NCT03729596

STATISTICAL ANALYSIS PLAN
VERSION 2.0

PROTOCOL CP-MGC018-01

A PHASE 1/2, FIRST-IN-HUMAN, OPEN-LABEL, DOSE-ESCALATION STUDY OF MGC018 (ANTI–B7-H3 ANTIBODY DRUG CONJUGATE) ALONE AND IN COMBINATION WITH MGA012 (ANTI–PD-1 ANTIBODY) IN PATIENTS WITH ADVANCED SOLID TUMORS

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LIST OF ABBREVIATIONS

ADA	Anti-drug antibodies
AUC	Area under the curve
BOR	Best overall response
BPI-sf	Brief Pain Inventory-short form
CI	Confidence interval
CR	Complete response
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
DLT	Dose limiting toxicity
DoR	Duration of response
ECG	Electrocardiogram
eCRF	Electronic case report form
EOTV	End of treatment visit
ICD	Immunological cell death
IFNγ	Interferon gamma
IHC	Immunohistochemistry
IV	Intravenous
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulated Activities
MAD	Maximum administered dose
mCRPC	Metastatic castration-resistant prostate carcinoma
MRI	Magnetic resonance imaging
MSI-H	Microsatellite instability-high

MTD	Maximum tolerated dose
NCI	National Cancer Institute
NE	Not evaluable
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
PD	Progressive disease
PD-1	Programmed death-1
PD-L1	Programmed death ligand-1
PK	Pharmacokinetic(s)
PR	Partial response
PRO	Patient-reported outcome
PSA	Prostate-specific antigen
PT	Preferred term
Q3W	Once every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
rPFS	radiographic progression-free survival
SAE	Serious adverse event
SAP	Statistical analysis plan
SCCHN	Squamous cell carcinoma of the head and neck
SD	Stable disease
SOC	System organ class
SPP	Statistical programming plan
SSE	Symptomatic skeletal event

TCR	T cell receptor
TEAE	Treatment emergent adverse event
TNBC	Triple-negative breast cancer

1 INTRODUCTION

This study is an open-label, Phase 1/2, dose escalation, and cohort expansion study designed to characterize the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, immunogenicity, and preliminary antitumor activity of MGC018 alone (Module A) and in combination with MGA012 (Module B), each administered by IV infusion, in participants with advanced solid tumors.

This statistical analysis plan (SAP) describes in detail the statistical methods to be used for analysis of the primary and secondary efficacy endpoints, the safety endpoints, and the PK parameters to be collected from this study.

2 STUDY OBJECTIVES

2.1 Primary Objective

To characterize the safety, tolerability, dose-limiting toxicities (DLTs), and maximum tolerated dose (MTD) or maximum administered dose (MAD) (if no MTD is defined) for MGC018 administered as monotherapy or in combination with MGA012, each administered intravenously (IV), in participants who have relapsed/refractory, unresectable locally advanced, or metastatic solid tumors.

2.2 Secondary Objectives

- To characterize the PK and immunogenicity of MGC018 alone and in combination with MGA012.
- To describe antitumor activity of MGC018 administered as monotherapy or in combination with MGA012 in participants with advanced solid tumors using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1).
- To describe the radiographic progression-free survival (rPFS) in metastatic castration-resistant prostate carcinoma (mCRPC).
- To describe the prostate-specific antigen (PSA) response rate and the best PSA percent change in mCRPC.

2.3 Exploratory Objectives

- To explore patient-reported outcome (PRO) using the Brief Pain Inventory-short form (BPI-sf) in Cohort Expansion (Module A).
- To explore effect of MGC018 on symptomatic skeletal events (SSEs) in participants with mCRPC in Cohort Expansion (Module A).
- To explore the relationships between PK, pharmacodynamics of MGC018 alone and in combination with MGA012, and antitumor activity (Modules A and B).
- To explore the impact of MGC018 alone and in combination with MGA012 on progression-free survival (PFS) and overall survival (OS) in participants with advanced solid tumors (Modules A and B).
- To determine programmed death–ligand 1 (PD-L1) expression via immunohistochemistry (IHC) staining of formalin-fixed, paraffin-embedded tumor biopsy specimens on archival tissue (Module B) and on optional paired tumor biopsy specimens (pre/on-treatment post Cycle 1 biopsies) in Cohort Expansion (Modules A and B).
- To explore the relationship between B7-H3 expression (H-score) and clinical response using a qualified B7-H3 IHC assay (Modules A and B).

- To assess whether MGC018 in combination with MGA012 induces immunological cell death (ICD) within optional paired tumor biopsy specimens (pre/on-treatment post cycle 1 biopsies) from participants in Cohort Expansion (Module B) as assessed by IHC.
- To assess whether MGC018 in combination with MGA012 modulates immune cell subset phenotype (including PD-1 expression) (Module B).
- To explore whether MGC018 modulates T cell response within optional paired tumor biopsy specimens (pre/on-treatment post Cycle 1 biopsies) from participants in Cohort Expansion (Modules A and B) as assessed by IHC and/or T cell receptor (TCR) spectratyping.
- To assess whether MGC018 alone or in combination with MGA012 induces an interferon gamma (IFNγ) gene expression signature in the optional paired tumor biopsy specimens (pre/on-treatment post Cycle 1 biopsies) from participants in Cohort Expansion (Modules A and B) via transcript profiling.
- To explore serum biomarkers including, but not limited to, IFNγ protein signature, in the peripheral circulation within the Cohort Expansion only (Modules A and B).
- To assess whether MGC018 modulates serum cytokine levels in Dose Escalation and Cohort Expansion phases (Modules A and B).
- To determine MGA012 receptor occupancy on immune cells in participants treated with the combination of MGC018 and MGA012 (Module B only).

The results of the exploratory objectives may not be included in the Clinical Study Report (CSR) or database lock unless they represent meaningful findings.

3 STUDY DESIGN AND PLAN

3.1 Overall Study Design and Plan

This study is a Phase 1/2, first-in-human, open-label, dose-escalation and cohort expansion study designed to characterize the safety, tolerability, PK, pharmacodynamics, immunogenicity, and preliminary antitumor activity of MGC018 administered by IV infusion, alone (Module A) and in combination with MGA012 (Module B) (see **Figure 1**); Module B will commence only after the MTD or MAD of MGC018 monotherapy (Module A) has been defined. Each module of the study consists of a Dose Escalation Phase to determine the MTD (or MAD, if no MTD is defined), followed by a Cohort Expansion Phase to further define the safety and initial antitumor activity of the respective monotherapy (Module A) and combination (Module B) regimens, using doses defined in the Dose Escalation Phase of each respective module. Module B will commence only upon notification to all the study investigators/institutions.

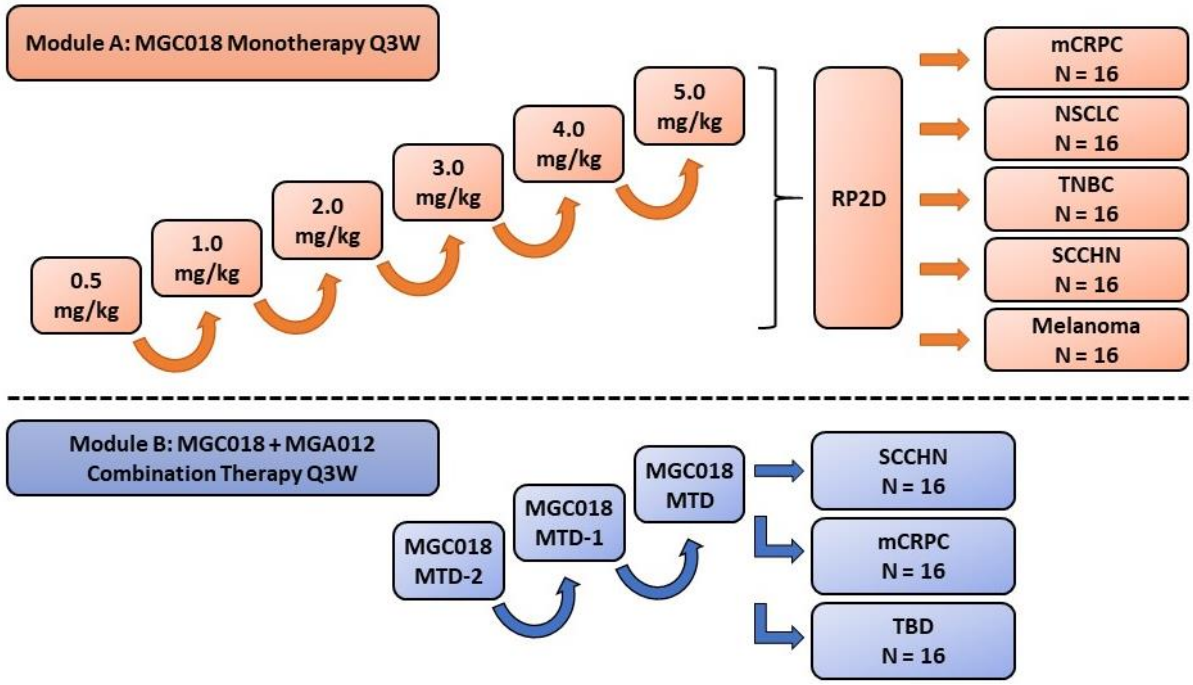
Participants with relapsed/refractory, unresectable locally advanced, or metastatic solid tumors of any histology will be enrolled in the Dose Escalation Phase of each module. The Module A Cohort Expansion Phase will be limited to mCRPC, non-small cell lung cancer (NSCLC), triple negative breast cancer (TNBC), squamous cell carcinoma of the head and neck (SCCHN), and melanoma. The Module B Cohort Expansion Phase will be limited to specific cohorts of participants with SCCHN, mCRPC, and a cohort to be determined (TBD) at a later date, guided by evolving experience from the Dose Escalation Phase of the study.

MGC018 will be administered alone or in combination with MGA012 (also known as INCMGA00012), as illustrated below in **Figure 2** and **Figure 3**, respectively. For Module A, MGC018 alone will be administered IV over 60 minutes on Days 1 and 22 of Cycle 1 and every subsequent 42-day cycle thereafter. For Module B, MGC018 alone will be administered IV over 60 minutes on Day 1 of Cycle 1 and with MGA012 on Day 22 of Cycle 1. Both MGC018 and MGA012 will be administered on Days 1 and 22 of every subsequent 42-day cycle thereafter, at the assigned dose for each cohort. Similar to MGC018, MGA012 will be administered IV over 60 minutes. On days when the MGC018 and MGA012 are to be administered on the same day (Module B only), MGA012 should be given first, followed immediately thereafter by MGC018.

For both the Dose Escalation Phase of Module A and Module B and the Cohort Expansion Phase of Module B, tumor assessments will occur at Day 42 of each cycle, for the first 4 cycles, and every other cycle thereafter. For the Cohort Expansion Phase of Module A, the tumor assessments will occur every 9 weeks (63 days). For Module A, the DLT evaluation period will be 21 days in duration; for Module B, the DLT evaluation period will be 42 days in duration. Participants who complete a given cycle, remain clinically stable, do not experience a DLT or other unacceptable toxicity, and do not otherwise meet the criteria for permanent treatment discontinuation may be eligible for additional treatment with MGC018 alone or in combination with MGA012 for up to a total of 18 cycles (approximately 2 years).

Following the last dose of study drug, all participants in Module A and Module B Cohort Expansion Phases will be followed every 3 months (90 days) for survival during a 2-year Survival Follow-up Period, until criteria are met for study discontinuation. Participants in Module A Dose Escalation Phase will be followed similarly for survival status until approval of Amendment 3, at which point they will be discontinued from follow up.

Figure 1 Overall Study Design



Note: MTD-2 = the dose level that is 2 dose levels below the MTD defined for MGC018 monotherapy.
MTD-1 = the dose level that is 1 dose level below the MTD defined for MGC018 monotherapy.
Abbreviations: mCRPC = metastatic castrate-resistant prostate carcinoma; MTD = maximum tolerated dose; NSCLC = non-small cell lung cancer; Q3W = every 3 weeks; RP2D = recommended phase II dose; SCCHN = squamous cell carcinoma of the head and neck; TBD = to be determined; TNBC = triple negative breast cancer.

Figure 2 MGC018 Monotherapy Dosing Schedule (Module A)

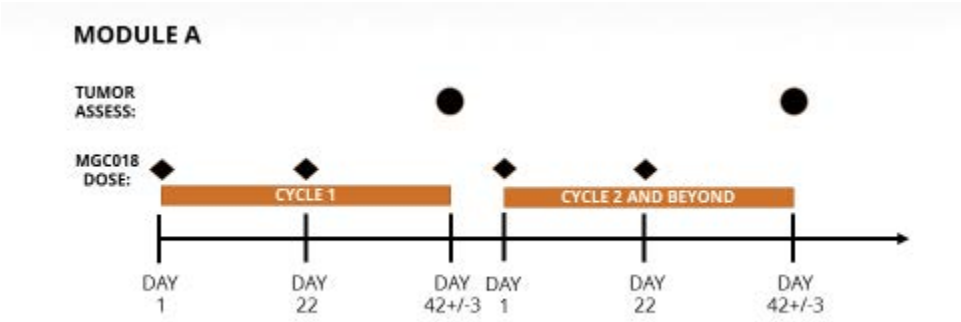
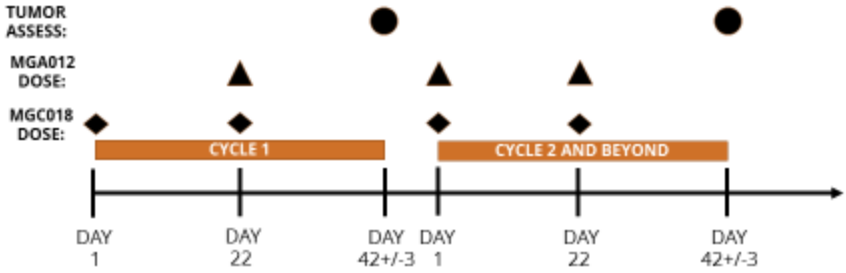


Figure 3 MGC018 and MGC012 Combination Dosing Schedule (Module B)



3.2 Sample Size

The study plans to enroll approximately up to 182 participants (107 in Module A and 75 in Module B). This number of participants does not take into account participants who may be replaced for non-evaluable participants or the possibility of expanding the mCRPC cohort with an additional 24 participants at the discretion of the sponsor.

In Module A, 27 participants were enrolled, of which 26 participants were treated with MGC018 monotherapy in the Dose Escalation Phase. Up to 80 participants with mCRPC, NSCLC, TNBC, SCCHN, or melanoma (up to 16 in each) will be enrolled to the Cohort Expansion Phase of Module A. Up to an additional 4 participants may be added per cohort. In Module B, up to 27 participants will be enrolled in the Dose Escalation Phase based on a 3+3+3 design with planned 3 dose cohorts in MGC018 and MGA012 combination therapy. The Cohort Expansion Phase of Module B will enroll up to 16 participants into each of 3 tumor specific cohorts (SCCHN, mCRPC, and participants with a tumor type TBD at a later date) treated with MGC018 in combination with MGA012. The sample size for each tumor specific cohort is primarily based on providing preliminary estimation of responses. **Table 1** provides the 2-sided 95% confidence interval (CI) for a number of potential responses among 16 participants.

The sample size for the mCRPC cohort expansion is primarily based on providing preliminary estimation of a 6-month rPFS rate.

Table 1 Response Rates and 95% Confidence Intervals

Sample Size	Number of Responses	Response Rate (%)	95% Confidence Interval (%)
16	1	6.3	0.2, 30.2
16	2	12.5	1.6, 38.3
16	3	18.8	4.0, 45.6
16	4	25.0	7.3, 52.4
16	5	31.3	11.0, 58.7
16	6	37.5	15.2, 64.6

During the Cohort Expansion Phase, participants who withdraw before completing the first tumor assessment for a reason other than clinical disease progression or death are considered unevaluable for response. In these cases, additional participants may be enrolled.

4 ANALYSIS POPULATIONS

4.1 Analysis Populations

The study analyses will be performed on the following populations:

- Safety Population: All participants who received at least one dose of any study drug. This population will be used for analyses of safety, pharmacodynamics, and immunogenicity. It will also be used for summary of baseline data and analyses of PFS, rPFS, and OS.
- Response Evaluable Population: All participants who received at least one dose of any study drug, had baseline measurable disease, and had at least one post-baseline radiographic tumor assessment or discontinued treatment due to clinical progressive disease or death. This population will be used for summary of tumor assessment data and analyses of response rates.
- PSA Response Evaluable Population: mCRPC participants with a baseline PSA ≥ 2 ng/ML and at least 1 post-baseline PSA measurement. This population will be used to calculate and summarize the PSA response rates.

5 ENDPOINTS

5.1 Efficacy Endpoints

5.1.1 Response Endpoints

Response by RECIST v1.1: The best overall response (BOR) will be categorized as complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), or not evaluable (NE). To be qualified as BOR, CR and PR require confirmation at least 4 weeks after initial observation of such response, and SD requires to be observed at least once after 6 weeks from the start of MGC018 treatment for Module A or MGC018 and MGA012 combination treatment for Module B.

5.1.2 Time-to-event Endpoints

- PFS: PFS is defined as the time from the first dose date of MGC018 treatment (Module A) or MGC018 and MGA012 combination treatment (Module B) to the date of first documented progression or death from any cause, whichever occurs first. The documented progression is determined by radiographic assessment using RECIST v1.1. PFS will be calculated as:

  PFS (months) = (date of event [documented progression or death] or date of censoring – first dose date +1) / (365.25/12)

- Duration of response (DoR): DoR is defined as the time from the date of initial response (CR or PR) to the date of first documented progression or death from any cause, whichever occurs first. DoR is calculated only for the responders (i.e., participants who have CR or PR). The documented progression is determined by radiographic assessment using RECIST v1.1. DoR will be calculated as:

  DoR (months) = (date of event [documented progression or death] or date of censoring – date of initial response+1) / (365.25/12)

- OS: OS is defined as the time from the first dose date of MGC018 treatment for Module A or MGC018 and MGA012 combination treatment for Module B to the date of death from any cause. OS will be calculated as:

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

5.1.3 Tumor Size Change Over Time Endpoints

The tumor size is defined as the sum of diameters of the target lesions. Tumor size change over time from baseline will be calculated.

5.1.4 Metastatic Castration-resistant Prostate Carcinoma-specific Endpoints

- Radiographic progression-free survival (rPFS): rPFS is defined as the time from the first dose of study drug to the first occurrence of one of these events: 1) Radiographic progression of soft tissue lesions using RECIST v1.1; 2) Radiographic progression of bone lesions: appearance of 2 or more new bone lesions; and 3) Death from any cause. rPFS is calculated as:

  rPFS (months) = (date of event [documented radiographic progression or death] or date of censoring – first dose date +1) / (365.25/12)

- PSA-related endpoints:

  PSA response: Defined as a ≥ 50% decline from baseline in PSA with confirmation at least 3 weeks later. The baseline PSA is defined as the last PSA value measured before the first administration of the study drug, or the value measured within 72 hours of the first dose, if elevated from the last PSA screening date.

  Change in PSA values from baseline: PSA measurements will be performed at baseline and then repeated at the times specified in the study protocol. Change in PSA from baseline will be calculated.

  PSA progression: PSA progression is defined as, if decline from baseline, a PSA increase that is ≥ 25% and ≥ 2 ng/mL above the nadir, and which is confirmed by a second value at least 3 weeks later; if no decline from baseline, a PSA increase that is ≥ 25% and ≥ 2 ng/mL above the baseline value after 12 weeks. Time to PSA progression is defined as the time from the first dose of study drug to the first documented PSA progression. Time to PSA progression is calculated as:

  Time to PSA progression (months) = (date of PSA progression or date of censoring – first dose date +1) / (365.25/12)

- Symptomatic Skeletal Events (SSE): SSEs are a clinical trial endpoint to describe skeletal morbidity defined as symptomatic fracture, surgery or radiation to bone, or spinal cord compression. SSEs include new symptomatic pathological fracture, use of external beam radiation to relieve bone pain, spinal cord compression, or tumor-related orthopedic surgical intervention. Time to SSE is defined as the time from the first dose of study drug to the first occurrence of SSE.

5.1.5 Patient-reported Outcome Endpoints:

PRO will be assessed using the Brief Pain Inventory-short form (BPI-sf). The BPI-sf is an exploratory 9 item self-administered written questionnaire used to evaluate the severity of a participant's pain and the impact of the pain on daily functioning.

5.2 Safety Endpoints

5.2.1 Adverse Events

Safety will primarily be addressed by evaluations of adverse events (AEs). An AE is defined as any untoward medical occurrence in a participant or clinical trial participant 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 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 informed consent form (ICF) is obtained through 30 days following the last dose of study drug or until the start of a subsequent systemic anticancer therapy (whichever occurs first). These events will be recorded by the Investigators in the 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 NCI-CTCAE Version 4.03.

Both protocol-related AEs and serious adverse events (SAEs) will be collected from the time the participant has consented to study participation. AEs and SAEs reported between the time the participant 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. After 30 days following the last dose of study drug administration, if an investigator becomes aware of an SAE that s/he suspects is related to study drug, the investigator should report the event to the sponsor.

5.2.2 Laboratory Evaluations

Standard safety laboratory parameters collected via a local laboratory will be summarized and graded according to CTCAE Version 4.03.

5.2.3 Physical Examinations

Physical examinations including weight and height will be performed according to the schedules outlined in the latest version of the protocol.

5.2.4 Vital Signs and Performance Status

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

5.2.5 Electrocardiograms

All electrocardiograms (ECGs) should be obtained in triplicate (3 ECGs per time point at approximately 1-minute intervals) according to the schedules outlined in the latest version of the protocol in order to evaluate the potential cardiac effects of study drug, including QTc interval prolongation. Central interpretation of ECGs will be used for data analysis purposes.

5.2.6 Echocardiography/MUGA scan

An echocardiogram or multigated acquisition (MUGA) scan to evaluate left ventricular ejection fraction (LVEF) will be performed according to the schedules outlined in the latest version of the protocol.

5.3 Pharmacokinetic, Pharmacodynamic, and Immunological Endpoints

PK samples, ADA samples, and pharmacodynamic biomarker specimens will be collected according to the schedules outlined in the latest version of the protocol.

6 STATISTICAL METHODOLOGY

6.1 General Considerations

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 expansion cohorts where appropriate. Response rates will be calculated for the response evaluable population.

Unless otherwise specified, the following general considerations are applied in data analyses:

- The baseline value is defined as the latest value on or prior to the first dose of study treatment.
- Categorical data will be summarized by the number and percent of participants falling within each category.
- Continuous variables will be summarized by descriptive statistics, including mean, standard deviation, median, minimum, and maximum.
- Time-to-event endpoints will be summarized by the number and percent of the event, median time and corresponding 95% confidence interval (CI), and event free rate and corresponding 95% CI at the specified time points of interest.
- The impact of COVID-19 may be assessed and analyzed on a case-by-case basis. In particular, the following analyses may be performed if there are enough COVID-19 positive participants to render the analyses meaningful:
    - Number of participants discontinued study treatment and/or discontinued from study due to COVID-19, if such a reason is collected
    - Summary of tumor response, PFS, rPFS and OS
    - Summary of study drug interruption, delay or withdrawal due to COVID-19, if such a reason is collected
    - Listing of protocol deviations due to COVID-19
- All data summaries and tabulations will be conducted using SAS® software Version 9.4 or higher.

6.2 Missing Data

Data that are reported as missing will be treated as missing in all data summaries. Imputation rules for partially recorded dates, in case that the 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 Participant Disposition and Baseline Characteristics

6.3.1 Participant Disposition

For participant disposition, the number and percentage of participants who reach various study milestones are summarized: All screened participants are broken down by screen failures (with reasons if collected) and enrolled. Then the category of enrolled is broken down by never treated (with reasons if collected) and treated. The category of treated will further be broken down by treatment ongoing and treatment discontinuation (with reasons for discontinuation, which also include protocol-defined treatment completion, if any). The end of study status for all enrolled participants will also be included. Duration of follow-up since first dose of study treatment, defined as from the date of first dose of MGC018 treatment (Module A) or MGC018 and MGA012 combination treatment (Module B) to the date of withdraw of consent, lost to follow up, death, or the last contact date, will be summarized.

6.3.2 Participant Demographics and Baseline Characteristics

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

6.4 Study Drug Exposures and Concomitant Medications

Study drug exposure, dose delay (including number and duration of delay), dose reduction, study drug withdrawals 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 administered as well as the total dose intended, and the dose intensity, which is calculated as percentage of total dose actually administrated divided by total dose intended during whole treatment period.

Duration of study treatment in months will be calculated as:

- (end of treatment visit (EOTV) date – first dose date + 1)/(365.25/12) for participants who have discontinued treatment;
- (data cutoff date– first dose date + 1)/(365.25/12) for participants whose treatment is ongoing.

The summary of concomitant medications will include the number and percentage of participants who receive any concomitant medications as well as each concomitant medication by drug class.

6.5 Subsequent Anti-cancer Therapy

Systemic anti-cancer therapies received after study drug discontinuation may include chemotherapy, immunotherapy, biologic therapy, targeted small molecules, radiotherapy, and surgery. Number and percentage of participants with any subsequent anti-cancer therapy will be summarized.

6.6 Protocol Deviations

Major protocol deviations will be identified prior to database lock for final analysis and will be listed and summarized.

6.7 Efficacy Endpoint Analyses

6.7.1 Analyses of Response Endpoints

The number and percent of participants with their BOR will be summarized. The objective response rate (ORR) per RECIST v1.1 is estimated as the proportion of participants in the response evaluable population who achieve BOR of CR or PR. The 2-sided 95% exact binomial CIs of the response rates will be calculated.

6.7.2 Analyses of Time-to-event Endpoints

6.7.2.1 Analyses of Progression-free Survival

The Kaplan-Meier method will be applied to estimate PFS curve, median PFS, and PFS rates at 3 and 6 months. The method of Brookmeyer and Crowley (**1**) will be used to construct 95% CI for median PFS. The 95% CIs for PFS rate will be calculated by normal approximation after log(-log) transformation.

For patients who are not known to be dead or progressed at the time of data cut-off for PFS analysis, the PFS will be censored at the date of the last tumor assessment. For primary PFS analysis, Table 2 describes the censoring rules.

Table 2 Censoring Rules for Primary Progression-free Survival Analysis

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

PFS will be analyzed by tumor type when sample size warrants. A sensitivity analysis for PFS may be performed to assess the robustness of above primary PFS analysis. For this sensitivity analysis, the censoring rules are the same as in **Table 2** except that the documented progression or death will be considered as an event, regardless when it occurs during the study.

6.7.2.2 Analyses of Duration of Response

The Kaplan-Meier method will be applied to estimate DoR curve and median DoR. The last three censoring rules described in **Table 2** will be applied for handling censorings. For responders (see definition in **Section 5.1.2**) who are not known to be dead or progressed at the time of data cut-off for DoR analysis, the DoR will be censored at the date of the last tumor assessment. The method of Brookmeyer and Crowley **(1)** will be used to construct 95% CI for median DoR. The DoR analyses will be performed only if there are enough responders to render the analyses meaningful.

6.7.2.3 Analyses of Overall Survival

The Kaplan-Meier method will be applied to estimate OS curve, median OS, and OS rates at 6 and 12 months. For patients who are not known to be dead at the time of data cut-off for OS analysis, the OS will be censored at the time they are last known to be alive. The method of Brookmeyer and Crowley (**1**) will be used to construct 95% CI for median OS. The 95% CIs for OS rate at 6 and 12 months will be calculated by normal approximation after log(-log) transformation. OS will be analyzed by tumor type when sample size warrants.

6.7.3 Subgroup and B7-H3 Expression Analyses

Subgroup analysis of efficacy (e.g., objective response rate, PFS and OS) may be conducted based on the following biomarkers:

Microsatellite instability-high (MSI-H) status

BRCA-1 mutation

BRCA-2 mutation

BRAF mutation (melanoma only)

Human papilloma viral status (SCCHN only)

The relationship between B7-H3 expression IHC score and clinical response will be explored.

6.7.4 Tumor Size Change Over Time

The tumor size percent change from baseline over time will be summarized and presented by spider plot. The best tumor size percentage change from baseline will be presented by waterfall plot.

6.7.5 Analyses of Metastatic Castration-resistant Prostate Carcinoma-specific Endpoints

- rPFS: The censoring rules in **Table 2** will be applied to rPFS analysis. The analysis of rPFS will be the same as that described for PFS.
- PSA:

  PSA response rate will be calculated for participants with a baseline PSA $\geq$ 2 ng/mL and at least 1 post-baseline value (i.e. PSA response evaluable population). The PSA response rate will be summarized at 12 weeks from baseline. The 2-sided 95% exact binomial CI of the response rate will be calculated.

  The percent change in PSA from baseline overall time will be summarized by visit and presented individually by spider plot. The percentage of change in PSA from baseline to 12 weeks (or earlier if treatment is discontinued), and the best PSA percent change from baseline will be presented by waterfall plots.

  The Kaplan-Meier method will be applied to estimate time to PSA progression in the PSA response evaluable population. PSA measurements are performed at baseline and then repeated prior to each dose of each treatment visit, approximately 30 days after the last study treatment administration (EOTV), and every 12 weeks (± 7 days) during the follow-up period until disease progression, start of another cancer therapy, or the study cutoff date, whichever comes first.

Participants without PSA progression at the time of analysis will be censored to the date of their last PSA assessment. The last three rules in **Table 2** will be applied to PSA progression analysis, with the changes from "progression" and "tumor assessment" to "PSA progression" and "PSA assessment", respectively.

- SSE: SSE rate will be summarized. Specifically, SSE rate per 100 patient-year will be calculated as the number of each of the SSEs, including the occurrence of new symptomatic pathological fracture, use of external beam radiation to relieve bone pain, spinal cord compression, or tumor-related orthopedic surgical intervention, divided by the total patient-years in the mCRPC cohort The Kaplan-Meier method will be applied to estimate time to SSE. Participants without SSE at the time of analysis will be censored at the last assessment. For each participant, the eCRF documenting any SSEs is scheduled to be completed pre-dose of each treatment. Participants without any SSE assessment will be excluded for the SSE endpoint analysis.

6.7.6 Patient-reported Outcome

The BPI-sf will be used to assess pain. A mean pain severity score will be calculated from the average of 4 pain intensity item scores: items 3 (worst), 4 (least), 5 (average), and 6 (right now). Changes from baseline in pain intensity item scores, mean pain severity score, and pain interference scores will be summarized. Imputation of missing values will be used for BPI-sf. If at least two out of the four pain intensity items are answered, any missing items will be assigned the mean value of the completed pain intensity items. If at least four out of the seven pain interference items are answered, the missing pain interference items will be assigned the mean value of the completed paint interference items.

6.8 Safety Endpoint Analyses

6.8.1 Treatment Emergent Adverse Events

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

- All AEs
- AEs with CTCAE severity grade ≥ 3
- Study drug–related AEs
- Study drug–related AEs with CTCAE severity grade ≥ 3
- SAEs
- Study drug–related SAEs
- AEs that result in discontinuation of study treatment

- AEs that led to dose interruption, dose delay, or discontinuation of individual study drug
- Fatal AEs
- Immediately reportable AEs (if applicable)
- AEs of special interest (AESIs)

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

6.8.2 Laboratory Values

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

6.8.3 Other Safety Endpoints

6.8.3.1 Electrocardiogram and Left Ventricular Ejection Fraction

ECGs will be collected and analyzed for evidence of cardiac toxicity, especially prolongation of QTc interval. The following categories for QTcF interval and maximum post dose change from baseline QTcF interval (ΔQTcF) will be used in summary and shift tables:

QTcF: ≤ 450 msec, >450 to 480 msec, >480 to 500 msec, and >500 msec

ΔQTcF: ≤ 30 msec, >30 to 60 msec, and >60 msec

Summaries of mean and change from baseline in LVEF will be provided.

6.8.3.2 Vital Signs and ECOG Performance Status

Vital signs and ECOG performance status will be summarized with descriptive statistics at each visit and time point where they are collected. Vital sign shift tables may be produced to summarize changes. The ECOG shift from baseline to highest score during the on-treatment period may be summarized.

6.9 Pharmacokinetic, Pharmacodynamic, and Immunological Parameter Endpoint Analyses

Pharmacokinetic Analysis: Summary statistics will be tabulated separately for serum PK parameters by MGC018 and MGA012 dose. Geometric means and percent coefficients of variation will be reported for maximum concentration (C_{max}), area under the curve from time 0 to time ($AUC_{(0-T)}$), AUC in a dosing interval ($AUC_{(TAU)}$), AUC from time 0 to infinity ($AUC_{(inf)}$), lowest concentration (C_{trough}) and accumulation index (AI); arithmetic means and standard deviations will be reported for apparent terminal half-life ($t_{1/2}$), clearance (CL), and volume of distribution at steady state (V_{ss}); and medians, minimum, and maximum will be reported for time to reach C_{max} (T_{max}). Separate scatter plots of C_{max} and AUC will be provided versus dose to assess dose dependency. Dose proportionality may be assessed using a power model.

Immunogenicity Analysis: The proportion of participants who are negative for anti-drug antibodies (ADAs) at baseline and become positive in this assay, the proportion of participants who are negative at baseline and remain negative, and those who have positive ADA at baseline that increases or decreases in titer over the course of treatment will be summarized. Analysis will be conducted separately for MGC018 and MGA012.

Pharmacodynamic Analysis: Summary statistics for pharmacodynamic parameters and corresponding changes from baseline will be summarized and/or may also be presented graphically. In addition, possible associations between changes in pharmacodynamic measures of interest and MGC018 monotherapy and in combination with MGA012 dose and exposure may be explored.

7 LIST OF TABLES, LISTINGS, AND FIGURES

The list of tables, listings, and figures (TLFs) and associated shells planned for the clinical study report based on the analyses described in this SAP will be provided in a separate statistical programming plan (SPP), which will also include data reporting conventions and programming specifications for the development of these TLFs.

8 REFERENCES

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