H3 expression and no archived sample obtained)
- Soluble B7-H3 over time analyzed by enzyme-linked immunosorbent assay (ELISA); in addition to other potential circulating serum biomarkers indicative of potential tumor response

Note: Cohort 4 will not have PD-L1 testing.

7.11.4.2 Tests Performed for Cohort Expansion Patients:

- Determination of B7-H3 tumor cell and tumor vasculature expression, PD-L1 tumor cell membranous expression, and immune cell infiltration into the tumor bed via IHC staining (or other method for immune cell infiltration) of archival tissue and/or of optional paired pre- and on-treatment tumor biopsy specimens when available. The optional pre-treatment and on-treatment tumor biopsies will be carried out for cohort expansion patients who elect to undergo pre- and on-treatment biopsy.
- Assessment of PD-L1 tumor expression levels.
- Characterization of T cell repertoire using T cell receptor (TCR) spectratyping of PBMCs on selected samples may be carried out depending on observed anti-tumor activity.
- An assessment of the ability of patient's PBMCs to support MGA271-mediated antibody dependent cellular cytotoxicity (ADCC) activity in pre- and on-treatment samples using a non-isotopic assay with the patient's PBMCs as effector cells and B7-H3 expressing tumor cell lines as target cells may be carried out depending on observed anti-tumor activity.

7.11.4.3 Archival Tumor Biopsy Specimens

Patients who have not had tumor B7-H3 expression levels previously determined using IHC analysis performed at the Sponsor-designated central laboratory will be required to have identified an archival tumor specimen (FFPE) or 5 unstained slides for the determination of B7-H3 expression within tumor specimens using an IHC staining assay. Tumor specimens should be sufficient to provide a minimum of 5 slides to enable determination of B7-H3 expression using IHC staining. If a tumor biopsy is performed at baseline with resulting sample adequate to make 5 slides, the archived sample requirement will be waived, but it is still strongly encouraged to obtain the archived sample so that comparisons in B7-H3 staining can be made between FFPE slides from archived and FFPE slides from fresh tissue. Additional archival slides will be required for assessment of PD-L1 expression if the patient has not already had the level of PD-L1 expression assessed.

7.11.4.4 Optional Paired Pre-Treatment and On-Treatment Tumor Biopsy Specimens

Patients in the Cohort Expansion Phase who have one lesion considered to be potentially amenable to biopsy have the option of providing consent for paired biopsy samples. Baseline and on-treatment biopsy samples are to be done during the screening period and Day 42 ± 3 days, respectively. Tumor lesions used for biopsy should be lesions that are felt to be accessible with acceptable clinical risk in the judgment of the investigator and should not be lesions used as RECIST target lesions, unless there are no other lesions suitable for biopsy. If a RECIST target lesion is used for biopsy, the lesion must be ≥ 2 cm in longest diameter. Lesions to be biopsied should not have been previously irradiated, unless the lesion has grown in size beginning at least 14 days since the last radiation dose. Note that multiple lesions may be used to obtain the biopsy sample.

Lesions to be biopsied should be of sufficient size to enable acquisition of at least 2 tumor biopsy cores using a 16-gauge biopsy needle. Exceptions to the gauge of the needle may be considered after consultation with the Sponsor's Medical Monitor. Up to 2 additional biopsy cores may be obtained if this can be performed with acceptable clinical risk in the judgment of the Investigator. Punch biopsies or excisional biopsies are allowed if these can be performed with acceptable clinical risk in the judgment of the Investigator. Immediate confirmation of the adequacy of the biopsy specimen and the presence of malignant cells in the tumor biopsy is strongly encouraged. Additional unscheduled tumor biopsies may be obtained at interim or follow-up time points at the Investigator's discretion and in consultation with the Sponsor Medical Monitor if clinically indicated and/or to assess changes in tumor histopathology over time.

Additional instructions for the acquisition, processing, and storage of tumor biopsy specimens will be provided in the Laboratory Manual. The paired tumor biopsy specimens will be obtained to enable investigation of the pharmacodynamic effects of MGA271 within the local tumor microenvironment of patients with melanoma. Studies to be performed will include assessment of local T cell infiltration and the expression of tumor apoptosis markers. Tissue samples will be stored as described in **Section 7.12.2** by the Sponsor for potential retesting after the end of the study.

7.12 Other Study Procedures

7.12.1 Central Laboratory Evaluations

MacroGenics or its designee will provide blood sampling supplies such as polypropylene transport tubes, labels, and log sheets. Serum tubes should be labeled with the patient's number, date, and time of sampling. The Investigator will maintain a log with the same data.

Specimens must be appropriately prepared, divided if appropriate, frozen, and shipped (while often retaining certain replicate samples at the site) according to the instructions in the Laboratory Manual.

7.12.2 Sample Retention and Further Testing

Samples acquired for protocol-specified assays (except for the tissue sample from the biopsy as described in **Section 7.11.4.4** that will be stored indefinitely) may be retained up to 2 years after last approval of a marketing application in an International Conference on Harmonisation (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. Samples may also be used for additional future research use (including assay development/optimization) and may be retained up to 15 years from the end of study for these future research purposes; however, patients must provide consent for additional future research uses.

7.13 Appropriateness of Measurements

Routine laboratory evaluations including hematology, chemistry, special 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.

Serum concentrations of MGA271 will be monitored using an ELISA based assay. Standard bridging ELISAs will be carried out in the Sponsor's designated central laboratory to characterize the immunogenicity of MGA271. 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.

7.13.1 Rationale for Use of Immune Response Criteria

Patients will be managed according to irRC (i.e., irRECIST) principles. 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 considers that the patient may still derive benefit from continuation of therapy. Treatment of patients according to irRC (i.e., irRECIST) principles is supported by well-documented evidence that in some patients treated with T cell directed, immune-modulatory agents, their tumors can evolve to an objective response after an initial period

characterized by either growth of target lesions or the development of new target lesions that would otherwise meet the criteria for disease progression using conventional response criteria (**68**) (see also **Appendix 6**). Further details regarding the application of this approach are described in **Section 7.11.1**.

8 STUDY ACTIVITIES

A table of study activities including screening, on-study and end-of study visits is presented in **Appendix 1**, Time and Events Table.

8.1 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.

8.2 Registration

Each patient must be registered with MacroGenics prior to enrollment. The following information should be provided during registration:

- Date of birth
- Date of signed informed consent
- Planned date of first of pembrolizumab and MGA271 or of MGA271+MGA012 administration

The instructions for the registration process are provided in the Study Manual.

8.3 End of Treatment Visit

A list of evaluations to be performed for the End of Treatment visit is provided in **Appendix 1**. Criteria for triggering the End of Treatment visit are specified in **Section 5.3**. The End of Treatment Visit should be performed after the patient has met off-study criteria or has been followed for at least 28 days after the last dose of study drug depending on ability to follow the patient and duration and severity of ongoing AEs. It is recognized that certain patients (such as those experiencing progression of disease) may be cared for in facilities other than the participating investigational site, may proceed to receive other cancer therapy, and/or may elect not to return to the investigational site. Therefore, this visit is considered optional, but should be carried out whenever possible.

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

This Phase 1 study is primarily observational and, thus, the majority of the statistical summaries will be descriptive. Summary statistics will consist of absolute and relative frequencies of each category of discrete variables and of means, standard deviations, medians, minimums and maximums for continuous variables.

Safety and efficacy summaries will be provided for each dose level cohort during dose escalation and for all dose level cohorts combined, as well as for each expansion cohort (melanoma, SCCHN, NSCLC, and urothelial cancer) and all expansion cohorts combined. Response rates may be calculated for specific disease sub-groups, if appropriate.

Baseline will be considered the closest value obtained prior to first dose. Data that are reported as missing will be treated as missing in all data summaries. Incomplete dates will be imputed and defined in the Statistical Analysis Plan. In descriptive summaries for safety, observations that are spurious (extreme relative to the majority of the data) will not be altered or removed from the summary.

9.2 Determination of Sample Size

This study plans to enroll approximately up to 157 patients (up to approximately 45 in the dose escalation phase and 112 in the MTD expansion cohorts). This sample size is considered sufficient to evaluate the primary objective of this study (toxicity). In addition,

in select solid tumors.

Additional patients may be enrolled in study groups to meet sample size requirements if discontinuations unrelated to treatment-emergent signs and symptoms occur.

For the Cohort Expansion Phase, up to 16 patients each will be enrolled into melanoma and urothelial expansion cohorts, respectively, and up to 20 patients will be enrolled into each of 2 cohorts for NSCLC and SCCHN, respectively. The sample size is primarily based on providing preliminary estimation of responses.

9.2.1 Analysis Populations

Two populations will be used for analysis, the **Safety Population** and **the Response Evaluable Population**, as defined below:

- **Safety Population**: All patients who received at least one dose of either MGA271 or pembrolizumab or MGA012. Safety Population will be used to summarize baseline data, safety data and for assessment of OS and PFS. Patients who receive at least one dose of MGA271 or MGA012 will be included in PK, PD, and immunogenicity analyses.
- **Response Evaluable Population:** All patients who received MGA271 and pembrolizumab or MGA271 +MGA012 and had at least 1 post-infusion radiographic tumor assessments. Patients who meet these criteria will be eligible for the determination of best overall response and will be included in the response evaluable population used for the calculation of ORRs using both conventional RECIST 1.1 (**Appendix 5**) and irRC (i.e., irRECIST as defined in **Appendix 6**) criteria.

Patients who withdraw before receiving all protocol-specified treatment before completion of the DLT evaluation period, for a reason unrelated to drug toxicity will be considered to have inadequate data to support dose escalation. In this case, replacement patients may be enrolled at the same dose level and schedule as necessary to complete the cohort.

9.3 Demographics and Baseline Characteristics

Patient disposition, demographics, baseline characteristics, disease history, medical history, concomitant medications, and study drug exposure data will be summarized using descriptive statistics.

9.4 Safety Endpoint(s)

9.4.1 Adverse Events

Adverse events will be coded to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Only treatment-emergent AEs, as defined in **Section 7.8.2**, will be summarized in tables. Events prior to treatment (e.g., due to study-related procedure) will be listed in an appendix to the final study report.

The following tables of adverse event data will be created to summarize the number and percent of patients who experience at least one event of each of the following types:

- All AEs by CTCAE grade
- Drug related AEs by CTCAE grade
- AEs with CTCAE Grade severity Grade ≥ 3
- All drug related AEs by CTCAE Grade severity Grade ≥ 3
- All SAE (this may be a listing if there are few events)
- Drug related SAE
- Fatal AEs (this may be a listing if there are few events)
- AESIs
- AEs that result in study discontinuation
- AEs which lead to dose interruption
- AEs that lead to withdrawal of study drug

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. Events will be displayed alphabetically for SOC and Preferred Term. An overall summary of AEs will display the number and percent of patient/patients who experience at least one event of each of the following types:

- All AEs
- Drug Related AEs
- AEs with CTCAE severity ≥ Grade 3

- Drug-related AE with CTCAE severity Grade ≥ 3
- All SAE
- Drug-related SAE
- AEs that lead to dose interruption
- AE that results in study or study drug discontinuation
- Fatal AEs
- AESIs

9.4.2 Laboratory Values

Summaries of laboratory values will display descriptive statistics for numerically quantified labs. Summaries will be grouped by laboratory panel (e.g., hematology, blood chemistry, and urinalysis) and will be displayed by visit for each laboratory parameter.

A list of repeated labs including original values and repeat values will be included.

Graphs of mean values over time may also be generated.

9.4.3 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.

9.5 Efficacy Endpoints

Response will be categorized as CR, PR, SD, or PD and evaluated using RECIST 1.1 criteria (**Appendix 5**) and as irCR, irPR, irSD, or irPD using the immune-related response criteria (i.e., irRECIST as defined in **Appendix 6**). The ORR will be the proportion of patients in the response evaluable population achieving CR or PR when such responses are confirmed at least 28 days after the initial observation of an objective response. A two-sided 95% exact binomial confidence interval will be calculated around the ORR for each expansion cohort.

Response duration will be calculated for responders as the time from initial response (CR or PR) to the time of PD or death, whichever occurs first. Kaplan-Meier methods will be used to estimate response duration over time and the median response duration. Responders who complete the study without documented PD will be censored at the date of their last tumor assessment.

PFS and irPFS will be calculated as the time from the initial infusion of pembrolizumab or MGA271 until documented disease progression, or death from any cause. Patients with no PFS event (disease progression or death from any cause) will be censored at the date of their last tumor assessment. In addition, PFS and irPFS rates will be calculated at 3-month and 6-

month time points from the first dose of study drug. Kaplan-Meier methods will be used to estimate PFS over time and the median duration of PFS. The method of Brookmeyer and Crowley **(9)** will be used to construct 95% CIs around PFS estimates of the median and other quartiles for each expansion cohort.

Incomplete and missing data can complicate interpretation of PFS. **Appendix 3** describes the handling of these data for the PFS analysis.

Overall survival is defined as the time from the initial infusion of pembrolizumab or MGA271 to death from any cause. Kaplan-Meier methods will be used to estimate the overall survival function. Patients who do not die will be censored at the date that the patient was last known to be alive. In addition, OS will be calculated at 6 months from the first dose of study drug.

9.6 Other Assessments or Analyses

Pharmacokinetic Analysis: Summary statistics will be tabulated for PK parameters by MGA271 dose. Geometric means and percent coefficients of variation will be reported for C_{max}, AUC_{tau}, and C_{trough}; arithmetic means and standard deviations will be reported for terminal half-life ($t_{1/2}$), 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.

Immunogenicity Analysis: The proportion of patients who are negative for MGA271 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.

Pharmacodynamic Analysis: Summary statistics for pharmacodynamics parameters such as, but not limited to, those listed under section, “Pharmacodynamics/Biomarkers/Tumor Biopsy” **(Section 7.11.4)** and corresponding changes from baseline, will be summarized and/or may also be presented graphically as will possible associations between changes in pharmacodynamics measures of interest and MGA271 dose and exposure may be explored.

10 QUALITY CONTROL AND ASSURANCE

Quality review activities will be undertaken to ensure accurate, complete, and reliable data. MacroGenics, Inc. 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.

10.1 Monitoring, Auditing and Inspections

To ensure the safety of participants 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 (refer to **Section 11.5** for additional information on source documents).

MacroGenics, Inc. 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 a sample 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 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.).

10.2 Data Entry and Computerized Systems

An electronic data capture system will be used in this trial. Other data assessments, such as central laboratory assays, immunochemistry, and ECG data, will be managed by central vendors for transfer to MacroGenics, Inc. or representative for use in the study analysis database.

11 ADMINISTRATIVE CONSIDERATIONS

11.1 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 unconditional 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 unconditional 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; 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 violations or deviations
- Notification when the study has been completed.

- Proof of indemnity/liability insurance.
- Other documents required by the IRB/IEC

11.2 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.

The protocol and the informed consent document will be reviewed and approved by the IRB/IEC of each participating center before study initiation. Serious adverse events, regardless of causality, will be reported to the Sponsor/designee and to the IRB/IEC, if required by local regulations. The Investigator will keep the IRB/IEC informed regarding the progress of the study.

11.3 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.

11.4 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, except as necessary for monitoring by the relevant regulatory authorities, the Sponsor of the clinical trial, 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.

11.5 Case Report Forms and Study Records

Source data in a clinical trial 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 onto CRFs designed to capture all observations and other data pertinent to the clinical investigation. Data should be recorded on source documents and entered onto eCRFs. Electronic CRFs should be filled out completely 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.

11.6 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.

The Investigator may be subjected to a field audit by MacroGenics, Inc. (or designee) and/or regulatory inspectors in order to validate the participation of patients in the study and to verify the data reported on the eCRFs on file at MacroGenics, Inc. MacroGenics should be notified immediately of any audits scheduled by any regulatory authorities. Copies of audit reports, findings and/or correspondence from regulatory authorities for audits conducted on a MacroGenics-sponsored study should be promptly forwarded to MacroGenics.

11.7 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, Inc. is required to maintain study records for longer periods (e.g., applicable local regulations); therefore, MacroGenics, Inc. should be contacted before study records are removed from the

control of the investigational site for any reason. The Investigator must obtain written permission from MacroGenics, Inc. prior to destruction of study documents.

11.8 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: 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 MGA271; 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 (as defined in **Section 4.7.2**).

In consideration of participation in the study, MacroGenics, Inc. 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.

11.9 Publication and Disclosure Policy

Data collected in this clinical study belong to the study Sponsor which will formulate a policy on the use of study data. This policy will be codified in the Clinical Trial Agreement. This includes authorship issues: scheduling and prioritizing analyses for reports, publications, and presentations; and developing a review and approval process.

11.10 Discontinuation of the Study or Study Sites

11.10.1 Discontinuation of Study Sites

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

11.10.2 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.

11.11 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 CSR. Agreement with the final CSR will be documented by the dated signature of the Coordinating Principal Investigator.

12 REFERENCE LIST

1. **Aggarwal, C, Joshua, A, Ferris, R, Antonia, S, Rahma, O, Tolcher, A et al**. A Phase 1, Open-Label, Dose Escalation Study of Enoblituzumab in Combination with Pembrolizumab in Patients with Select Solid Tumors. SITC Poster, 2018.

2. **Amarnath S, Mangus CW, Wang JC, Wei F, He A, Kapoor V, et al.** The PDL1-PD1 axis converts human TH1 cells into regulatory T cells. Sci Transl Med 2011 Nov 30;3(111):111ra120.

3. **American Cancer Society.** Cancer Facts & Figures. Atlanta: American Cancer Society 2014.

4. **Bai, S, Jorga, K, Xin, Y, Jin, D, Zheng, Y, Damico-Beyer, L A, et al**. A guide to rational dosing of monoclonal antibodies. Clin. Pharmacokinet, 2012. 51(2): p. 119-135

5. **Barber DL, Wherry EJ, Masopust D, Zhu B, Allison JP, Sharpe AH, et al.** Restoring function in exhausted CD8 T cells during chronic viral infection. Nature 2006 Feb 9;439(7077):682-7.

6. **Boland JM, Kwon ED, Harrington SM, Wampfler JA, Tang H, Yang P, et al.** Tumor B7-H1 and B7-H3 expression in squamous cell carcinoma of the lung. Clin Lung Cancer 2013 Mar;14(2):157-63.

7. **Boorjian SA, Sheinin Y, Crispen PL, Farmer SA, Lohse CM, Kuntz SM, et al.** T-Cell Coregulatory Molecule Expression in Urothelial Cell Carcinoma: Clinicopathologic Correlations and Association with Survival. Clin Cancer Res 2008;14(15):4800-7.

8. **Brahmer J, rizvi N, Lutzky J, Khleif S, Blake-Haskins A, Li X, et al.** Clinical activity and biomarkers of MEDI4736, an anti-PD-L1 antibody, in patients with NSCLC. J Clin Oncol 2014;32(5s).

9. **Brookmeyer R, Crowley J. A** Confidence Interval for the Median Survival Time. Biometrics 1982;38:29-41.

10. **Castriconi R, Dondero A, Augugliaro R, Cantoni C, Carnemolla B, Sementa AR, et al.** Identification of 4Ig-B7-H3 as a neuroblastoma-associated molecule that exerts a protective role from an NK cell-mediated lysis. PNAS 2004;101(34):12640-5.

11. **Chapoval AI, Ni J, Lau JS, Wilcox RA, Flies DB, Liu D, et al.** B7-H3: a costimulatory molecule for T cell activation and IFN-gamma production. Nat Immunol 2001 Mar;2(3):269-74.

12. **Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, et al.** Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J Clin Oncol 2011 Nov 10;29(32):4294-301.

13. **Chavin G, Sheinin Y, Crispen PL, Boorjian SA, Roth TJ, Rangel L, et al.** Expression of immunosuppresive B7-H3 ligand by hormone-treated prostate cancer tumors and metastases. Clin Cancer Res 2009 Mar 15;15(6):2174-80.

14. **Chen X, Wang P, Kaul S, Sumrow B, Yeleswaram S**. Assessment of Flat Dosing Strategy for INCMGA00012 in Patients With Advanced Tumors. AACR Annual Meeting 2019. 2019

15. **Condamine T, Owens S, Feldmam P, La Motte-Mohs R, Muth J, Sumrow B, et al**. PharmacodynamicCorrelates in a Phase 1 Study of INCMGA00012, a a PD-1 Antagonistic Monoclonal Antibody. AACR Annual Meeting 2019. 2019

16. **Clynes RA, Towers TL, Presta LG, Ravetch JV.** Inhibitory Fc receptors modulate in vivo cytoxicity against tumor targets. Nat Med 2000 Apr;6(4):443-6.

17. **Collins M, Ling V, Carreno BM.** The B7 family of immune-regulatory ligands. Genome Biol 2005;6(6):223.

18. **Crispen PL, Sheinin Y, Roth TJ, Lohse CM, Kuntz SM, Frigola X, et al.** Tumor cell and tumor vasculature expression of B7-H3 predict survival in clear cell renal cell carcinoma. Clin Cancer Res 2008 Aug 15;14(16):5150-7.

19. **Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al.** New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur Journal of Cancer 2009;45(2):228-47.

20. **Francisco LM, Salinas VH, Brown KE, Vanguri VK, Freeman GJ, Kuchroo VK, et al.** PD-L1 regulates the development, maintenance, and function of induced regulatory T cells. J Exp Med 2009 Dec 21;206(13):3015-29.

21. **Freeman GJ, Long AJ, Iwai Y, Bourque K, Chernova T, Nishimura H, et al.** Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. J Exp Med 2000 Oct 2;192(7):1027-34.

22. **Freshwater, T, Kondic, A, Ahamadi, M, Li, C H, de Greef, R, de Alwis, D, et al**. Evaluation of dosing strategy for pembrolizumab for oncology indications. J Immunother Cancer, 2017. 5: p. 43.

23. **Garon EB, Gandhi L, Rizvi N, Hui R, Balmanoukian AS, Patnaik A, et al.** LBA43 - Antitumor activity of pembrolizumab (Pembro; MK-3475) and correlation with programmed death ligand 1 (PD-L1) expression in a pooled analysis of patients (pts) with advanced non-small cell lung carcinoma (NSCLC). European Society for Medical Oncology . 9-28-0014. Ref Type: Abstract

24. **Gettinger SN, Shepherd FA, Antonia SJ, Brahmer JR, Chow L, Juergens RA, et al.** First-line nivolumab (anti-PD-1; BMS-936558, ONO-4538) monotherapy in advanced NSCLC: Safety, efficacy, and correlation of outcomes with PD-L1 status. J Clin Oncol 2014;32(5s).

25. **Gillison ML, D'Souza G, Westra W, Sugar E, Xiao W, Begum S, et al.** Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers. J Natl Cancer Inst 2008 Mar 19;100(6):407-20.

26. **Gregorio A, Corrias MV, Castriconi R, Dondero A, Mosconi M, Gambini C, et al.** Small round blue cell tumours: diagnostic and prognostic usefulness of the expression of B7-H3 surface molecule. Histopathology 2008;53:73-80.

27. **Hemon P, Jean-Louis F, Ramgolam K, Brignone C, Viguier M, Bachelez H, et al.** MHC class II engagement by its ligand LAG-3 (CD223) contributes to melanoma resistance to apoptosis. J Immunol 2011 May 1;186(9):5173-83.

28. **Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al.** Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010 Aug 19;363(8):711-23.

29. **Hofmeyer KA, Ray A, Zang X.** The contrasting role of B7-H3. Proc Natl Acad Sci U S A 2008 Jul 29;105(30):10277-8.

30. **JanssenBiotech. Remicade (infliximab) Prescribing Information**, Revised November 2013. JanssenBiotech Pamphlet 2013.

31. **Katayama A, Takahara M, Kishibe K, Nagato T, Kunibe I, Katada A, et al.** Expression of B7-H3 in hypopharyngeal squamous cell carcinoma as a predictive indicator for tumor metastasis and prognosis. Int J Oncol 2011 May;38(5):1219-26.

32. **Keir ME, Butte MJ, Freeman GJ, Sharpe AH.** PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol 2008;26:677-704.

33. **Kohrt HE, Houot R, Marabelle A, Cho HJ, Osman K, Goldstein M, et al.** Combination strategies to enhance antitumor ADCC. Immunotherapy 2012 May;4(5):511-27.

34. **Lakhani, N, Mehnert, J M, Rasco, D, Gordon, M, Lohr, J, Sharma, S, et al**. A Phase 1 Study of the Safety, Tolerability, and Pharmacokinetics (PK) of MGA012 (anti-PD-1 antibody) in Patients with Advanced Solid Tumors. 2017.

35. **Loo D, Alderson RF, Chen FZ, Huang L, Zhang W, Gorlatov S, et al.** Development of an Fc-enhanced Anti-B7-H3 Monoclonal Antibody with Potent Antitumor Activity. Clin Cancer Res 2012 Jul 15;18(14):3834-45.

36. **Mahnke K, Ring S, Johnson TS, Schallenberg S, Schonfeld K, Storn V, et al.** Induction of immunosuppressive functions of dendritic cells in vivo by CD4+CD25+ regulatory T cells: role of B7-H3 expression and antigen presentation. Eur J Immunol 2007 Aug;37(8):2117-26.

37. **Mehnert, J M, Joshua, A M, Lakhani, N, Banerji, U, Rasco, D, Lugowska, I, et al.**, First-in-Human Phase 1 Study of INCMGA00012 in Patients With Advanced Solid Tumors: Interim Results of the Cohort Expansion Phase. SITC Poster, 2018.

38. **Merck. KEYTRUDA (pembrolizumab) Prescribing Information.** Merck pamphlet 2015 Jan.

39. **Modak S, Kramer K, Gultekin SH, Guo HF, Cheung NK**. Monoclonal antibody 8H9 targets a novel cell surface antigen expressed by a wide spectrum of human solid tumors. Cancer Res 2001 May 15;61(10):4048-54.

40. **Musolino A, Naldi N, Bortesi B, Pezzuolo D, Capelletti M, Missale G, et al.** Immunoglobulin G fragment C receptor polymorphisms and clinical efficacy of trastuzumab-based therapy in patients with HER-2/neu-positive metastatic breast cancer. J Clin Oncol 2008 Apr 10;26(11):1789-96.

41. **NCCN. Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer.** [2014 Available from: NCCN.org.

42. **Olsen KD, Kwon ED, Sheinin Y, Lohse CM, Kasperbauer JL, Moore EJ.** B7-H1, B7-H3, and CA1X Expression in squamous Cell Carcinoma of Head and Neck Tumors.: 7th International Conference on Head and Neck Cancer; 2008.

43. **Plimack ER, Bellmunt J, Gupta S, Berger R, Montgomery RB, Heath K, et al.** Pembrolizumab (MK-3475) for advanced urothelial cancer: Updated results and biomarker analysis from KEYNOTE-012. J Clin Oncol 2015;33.

44. **Plimack ER, Gupta S, Bellmunt J, Berger R, Montgomery B, Gonzalez EJ, et al.** LBA23 - A phase 1b study of pembrolizumab (Pembro; MK-3475) in patients (Pts) with advanced urothelial tract cancer. European Society for Medical Oncology . 9-29-2014. Ref Type: Abstract

45. **Rizvi NA, et al.** Safety and clinical activity of MK-3475 as initial therapy in patients with advanced non-small cell lung cancer (NSCLC). J Clin Oncol . 2014. Ref Type: Abstract

46. **Robert C, Ribas A, Wolchok JD, Hodi FS, Hamid O, Kefford R, et al**. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. Lancet 2014 Sep 20;384(9948):1109-17.

47. **Roth TJ, Sheinin Y, Lohse CM, Kuntz SM, Frigola X, Inman BA, et al.** B7-H3 ligand expression by prostate cancer: a novel marker of prognosis and potential target for therapy. Cancer Res 2007 Aug 15;67(16):7893-900.

48. **Schneider T, Hoffmann H, Dienemann H, Schnabel PA, Enk AH, Ring S, et al.** Non-small cell lung cancer induces an immunosuppressive phenotype of dendritic cells in tumor microenvironment by upregulating B7-H3. J Thorac Oncol 2011 Jul;6(7):1162-8.

49. **Schwarz A, Schwarz T.** UVR-Induced Regulatory T Cells Switch Antigen-Presenting Cells from a Stimulatory to a Regulatory Phenotype. J Invest Dermatol 2010;130:1914-21.

50. **Segal NH, Antonia SJ, Brahmer JR, Maio M, Blake-Haskins A, Li X, et al.** Preliminary data from a multi-arm expansion study of MEDI4736, an anti-PD-L1 antibody. J Clin Oncol 2014;32(5s).

51. **Seiwert TY, Burtness B, Weiss J, Gluck I, Eder JP, Pai SI, et al.** A phase Ib study of MK-3475 in patients with human papillomavirus (HPV)-associated and non-HPV-associated head and neck (H/N) cancer. J Clin Oncol 2014;32(5s).

52. **Shin EC, Protzer U, Untergasser A, Feinstone SM, Rice CM, Hasselschwert D, et al.** Liver-directed gamma interferon gene delivery in chronic hepatitis C. J Virol 2005 Nov;79(21):13412-20.

53. **Steinberger P, Majdic O, Derdak SV, Pfistershammer K, Kirchberger S, Klauser C, et al.** Molecular characterization of human 4Ig-B7-H3, a member of the B7 family with four Ig-like domains. J Immunol 2004;172(4):2352-9.

54. **Suh WK, Gajewska BU, Okada H, Gronski MA, Bertram EM, Dawicki W, et al.** The B7 family member B7-H3 preferentially down-regulates T helper type 1-mediated immune responses. Nat Immunol 2003 Sep;4(9):899-906.

55. **Sun J, Chen LJ, Zhang GB, Jiang JT, Zhu M, Tan Y, et al.** Clinical significance and regulation of the costimulatory molecule B7-H3 in human colorectal carcinoma. Cancer Immunol Immunother 2010 Mar 24.

56. **Sun Y, Wang Y, Zhao J, Gu M, Giscombe R, Lefvert AK, et al.** B7-H3 and B7-H4 expression in non-small-cell lung cancer. Lung Cancer 2006 Aug;53(2):143-51.

57. **Sznol M, Kluger HM, Callahan MK, Postow MA, Gordon RA, Segal NH, et al.** Survival, response duration, and activity by BRAF mutation (MT) status of nivolumab (NIVO, anti-PD-1, BMS-936558, ONO-4538) and ipilimumab (IPI) concurrent therapy in advanced melanoma (MEL). J Clin Oncol 2014;32(5s).

58. **Tekle C, Nygren MK, Chen YW, Dybsjord I, Nesland JM, Maelandsmo GM, et al.** B7-H3 contributes to the metastatic capacity of melanoma cells by modulation of known metastasis-associated genes. Int J Cancer 2012 May 15;130(10):2282-90.

59. **Thompson RH, Kwon ED, Allison JP.** Inhibitors of B7-CD28 costimulation in urologic malignancies. Immunotherapy 2009 Jan;1(1):129-39.

60. **Topalian SL, Drake CG, Pardoll DM.** Targeting the PD-1/B7-H1(PD-L1) pathway to activate anti-tumor immunity. Curr Opin Immunol 2012 Apr;24(2):207-12.

61. **Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al.** Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012 Jun 28;366(26):2443-54.

62. **Vermorken JB, Trigo J, Hitt R, Koralewski P, Diaz-Rubio E, Rolland F, et al.** Open-label, uncontrolled, multicenter phase II study to evaluate the efficacy and toxicity of cetuximab as a single agent in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck who failed to respond to platinum-based therapy. J Clin Oncol 2007 Jun 1;25(16):2171-7.

63. **Wang, D D, Zhang, S, Zhao, H, Men, A Y, and Parivar, K**. Fixed dosing versus body size-based dosing of monoclonal antibodies in adult clinical trials. J Clin Pharmacol, 2009. 49(9): p. 1012-24

64. **Wang L, Kang FB, Shan BE.** B7-H3 mediated tumor immunology: Friend or foe? Int J Cancer 2013 Sep 7.

65. **Weng WK, Levy R.** Two immunoglobulin G fragment C receptor polymorphisms independently predict response to rituximab in patients with follicular lymphoma. J Clin Oncol 2003 Nov 1;21(21):3940-7.

66. **Wilke CM, Wei S, Wang L, Kryczek I, Kao J, Zou W**. Dual biological effects of the cytokines interleukin-10 and interferon-gamma. Cancer Immunol Immunother 2011 Nov;60(11):1529-41.

67. **Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbe C, et al.** Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009 Dec 1;15(23):7412-20.

68. **Woo SR, Turnis ME, Goldberg MV, Bankoti J, Selby M, Nirschl CJ, et al.** Immune inhibitory molecules LAG-3 and PD-1 synergistically regulate T-cell function to promote tumoral immune escape. Cancer Res 2012 Feb 15;72(4):917-27.

69. **Wu CP, Jiang JT, Tan M, Zhu YB, Ji M, Xu KF, et al.** Relationship between co-stimulatory molecule B7-H3 expression and gastric carcinoma histology and prognosis. World J Gastroenterol 2006 Jan 21;12(3):457-9.

70. **Zang X, Sullivan PS, Soslow RA, Waitz R, Reuter VE, Wilton A, et al.** Tumor associated endothelial expression of B7-H3 predicts survival in ovarian carcinomas. Mod Pathol 2010 May 21.

71. **Zang X, Thompson RH, Al-Ahmadie HA, Serio AM, Reuter VE, Eastham JA, et al.** B7-H3 and B7x are highly expressed in human prostate cancer and associated with disease spread and poor outcome. Proc Natl Acad Sci U S A 2007 Dec 4;104(49):19458-63.

Appendix 1 Time and Events Schedule

Time and Events Schedule: MGA271 and Pembrolizumab

Cycle		**Initial Tumor Assessment Cycle**									**Cycle 2 and beyond**					
Treatment Day of the Cycle (Visits occur ± 3 days of scheduled visit, unless otherwise noted)	**-28**	**1**	**2**	**3**	**8**	**15**	**22**	**29**	**36**	**42**	**1**	**8 15 29 36 50 57**	**22**	**43**	**63**	**EOTV**
Evaluation or Procedure [20]																
STUDY DRUG ADMINISTRATION																
Pembrolizumab		X					X				X		X	X		
MGA271		X [1]			X	X	X [1]	X	X		X [1]	X	X [1]	X [1]		
ELIGIBILITY																
Informed Consent (obtained prior to registration; no time constraint)	X															
Patient registration[18]	X															
Identify available archival tissue samples for B7-H3 and PD-L1 testing or consent to a fresh biopsy [2]	X															
Confirmed PD-L1 Expression < 1% (for NSCLC Cohort 1 only) [2]	X															
Medical history	X															
Review of concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG PS	X	X								X					X	X
ECG [20]	X [3]	X [3]	X [3]		X [3]	X [3]	X [3]				X [15]					

Time and Events Schedule: MGA271 and Pembrolizumab

Cycle		**Initial Tumor Assessment Cycle**									**Cycle 2 and beyond**					
Treatment Day of the Cycle **(Visits occur ± 3 days of scheduled visit, unless otherwise noted)**	**-28**	**1**	**2**	**3**	**8**	**15**	**22**	**29**	**36**	**42**	**1**	**8** **15** **29** **36** **50** **57**	**22**	**43**	**63**	**EOTV**
Evaluation or Procedure [20]																
β-hCG pregnancy test	X [4]						X				X					
Pre-Treatment Tumor Biopsy (Cohort Expansion Phase Only)	X															
Optional On-Treatment Tumor Biopsy (Cohort Expansion Phase Only)										X [5]						
SAFETY & PD EVALUATION																
Physical examination [6, 20]	X	X			X	X	X	X	X		X	X	X	X	X	X
Monitor for AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC with differential, platelet count [8, 20]	X	X			X	X	X	X	X		X		X		X	X
Chemistry panel [8, 9, 20]	X	X			X	X	X	X	X		X		X		X	X
Special Chemistry [8,10, 20]	X	X			X	X	X	X	X		X		X		X	
Free T4 and TSH [8, 20]		X					X				X					
Prothrombin time; Activated partial thromboplastin time [8, 20]		X									X					
Urinalysis [8, 20]	X	X					X				X		X		X	X
Flow Cytometry: Lymphocyte subsets, NK cells and activation markers [7, 20]		X	X				X			X						

Time and Events Schedule: MGA271 and Pembrolizumab

Cycle		**Initial Tumor Assessment Cycle**									**Cycle 2 and beyond**					
Treatment Day of the Cycle (Visits occur ± 3 days of scheduled visit, unless otherwise noted)	**-28**	**1**	**2**	**3**	**8**	**15**	**22**	**29**	**36**	**42**	**1**	**8 15 29 36 50 57**	**22**	**43**	**63**	**EOTV**
Evaluation or Procedure [20]																
PBMC Collection: T-cell Repertoire/ADCC (Expansion only) [7, 20]		X					X						X[19]			
Soluble B7-H3 and other soluble proteins [7, 20]		X	X				X			X						
Serum Cytokine Sampling [11, 20]		X	X	X	X											
Vital signs [20] (pulse, respirations, blood pressure, temp)	X [12]	X [12]	X [12]		X [12]	X [12]	X [12]	X [12]	X [12]		X [16]	X [16]	X [16]	X [16]	X [16]	
THERAPEUTIC ACTIVITY																
Disease assessment by RECIST and irRECIST: CT/MRI Chest, Abdomen and Pelvis [20]	X									X					X	X
CT/MRI Brain [13, 20]	X									X					X	X
PK/IMMUNOGENICITY																
MGA271 PK sampling [14, 20]		X	X	X	X		X				See Table 6 for Cycles 2 - 6					X
ADA blood sample (anti-MGA271 Antibodies[20]		X [7]					X [7]				X [17]			X [17]		X

1. On days when both pembrolizumab and MGA271 are to be administered, pembrolizumab must be administered first. An effort should be made to begin the MGA271 infusion between 30 minutes to 120 minutes after the completion of the pembrolizumab infusion. It is understood that this window may not always be attainable, but it is the preferred window of time to administer MGA271. On days when MGA271 is administered after pembrolizumab, MGA271 may be administered the next day for safety reasons or scheduling purposes. The start and stop time of each pembrolizumab and MGA271 infusion must be documented. A minimum of 6-day interval should occur between doses of MGA271 when given on a weekly schedule.

2. Tissue samples or slides for B7-H3 testing should be identified before initiating therapy, but do not need to be submitted or resulted in advance of initiating therapy and may be submitted by C1 D43. B7-H3 expression is not required for eligibility in this study; however, tumor expression of B7-H3 will be evaluated for all patients. Patients should have a formalin-fixed, paraffin embedded (FFPE) tumor specimen or unstained slides identified for analysis, to enable determination of the expression of B7-H3 within tumor specimens using IHC staining. If an archived tumor specimen is not available, patients who undergo a fresh tumor biopsy (**Section 7.11.4.3**) can have B7-H3 expression evaluated from a FFPE sample obtained from the fresh tumor biopsy. In this case, the biopsy should be obtained prior to initiating study therapy. In cases in which an archived sample and fresh tumor sample are both available, B7-H3 expression can be confirmed with either FFPE sample. PD-L1 tumor expression status for **NSCLC Cohort 1** to be obtained before registration (no time constraint) either by historical documented IHC expression, or if no prior PD-L1 expression level available, obtained by IHC PD-L1 testing on archival or new tumor sample. PD-L1 testing for all other Cohort Expansion Phase cohorts can have PD-L1 tumor expressions determined prior to or after enrollment. All PD-L1 testing to be done with a sponsor approved method. Tumor immune cell infiltration evaluation will be determined prior to or after enrollment for all patients if enough sample is available for testing.
3. Pembrolizumab infusion on Days 1 and 22: ECGs will be obtained immediately before the pembrolizumab infusion (pre-dose) and at 30 minutes (end of infusion).

MGA271 infusion on Day 1 (intensive PK day): ECGs will be taken immediately before MGA271 infusion (pre-dose); at 120 minutes (end of infusion); at 3 hours and 24 hours after the start of infusion. If infusion is interrupted, ECGs will be done based on the time of re-starting infusion. MGA271 infusion on Days 8, 15 and 22: ECGs will be taken immediately before MGA271 infusion (pre-dose) and at 120 minutes (end of infusion).

4. For women of childbearing potential, to be obtained within 72 hours prior to initial dose of pembrolizumab.
5. Can be done +/- 3 days from Day 42.
6. Includes height (screening only) and weight. Note that full physical exams to be done on screening, Day 1 (baseline), and at the EOTV. All other physical exams will be directed physical exams based on patient symptoms, tumor location and as clinically indicated.
7. Day 1 sample will be collected prior to pembrolizumab infusion; all other days, prior to MGA271 infusion. See **Table 5** for ADA sample Days and times.
8. Samples will be drawn prior to infusion and analyzed by the LOCAL laboratory. Day 1 of Cycle 1 safety labs do not need to be repeated if done within 3 days of Day 1.
9. Includes ALB, ALK-P, ALT, AST, bicarbonate, BUN, Ca, Cl, creatinine, glucose, magnesium, phosphorus, K, Na, total protein, uric acid.
10. Includes amylase, total and direct bilirubin, lipase.
11. For Cytokine samples: Day 1 sample will be collected prior to pembrolizumab infusion and then collected with the 5 hours after start of MGA271 infusion PK sample, and with the PK sample on Days 2 and 3, and with the PK end of infusion sample on Day 8. Additional samples may be obtained selectively at additional timepoints in patients who experience signs and symptoms of cytokine release.
12. Initial Tumor Assessment Cycle: Vital signs include temperature, pulse, blood pressure, and respiratory rate and are obtained as follows:

Pembrolizumab infusion on Days 1 and 22: Vital signs will be taken immediately before the pembrolizumab infusion (pre-dose); at 15 minutes after the start of infusion; at 30 minutes (end of infusion); and at 90 minutes after start of infusion if the MGA271 dose has not already commenced.

MGA271 infusion on Days 1, 8, 15, 22, 29 and 36: Vital signs will be taken immediately before MGA271 infusion (pre-dose); at 60 minutes after the start of infusion; at end of infusion; and at 3 hours after the start of infusion. If infusion is interrupted, vitals will be based on time of restarted infusion. NOTE: The vital signs taken at 3 hours after the start of the infusion (i.e., 1 hour after the end of the infusion) and may be deferred if continued monitoring is not clinically indicated. Vital signs will also be taken at 24 hours after the start of infusion on Day 1 (PK day).

13. A CT or MRI of the brain will be performed in cases where clinically indicated (e.g., suspicion of brain metastases) and repeat brain scans will only be performed if the Screening brain scan was positive or as clinically indicated.
14. Pharmacokinetic sampling to be performed according to **Table 6**.
15. Treatment Tumor Assessment Cycles 2 and beyond.

ECGs will be obtained prior to the first pembrolizumab infusion on the first day of each cycle (Day 1). For Cycle 2, Day 1 only, (intensive PK day): ECGs will be taken immediately before MGA271 infusion (pre-dose) and at 120 minutes (end of infusion).

16. Treatment Assessment Cycles 2 and beyond: Vital signs include temperature, pulse, blood pressure, and respiratory rate and are obtained as follows:

Pembrolizumab infusion days: Vital signs including temperature, pulse, blood pressure and respiratory rate will be taken immediately before the pembrolizumab infusion (pre-dose); at 15 minutes after the start of infusion; at 30 minutes (end of infusion).

MGA271 infusion (both on days with and without pembrolizumab infusion): Vital signs will be taken immediately before MGA271 infusion (pre-dose); at 60 minutes after the start of infusion; and at end of infusion; and at 3 hours after the start of infusion. NOTE: The vital signs taken at 3 hours after the start of the infusion (i.e., 1 hour after the end of the infusion) and may be deferred if continued monitoring is not clinically indicated. Vital signs will also be taken at 24 hours after the start of infusion on Day 1 (PK day).

17. ADA samples will be obtained on Day 1 of Cycles 2, 3, 4, and 5. The ADA sample will be obtained on Day 43 of Cycle 6. See **Table 5** for ADA sample Days and times.
18. To be done within 3 days of Day 1.
19. Cycles 2 and 3 only.
20. For time window allowances for specific evaluations or procedures, refer to the **Table 8**.

Time and Events Schedule: MGA271+MGA012 (Cohort 4 Only)

Cycle		Initial Tumor Assessment Cycle								Cycle 2 and beyond								
Treatment Day of the Cycle (Visits occur ± 3 days of scheduled visit, unless otherwise noted)	**-28**	**1**	**2**	**4**	**8**	**15**	**22**	**42**		**1**	**2**	**4**	**8**	**15**	**22**	**43**	**63**	**EOTV**
Evaluation or Procedure [11]																		
STUDY DRUG ADMINISTRATION																		
MGA012		X					X			X					X	X		
MGA271		X [1]					X [1]			X [1]					X [1]	X [1]		
ELIGIBILITY																		
Informed Consent (obtained prior to registration; no time constraint)	X																	
Patient registration	X																	
Identify available archival tissue samples for B7-H3 testing or consent to a fresh biopsy [2]	X																	
Medical history	X																	
Review of concomitant medications	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
ECOG PS	X	X						X									X	X
ECG [3, 11]	X[3]	X[3]					X[3]			X[3]								
β-hCG pregnancy test	X[4]						X			X								
SAFETY & PD EVALUATION																		
Physical examination [5, 11, 12]	X	X					X			X					X	X	X	X
Monitor for AEs		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
CBC with differential, platelet count [6, 11, 12]	X	X					X			X					X		X	X

Time and Events Schedule: MGA271+MGA012 (Cohort 4 Only)

Cycle		Initial Tumor Assessment Cycle								Cycle 2 and beyond								
Treatment Day of the Cycle (Visits occur ± 3 days of scheduled visit, unless otherwise noted)	**-28**	**1**	**2**	**4**	**8**	**15**	**22**	**42**		**1**	**2**	**4**	**8**	**15**	**22**	**43**	**63**	**EOTV**
Evaluation or Procedure [11]																		
Chemistry panel [6, 7, 11, 12]	X	X					X			X					X		X	X
Special Chemistry [6, 8, 11, 12]	X	X					X			X					X		X	
Free T4 and TSH [6, 11, 12]		X					X			X								
Prothrombin time; Activated partial thromboplastin time [6, 11]		X								X								
Urinalysis [6, 11, 12]	X	X					X			X					X		X	X
Flow Cytometry Occupancy	See **Appendix 2** and **Table 9**																	
Flow Cytometry subsets	See **Appendix 2** and **Table 9**																	
Soluble B7-H3 and other soluble proteins	See **Appendix 2 and Table 9**																	
Serum Cytokine Sampling	See **Appendix 2 and Table 9**																	
Vital signs (pulse, respirations, blood pressure, temp) [9, 11]	X	X					X			X					X	X	X	
THERAPEUTIC ACTIVITY																		
Disease assessment by RECIST and irRECIST: CT/MRI Chest, Abdomen and Pelvis [11]	X							X									X	X
CT/MRI Brain [10, 11]	X							X									X	X
PK sampling	See **Appendix 2** and **Table 9**																	
ADA blood sample	See **Appendix 2** and **Table 9**																	

1. An effort should be made to begin the MGA271 infusion between 30 minutes to 120 minutes after the completion of the MGA012 infusion. It is understood that this window may not always be attainable, but it is the preferred window of time to administer MGA271. MGA271 may be

administered the next day for safety reasons or scheduling purposes. The start and stop time of each MGA012 and MGA271 infusion must be documented. MGA271 is administered Q3W ± 3 days. An interval of at least 18 days should occur since the previous administration.

2. B7-H3 expression are not required for eligibility in this study; however, tumor expression of B7-H3 will be evaluated for all patient tissue samples or slides for B7-H3 and tissue should be identified before initiating therapy, but do not need to be submitted or resulted in advance of initiating therapy and may be submitted by C1 D43. Patients should have a formalin-fixed, paraffin embedded (FFPE) tumor specimen or unstained slides identified for analysis, to enable determination of the expression of B7-H3 within tumor specimens using IHC staining. If an archived tumor specimen is not available, patients who undergo a fresh tumor biopsy **(Section 7.11.4.3)** can have B7-H3 expression evaluated from a FFPE sample obtained from the fresh tumor biopsy. In this case, the biopsy should be obtained prior to initiating study therapy. In cases in which an archived sample and fresh tumor sample are both available, B7-H3 expression can be confirmed with either FFPE sample.
3. MGA012 infusion on Days 1 and 22: ECGs will be obtained before both the MGA012 and MGA271 infusions, at the end of both MGA012 and MGA271 infusions. **C1D1:** 3 hours after start of MGA271 infusion. **C2 and beyond: D1** pre-infusion MGA012. If infusion is interrupted, ECGs will be done based on the time of re-starting infusion.
4. For women of childbearing potential, to be obtained within 72 hours prior to initial dose of MGA012.
5. Includes height (screening only) and weight. Note that full physical exams to be done on screening, Day 1 (baseline), and at the EOTV. All other physical exams will be directed physical exams based on patient symptoms, tumor location and as clinically indicated.
6. Samples will be drawn prior to infusion and analyzed by the LOCAL laboratory. Day 1 of Cycle 1 safety labs do not need to be repeated if done within 3 days of Day 1.
7. Includes ALB, ALK-P, ALT, AST, bicarbonate, BUN, Ca, Cl, creatinine, glucose, magnesium, phosphorus, K, Na, total protein, uric.
8. Includes amylase, total and direct bilirubin, lipase.
9. The 2 hour after start of MGA012 infusion and 3 hour after start of MGA271 infusion vital signs measurements may be deferred if continuing monitoring is not clinically indicated. If infusion is interrupted, vital signs will start from the beginning when infusion resumes.
10. A CT or MRI of the brain will be performed in cases where clinically indicated (e.g., suspicion of brain metastases) and repeat brain scans will only be performed if the Screening brain scan was positive or as clinically indicated.
11. For time window allowances for specific evaluations or procedures, refer to **Table 9.**
12. Assessments are shared between Day 63 and Day 1 of the subsequent cycle and do not need to be repeated if Day 1 occurs within 3 days of Day 63. If two scheduled visits have shared data (i.e., the visits occur on the same date because overlapping window allowances permit combined visits), enter all required assessments and procedures in the forms for the earlier scheduled visit first. Any additional assessments and procedures unique to the later visit should be entered in that visit. Do not enter duplicate forms (e.g., laboratory results) in both scheduled visits.

Table 8 Time Window Allowances for Study Evaluations and Procedures for MGA271 and Pembrolizumab

Procedure	Study Day	Time Point	Window Allowance
Cytokines	C1D1	Pre-Infusion	-1 hour to 0 min before SOI
		5 hours after Start of MGA271 Infusion	+/-30 min (must match PK time)
	C1D2	24 hours after Start of MGA271 Infusion	+/-3 hours (must match PK time)
	C1D3	48 hours after Start of MGA271 Infusion	+/-3 hours (must match PK time)
	C1D8	End of Infusion (MGA271)	-10 min to 0 min (EOI) (must match PK time)
ECG	C1D1, C1D22	Pre-Infusion (pembrolizumab)	-1 hour to 0 min before SOI
	C1D1, C1D22	End of Infusion (pembrolizumab)	0 min to +20 min after EOI
	C1D1	Pre-Infusion (MGA271)	-1 hour to 0 min before SOI (Note: must be taken after post pembrolizumab ECG)
	C1D1	End of Infusion (MGA271)	0 min to +20 min
	C1D1	3 hours after Start of MGA271 Infusion	+/- 30 min
	C1D2	24 hours after Start of MGA271 Infusion	+/- 3 hour
	C1: D8, 15, 22	Pre-Infusion (MGA271)	-1 hour to 0 min before SOI
	C1: D8, 15, 22	End of Infusion (MGA271)	0 min to +20 min after EOI
	C2D1	Pre-Infusion (pembrolizumab)	-1 hour to 0 min before SOI
	C2D1	Pre-Infusion (MGA271)	-1 hour to 0 min before SOI (Note: must be taken after post pembrolizumab ECG)
	C2D1	End of Infusion (MGA271)	0 min to +20 min
	C2 and beyond: D1	Pre-Infusion (pembrolizumab)	-1 hour to 0 min before SOI

	C1D1, D22	Pre-Infusion (pembrolizumab)	Any time before dosing on visit day (dosing day) or day before (must match PK time)
Flow cytometry, sB7-H3	C1D2	24 hours after Start of MGA271 Infusion	+/-3 hours (must match PK time)
	C1D1, D8, D22; C2D1; C3-5D1; C6D43	Pre-Infusion	Any time before dosing on visit day (dosing day) or day before
PK	C1D1, D8, D22; C2D1	End of MGA271 Infusion	-10 min to 0 min (EOI)
	C1D1; C2D1	3 hours after Start of MGA271 Infusion	+/-30 min
	C1D1; C2D1	5 hours after Start of MGA271 Infusion	+/-30 min
	C1D1; C2D1	8 hours after Start of MGA271 Infusion	+/-30 min
	C1D2; C2D2	24 hours after Start of MGA271 Infusion	+/-3 hours
	C1D3; C2D3	48 hours after Start of MGA271 Infusion	+/-3 hours
	C1: D1, 22	Pre-Infusion (pembrolizumab)	-15 min to 0 min before SOI
Vital Signs		15 minutes after Start of Pembrolizumab Infusion	+/-5 min
		End of Infusion (pembrolizumab)	0 min to +15 min after EOI
		90 minutes after Pembrolizumab Infusion	+/-15 min
	C1: D1, 8, 15, 22, 29, 36	Pre-Infusion (MGA271)	-15 min to 0 min before SOI (Note: must be taken after post pembrolizumab vitals)
		60 minutes after Start of MGA271 Infusion	+/-15 min
		End of Infusion (MGA271)	0 min to +15 min
		3 hours after Start of MGA271 Infusion	+/-30 min
	C1D2	24 hours after Start of MGA271 Infusion	+/-3 hour
	C2 and beyond: D1, 22, 43	Pre-Infusion (pembrolizumab)	-15 min to 0 min before SOI

		15 minutes after Start of Pembrolizumab Infusion	+/-5 min
		End of Infusion (pembrolizumab)	0 min to +15 min after EOI
		Pre-Infusion (MGA271)	-15 min to 0 min before SOI (Note: must be taken after post pembrolizumab vitals)
		60 minutes after Start of MGA271 Infusion	+/-15 min
		End of Infusion (MGA271)	0 min to +15 min
		3 hours after Start of MGA271 Infusion	+/-30 min
	C2 and beyond: D1, 8, 15, 29, 36, 50, 57	Pre-Infusion (MGA271)	-15 min to 0 min before SOI
		60 minutes after Start of MGA271 Infusion	+/-15 min
		End of Infusion (MGA271)	0 min to +15 min
		3 hours after Start of MGA271 Infusion	+/-30 min
	C1D1, C1D22, C2-5: D1, C6D43	Pre-Infusion (pembrolizumab)	Any time before dosing on visit day (dosing day) or day before
	C1: D1, 8, 15, 22, 29, 36; C2 and beyond: D1, 8, 15, 22, 29, 36, 43, 50, 57, 63	Pre-Infusion	-3 to 0 days prior to dosing
ADA	C1: D42; C2 and beyond: D63	Pre-Infusion	-3 to 0 days prior to dosing
Physical Examination	C1: D1, 8, 15, 22, 36; C2 and beyond: D1, 22, 63	Pre-Infusion	-3 to 0 days prior to dosing
Disease Assessment	C1: D1, 8, 15, 22, 36; C2 and beyond: D1, 22, 63	Pre-Infusion	-3 to 0 days prior to dosing
CBC with differential, platelet count	C1: D1, 8, 15, 22, 36; C2 and beyond: D1, 22, 63	Pre-Infusion	-3 to 0 days prior to dosing
Chemistry panel	C1: D1, 22; C2 and beyond: D1	Pre-Infusion	-3 to 0 days prior to dosing
Special chemistry	C1: D1; C2 and beyond: D1	Pre-Infusion	-3 to 0 days prior to dosing

Free T4 and TSH	C1: D1, 22; C2 and beyond: D1, 22, 63	Pre-Infusion	-3 to 0 days prior to dosing
Prothrombin time; Activated partial thromboplastin time	C1: D1, 8, 15, 22, 29, 36; C2 and beyond: D1, 8, 15, 22, 29, 36, 43, 50, 57	Pre-Infusion	+10 min
Urinalysis	C1: D1, 22; C2 and beyond: D1, 22, 63	Pre-Infusion	-3 to 0 days prior to dosing
Study Drug Infusion Duration	C1: D1, 8, 15, 22, 29, 36; C2 and beyond: D1, 8, 15, 22, 29, 36, 43, 50, 57	NA	+10 min

Abbreviations: ADA= Anti-drug antibodies; C=cycle; D=day; min=minutes; EOI=end of infusion; NA=not applicable; SOI=start of infusion;

Table 9 Time Window Allowances for Study Evaluations and Procedures for MGA271 and MGA012 (Cohort 4 Only)

Procedure	Study Day	Time Point	Window Allowance
Cytokines	C1D1, C2D1	Pre-Infusion MGA012	**-1 hour to 0 min before SOI**
	C1D1, C2D1	5 hours after start of MGA271 Infusion	+/-30 min (must match PK time)
	C1D2, C2D2	No specific timepoint	No specific window
ECG	C1D1, C1D22	Pre-Infusion MGA012	-1 hour to 0 min before SOI
	C1D1, C1D22	End of Infusion MGA012	0 min to +20 min after EOI
	C1D1, C1D22	Pre-Infusion MGA271	-1 hour to 0 min before SOI (Note: must be taken after post MGA012 ECG)
	C1D1, C1D22	End of Infusion MGA271	0 min to +20 min after EOI
	C1D1	3 hours after Start of MGA271 Infusion	+/- 30 min
	C2 and beyond: D1	Pre-Infusion MGA012	-1 hour to 0 min before SOI
Flow cytometry, Occupancy	C1D1, C1D22 C2D1, C2D22, C3 and beyond: D1 and D22	Pre-Infusion MGA012	Any time before dosing on visit day (dosing day) or day before (must match PK time)
	C1D1, C2D1	5 hours after start of MGA271 infusion	+/-30 min (must match PK time)
	C1D2, C2D2 C1D8, C2D8 C1D15, C2D15	No specific timepoint	No specific window
	C1D22, C2D22, C3 and beyond: D1 and D22	End of MGA271 Infusion	-10 min to 0 min (EOI)
Flow Cytometry Subsets	C1D1, C2D1 C1D22, C2D22 C3 and beyond: D1 and D22	Pre-Infusion MGA012	Any time before dosing on visit day (dosing day) or day before (must match PK time)
	C1D1, C2D1	5 hours after start of MGA271 infusion	+/-30 min (must match PK time)
	C1D2, C2D2 C1D15, C2D15	No specific timepoint	No specific window
Soluble B7 H3 and Other Soluble Proteins	C1D1, C2D1 C1D22, C2D22	Pre-Infusion MGA012	Any time before dosing on visit day (dosing day) or day before (must match PK time)
	C1D8, C2D8	No specific timepoint	No specific window

Table 9 Time Window Allowances for Study Evaluations and Procedures for MGA271 and MGA012 (Cohort 4 Only)

Procedure	Study Day	Time Point	Window Allowance
PK	C1D1, C1D22 C2D1, C2D22 C3 and beyond: D1 and D22	Pre-Infusion MGA012	Any time before dosing on visit day (dosing day) or day before
	C1D1, C1D22 C2D1, C2D22 C3 and beyond: D1 and D22	End of MGA012 infusion	-10 min to 0 min (EOI)
	C1D1, C1D22 C2D1, C2D22 C3 and beyond: D1 and D22	End of MGA271 Infusion	-10 min to 0 min (EOI)
	C1D1, C2D1	5 hours after Start of MGA271 Infusion	+/-30 min
	C1D2, C1D4, C1D8, C1D15	No specific timepoint	No specific window
	C2D2, C2D4, C2D8, C2D15	No specific timepoint	No specific window
Vital Signs	C1D1, C1D22	Pre-Infusion MGA012	-15 min to 0 min before SOI
		30 minutes after Start of MGA012 Infusion	+/-15 min
		End of Infusion (MGA012)	0 min to +15 min after EOI
		2 hours after Start of MGA012 Infusion	+/-15 min
	C1D1, C1D22	Pre-Infusion MGA271	-15 min to 0 min before SOI (Note: must be taken after post MGA012 vitals)
		60 minutes after Start of MGA271 Infusion	+/-15 min
		End of Infusion MGA271	0 min to +15 min
		3 hours after Start of MGA271 Infusion	+/-30 min
	C2 and beyond: D1, D22, D43	Pre-Infusion MGA012	-15 min to 0 min before SOI
		30 minutes after Start of MGA012 Infusion	+/-15 min
		End of Infusion MGA012	0 min to +15 min after EOI

Table 9 Time Window Allowances for Study Evaluations and Procedures for MGA271 and MGA012 (Cohort 4 Only)

Procedure	Study Day	Time Point	Window Allowance
		2 hours after Start of MGA012 Infusion	+/-15 min
		Pre-Infusion MGA271	-15 min to 0 min before SOI (Note: must be taken after post MGA012 vitals)
		60 minutes after Start of MGA271 Infusion	+/-15 min
		End of Infusion MGA271	0 min to +15 min
		3 hours after Start of MGA271 Infusion	+/-30 min
ADA	Days 1 and 22 all Cycles	Pre-Infusion (MGA012)	Any time before dosing on visit day (dosing day) or day before
Physical Examination	C1: D1, 22, C2 and beyond: D1, 22, 43	Pre-Infusion	-3 to 0 days prior to dosing
Disease Assessment	C1: D42; C2 and beyond: D63	Pre-Infusion	-3 to 0 days prior to dosing
CBC with differential, platelet count	C1: D1, 22, C2 and beyond: D1, 22	Pre-Infusion	-3 to 0 days prior to dosing
Chemistry panel	C1: D1, 22, C2 and beyond: D1, 22	Pre-Infusion	-3 to 0 days prior to dosing
Special chemistry	C1: D1, 22, C2 and beyond: D1, 22	Pre-Infusion	-3 to 0 days prior to dosing
Free T4 and TSH	C1: D1, 22; C2 and beyond: D1	Pre-Infusion	-3 to 0 days prior to dosing
Prothrombin time; Activated partial thromboplastin time	C1: D1; C2 and beyond: D1	Pre-Infusion	-3 to 0 days prior to dosing
Urinalysis	C1: D1, 22; C2 and beyond: D1, 22	Pre-Infusion	-3 to 0 days prior to dosing
Study Drug Infusion Duration	C1: D1, 22, C2 and beyond: D1, 22, 43	NA	+10 min

Abbreviations: ADA= Anti-drug antibodies; C=cycle; D=day; min=minutes; EOI=end of infusion; NA=not applicable; SOI=start of infusion;

Appendix 2 Pharmacokinetics, Immunogenicity, and Pharmacodynamic Biomarkers Blood Sampling Schedule for MGA271+MGA012 (Cohort 4 Only)

Tumor Assessment Cycle	Day	Time Points	PK MGA271 And MGA012	ADA MGA271 and MGA012	Cytokines	Flow Cytometry Occupancy	Flow Cytometry Subsets	Soluble B7-H3 and Other Soluble Proteins
Cycle 1 and 2	1	Pre MGA012	x	x	x	x	x	x
		EOI MGA012	x					
		EOI MGA271	x					
	1	5 hr. after start of MGA271 infusion	x		x	x	x	
	2	No specific time point	x		x	x	x	
	4	No specific time point	x					
	8	No specific time point	x			x		x
	15	No specific time point	x			x	x	
	22	Pre MGA012	x	x		x	x	x
	22	EOI MGA012	x					
	22	EOI MGA271	x			x		
Cycle 3 and Beyond	1	Pre MGA012	x	x		x	x	
		EOI MGA012	x					
		EOI MGA271	x			x		
	22	Pre MGA012	x	x		x	x	
		EOI MGA012	x					
		EOI MGA271	x			x		
IRR/CRS		No specific time point			x			
EOTV		No specific time point	x	x			x	x

- Actual start and end of infusion times and PK sample collection times will be recorded on the CRFs.
- All Pre-dose samples will be collected prior to MGA012 infusion. ADA samples will be collected simultaneously with pre-infusion PK samples.
- Flow cytometry samples (occupancy and subset) will be collected through Cycle 4.

- Cytokine samples will be performed according to the table above. Additional samples should be obtained selectively at additional time points in patients who experience signs and symptoms of cytokine release at the time of the adverse event, with the goal to obtain a cytokine sample immediately at the time of onset of adverse event; specific dates and times of blood draws must be recorded.

Abbreviations: ADA= Anti-drug antibodies; C=cycle; D=day; min=minutes; EOI=end of infusion; NA=not applicable; SOI=start of infusion;

Appendix 3 Definition of PFS

Situation	Date	Outcome
No baseline tumor assessments	Date of 1st dose	Censored
Death prior to the 1st scheduled tumor assessment	Date of death	Progressed
No post-baseline tumor assessments in absence of death prior to the 1st scheduled tumor assessment	Date of 1st dose	Censored
Documented disease progression	Date of disease progression	Progressed
Initiation of alternative anti-cancer treatments in absence of PD	Date of last tumor assessment prior to initiation of such treatment	Censored
Death or progression immediately after missing two or more consecutive scheduled tumor assessments	Date of last tumor assessment prior to missed assessments	Censored

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 (**19**))

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

MEASURABILITY OF TUMOR AT BASELINE

DEFINITIONS

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

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-measurable).
- 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 non-target lesions' for information on lymph node measurement.

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-measurable 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.

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 measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic 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.

SPECIFICATIONS BY METHODS OF MEASUREMENTS

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.

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.

TUMOR RESPONSE EVALUATION

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).

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').

RESPONSE CRITERIA

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

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.

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'.

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 measurable, 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 non-target lesions. All lymph nodes must be non-pathological in size (<10mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target 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).

Special notes on assessment of progression of non-target disease

The concept of progression of non-target 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.

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.

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.

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 measurable disease at baseline.

Missing assessments and unevaluable 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.

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.

a 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.

CONFIRMATION/DURATION OF RESPONSE

Confirmation

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

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.

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

(Adapted from Wolchok 2009 (**67**))

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

MEASURABILITY OF TUMOR AT BASELINE

DEFINITIONS

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

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-measurable).
- 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 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.

Non-measurable

All other lesions, including small lesions (longest diameter < 10mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable 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.

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 measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic 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.

SPECIFICATIONS BY METHODS OF MEASUREMENTS

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.

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.

TUMOR RESPONSE EVALUATION

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).

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’).

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).

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.

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'.

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 measurable, 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 (<10mm 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.

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.

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.

Time point response

It is assumed that at each protocol specified timepoint, 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 measurable lesions has increased by ≥ 20% from the nadir sum of diameters

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.

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.

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**.

CONFIRMATION/DURATION OF RESPONSE

Confirmation

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

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.

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 1, Open-Label, Dose Escalation Study of MGA271 in Combination with Pembrolizumab and in Combination with MGA012 in Patients with Melanoma, Squamous Cell Cancer of the Head and Neck, Non-Small Cell Lung Cancer, Urothelial Cancer, and Other Cancers

Study Number: CP-MGA271-03

I have read the protocol described above.

I have fully discussed the objectives of this trial 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, subject to ethical and safety considerations and guidelines, and to conduct the trial 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 trial 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 trial, I will communicate my intention immediately in writing to the Sponsor.

Signed: _____ **Date:** _____

PI Name (printed): _____

PI Affiliation: _____

PI Address: _____

PI Phone Number: _____

CP-MGA271-03 Protocol Amendment 6 (26-Aug-2020)
This is the electronic signature page for the above referenced document.

User Task: eSignatories Approval	– Data Management/Statistics Approval (Intended or Designee) 27-Aug-2020 17:11:49 GMT+0000

User Task: eSignatories Approval	roval (Intended or Designee) 27-Aug-2020 18:00:44 GMT+0000