STATISTICAL ANALYSIS PLAN

VERSION 2.0

PROTOCOL CP-MGA271-03

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

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LIST OF ABBREVIATIONS

ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse event of special interest
B7-H3	Homolog 3 of the B7 ligand
CI	Confidence interval
CR	Complete response
CTCAE	Common terminology criteria for adverse events
DLT	Dose limiting toxicity
DoR	Duration of response
ECG	Electrocardiogram
eCRF	Electronic case report form
irPFS	Immune-related progression-free survival
irRC	Immune-related response criteria
MedDRA	Medical Dictionary for Regulated Activities
MAD	Maximum administered dose
MTD	Maximum tolerated dose
NSCLC	Non-small cell lung carcinoma
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
PD	Progressive disease
PT	Preferred term
PR	Partial response
RECIST	Response evaluation criteria in solid tumors

SAE	Serious adverse event
SAP	Statistical analysis plan
SPP	Statistical programming plan
SCCHN	Squamous cell carcinoma of the head and neck
SOC	System organ class
TEAE	Treatment emergent adverse event
TLF	Tables, listings, and figures

1 INTRODUCTION

This study evaluates novel combinations of immunotherapies in patients with advanced cancer and is designed to investigate whether combined administration of MGA271 and pembrolizumab, or combined administration of MGA271 and MGA012, through coordinately blocking two distinct B7-H3 and PD-1 pathways, can further potentiate the promising antitumor activity observed with pembrolizumab or MGA012 alone. The statistical analysis plan (SAP) v1.0 aligns with amendment 6 of the study protocol and describes in detail the statistical methods used for analysis of the efficacy endpoints, the safety endpoints, as well as the pharmacokinetic (PK) and pharmacodynamic (PD) parameters collected from the study.

2 STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives of this study are:

To characterize the safety, tolerability, dose limiting doxicity (DLT), and maximum tolerated dose (MTD), or maximum administered dose (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, squamous cell carcinoma of the head and neck (SCCHN), or non-small cell lung carcinoma (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 administered IV Q3W to patients with unresectable locally advanced or metastatic melanoma, SCCHN, or NSCLC, urothelial cancer, and other cancers as stipulated in inclusion criteria.

2.2 Secondary Objectives

The 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 Q3W.
- To characterize the PD activity of MGA271 when administered IV weekly in combination with IV 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 and immune-related response criteria (irRC).

2.3 Exploratory Objectives

The exploratory objectives of the study are:

- 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.

3 STUDY DESIGN AND PLAN

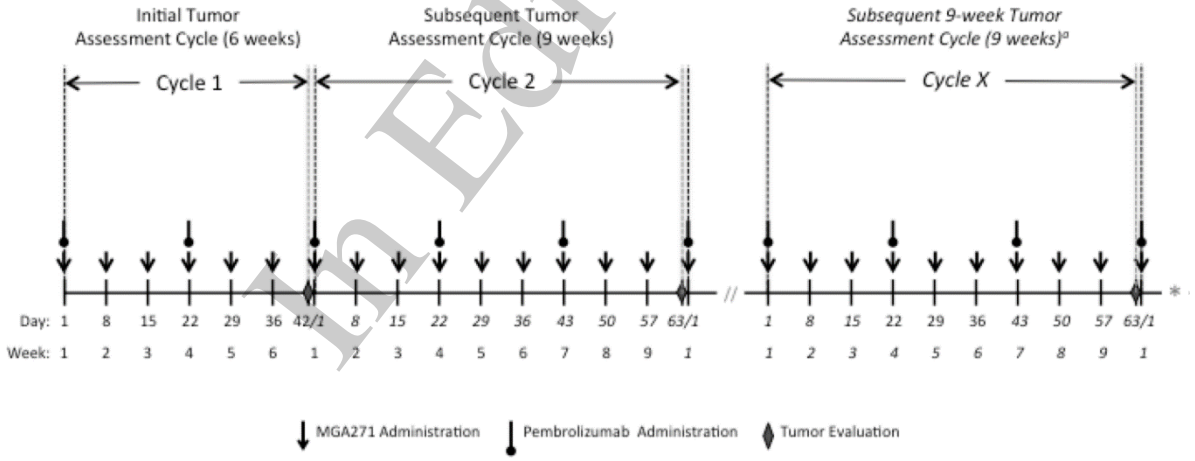
3.1 Overall Study Design and Plan

3.1.1 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 Q3W. Beginning with Amendment 5, this study also characterizes the safety and tolerability of MGA271 administered IV Q3W in combination with MGA012, both administered IV Q3W (cohort 4).

This 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 1**.

Figure 1 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.**

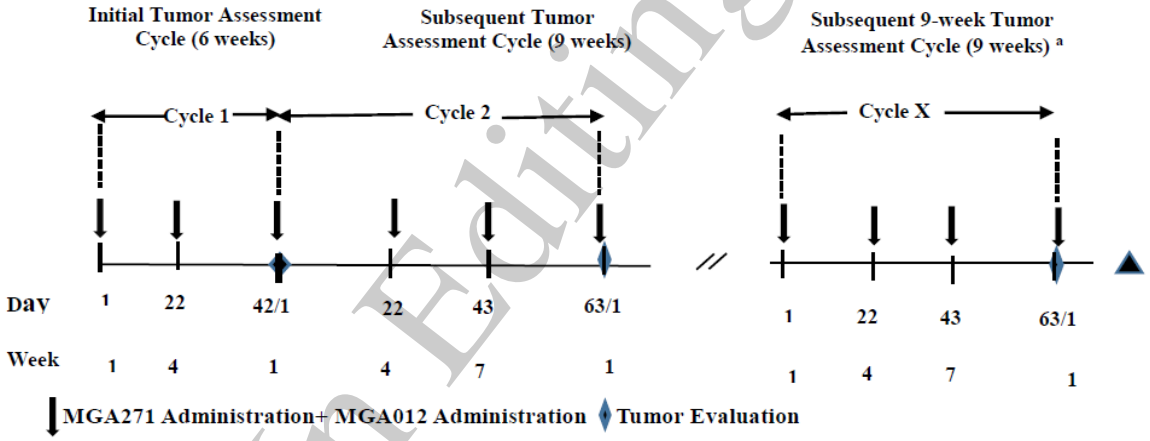
MGA271 will be administered as an IV infusion over 120 minutes on a once-weekly schedule. Pembrolizumab will be administered at 2 mg/kg as an IV infusion over 30 minutes Q3W. On the days that both agents are administered, pembrolizumab will be administered first, followed by MGA271.

For both the Dose Escalation and Cohort Expansion phases, the 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 2**.

Figure 2 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 my receive up to 5 additional 9-week treatment cycles during Subsequent Tumor Assessment Cycles, for a maximum total of 17 does 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.

3.1.2 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, melanoma, thyroid cancer, TNBC, 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).

The 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 drug doses in each cohort are listed in **Table 1**.

Table 1 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.

Beginning with Amendment 5, a new cohort, Cohort 4, wasadded 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 (**Table 1**).

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. 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.

3.1.3 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 each), 2 cohorts of SCCHN (up to n=20 each), 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.

3.1.4 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.

3.2 Sample Size Justification

This study may enroll 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,

mors.

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.

4 STUDY POPULATIONS AND SUBGROUPS

4.1 Study 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 MGA271, pembrolizumab or MGA012. Safety Population will be used to summarize baseline data, safety data and for assessment of overall survival (OS) and progression-free survival (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 and 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 objective response rates (ORRs) using both conventional RECIST 1.1 and irRC 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.

4.2 Important Subgroups

Each dose cohort will be summarized as an independent subgroup. Other subgroups may be defined as needed.

5 ENDPOINTS AND COVARIATES

5.1 Efficacy Endpoints

Response will be categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) and evaluated using RECIST 1.1 criteria and as immune-related complete response (irCR), immune-related partial response (irPR), immune-related stable disease (irSD), or immune-related progressive disease (irPD) using irRC. 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.

Duration of response (DoR) 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 DoR over time and the median DoR. 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 year 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 **(1)** 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. **Table 3** describes the handling of these data for the PFS analysis.

Overall survival (OS) 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.

Table 3 Censoring Rules for PFS Analysis

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	Date of 1st dose	Censored

Situation	Date	Outcome
prior to the 1st scheduled tumor assessment		
Documented disease progression	Date of disease progression	Progressed
Initiation of alternative anti-cancer treatments in absence of disease progression	Date of last tumor assessment prior to initiation of such treatment	Censored
Death or disease progression immediately after missing two or more consecutive scheduled tumor assessments	Date of last tumor assessment prior to missed assessments	Censored

5.2 Safety Endpoints

5.2.1 Adverse Events

Adverse event (AE) means any untoward medical occurrence in a patient or clinical trial patient associated with the use of a drug in humans, whether or not considered drug related. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Only treatment emergent adverse events (TEAEs) will be summarized as safety endpoints. A TEAE is defined as any event that is newly occurring on or after the administration of study drug or an event that existed before but increased in severity on or after study drug administration.

All adverse events whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained through the end of treatment visit (EOTV) or 28 days following the last dose of study (whichever occurs later). These events will be recorded by the Investigators in the electronic case report forms (eCRFs). AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). An assessment of severity grade will be made using National Cancer Institute- Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03.

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

5.2.2 Laboratory Values

Safety laboratory assessments will be carried out locally and evaluated by the Investigator to ensure patient safety. 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. 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).

5.2.3 Other Safety Endpoints

Physical examination will be performed (including weight and height) for all patients according to the schedules outlined in the protocol.

Vital signs (include temperature, pulse, blood pressure, and respiratory rate) and Eastern Cooperative Oncology Group (ECOG) performance status will be performed according to the schedules outlined in the protocol.

Twelve-lead electrocardiograms (ECGs) will be obtained according to the protocol to evaluate the potential cardiac effects of the combination of MGA271 and pembrolizumab and of MGA271+MGA012, including QT interval. 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. For Cohort 4 only, ECGs will be read locally.

5.3 Pharmacokinetic, Pharmacodynamic, and Immunological Parameter Endpoints

Central laboratories will be used to measure serum concentrations (for PK evaluations), cytokines, T-cell repertoire, anti-drug antibodies (ADA, anti-MGA271 and anti-MGA012 antibodies) as well as the other pharmacodynamic parameters. The timepoints for collection of blood samples for each of these tests are included in the study protocol.

6 STATISTICAL METHODOLOGY

6.1 General Considerations

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 for continuous variables. Categorical data will be summarized by the number and percent of subjects falling within each category. Continuous variables will be summarized by descriptive statistics, including the mean, standard deviation, median, minimum, and maximum. Time-to-event endpoints will be summarized with median durations and corresponding 95% confidence intervals.

For change from baseline calculations, baseline is defined as the most recent value prior to the first infusion of any of the study drugs among MGA271, pembrolizumab or MGA012.

6.2 Missing Data

Data reported as missing will be treated as missing in all data summaries. Imputation rules for partially recorded dates, where complete dates are required to carry out an analysis, will be provided in the statistical programming plan (SPP). 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.

6.3 Patient Disposition and Baseline Characteristics

6.3.1 Patient Disposition

For patient disposition, the number and percentage of patients who reach various study

milestones are summarized in each patient category. All screened patients are categorized into two groups: patients with screen failures (with reasons if collected) and enrolled. Then the enrolled patient group is further categorized into two subgroups: never treated (with reasons if collected) and treated with any of the study drugs. The “treated with any study drugs” category will further be divided into the treatment ongoing (if any) and treatment discontinuation (with reasons for discontinuation, which also include protocol-defined treatment completion, if any) categories. The end of study status for all enrolled patients will also be included.

6.3.2 Patient Demographics and Baseline Characteristics

Patient demographics, baseline characteristics, disease history, medical history, prior cancer therapy, and other collected baseline data will be summarized using descriptive statistics.

6.4 Study Drug Exposure and Concomitant Medications

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

Duration of study treatment (months) will be calculated as:

(date decided to discontinue treatment – date of first dose + 1)/(365.25/12) for patients who have discontinued treatment.

The summary of concomitant medications will include the number and percentage of patients who receive any concomitant medications as well as each concomitant medication by World Health Organization Anatomical Therapeutic Chemical (ATC) first level and Preferred Term (PT).

6.5 Protocol Deviations

Major protocol deviations will be documented and filed prior to database lock. The major protocol deviations will be listed and summarized in the final analysis.

6.6 Efficacy Endpoint Analyses

6.6.1 Objective Response

Objective response rate (ORR), determined by RECIST and irRC criteria, will be calculated by [redacted] tumor type and will be based on a confirmed response at least 28 days after initial observation of response. Two-sided 95% exact binomial confidence intervals (CIs) will be calculated around the ORRs. [redacted] For SCCHN and NSCLC, ORR from participants with or without prior PD-1/PD-L1 treatments will be summarized in separate tumor type groups. [redacted]

Objective responses that are not subsequently documented with a confirmed response by 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 rate will be calculated as:

Objective response rate (ORR) = number of patients with confirmed response (CR or PR) / number of patients with response evaluable

6.6.2 Tumor Size Change from Baseline

The tumor size percent change from baseline over time will be summarized and presented by spider plot. The best tumor size percent change from baseline prior to the date of first PD or initiation of new anticancer therapy will be presented by waterfall plot. Patients with CR or PR at time of last assessment will be censored at the time of their last tumor assessment. Using statistical notation, if y_t denotes the sum of the measurements at some post-baseline timepoint and y_0 denotes the sum of the measurements at baseline, the percent change from baseline will be calculated as:

$$(y_t - y_0) / y_0 \times 100$$

6.6.3 Time-to-Event Analyses

Kaplan-Meier methods will be used to estimate cumulative probabilities and quartiles (25th percentile, median, and 75th percentile) of time-to-event endpoints (DoR, PFS, irPFS, and OS). The method of Brookmeyer and Crowley (**1**) will be used to construct two-sided 95% CIs around the quartile estimates. These calculations will be performed for all patients in cohort expansion by tumor type. Additional analysis may be carried out, by tumor type, on patients in the dose escalation cohort combined with those in the expansion cohort.

DoR 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. Patients with CR or PR at time of last assessment will be censored at the time of their last tumor assessment. DoR will be calculated as follows:

DoR (months) = (progression date or death date or date of last tumor assessment – date of initial response+1) / (365.25/12)

PFS is defined as the time from first dose of study drug until documented disease progression or death from any cause, or date of last tumor assessment. A patient will be censored at the time of last assessment if the patient remains progression free at that time. Progression will be assessed using both RECIST 1.1 and irRC. PFS will be calculated as follows:

PFS (months) = (date of progression or date of death or date of last tumor assessment – date of first dose+1) / (365.25/12)

Overall survival (OS) is calculated from the time of first dose until death from any cause. Patients alive at study completion will be censored for analysis purposes. OS will be calculated as follows:

OS (months) = (date of last contact or death date – date of first dose+1) / (365.25/12)

6.7 Safety Endpoint Analyses

6.7.1 Adverse Events

As mentioned in **Section 5.2**, only TEAEs will be summarized in tables.

The following summaries of adverse event data will be created:

- All AEs
- Drug related AEs
- 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 SAEs (this may be a listing if there are few events)
- Drug related SAEs
- Fatal AEs (this may be a listing if there are few events)
- Adverse events of special interest (AESIs)
- AEs that result in study discontinuation
- AEs which lead to dose interruption
- AEs that lead to withdrawal of study drug

All of these summaries will display the number and percent of patients that experience the given event and will display events by System Organ Class (SOC) and Preferred Term (PT) from the MedDRA dictionary. Events will be displayed in alphabetically for SOC incidence and in descending order of overall PT incidence within each SOC.
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
- AEs by CTCAE Grade
- Drug related AEs by CTCAE Grade
- All SAEs
- Drug-related SAEs
- AEs that lead to dose interruption
- AE that results in study discontinuation
- AE that results in study drug withdrawal
- Fatal AEs
- AESIs

6.7.2 Laboratory Values

Summaries of laboratory values will display descriptive statistics for numerically quantified labs. Absolute values and changes from baseline will be summarized and grouped by lab panel (e.g., hematology, blood chemistry, and urinalysis). For each panel, the data will be displayed by lab parameter and visit. Shift tables may be generated.

6.7.3 Electrocardiograms

Within each patient, the values provided in triplicate at each timepoint will be averaged by the mean. These intra-patient averages will be used for calculating changes from baseline and will be used to calculate summary statistics.

For each relevant visit and timepoint, summary statistics will be calculated for the heart rate, QT interval, QT interval with Fridericia's correction (QTcF), and maximum post dose change from baseline QTcF interval (ΔQTcF).

An additional summary will display the number and percent of patients with QTcF intervals >450 msec and ≤450 msec at each timepoint.

An ECG data listing will display all abnormal clinical interpretations.

6.7.4 Vital Signs and Weight

Vital signs and weight will be summarized at each timepoint. Absolute values and changes from baseline will be summarized.

Abnormal vital sign values will be identified using the normal ranges displayed in **Table 4**. Shift tables displaying the number and percent of subjects with Low, Normal, and High values at baseline that shift or remain Low, Normal, or High at post-baseline visits will be created.

6.7.5 Physical Examinations

Physical examination data will not be summarized. Abnormal physical examination findings discovered or becoming progressively abnormal after enrollment are to be noted as adverse events and will be summarized as such.

Table 4 Vital Sign Normal Ranges

Vital Sign (unit)	Normal Range (Inclusive)
Systolic Blood Pressure (mmHg)	90 – 140
Diastolic Blood Pressure (mmHg)	60 – 90
Respiration Rate (breaths/min)	12 – 20
Heart Rate (beats/min)	60 – 100
Temperature (°C)	34.0 – 38.0

6.8 Pharmacokinetic, Pharmacodynamic, and Immunological Parameter Endpoints

Serum concentrations of MGA271 and MGA012, and PK parameters, will be summarized by study visit using descriptive statistics and graphs over time. Any statistical modeling using population PK may be performed by an external consultant. An analysis plan will be provided.

The proportion of patients who are negative for MGA271 or MGA012 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. The impact of ADA on PK, safety, and efficacy will be assessed to the extent possible.

Summary statistics for pharmacodynamics parameters including, but not limited to, those listed under Protocol section 7.11.4, “Pharmacodynamics/Biomarkers” 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/MGA012 dose and exposure may be explored.

6.9 Data Standards

Clinical Data Interchange Standards Consortium (CDISC) standards will be used. The latest version of Study Data Tabulation Model (SDTM) will be used for data tabulations of the eCRF data. The latest version of Analysis Dataset Model (ADaM) will be used for the analysis datasets.

7 LIST OF TABLES AND FIGURES

The list of tables, listings, and figures (TLFs) and associated shells planned for the CSR based on the analyses described in this SAP are provided in a separate SPP, which also includes data reporting conventions and programming specifications for the development of the TLFs.

8 REFERENCES

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

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