# CLINICAL STUDY PROTOCOL: CP-MGC018-01
# PROTOCOL AMENDMENT 6

| | |
|---|---|
| **Study Title:** | 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 |
| **Study Number:** | CP-MGC018-01 |
| **Study Phase:** | Phase 1/2 |
| **Product Number:** | MGC018, MGA012 |
| **IND Number:** | |
| **EudraCT Number:** | 2018-003555-38 |
| **Indication:** | Advanced Solid Tumors |
| **Coordinating Principal Investigator:** | TBD |
| **Sponsor:** | MacroGenics, Inc.<br>9704 Medical Center Drive<br>Rockville, MD 20850<br>301-251-5172 |
| **Sponsor's Medical Monitor:** | Refer to study contact list |

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**Study Number:** CP-MGC018-01

This clinical study protocol has been approved by the sponsor:

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

Executive Clinical Research Director
MacroGenics, Inc.

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

Senior Principal Biostatistician, Biostatistics
MacroGenics, Inc.

# RATIONALE FOR PROTOCOL AMENDMENT 6

# LIST OF ABBREVIATIONS

| | |
|---|---|
| ADA | anti-drug antibody |
| ADC(s) | antibody-drug conjugate(s) |
| AE | adverse event |
| AESI | adverse event of special interest |
| AI | accumulation index |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| AML | acute myeloid leukemia |
| ASCO | American Society of Clinical Oncology |
| AST | aspartate aminotransferase |
| AUC | area under the curve |
| $AUC_{(0\text{-}T)}$ | AUC from time 0 to time |
| $AUC_{(INF)}$ | AUC from time 0 to infinity |
| $AUC_{(TAU)}$ | AUC in a dosing interval |
| BOR | best overall response |
| BPI-sf | Brief Pain Inventory-Short Form |
| BW | body weight |
| $C_{max}$ | maximum concentration |
| $C_{trough}$ | lowest concentration |
| CAP | College of American Pathologists |
| CBC | complete blood count |
| CI | confidence interval |
| CL | clearance |
| COVID-19 | coronavirus disease 2019 |
| CR | complete response |
| CRF | case report form |
| CRP | C-reactive protein |
| CRS | cytokine release syndrome |
| CT | computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTFG | Clinical Trial Facilitation Group |
| CTL | cytotoxic T lymphocyte |

| | |
|---|---|
| CTLA-4 | cytotoxic T-lymphocyte–associated protein 4 |
| DCs | dendritic cells |
| DLT | dose-limiting toxicity |
| DoR | duration of response |
| DNA | deoxyribonucleic acid |
| eCRF | electronic case report form |
| ECG | electrocardiogram |
| EDC | electronic data capture |
| EOI | end of infusion |
| EOTV | end of treatment visit |
| FDA | Food and Drug Administration |
| FIH | first-in-human |
| G-CSF | granulocyte colony stimulating factor |
| GLP | Good Laboratory Practice |
| GM-CSF | granulocyte-macrophage colony stimulating factor |
| HER2 | human epidermal growth factor receptor 2 |
| HNSTD | highest non-severely toxic dose |
| HPV | human papillomavirus |
| hr | hour(s) |
| ICD | immunologic cell death |
| ICF | informed consent form |
| IEC | Independent Ethics Committee |
| IFNγ | interferon gamma |
| IL | interleukin |
| IHC | immunohistochemistry |
| irAEs | immune-related adverse events |
| IRB | Institutional Review Board |
| IRE | immediately reportable event |
| IP | intraperitoneal |
| IRR | infusion-related reaction |
| IV | intravenous(ly) |
| LAG-3 | lymphocyte-activation gene 3 |
| LTFU | lost to follow-up |
| LVEF | left ventricular ejection fraction |

| | |
|---|---|
| mAb | monoclonal antibody |
| MAD | maximum administered dose |
| mcg | microgram |
| mCRPC | metastatic castration-resistant prostate carcinoma |
| mL | milliliter |
| MRI | magnetic resonance imaging |
| MSI-H | microsatellite instability – high |
| MTD | maximum tolerated dose |
| MUGA | multigated acquisition (scan) |
| n | number |
| NA or N/A | not applicable |
| NE | not evaluable |
| nM | nanomolar |
| NSCLC | non-small cell lung cancer |
| ORR | objective response rate |
| OS | overall survival |
| PBS | phosphate buffered saline |
| PGWG2 | Prostate Cancer Working Group 2 |
| PD | progressive disease |
| PD-1 | programmed death–1 |
| PD-L1 | programmed death–ligand 1 |
| PET | positron emission tomography |
| PFS | progression-free survival |
| pg | picogram |
| Ph. Eur. | European Pharmacopoeia |
| PK | pharmacokinetic(s) |
| PPE | palmar-plantar erythrodysesthesia |
| PQC | product quality complaint |
| PR | partial response |
| PRO | patient-reported outcome |
| PSA | prostate-specific antigen |
| PT | preferred term; prothrombin time |
| PTT | partial thromboplastin time |
| QW | once weekly |

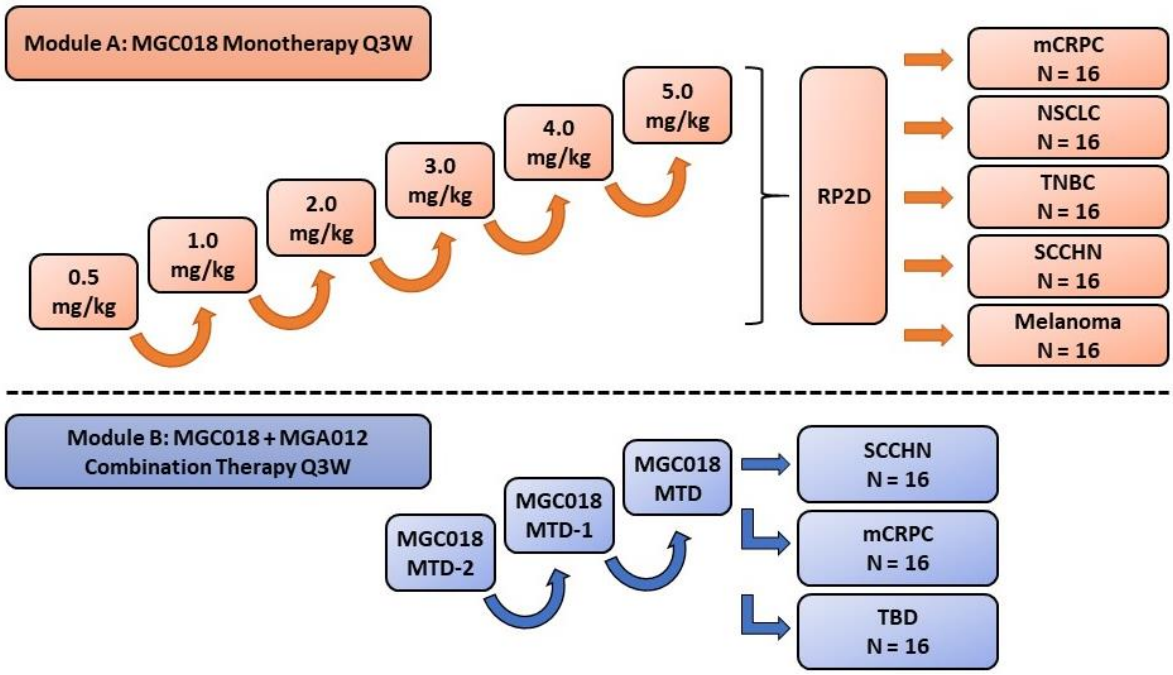
| | |
|---|---|
| Q2W | once every 2 weeks |
| Q3W | once every 3 weeks |
| Q4W | once every 4 weeks |
| Q6W | once every 6 weeks |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RP2D | recommended phase II dose |
| rPFS | radiographic progression-free survival |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SARS-CoV-2 | severe acute respiratory syndrome coronavirus 2 |
| SCCHN | squamous cell cancer of the head and neck |
| SEM | standard error of the mean |
| SD | stable disease |
| SJS | Stevens Johnson syndrome |
| SOC | system organ class |
| SPP | statistical programming plan |
| SSE | symptomatic skeletal event |
| TAB | total antibody |
| TBD | to be determined |
| TBSE | total body skin examination |
| TCR | T-cell receptor |
| TEAEs | treatment emergent adverse events |
| TEN | toxic epidermal necrolysis |
| TILs | tumor-infiltrating lymphocytes |
| TK | toxicokinetic |
| TNBC | triple negative breast cancer |
| TNFα | tumor necrosis factor alpha |
| ULN | upper limit of normal |
| US | United States |
| USP-NF | United States Pharmacopeia-National Formulary |
| v | version |

# 1 SYNOPSIS

| | |
|---|---|
| **Sponsor:** MacroGenics, Inc. | |
| **Name of Product:** MGC018 (Anti–B7-H3 Antibody Drug Conjugate) | |
| **Study Title:** 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 | |
| **Study Number:** CP-MGC018-01 | |
| **Study Phase:** Phase 1/2 | |
| **Investigator(s)/Centers:**<br>The study will be conducted at approximately 30 institutions globally. | |
| **Primary Objective(s):** 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. | |
| **Secondary Objective(s):**<br>• To characterize the pharmacokinetics (PK) and immunogenicity of MGC018 alone and in combination with MGA012.<br>• 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) (**Appendix 5**).<br>• To describe the radiographic progression free survival (rPFS) in metastatic castration-resistant prostate carcinoma (mCRPC).<br>• To describe the prostate-specific antigen (PSA) response rate and best PSA percent change in mCRPC. | |
| **Study Drug:**<br>• MGC018 is a humanized B7-H3 antibody drug conjugate (ADC). The duocarmycin-based linker/payload incorporated into MGC018 is licensed from Byondis (formerly known as Synthon Biopharmaceuticals).<br>• MGA012 (also known as INCMGA00012) is an anti–programmed death–1 (anti–PD-1) monoclonal antibody (mAb) protein produced in . | |
| **Study Design:**<br>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 below); Module B will commence upon sponsor notification 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.<br>Module B will commence only upon sponsor notification to all the study investigators/institutions. | |

Participants with relapsed or 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, NSCLC, TNBC, squamous cell cancer 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 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.

MGC018 will be administered alone or in combination with MGA012. 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. The first administration of MGC018 in participants in the first 2 dose levels in Module A will be staggered by at least 48 hours. 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. 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 the Dose Escalation Phase tumor assessments will occur at Day 42 of each cycle, for the first 4 cycles, and every other cycle thereafter. For the Module A Cohort Expansion Phase the tumor assessments will be 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 (see **Section 4.1.1** for more details). 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 or Module B Cohort Expansion Phases will be followed every 3 months (90 days) for survival during a 2-year Survival Follow-up Period. Participants in Module A Dose Escalation will be followed similarly for survival status until approval of Amendment 3, at which point they will be discontinued from follow up.

**Dose-Limiting Toxicities:**

For the purpose of guiding study decisions regarding dose escalation, DLTs will be defined based on drug-related adverse events (AEs) (or laboratory abnormalities) that occur up to Study Day 21 of Cycle 1 in the Dose Escalation Phase only for Module A, and Study Day 42 of Cycle 1 in the Dose Escalation Phase only for Module B. The severity of AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (NCI CTCAE v4.03). DLTs will be defined separately for hematologic, non-hematologic, and hepatic non-hematologic events.

**Number of Participants Enrolled:**

The maximum to be enrolled in this study will be approximately up to 182 participants. This number does not take into account participants who may be replaced or the possibility of expanding the mCRPC cohort with an additional 24 participants at the discretion of the sponsor.

The number of participants enrolled in the Dose Escalation Phase could range from 6 up to 54 participants depending on results during the course of the study and the number of dose levels explored. This participant number does not take into account participant replacement for non-evaluable participants or the possibility of expanding an individual dose escalation cohort up to 15 participants to allow for further evaluation of safety, PK, and antitumor activity of the study drugs at the dose level in that cohort.

The Cohort Expansion Phase of the study will enroll up to 128 participants.

- Module A Cohort Expansion Phase will include 5 cohorts of up to 16 participants each with mCRPC, NSCLC, TNBC, SCCHN, and melanoma.
- Module B Cohort Expansion Phase will include 3 cohorts of up to 16 participants each with SCCHN, mCRPC and a tumor type TBD at a later date, based on the experience during dose escalation.

During the Cohort Expansion Phase of the study, participants 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, additional participants may be enrolled. In addition, up to 4 participants may be added per cohort.

**Participant Population/Key Entry Criteria:**

The participant population to be enrolled in the Dose Escalation Phase of this study will consist of adult participants with relapsed or refractory, unresectable locally advanced or metastatic solid tumors of any histology. The Cohort Expansion Phase will include participants with mCRPC, NSCLC, TNBC, SCCHN, and melanoma (Module A), and unresectable, locally advanced or metastatic SCCHN, mCRPC, and a cohort TBD at a later date (Module B). Tumor specimens for determination of B7-H3 and PD-L1 expression via IHC staining will be collected on all participants during both Dose Escalation and Cohort Expansion and will be assayed at a central laboratory designated by the sponsor. Determination of B7-H3 and PD-L1 IHC testing results will not be required prior to protocol enrollment.

**Duration of Treatment and Study Duration:**

Treatment for all participants may continue for up to 18 cycles, with each cycle consisting of 6 weeks (42 days). For participants with a dose delay > 21 days, the total number of cycles may be < 18 cycles and the time on MGC018 will be no more than 2 years.

It is expected that enrollment of the Dose Escalation Phase of the study (including Module A and Module B) will occur over approximately 18 months, and that enrollment of the Cohort Expansion Phase of the study will

take approximately 12 months from the time of initiation of the Cohort Expansion Phase for each Module A and Module B.

The total time for conduct of the trial is expected to be approximately 78 months (which includes 2 years of survival follow-up). These estimates of the timing for study conduct may vary from that observed in the actual conduct of the trial.

**Criteria for Evaluation:**

Safety Assessments:

The safety assessment will be based on the evaluation of adverse events (AEs) that occur from the time of initiation of administration of study drug through 30 days following the last dose of study drug or until the start of a subsequent systemic anticancer therapy (whichever occurs first) and will be determined based on signs, symptoms, physical examination findings, and/or laboratory test results from enrolled participants as appropriate. Progression of the underlying tumor resulting in hospitalization or death (e.g., participant hospitalized for or dies from progressive disease [PD]) will be documented as a tumor response and not as a serious adverse event (SAE).

Response Assessments:

Tumor assessments will be obtained using computed tomography (CT) or positron emission tomography/CT (PET/CT) and/or magnetic resonance imaging (MRI) scans. For mCRPC participants a bone scan will be obtained in addition to CT and/or MRI scans at baseline and on study. Target and non-target lesions will be designated at screening and then evaluated at every 6 weeks (42 days) for the first four cycles, and every other cycle thereafter while the participant in Module A Dose Escalation and Module B is on study treatment. Target and non-target lesions will be designated at screening and then evaluated every 9 weeks (63 days) while the participant is on study treatment in Cohort Expansion Phase for Module A. For mCRPC a lymph node is to be ≥ 20 mm to be a target lesion. In situations where the bone scan findings are suggestive of a flare reaction or apparent new lesion(s) may represent trauma, additional imaging to confirm these results with other imaging modalities such as MRI or fine-cut CT should be obtained. At each tumor assessment time point, the overall response status will be determined based on assessment of target and non-target lesions as well as appearance of any new lesions. For RECIST v1.1 (**Appendix 5**), the overall responses will be categorized as complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), or not evaluable (NE).

Survival Assessments:

All participants in Module A or Module B Cohort Expansion Phases who have discontinued study treatment will be followed for survival status every 3 months (90 days) for a 2-year survival follow-up period following the last dose of MGC018 alone (Module A) or in combination with MGA012 (Module B), until criteria are met for study discontinuation. Participants in Module A Dose Escalation will be followed similarly for survival status until approval of Amendment 3, at which point they will be discontinued from follow up.

Pharmacokinetic Assessments:

Serum concentrations of conjugated antibody and total antibody following administration of MGC018 and serum concentrations of MGA012 will be monitored using quantitative bioanalytical methods. SYD986 levels will be measured from plasma using a liquid chromatography-tandem mass spectrometry assay. Single- and multiple-dose PK parameters will be derived from MGC018 and MGA012 serum concentrations and SYD986 plasma concentration versus time data.

Immunogenicity Assessments:

The anti-drug antibody (ADA) against MGC018 and the ADA against MGA012 will each be detected using validated bridging assay methods.

Pharmacodynamics/Biomarkers:

Tests to be performed for PD/biomarker assessments are indicated in **Section 10.3**.

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

Safety Population: All participants who received at least one dose of 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 progression-free survival (PFS), rPFS, and overall survival (OS).

Response Evaluable Population: All participants who received at least one dose of study drug, had baseline measurable or non-measurable disease, and had at least one post-baseline radiographic tumor assessment or discontinued from 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 PSA response rates.

**STATISTICAL METHODS:**

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

Sample Size: The study plans to enroll approximately up to 182 participants (107 in Module A and 75 in Module B). 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, and melanoma (up to 16 in each) will be enrolled to the Cohort Expansion Phase of Module A. 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 with MGC018 and MGA012 combination therapy. The Cohort Expansion Phase of Module B will enroll up to 16 participants in 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.

Safety: Treatment-emergent AEs will be summarized by system organ class (SOC) and preferred term (PT), by relationship to study drugs, and by highest severity. For laboratory tests, number and percent of participants shifted from baseline to post-baseline maximum severity in Common Terminology Criteria for Adverse Events (CTCAE) grade will be summarized.

Efficacy: Number and percent of participants with their best overall response (BOR) will be summarized. Objective response rate will be calculated as the proportion of participants in the response evaluable population achieving a best response of CR or PR. The response rates will be determined using RECIST v1.1. PSA response rate (a ≥ 50% decline from baseline in PSA with confirmation at least 3 weeks later) will be summarized. The best PSA percent change from baseline will be presented by waterfall plot. Two-sided 95% exact binomial confidence intervals (CIs) will be calculated around the response rates. Kaplan-Meier methods will be used to estimate the time-to-event endpoints.

# 2 BACKGROUND INFORMATION

## 2.1 Rationale for Study

Antibody-drug conjugates (ADCs) have emerged as a powerful class of therapeutic agents for the targeted treatment of cancer. ADCs combine the tumor target specificity of a monoclonal antibody (mAb) with highly potent cytotoxic "payloads" for the selective delivery of cytotoxic agents to cancer cells. The targeted delivery of cytotoxic agents to cancer cells offers the potential for increased efficacy, while at the same time minimizing exposure to normal tissues, thereby expanding the therapeutic window.

Immune-checkpoint blockade has emerged as a promising approach for the treatment of patients with various solid tumors or hematologic malignancies. Inhibitors of programmed death–1 (PD-1), programmed death–ligand 1 (PD-L1), and cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) are currently approved for use in patients with advanced stage melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), squamous cell carcinoma of head and neck (SCCHN), urothelial cancer, Hodgkin's lymphoma, and microsatellite instability – high (MSI-H) or mismatch repair (MMR) deficient solid tumors. However, there is a significant proportion of patients that do not derive clinical benefit from these agents. Combination immunotherapies may enhance the ability to prevent immune escape by targeting multiple mechanisms of resistance of tumor cells to the immune system (**45**). Data from clinical studies suggest a relationship between patient response and intratumoral level of CD8+ T-cells prior to treatment (**66**, **69**). Further, an increased number of CD3+ T-cells as well as an increased ratio of cytotoxic CD8+ T-cells (CTLs) over FOXP3+ regulatory T-cells (Tregs) within tumors following chemotherapy treatment was predictive of therapeutic responses in breast and colorectal cancer patients treated with anthracyclines and oxaliplatin, respectively (**20**, **29**, **75**). In addition to direct activation and maturation of dendritic cells (DCs) (**47**), cytotoxic agents may induce antitumor immunity by inducing immunologic cell death (ICD). ICD is characterized by endoplasmic reticulum stress leading to cell surface expression of calreticulin, followed by release of the soluble mediators high mobility group box 1 protein and adenosine triphosphate, and type I interferon (**26**). Both activation and maturation of DCs and induction of ICD trigger an immune response toward tumors via engagement of the adaptive immune response through cross-presentation of tumor derived antigens and priming of specific CD8+ effector T-cells. Importantly, several recent reports indicate that several classes of ADC payloads with varied mechanisms of action, including tubulin agents and DNA disrupting agents, can induce ICD and elicit antitumor immunity. Increases in tumor-infiltrating lymphocytes (TILs), particularly T cells, were observed within tumors in a preclinical orthotopic breast cancer model following treatment with ado-trastuzumab emtansine. Treatment with the combination of ado-trastuzumab emtansine and CTLA-4– and PD-1–blocking antibodies in this model resulted in strong antitumor efficacy and protection from tumor rechallenge, indicating a strong, T cell–directed, immunological memory response in the treated mice. Consistent with these observations, ado-trastuzumab emtansine treatment of patients with HER2-positive/estrogen receptor (ER)-positive breast cancer has been shown to elicit intratumoral recruitment of TILs (**48**). Similarly, ADCs carrying the tubulin disrupting agent tubulysin or the DNA disrupting agent pyrrolobenzodiazepine dimer (PBD) payload have been shown to induce ICD, immunologic

modulation and memory, and synergistic antitumor efficacy when combined with several different checkpoint inhibitors in mouse models (**57**). Additionally, CD30-targeted lymphoma therapy with brentuximab vedotin has been shown to induce activation of patient DCs, T cells, and B cells, leading to sustained clinical responses and tumor-specific immunity in an allogenic setting (**67**). Taken together, these observations and the complementary mechanisms of action of these agents, provides strong rationale for combining ADCs with immune checkpoint blockade, and is currently being investigated clinically for a number of ADCs. It is hypothesized that in combination, MGC018 (anti–B7-H3 ADC) and MGA012 (anti-PD-1 antibody [also known as INCMGA00012]), could mediate antitumor activity that is greater than that achieved with either single agent alone.

MGC018, also known as AEX4089DC1, is an ADC targeted against B7-H3 (see **Section 2.3**). MGC018 is comprised of the cleavable linker-duocarmycin payload, valine-citrulline-*seco*-Duocarmycin hydroxyBenzamide-Azaindole (vc-*seco*-DUBA; SYD980) (**21**, **23**), conjugated through reduced interchain disulfides, to the anti–B7-H3 humanized immunoglobulin G 1 (IgG1) kappa mAb MGA017. MGA017, which is based on the mouse mAb PRCA157, is cross-reactive with human and cynomolgus monkey B7-H3.

MGC018 has an average drug-to-antibody ratio (DAR) of ~ 2.7, and an average molecular weight of ~ 150 kDa. MGC018 is designed to bind to cell-surface B7-H3, internalize into cells, and release the cytotoxic duocarmycin drug. Following binding to cell-surface B7-H3 and internalization of MGC018 through endocytosis, the peptide linker is cleaved by lysosomal proteases, such as cathepsin B. Subsequently, 2 self-elimination reactions occur on the duocarmycin moiety to generate *seco*-DUBA (SYD978), which then spontaneously rearranges to form the activated duocarmycin drug (also known as DUBA or SYD986), which can then bind and alkylate DNA (**Figure 1**). The irreversible alkylation of DNA disrupts the nucleic acid architecture, ultimately leading to cell death. Due to the nature of the “cleavable” linker/payload, the protease-cleaved, activated DUBA is membrane permeable and, when released by dying cells, can cause bystander killing of neighboring tumor cells, irrespective of B7-H3 expression (**70**) (**Figure 2**). Importantly, the bystander killing property of the vc-*seco*-DUBA linker/payload may afford MGC018 therapeutic benefit toward heterogeneous B7-H3–expressing tumors.

**Figure 1** **Schematic Representation of MGC018 and Mechanism of Release of Prodrug from MGC018 and Conversion to the Active Duocarmycin Drug DUBA**

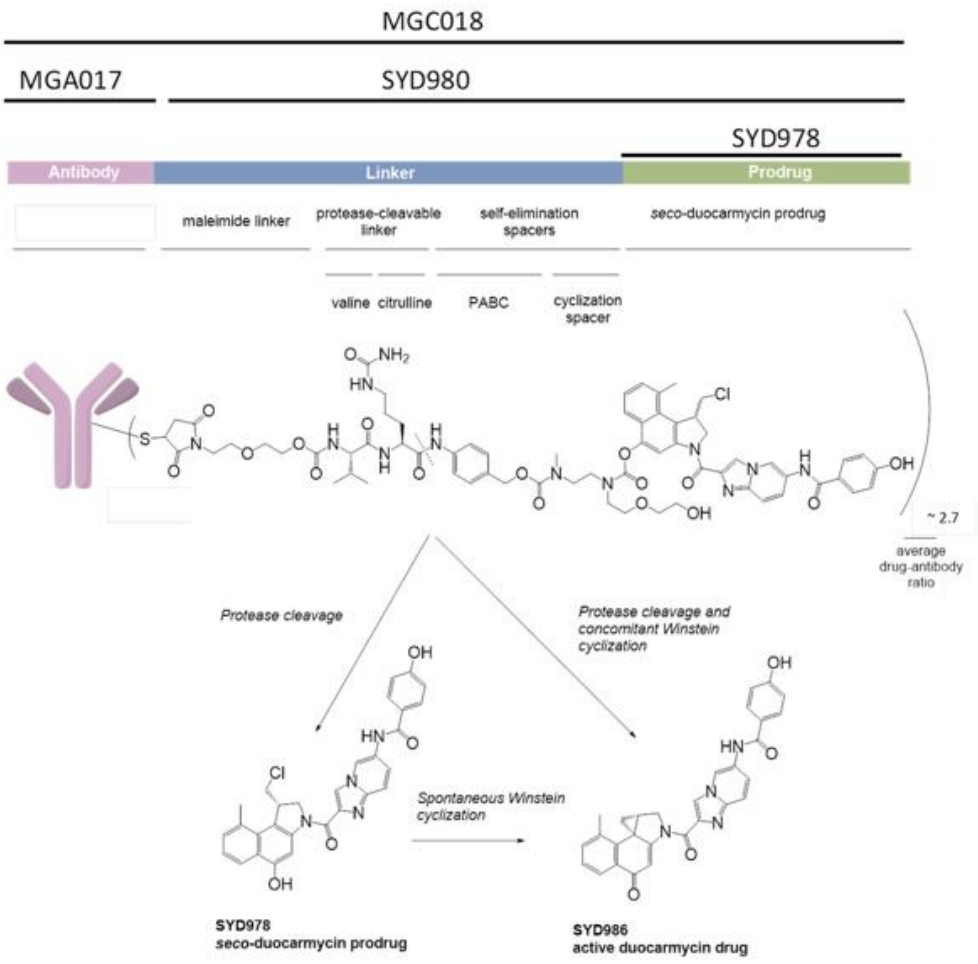
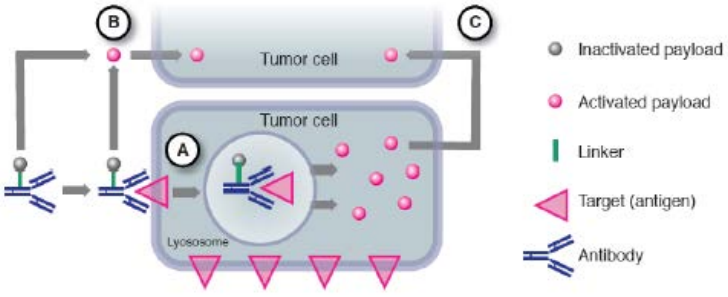



**Figure 2** **MGC018 Mode of Action**



MGC018 binds to its target antigen with a binding affinity of 22.7 nM. In support of the cynomolgus monkey as a relevant species for nonclinical toxicology evaluation, MGC018 exhibited equivalent binding affinity (22.1 nM) toward B7-H3 of this species as that observed for human B7-H3.

In vitro studies on cell lines and xenograft studies in CD-1 Nude (homozygous) mice have characterized the biological activity of MGC018. Consistent with its binding properties, MGC018 exhibited potent cytotoxic activity toward human tumor cell lines expressing a range of B7-H3 levels, and the cytotoxic activity of MGC018 was dependent on B7-H3 expression. In vivo efficacy studies with MGC018 established dose response profiles following single- and repeat-dose administration and identified cancer types that exhibit sensitivity to MGC018, which may serve as therapeutic indications for clinical studies. In single-dose experiments, MGC018 exhibited antitumor activity toward human tumor xenografts representing breast, lung, and ovarian cancer, as well as melanoma. Antitumor activity (reduction in percentage of mean tumor size in the treatment group relative to mean tumor size of the vehicle control group [% T/C] and number of complete responses) was generally observed at the lowest dose levels tested (1 or 3 mg/kg), depending on the study. Repeat-dose administration of MGC018 led to greater antitumor activity in ovarian, breast, and lung cancer xenograft studies compared to a single dose administration. Dose-dependent antitumor activity was observed in all 3 models, with a minimal efficacious dose established at 1.0 mg/kg for Calu-6 lung cancer and 0.3 mg/kg for PA-1 ovarian cancer and MDA-MB-468 breast cancer.

A Good Laboratory Practice (GLP) tissue cross-reactivity study of human tissues with MGC018 revealed that plasma membrane and cytoplasmic reactivity was observed in mononuclear cells in lymphoid tissues, including reticulo-endothelium in the spleen, heart, and stomach, as well as the membrane and cytoplasm of the following epithelial cell types: liver hepatocytes, the epidermis and hair follicle epithelium in the skin, and extravillous trophoblasts and amniotic epithelium in the human placenta. The reactivity was generally weak, or weak to moderate in intensity, and rare to occasional in frequency. All other reactivity was cytoplasmic in nature.

MGC018 administered as a 1-hour intravenous (IV) infusion once every 3 weeks (Q3W) (total of 3 doses) was tolerated in cynomolgus monkeys up to 10 mg/kg/dose, the highest dose tested in the GLP toxicology study. As there were no MGC018-related life-threatening toxicities, irreversible findings, or mortality, the highest non-severely toxic dose (HNSTD) for this study was determined to be 10 mg/kg/dose.

MGC018 demonstrated favorable binding properties, potent cytotoxic activity toward multiple B7-H3–expressing human tumor cells in vitro, and antitumor activity in B7-H3 human tumor xenografts representing breast cancer, ovarian cancer, lung cancer and melanoma in vivo. Further, MGC018 exhibited a favorable tissue cross-reactivity profile across a panel of 34 normal human tissues and an acceptable safety profile following repeat-dose administration in cynomolgus monkeys. The data from the nonclinical pharmacology studies provide strong scientific rationale for the evaluation of MGC018 as a therapeutic candidate for the treatment of B7-H3–expressing malignancies.

## 2.2 Disease Background

### 2.2.1 SCCHN

Head and neck cancer accounts for about 3% of malignancies in the United States (US). Approximately 62,000 patients are diagnosed annually in the US and approximately 13,000 deaths occur annually secondary to SCCHN (**60**). Globally, over 500,000 patients are diagnosed with this disease annually (**34**). 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 (**13**, **27**). In the US, the incidence of oropharyngeal cancers caused by HPV infection is increasing, whereas the incidence of oropharyngeal cancers related to other causes is falling (**13**).

Treatment for patients with locally advanced SCCHN remains unsatisfactory. Less than 40% of patients are cured with primary treatment with combination of radiation therapy and cisplatin-based chemotherapy. Survival is less than 20% at 2 years in patients with recurrent disease following treatment with radiochemotherapy. The combination of cetuximab, a blocking antibody for epidermal growth factor receptor (EGFR), with radiotherapy showed significant improvement in outcomes for patients with locally advanced disease when compared with radiotherapy alone. However, it failed to change the rate of distant metastasis. The combination of cetuximab with radiochemotherapy failed to improve progression-free survival (PFS) and overall survival (OS) in patients with advanced stage disease (**5**). In addition, there is evidence to suggest the role of immune checkpoints that limit T cell responses to tumors in SCCHN. Pembrolizumab has been recently approved for treatment of patients with recurrent or metastatic SCCHN with disease progression on or after platinum-containing chemotherapy, irrespective of the HPV status. The objective response rate (ORR) following pembrolizumab in this population is about 16%, with a CR rate of 5% (**4**, **16**). There is no significant difference in response rate based on HPV status of the tumor. Although this is an improvement over prior standard therapy, there is a need to identify new therapeutic options for patients with SCCHN.

B7-H3 is expressed on a high percentage of SCCHN tumors (**36**, **51**). In addition, 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 (**36**).

Collectively, these observations provide a supportive rationale for targeting B7-H3 with MGC018 in patients with SCCHN and for the exploration of combined administration of MGC018 with anti–PD-1 antibody (MGA012) in this population. Participants with SCCHN who have relapsed or who have refractory disease following treatment with platinum-based therapy will be enrolled in this study to assess the preliminary clinical activity of MGC018 alone or in combination with MGA012.

### 2.2.2 Prostate Cancer

Prostate cancer is the most commonly diagnosed cancer in men and is the second-leading cause of cancer-related deaths. In the US, it is estimated that 160,360 men in 2017 will be diagnosed with prostate cancer, and 26,730 deaths will occur secondary to prostate cancer (**61**). Although hormone therapy is associated with significant responses in metastatic and advanced disease, virtually all patients develop hormone-refractory disease and may receive docetaxel for metastatic castration-resistant prostate carcinoma (mCRPC). Newer androgen receptor therapies such as abiraterone have shown improved PFS over docetaxel in mCRPC; however, the need for novel treatments in this setting remains. Cross-resistance between taxanes and new hormonal agents abiraterone and enzalutamide, may affect drug sequence choices in mCRPC (**71**).

Based on a Phase 1 study (NCT01391143) of the Fc engineered anti–B7-H3 mAb enoblituzumab, 89% (88/99) of prostate cancer patients screened were B7-H3 positive. Thus, a very high proportion of patients with prostate cancer may be anticipated to have B7-H3-positive tumors, supporting targeting this disease with MGC018. Initial indications of clinical activity were noted in the Phase 1 trial of enoblituzumab in participants with prostate cancer, including one participant with a 23% tumor reduction per Response Evaluation Criteria in Solid Tumors (RECIST) and a 46% prostate-specific antigen (PSA) decrease following progression on sipuleucel-T, abiraterone, enzalutamide, radium 223, and Taxotere® and one patient post-radiotherapy with a 58% tumor reduction per RECIST and a 51% decrease in PSA (MacroGenics unpublished data).

PD-1 inhibitors have not shown significant activity as monotherapy in patients with metastatic prostate cancer. However, more recently, pembrolizumab given in combination with enzalutamide in a Phase 2 study showed evidence of clinical benefit in castration resistant prostate cancer (**28**). High expression of B7-H3 makes prostate cancer a good candidate for evaluation of MGC018. It is also hypothesized that cytoreduction mediated by administration of MGC018 could also serve to potentiate the immune stimulatory activity of MGA012. The combination of MGC018 and MGA012 could be synergistic and mediate greater antitumor activity than either single agent alone for patients with mCRPC.

### 2.2.3 Non-small Cell Lung Cancer

Lung cancer is the most commonly diagnosed cancer worldwide (**7**). In 2018, an estimated 2.1 million new cases of lung cancer were diagnosed globally, accounting for approximately 11.6% of the global cancer burden. An estimated 1.76 million lung cancer deaths occurred in 2018. In 2020, an estimated 228,820 adults (116,300 men and 112,520 women) in the US will be diagnosed with lung cancer (**62**). An IHC screen performed by MacroGenics, Inc. of NSCLC specimens revealed that 144 of 156 total specimens (100%) exhibited B7-H3 expression at any level, while 124 of 86 (70%) had H-scores > 100 (i.e., moderate or strong expression).

In the first-line treatment setting, due to the introduction of new drugs and patient selection based on histological subtypes and driver mutations that influence the biology of these

malignancies, median overall survival (OS) for patients with advanced NSCLC receiving platinum-based chemotherapy in combination with agents targeting specific histologies and mutations has improved to 12 months or longer in controlled studies (**56**). However, despite availability of multiple treatment options in the second-line setting, clinical outcomes remain poor. Response rates are, on average, less than 10%, and median OS is 7–9 months from start of second-line therapy (**80**).

In a meta-analysis, B7-H3 was significantly associated with lymph node metastasis, and advanced TNM stage in NSCLC (**77**). High levels of B7-H3 protein have a negative prognostic impact in lung carcinomas (**2**). These observations provide rationale for targeting B7-H3 with MGC018 in patients with NSCLC.

### 2.2.4 Triple Negative Breast Cancer

About 12% of breast cancers known as TNBC are negative for estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2. TNBC is associated with a poorer prognosis than other types of breast cancer (**63**). An IHC screen of TNBC specimens performed at MacroGenics, Inc., revealed that 12 of 17 (71%) exhibited B7-H3 expression at any level, while 8/17 (47%) exhibited ≥ 2+ B7-H3 expression.

Breast cancer demonstrates several characteristics that suggest that this tumor may elicit an immune response. These include the presence of infiltrating immune cells and lymphocytes within the tumor microenvironment; the prognostic value of an immunity-related gene signature; and genetic instability leading to increased number of mutations, translated into more neoantigens. The characteristics are more pronounced in TNBC and human epidermal growth factor receptor 2 HER2-positive tumors. These 2 are considered the most immunogenic subtypes of breast cancer (**17**).

TNBC has been divided into 6 molecular subtypes, including an immunomodulatory subtype characterized by an immune gene expression pattern, high number of immune cells infiltrating the tumor stroma, higher PD-L1 expression, and high mutation rate. These features make TNBC patients good candidates for immunotherapy (**24**, **38**).

Studies on TILs derived from tumor tissue from patients with TNBC have shown expression of lymphocyte-activation gene3 (LAG-3) and PD-1. In a study of 259 TNBC tumor samples, PD-1 and LAG-3 were expressed in TILs of 30% and 18%, respectively. Co-expression of PD-1 and LAG-3 was seen in 15% of tumors (**6**). Increased stromal TILs have been associated with increased relapse free survival and increased OS in patients with TNBC.

Some recent studies of immunotherapy agents have shown activity in TNBC. The ADC IMMU-132, which binds to the protein Trop2 and delivers SN-38, the active metabolite of irinotecan, to the tumor is in clinical trials for TNBC. A Phase 1/2 trial enrolled 60 participants with TNBC, with a 33% ORR and PFS of 5.6 months (**33**). Vantictumab (anti-Fzd7 mAb), in combination with paclitaxel, produced partial responses in 6 of 15 (40%) patients with TNBC (**1**). Antitumor activity has also been seen in early clinical trials with PD-1/PD-L1 inhibitors in TNBC (**30**), which further supports MGC018 and MGA012 combination therapy.

In the Cohort Expansion Phase of this study, the antitumor activity of MGC018 will be evaluated in a cohort of participants with TNBC, who have progressed after at least one systemic therapy for locally advanced unresectable or metastatic disease.

### 2.2.5 Melanoma

In 2018, an estimated 287,723 new cases of melanoma of the skin were diagnosed globally, with 60,712 deaths due to the disease (**7**). In the US, estimates for 2020 were 100,350 new cases and 6,850 deaths attributable to melanoma of the skin (**62**). 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. Despite 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 PFS for patients with advanced melanoma on pembrolizumab was approximately 5.5 months (median OS not reached at 12 months), and with ipilimumab treatment, the median OS and median PFS are approximately 10 months and 2.9 months, respectively (**31**) (see Keytruda® US prescribing information). Thus, although current treatment options such as pembrolizumab or ipilimumab monotherapy provide a survival benefit in advanced disease, there remains a medical need for continued improved treatment in advanced cases.

In addition to the above, a high percentage of melanoma tumors demonstrate membranous surface expression of B7-H3, whereas nevi have either no or low levels of membranous expression (**68**, **74**). In addition, B7-H3 expression levels on melanoma are 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 (**68**, **74**).

## 2.3 Background on B7-H3 and PD-L1

### 2.3.1 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 (**18**).

B7-H3, also referred to as CD276, is a novel member of the B7 family. B7-H3 is a type-1 transmembrane glycoprotein containing extracellular immunoglobulin-like domains. Although B7-H3 mRNA is widely distributed, B7-H3 protein expression in normal human tissues is limited, presumably due to the negative regulation of B7-H3 protein expression by the microRNA miR-29 (**78**). B7-H3 protein, however, is overexpressed in a variety of solid tumors, due in part to the downregulation of miR-29 in tumor tissues (**78**). B7-H3 has been implicated in the delivery of both co-stimulatory and co-inhibitory signals (**32**). 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 (**64**). 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, because of its overexpression in many malignant tumors and limited expression in normal tissues. A large number of solid tumor types have been reported to overexpress B7-H3, including, but not limited to, prostate cancer (**14**, **40**, **59**, **79**); melanoma (**40**, **54**, **73**); renal cell carcinoma (**19**, **40**, **53**), where B7-H3 is broadly expressed in tumor epithelium and tumor-associated vasculature; breast cancer (**39**, **40**, **42**); non-small cell lung cancer (NSCLC) (**35**, **40**, **43**, **65**); and oral squamous carcinoma (**15**). In the majority of cancers, overexpression of B7-H3 has been correlated with multiple adverse clinical and pathological features of disease, increased risk of recurrence, and reduced survival. A more extensive survey of published literature reporting B7-H3 expression in cancer, and correlation with clinical features and outcome is presented in the **MGC018 Investigator Brochure**.

### 2.3.1.1 MGC018 Nonclinical Experience

#### 2.3.1.1.1 MGC018 Pharmacology

The nonclinical pharmacology program for MGC018 was designed to characterize the binding affinity and biological activity of MGC018 in vitro and in vivo and is briefly summarized below. Further information can be obtained from the **MGC018 Investigator Brochure**.

The binding of MGC018 to its target antigen was characterized by surface plasmon resonance analysis using recombinant soluble B7-H3 (4Ig). MGC018 preserves the antigen-binding properties exhibited by the non-conjugated precursor molecule (MGA017) and exhibits a binding affinity of 22.7 nM toward human B7-H3. In support of the cynomolgus monkey as a relevant species for nonclinical toxicology evaluation, MGC018 exhibited equivalent binding affinity (22.1 nM) toward B7-H3 of this species as that observed for human B7-H3. MGC018 binding on various human B7-H3 cancer cell lines was confirmed and measured by quantitative flow cytometry.

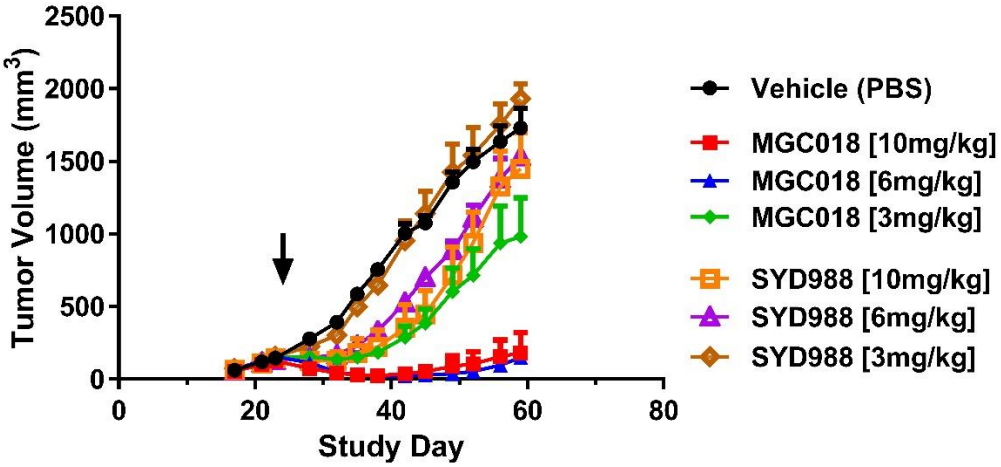
Consistent with its binding properties and designed mechanism of action, MGC018 exhibited potent cytotoxicity toward human B7-H3–expressing cancer cell lines in vitro. MGC018 exhibited potent cytotoxic activity toward human tumor cell lines expressing a range of B7-H3 levels, with half maximal inhibitory concentration values ranging from 181 to 1447 pM. The cytotoxic activity of MGC018 was dependent on B7-H3 expression, as cells with undetectable cell surface B7-H3 expression (Raji B cell lymphoma) remained insensitive to MGC018; moreover, tumor cell lines knocked out for B7-H3 (Hs700T/B7-H3 KO) were also insensitive to MGC018.

The antitumor activity of MGC018 was demonstrated in a series of in vivo pharmacology studies that evaluated the efficacy of MGC018 toward human tumor xenografts following single and repeat-dose administration. Human tumor cell line xenografts representing breast cancer (MDA-MB-468), lung cancer (Calu-6), ovarian cancer (PA-1), and melanoma (A375.S2) were tested in CD-1 Nude (homozygous) mice. MDA-MB-468 tumor cells were

implanted orthotopically in the mammary fat pad, whereas Calu-6, PA-1 and A375.S2 tumor cells were implanted subcutaneously. It is important to note that MGC018 exhibits poor stability in mouse serum and rapid clearance in mice following IV and intraperitoneal (IP) dose administration, due to the sensitivity of the vc-*seco*-DUBA linker payload moiety to the rodent-specific carboxylesterase (CES1c) which is not expressed by primates (**21**, **23**). The rapid clearance of MGC018 in mice may under-predict the anti-tumor activity of MGC018, making reliable extrapolations from exposure-response analyses difficult. Additionally, SYD988, a nontargeting anti-CD20 control ADC, which contains the same vc-seco-DUBA linker-payload as MGC018 and is similarly susceptible to CES1c cleavage and the release of free payload, may exhibit a background level of non-specific antitumor activity in some tumor xenograft models.

In single-dose experiments, MGC018 exhibited antitumor activity toward human tumor xenografts representing breast, lung, and ovarian cancer, as well as melanoma. Antitumor activity (reduction in percent mean tumor size in treatment group relative to mean tumor size of vehicle control group [% T/C] and number of complete responses) was observed at all dose levels and generally observed at the lowest dose levels tested (1 or 3 mg/kg depending on the study). **Figure 3** shows the results of a study with PA-1 ovarian cancer tumor xenografts treated with a single dose administration of MGC018. Antitumor activity was observed at all 3 dose levels of MGC018. A reduction in tumor volume of 89%, 91%, and 43%, with 3/6, 2/6, and 1/6 complete responses, respectively, was observed following treatment with MGC018 at 10, 6, and 3 mg/kg, respectively, on Day 59. The nontargeting SYD988 control ADC, which contains the same vc-*seco*-DUBA linker-payload as MGC018, exhibited minimal antitumor activity, with reductions in tumor volume of 16% and 11% following treatment at 10 and 6 mg/kg, respectively; a slight increase in tumor volume (12% increase) at 3 mg/kg; and no complete responses.

**Figure 3** **Antitumor Activity of MGC018 in CD1 Nude (Homozygous) Mice Bearing PA-1 Ovarian Cancer Xenografts: Single-Dose Administration**

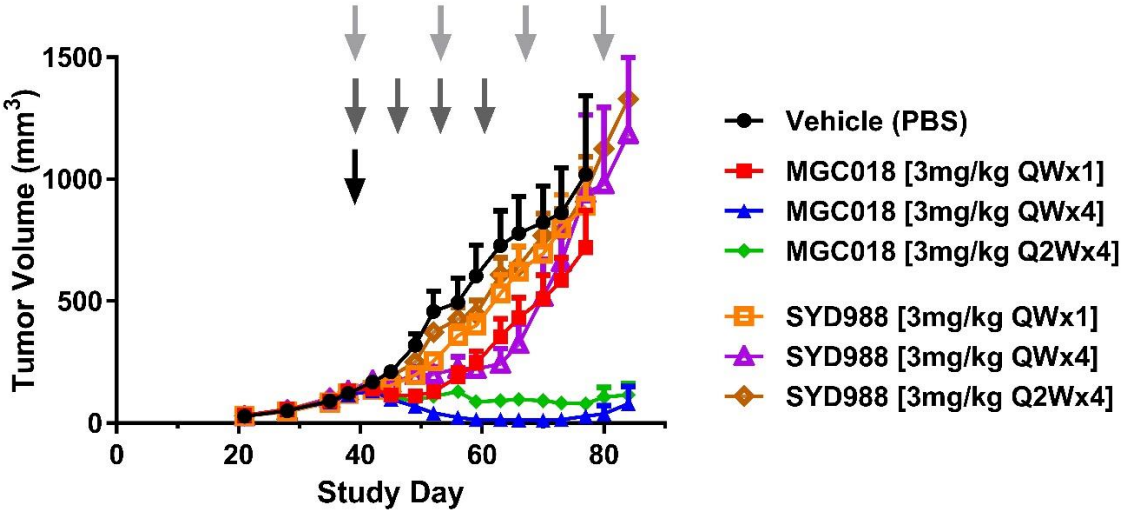



**Female CD1 Nude (homozygous) mice (n = 6/group) were implanted subcutaneously with PA-1 tumor cells ($5 \times 10^6$ cells). When tumors reached ~ 150 $mm^3$, mice were randomized and treated intraperitoneally with vehicle control (PBS), nontargeting control ADC (SYD988), and targeting ADC (MGC018) on Day 24 (arrow) at the dose levels indicated for a total of one dose. Tumor volume is shown as group mean ± SEM.**

**Abbreviations: PBS = phosphate buffered saline; SEM = standard error of the mean.**

The vast majority of ADCs are administered via a repeat-dose regimen in the clinical setting, with intervals ranging from once weekly (QW) to once every 6 weeks (Q6W). To evaluate the antitumor activity following repeat-dose administration, a study was performed in PA-1 ovarian cancer tumor xenografts comparing single-dose (QWx1) to once weekly, 4 times (QWx4) and once every 2 weeks, 4 times (Q2Wx4) administration. As shown in **Figure 4**, repeat-dose administration of MGC018 led to a much greater antitumor response than administration of a single dose. A single dose of 3 mg/kg MGC018 achieved short-term tumor stasis of approximately 10 days, followed by tumor regrowth, with a reduction in tumor volume of 29% on Day 77. Repeat-dose administration of 3 mg/kg MGC018 led to a decrease in tumor volume, resulting in a 97% and 92% reduction in tumor volume with 4/6 and 2/6 complete responses for QWx4 and Q2Wx4 treatment, respectively. SYD988 at 3 mg/kg exhibited minimal antitumor activity, with reductions in tumor volume of 13%, 8% and 7% for single, QWx4 and Q2Wx4 administration, respectively; only 1 animal treated with SYD988 (QWx4 group) showed a complete response.

**Figure 4** **Antitumor Activity of MGC018 in CD1 Nude (Homozygous) Mice Bearing PA-1 Ovarian Cancer Xenografts: Single- vs. Repeat-Dose Administration**




**Female CD1 Nude (homozygous) mice (n = 6/group) were implanted subcutaneously with PA-1 ovarian cancer tumor cells ($5 \times 10^6$ cells). When tumors reached ~ 150 $mm^3$, mice were randomized and treated intravenously with vehicle control (PBS), nontargeting control ADC (SYD988), and targeting ADC (MGC018) for a single-dose administration (QWx1) on Day 39 (black arrow); repeat-dose administration once weekly x 4 doses (QWx4) on Days 39, 46, 53, and 60 (dark gray arrows); or repeat-dose administration once every 2 weeks x 4 doses (Q2Wx4) on Days 39, 53, 67, and 81 (light gray arrows) at the dose level indicated for a total of 4 doses. Tumor volume is shown as group mean ± SEM.**

**Abbreviation: SEM, standard error of the mean.**

Additional repeat-dose administration in vivo efficacy studies with MGC018 in mice bearing breast cancer, ovarian cancer, and NSCLC are presented in the **MGC018 Investigator Brochure**.

### 2.3.1.1.2 MGC018 Pharmacokinetics and Toxicology

A summary of nonclinical pharmacokinetic (PK) and toxicology data with MGC018 are provided below; please reference the **MGC018 Investigator Brochure** for a more detailed description.

The nonclinical toxicology program for MGC018 was performed exclusively in the cynomolgus monkey as MGC018 does not bind to B7-H3 in mouse or rat. The cynomolgus monkey was selected as the most appropriate animal model for nonclinical safety evaluation of MGC018 given the homology of cynomolgus monkey and human B7-H3, the ability of MGC018 to bind with nearly identical affinity to human and cynomolgus monkey B7-H3, and the concordance of staining pattern for MGC018 toward panels of normal human and cynomolgus monkey tissues.

A GLP tissue cross-reactivity study, performed on a panel of normal human tissues, demonstrated that MGC018 staining the membrane and cytoplasm of mononuclear cells found in human lymphoid tissues (spleen, thymus, and tonsil), as well as rare or very rare cases of stomach or heart, respectively. Membrane and cytoplasm staining was observed in a few epithelial cell types: hepatocyte epithelium in liver (2 of 3 samples with weak intensity and occasional staining at the higher of 2 validated MGC018-biotinylated (MGC018-Bio) antibody concentrations); the epidermis and hair follicle epithelium in skin (2 of 3 samples with weak to moderate intensity and rare to occasional staining at both the high and low MGC018-Bio antibody concentrations); and extravillous trophoblasts and amniotic epithelium in the placenta. All staining in this study represented expected reactivity, and no unanticipated cross-reactivity of MGC018 was observed (**41**, **52**, **55**, **59**, **64**, **81**, **82**).

In the repeat-dose GLP toxicology study, MGC018 was administered at dose levels of 0 (vehicle control), 1, 3, 6, and 10 mg/kg/dose to cynomolgus monkeys (n = 5/sex/group) and was tolerated as 1-hour IV infusions on a Q3W schedule for a total of 3 doses. Other MGC018 studies included single-dose studies up to 27 mg/kg and an exploratory repeat-dose toxicology study with MGC018 dosed every 2 weeks (Q2W) at 6 or 20 mg/kg. There were no MGC018-related observations in animals evaluated at these dose levels for the following parameters: food consumption, ophthalmology, electrocardiograms (ECGs), body temperature, blood pressure, heart rate, respiration rate, or functional observation battery (FOB) examinations and assessment for autonomic, sensorimotor, reflexive motor, or physiological functions.

The 3 components of MGC018 (i.e., conjugated antibody, total antibody, or unconjugated SYD986) were examined in the toxicity GLP study. The maximum serum concentration ($C_{max}$) for conjugated and total antibody increased proportionally with increasing MGC018 dose level. Exposure of the conjugated and total antibody at MGC018 doses ranging from 1 to 6 mg/kg increased more than proportionally with dose level and the clearance (CL) decreased with increasing dose levels of MGC018. However, at MGC018 doses > 6 mg/kg, exposure of conjugated or total antibody increased proportionally with dose level and the CL was essentially unchanged.

Animals from the individual dose groups achieved comparable exposure of conjugated or total antibody during the first dose interval. However, exposure decreased in a few animals during the second dose interval and in most of the animals during the third dose interval due to ADA. There was no accumulation of ADC or total antibody after 3 MGC018 doses administered Q3W (observed accumulation ratio < 1). The $C_{max}$ of unconjugated SYD986 also increased proportionally with increasing dose level and was 2070- to 8862-fold lower than that of the SYD986 conjugated to MGC018 for the 1 to 10 mg/kg dose groups. Unconjugated SYD986 had an accumulation ratio of 1.37 to 1.96 for the 3, 6, and 10 mg/kg dose groups, which could be expected when SYD986 is released from MGC018 in serum, plasma, or blood.

MGC018-related clinical signs were predominantly dose dependent and included skin findings (hyperpigmentation, dry skin, erythema), occasional inappetence, soft/watery feces, thin body condition in single females at 6 and 10 mg/kg/dose, and sparse hair noted in a subset of animals particularly at ≥ 6 mg/kg/dose. Slight changes in body weight gain were noted but not considered adverse.

MGC018-related changes in hematology parameters were noted in neutrophil and lymphocyte counts, red blood cell parameters, and reticulocyte counts, all of which were not considered adverse as changes were within the historical control range for these parameters in cynomolgus monkeys. A trend toward transient but repeated decreases in neutrophil counts, relative to predose levels, was observed in 2 males at 6 mg/kg/dose and the majority of the males at 10 mg/kg/dose on Days 36, 48, or 53. Minimal to mild transient decreases in lymphocyte counts were observed in both sexes at 10 mg/kg/dose (up to -49%) relative to Day 1 predose mean values. These changes resolved prior to or during the recovery period and without microscopic correlates.

Minimal to mild decreases in red cell mass (erythrocyte count, hemoglobin concentration, and/or hematocrit) relative to predose values started on Day 3 and corresponded to mild to moderate increase in reticulocytes, reflecting an appropriate regenerative erythroid response attributed to repeated blood collections. Starting on Day 23, the decrease in red cell mass was more pronounced and associated with a less pronounced increase in reticulocyte counts in males administered ≥ 6 mg/kg/dose and to a lesser extent in females that received 10 mg/kg/dose. These are suggestive of diminished or suppressed erythropoiesis, although no microscopic correlates were observed at termination. Red cell mass and reticulocyte changes were fully resolved during the recovery period.

MGC018-related changes in clinical chemistry parameters were noted in in C-reactive protein (CRP), aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT), and alkaline phosphatase (ALP) and were not considered adverse as changes remained in or very close to the historical control range for cynomolgus monkeys. Increases in CRP concentrations were noted across all groups, including controls following each dose and considered related to dosing procedures. However, males at ≥ 3 mg/kg/dose (all 3 doses) and females at ≥ 1 mg/kg/dose had more pronounced CRP increases and was associated with concurrent fibrinogen increases at 10 mg/kg/dose following the last dose. This is suggestive of an inflammatory stimulus and may have been related to microscopic skin findings at termination. Transient, minimal to mild increases in AST and/or ALT levels were noted at all dose levels including control animals; however, greater increases in 1 or 2 individuals of each sex were observed at ≥ 1 mg/kg/dose. These changes were partially to fully resolved by the following sample collection and did not result in microscopic correlates at termination. Decreased ALP levels were observed at 6 mg/kg/dose, lacked correlative findings among other clinical pathology or microscopic endpoints, resolved during the recovery period, and were not likely biologically meaningful.

A spectrum of microscopic findings was present in the skin overlying the last infusion site, skin from the routine section of skin (flank), and additional locations including the forelimbs, hindlimbs, and head. The findings ranged in severity and/or presence within individuals and across animals, but the features of the findings were generally similar within a dose group and displayed a clear dose response in severity and extent of the findings, which were generally more prominent at ≥ 6 mg/kg/dose and included increases in pigment, lymphocytic inflammation, epidermal hyperplasia, and single cell necrosis. Complete reversal of lymphocytic inflammation and single cell necrosis was observed at the end of the recovery phase, and pigment changes and hyperplasia showed ongoing resolution.

In a non-GLP study, a higher repeat-dose level of 20 mg/kg/dose administered at a 2-week interval was associated with similar, but greater, clinical pathology MGC018-related changes that in some cases resulted in microscopic correlates. These included an inflammatory response (increased fibrinogen, CRP, and globulin concentrations and decreased albumin concentrations) that was likely associated with cutaneous skin lesions, suppressed hematopoiesis (decreased red cell mass and decreased reticulocyte, neutrophil, and platelet counts) that correlated with decreased hematopoietic cellularity of the sternal bone marrow, and decreased lymphocyte counts that correlated with lymphoid depletion of the thymus. Microscopic skin findings were more severe in animals administered the higher repeat-dose level of 20 mg/kg/dose. Skin erosion that consisted of separation of the epidermis from the underling basement membrane and dermis resulted in grossly visible ulcers and led to euthanasia in extremis in 1 out of 3 animals.

Animals that received MGC018 as a single dose at ≥ 20 mg/kg and necropsied 48 hours post-dose had microscopic findings not observed at later necropsy days or in animals that received 10 mg/kg.

Based on the GLP toxicology study, the HNSTD for MGC018 was 10 mg/kg/dose administered as a 1-hour IV infusion Q3W (total of 3 doses) as there were no MGC018-related life-threatening toxicities, irreversible findings, or mortality. This corresponds to a peak and systemic exposure of 260.27 mcg/mL ($C_{max}$) and 11821 hr*mcg/mL [area under the concentration-time curve $(AUC)_{0\text{-}504hr}$)] for the conjugated antibody, 233.85 mcg/mL ($C_{max}$) and 11475 hr*mcg/mL ($AUC_{0\text{-}504hr}$) for the total antibody and 309.5 pg/mL ($C_{max}$) and 11188 hr*pg/mL ($AUC_{0\text{-}504hr}$) for SYD986 (payload), respectively.

### 2.3.2 PD-1

The PD-1 receptor is an inhibitory receptor expressed by T cells, which is engaged by ligands including PD-L1 and PD-L2, expressed by antigen-presenting cells. Interaction of PD-1 with its ligands leads to the delivery of a negative signal to the T-cell expressing PD-1 and inhibits T-cell function. This pathway helps the body maintain self-tolerance. Many tumor cells, however, have co-opted this pathway and express high levels of PD-L1 and thereby evade T cell attack. Within the tumor microenvironment, PD-1/PD-L1 interactions limit inflammation and inhibit cytotoxic T lymphocyte (CTL) activity. PD-1 activation inhibits CD8+ CTL proliferation, survival, and their effector function and can also induce apoptosis of TILs and promote differentiation of CD4+ T cells into Treg cells.

Immune checkpoint blockade utilizing anti–PD-1 or anti–PD-L1 antibodies has now proven to have clinical benefit among numerous clinical indications, including both hematologic malignancies and solid tumors. Furthermore, anti–PD-1/PD-L1 directed therapeutics are now being investigated in combination studies across various indications. Existing literature suggests that cytotoxic therapy may be combined with checkpoint inhibition to achieve antitumor activity that is superior to either modality alone and has led to numerous clinical studies of chemotherapy in combination with checkpoint inhibition, including studies that have supported the recent FDA approval of the combinations of pembrolizumab and chemotherapy in patients with NSCLC. It is hypothesized that targeted delivery of a cytotoxic payload (duocarmycin) using MGC018 in various cancers known to express B7-H3 could also achieve additive or synergistic clinical activity when administered in combination with anti–PD-1 (MGA012).

#### 2.3.2.1 MGA012 Clinical Background

Study CP-MGA012-01 is a Phase 1, open-label, multicenter dose-escalation study to define the toxicity profile, maximum tolerated dose (MTD), immunogenicity, PK, and potential antitumor activity of MGA012 in participants with relapsed, refractory advanced solid tumors for whom no standard therapy is available. The study consists of a Dose Escalation Phase and a Cohort Expansion Phase. During the Dose Escalation Phase, 2 schedules of administration were evaluated, Q2W and once every 4 weeks (Q4W), using a standard 3 + 3 design. Cohort expansion to assess further activity in specific solid tumors (endometrial carcinoma, cervical carcinoma, NSCLC, and sarcoma) is ongoing.

Phase 1 dose-finding results in participants with advanced cancer (N = 37) have been presented (**37**). Based on a data cutoff of 23 September 2018, MGA012 demonstrated acceptable tolerability with no dose-limiting toxicity observed at doses ranging from 1 to 10 mg/kg Q2W (Q4W administration was also studied). An MTD was not reached. The $T_{½}$ (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 NSCLC, endometrial cancer, cervical cancer, and sarcoma cohorts, with subsequent evaluation of flat dosing in tumor-agnostic and MSI-H uterine cancer cohorts.

Interim results for the expansion cohorts have recently been presented (**44**). A total of 132 participants were enrolled into the disease-specific expansion cohorts and another 30 in the tumor agnostic flat dosing cohorts at 500 and 750 mg Q4W. Participants were predominantly Caucasian and female; the median age ranged from 44 for the sarcoma cohort to 64 for endometrial cancer. The most frequently reported treatment emergent adverse events (TEAEs) (> 10%) in participants receiving body-weight based dosing were fatigue, diarrhea, and dyspnea. The most frequently reported TEAEs (≥ 20%) in participants 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%) participants exposed to MGA012 in the study have experienced immune-related adverse events (irAEs). Most irAEs were transient, with the exception of 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 (eg, MSI or PD-L1 status). Specifically, 5/27 (19%) of the evaluable NSCLC participants had confirmed RECIST responses, as did 4/29 (14%) cervical cancer, 4/23 (17%) endometrial cancer, and 1 sarcoma. ORR and median DoRs have not yet been established.

## 2.4 Dose Selection MGC018

Using the Guidance-based approach (**10**), the maximum recommended starting dose (MRSD) for the proposed Phase 1/2 trial was determined as follows: The HNSTD in the GLP toxicology study in cynomolgus monkeys was determined to be 10 mg/kg administered by 1-hour IV infusion Q3W. The starting dose was defined as 1/6 the HNSTD (10 * 1/6 = 1.67 mg/kg) (**10**). The human equivalent of the starting dose, based on a body surface area conversion factor, was calculated as 0.5 mg/kg (i.e., 1.67 mg/kg * 0.32) (**11**). MGC018 has nearly identical single arm binding affinity to human and cynomolgus monkey B7-H3 ($K_D$ of 22.7 vs. 22.1 nM, respectively); thus, no further adjustment for affinity differential was undertaken. Because of high systemic exposure multiples, the 0.5 mg/kg dose was considered as the MRSD. Subsequent to the first dose level of 0.5 mg/kg, successive dose levels of 1.0, 2.0, 3.0, 4.0, and 5.0 mg/kg will be explored, guided by dose escalation rules outlined in **Section 4.3**.

### 2.4.1 Multiples of Monkey Exposure

Allometric scaling, modeling, and simulations were used to estimate exposure data ($C_{max}$ and AUC) in the human after the first dose of 0.5 to 5.0 mg/kg and compared to the mean cumulative exposure for the HNSTD in the cynomolgus monkey (10 mg/kg). The data are presented in **Table 1**. First-dose predicted exposure data suggested adequate multiples of monkey exposure for the proposed dose range (0.5 to 5.0 mg/kg) to be investigated in humans. Using exposure parameters for ADC, SYD986, and total antibody (TAB, which includes conjugated and unconjugated antibody), the safety margins at the starting dose of 0.5 mg/kg in humans were 23.0-, 22.6- and 20.7-fold, respectively, based on $C_{max}$ and 17.6-, 17.1-, and 7.6-fold, respectively, and based on cumulative AUC as calculated using human (predicted) and monkey (actual) exposure parameters. Multiples of monkey exposure at the proposed top dose of 5.0 mg/kg were in the range of 0.8- to 4.3-fold.

**Table 1 Predicted Exposure Parameters of ADC, SYD986, and TAB After the First Dose (at Steady-State) of MGC018 and Exposure Multiples in Humans**

| Species | Analyte | Dose (mg/kg) | Exposure Parameters [a] | | Multiples of Monkey Exposure Based on | |
|---|---|---|---|---|---|---|
| | | | $C_{max}$ (mcg/mL or pg/mL) | AUC (h•mcg/mL or h•pg/mL) | $C_{max}$ | AUC |
| Human | ADC [b] | 0.5 | 11.3 (11.5) | 671 (688) | 23.0 (22.6) | 17.6 (17.2) |
| | | 1.0 | 22.7 (23.2) | 1554 (1626) | 11.5 (11.2) | 7.6 (7.3) |
| | | 2.0 | 45.5 (46.9) | 3705 (4033) | 5.7 (5.5) | 3.2 (2.9) |
| | | 3.0 | 68.3 (71.1) | 6219 (7038) | 3.8 (3.7) | 1.9 (1.7) |
| | | 4.0 | 91.1 (96.0) | 9026 (10602) | 2.9 (2.7) | 1.3 (1.1) |
| | | 5.0 | 113.9 (121.8) | 12090 (12847) | 2.3 (2.1) | 1.0 (0.9) |
| | SYD986 [c] | 0.5 | 13.7 (13.9) | 1473 (1453) | 22.6 (22.3) | 7.6 (7.7) |
| | | 1.0 | 21.0 (21.3) | 2827 (2746) | 14.7 (14.5) | 4.0 (4.1) |
| | | 2.0 | 34.0 (34.9) | 5523 (5234) | 9.1 (8.9) | 2.0 (2.1) |
| | | 3.0 | 46.7 (48.4) | 8261 (7710) | 6.6 (6.4) | 1.4 (1.5) |
| | | 4.0 | 59.2 62.3) | 11034 (10266) | 5.2 (5.0) | 1.0 (1.1) |
| | | 5.0 | 71.8 (76.5) | 13819 (12959) | 4.3 (4.0) | 0.8 (0.9) |
| | TAB [b] | 0.5 | 11.3 (11.5) | 671 (689) | 20.7 (20.3) | 17.1 (16.7) |
| | | 1.0 | 22.7(23.2) | 1555 (1627) | 10.3 (10.1) | 7.4 (7.1) |
| | | 2.0 | 45.5 (46.9) | 3706 (4033) | 5.1 (5.0) | 3.1 (2.8) |
| | | 3.0 | 68.3 (71.1) | 6220 (7039) | 3.4 (3.3) | 1.8 (1.6) |
| | | 4.0 | 91.1 (96.0) | 9027 (10603) | 2.6 (2.4) | 1.3 (1.1) |
| | | 5.0 | 113.9 (121.8) | 12091 (14694) | 2.1 (1.9) | 0.9 (0.8) |
| Monkey [d] | ADC | 10 | 260.27 | 11821 | NA | NA |
| | SYD986 | 10 | 309.50 | 11188 | NA | NA |
| | TAB | 10 | 233.85 | 11475 | NA | NA |

NOTE: $C_{max}$ in monkeys represents the mean maximum observed concentration after the third dose. AUC in monkeys represents AUC0-50 4 hr after the third dose (Report 1020-013-SR-TK).

a Values in parentheses are steady-state values after Q3W dosing in humans.

b Units for ADC and TAB $C_{max}$ and AUC are mcg/ml and h•mcg/mL, respectively.

c Units for SYD986 $C_{max}$ and AUC are pg/mL and h•pg/mL, respectively.

d The 10 mg/kg dose in the monkeys is the HNSTD

Abbreviations: ADC = antibody drug conjugate; AUC = area under the serum concentration-time curve extrapolated to infinite time (first dose) or over a dosing interval of 3 weeks (steady-state); $C_{max}$ = maximum serum concentration; HNSTD = high non-severely toxic dose; NA = not applicable; Q3W = once every 3 weeks; SR = scientific report; SYD986 = drug (also known as payload); TAB = total antibody; TK = toxicokinetic.

Exposure safety margins in the human at steady-state were also estimated for the Q3W dosing regimen using $C_{max}$ and AUC. In this estimation, predicted exposure parameters in a dosing interval of 3 weeks in humans at steady-state were compared to the actual cumulative exposure parameters in monkeys following administration of the HNSTD dose (10 mg/kg). These data in humans are summarized in **Table 1**. Consistent with first-dose data, predicted

steady-state exposure data provided similar fold multiples of monkey exposure for the proposed dose range of 0.5 to 5.0 mg/kg MGC018 Q3W to be investigated in the FIH study.

### 2.4.2 Dose Selection: MGA012

With a few exceptions, in general, the doses of therapeutic mAbs have been traditionally administered on a body size basis (mg/kg or mg/m$^2$), with the supposition that this approach may reduce the intersubject variability in drug exposure compared with the flat (or fixed) dosing approach (**72**). However, recent studies recommend the use of flat dosing over body size–based dosing in clinical trials, as both approaches performed similarly in reducing variability in drug exposure, with flat dosing being superior for some mAbs (**3**, **72**). Furthermore, flat dosing offers the advantages of convenience, compliance, cost-effectiveness, and safety due to less risk of dosing errors (**3**). Consistent with this recommendation, a current strategy for dosing PD-1 inhibitors is to use flat dosing (mg) in addition to or instead of body weight–based dosing (mg/kg) (**25**, **49**, **50**). Since the degree of the impact of body weight (BW on the PK of MGA012 in humans has not been delineated and since it is unknown whether body size–based dosing would influence intersubject variability in drug exposure, the study design in the current study will utilize a flat dosing scheme. This approach will allow for the evaluation of the PK/pharmacodynamic parameters corresponding to participants treated with a flat dose of MGA012.

Aligned with the above premise, MGA012 dosing regimen of 375 mg IV given on a Q3W schedule as a 60-minute infusion will be investigated in this study. This dose was selected based on the safety profile, PK, and pharmacodynamics from the ongoing Phase 1, FIH dose escalation and expansion Study CP-MGA012-01. In the latter study, dose escalation was carried out from 1 mg/kg Q2W to 10 mg/kg Q2W or Q4W with no reported dose-limiting toxicities (DLTs) and, thus, no MTD was exceeded or defined. The safety profile of MGA012 based on a total of 169 participants exposed to MGA012 in Study CP-MGA012-01 demonstrated that the majority of AEs were mild or moderate (CTCAE Grade 1 or 2), with toxicities manageable by standard medical therapy. See **Section 2.3.2.1** for a more detailed description of the safety profile from Study CP-MGA012-01.

Modeling and simulations of the PK data of MGA012 were performed on 10 subjects treated with a 3 or 10 mg/kg Q4W schedule who had PK profiles characterized up to 672 hours. The mean BW of these subjects was 87.7 kg with a range from 50.0 to 109.8 kg. Based on the mean BW, the top dose of 10 mg/kg Q2W corresponds to a flat dose of 877 mg Q2W, and in a 6-week interval (because of difference in the dosing intervals, Q2W versus Q3W for the 10 mg/kg versus 375 mg, respectively), the total dose administered is 2631 mg (877 mg × 3). Over the same 6-week interval, the total dose administered for the 375 mg Q3W dose is 750 mg (375 mg × 2). Thus, the 375 mg Q3W dose is approximately 3.5-fold lower than the top dose investigated in Study CP-MGA012-01 (10 mg/kg Q2W), providing adequate safety margins. However, concerns may still remain that the dose exposure may be higher for subjects with low BW given a 375 mg Q3W dose. For example, the BW based dose for a subject weighing 50 kg, receiving 375 mg Q3W dose, will be 7.5 mg/kg Q3W. The latter dose is approximately 2-fold lower than the top dose investigated in Study CP-MGA012-01 (10 mg/kg Q2W), further supporting the adequacy of the safety margins.

Safety margins were also investigated based on MGA012 exposure data [$C_{max}$, $AUC_{(TAU)}$, and lowest concentration ($C_{trough}$)]. Modeling and simulations were performed, and the predicted first dose and steady-state exposure parameters for the flat dosing schedule (375 mg Q3W) were compared to the exposure parameters for the 10 mg/kg Q2W dose in Study CP-MGA012-01 (**Table 2**). In this analysis, comparison of AUC was made over a 6-week interval because of the differences in the frequency of administration. The mean or median first dose or steady-state $C_{max}$ and $C_{trough}$ values for the 375 mg Q3W dose were lower than the mean values for the 10 mg/kg Q2W dose. More importantly, the mean or median $AUC_{(TAU)}$ for the 375 mg Q3W dose was also lower than the mean value for the 10 mg/kg Q2W dose. Furthermore, there was minimal overlap in the $5^{th}$ to $95^{th}$ percentile intervals for the exposure parameters between the 375 mg Q3W and 10 mg/kg Q2W doses. These data suggest that the predicted exposure parameters in subjects treated with the flat dose of 375 mg Q3W was below the corresponding exposures for the MGA012 10 mg/kg Q2W, the clinically established safe and tolerable dose. Predicted exposures for the 375 mg Q3W dose were 2.3- to 4.1-fold lower than the exposures for the 10 mg/kg Q2W dose, suggesting adequate safety margins.

Based on receptor occupancy (RO) data, the 375 mg Q3W doses (~ 4 mg/kg Q3W dose [based on a mean BW of 87.7 kg]) should result in maximum RO on CD4+ and CD8+ T cells.

In summary, the totality of the safety, PK, and pharmacodynamic data support the investigation of MGA012 at the dose of 375 mg Q3W.

**Table 2 Predicted Exposure Parameters for the 375 mg Q3W Dose Compared to 10 mg/kg Q2W Dose and Multiples of Exposure**

| Interval | Exposure Parameter | 10 mg/kg Q2W (N=10) | | 375 mg Q3W (N=10) | | Multiples of 10 mg/kg Q2W Exposure |
|---|---|---|---|---|---|---|
| | | GeoMean (%CV) | Median (P05, P95) | GeoMean (%CV) | Median (P05, P95) | |
| First Dose | $C_{max}$ (mcg/mL) | 207.0 (17) | 198.5 (164.8, 282.6) | 90.4 (27) | 83.1 (67.6, 144.3) | 2.3 |
| | $AUC_{(TAU)}$ (mcg•h/mL) | 90801 (21) | 92385 (69225, 129567) | 32896 (36) | 30182 (21526, 68120) | 2.8 |
| | $C_{trough}$ (mcg/mL) | 50.9 (29) | 56.8 (32.0, 69.2) | 15.9 (51) | 16.6 (6.9, 38.5) | 3.2 |
| Steady State | $C_{max}$ (mcg/mL) | 330.8 (24) | 343.1 (223.8, 435.0) | 121.2 (32) | 108.5 87.2, 229.9) | 2.7 |
| | $AUC_{(TAU)}$ (mcg•h/mL) | 184905 (33) | 196776 (103326, 266811) | 53806 (45) | 49922 (32196, 133326) | 3.4 |
| | $C_{trough}$ (mcg/mL) | 118.5 (50) | 135.4 (40.7, 194.3) | 28.6 (71) | 37.3 (7.6, 86.1) | 4.1 |

Abbreviations: $AUC_{(TAU)}$ = area under the serum concentration-time curve in a dosing interval; $C_{max}$ = maximum observed serum concentration; $C_{trough}$ = trough serum concentration (concentration at the end of a dosing interval); CV = coefficient of variation; GeoMean = geometric mean; N = number of subjects; P05 = 5th percentile; P95 = 95th percentile; Q2W = once every 2 weeks: Q3W = once every 3 weeks.

NOTE: For the 10 mg/kg Q2W and 375 mg Q3W doses, $AUC_{(TAU)}$ was multiplied by 3 and 2, respectively, to report it over a 6-week interval.

## 2.5 MGC018 and MGA012 Combination Dose Selection

In the combination portion of the study (Module B, dose escalation), the initial dose for MGC018 will begin at 0.5 mg/kg or the MTD-2 (the dose level that is 2 dose levels below the MTD defined for MGC018 monotherapy), whichever is higher, and will also be administered as a 60-minute IV infusion every 3 weeks. Successive escalation to doses levels will range from 1.0 to 5.0 mg/kg may be performed as tolerated up to a maximum of 5 mg/kg and will be guided by decision rules outlined in **Section 4.3**. MGA012 will be administered at a flat dose of 375 mg as a 60-minute IV infusion Q3W. 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.

# 3 STUDY PURPOSE AND OBJECTIVES

## 3.1 Primary Objective

The primary objective of this study is as follows:

- To characterize the safety, tolerability, DLTs, and 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.

## 3.2 Secondary Objectives

The secondary objectives of this study are as follows:

- 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) (**Appendix 5**).
- To describe the radiographic progression free survival (rPFS) in mCRPC.
- To describe the prostate-specific antigen (PSA) response rate and best PSA percent change in mCRPC.

## 3.3 Exploratory Objectives

Exploratory objectives are as follows:

- 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 immunohistochemistry and/or 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 or database lock unless they represent meaningful findings.

# 4 STUDY DESIGN

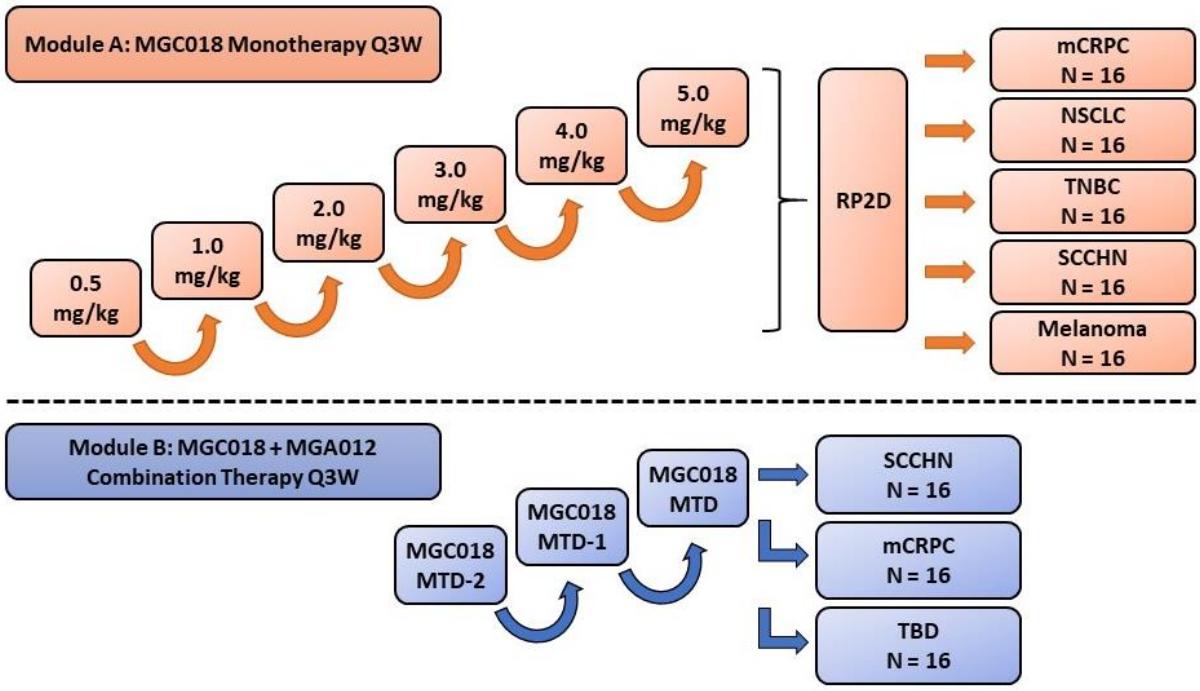
## 4.1 Overall Study Design and Plan

This study is a Phase 1/2, FIH, 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 5**); 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 sponsor notification to all the study investigators/ institutions.

Participants with unresectable, relapsed or refractory, 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, NSCLC, TNBC, 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; see **Section 4.1.2**.

**Figure 5 MGC018 Overall Study Design**

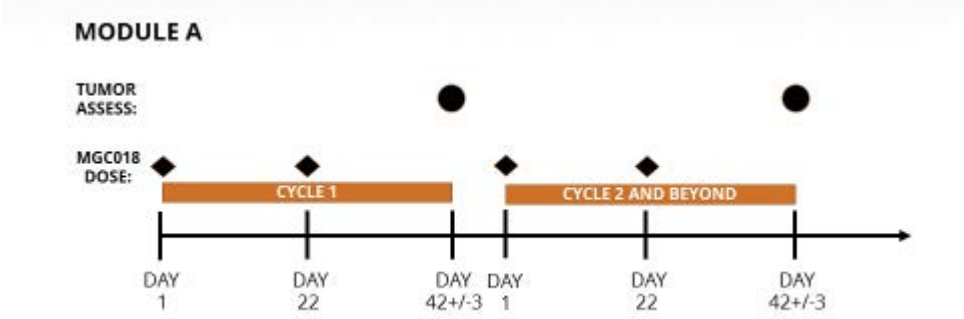



**Note: MTD-2 = the dose level that is 2 dose levels below the MTD defined for MGC018 monotherapy.**
**MTD-1 = the dose level that is 1 dose level below the MTD defined for MGC018 monotherapy.**

**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.**

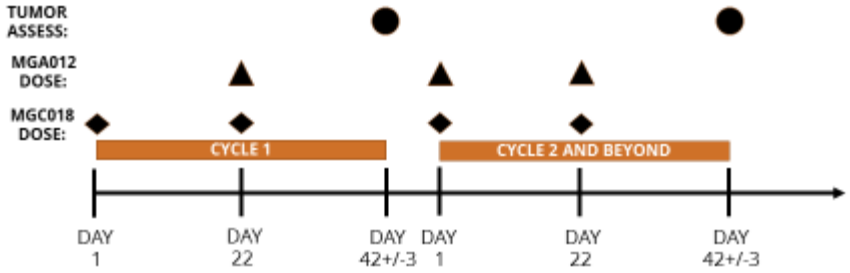
MGC018 will be administered alone or in combination with MGA012 (also known as INCMGA00012), as illustrated below in **Figure 6** and **Figure 7**, respectively. For Module A, MGC018 alone will be administered IV over 60 minutes on Days 1 and 22 of Cycle 1 and every subsequent 42-day cycle thereafter. 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.

**Figure 6 MGC018 Monotherapy Dosing Schedule (Q3W) (Module A)**




**Note: Imaging for tumor assessments will be every 9 weeks (63 days) during the Cohort Expansion Phase for Module A.**

**Figure 7 MGC018 and MGA012 Combination Dosing Schedule (Q3W) (Module B)**




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 (see **Section 4.1.1** below for more details). 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). For participants with a dose delay > 21 days, the total number of cycles may be < 18 cycles and the time on MGC018 will be no more than 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.

### 4.1.1 Dose Escalation Phase

The goal of the Dose Escalation Phase of this study is to initially characterize the safety and tolerability of MGC018 administered alone or in combination with MGA012 and, more specifically, to define the MTD of these respective monotherapy and combination regimens. If no MTD is defined during the dose escalation of MGC018 monotherapy (Module A) after escalation to the maximum protocol-specified dose, then that dose level will be designated as the MAD for MGC018 monotherapy. Similarly, if no MTD is defined during dose escalation of the combination of MGC018 and MGA012 (Module B), after escalation to the maximum protocol-specified dose, then that dose level will be designated as the MAD for MGC018 and MGA012 combination therapy.

For the purposes of guiding decisions regarding dose escalation, the **DLT Evaluation Period** for Module A (monotherapy) will be 21 days following administration of the first dose of MGC018. For Module B (combination therapy), the DLT evaluation period will be 42 days in duration.

Dose escalation will follow a conventional 3+3+3 design: successive cohorts of 3 to 9 participants each will be evaluated in sequential escalating doses of MGC018 administered alone (Module A) or in combination with MGA012 (Module B) as shown below (**Table 3** and **Table 4**).

Sentinel dosing will be used for the first 2 dose levels. The first administration of MGC018 in participants in the first 2 dose levels in Module A will be staggered by at least 48 hours.

In Module B, MGA012 will be administered at a dose of 375 mg (flat dose) Q3W, beginning on Day 22 of Cycle 1, and continuing on Days 1 and 22 of every cycle thereafter.

Participants who require dose delays greater than 21 days secondary to AEs considered unrelated to study treatment or any other cause unrelated to study treatment are considered unevaluable for safety and toxicity during the DLT evaluation period and will be replaced.

Intermediate dose levels may be explored based on review of the cumulative safety data and upon agreement between the investigators and the sponsor.

**Table 3 MGC018 Dose Levels: Module A Dose Escalation Phase**

| Cohort | MGC018 Dose (Q3W) |
|---|---|
| Cohort -1 | 0.3 mg/kg |
| Cohort 1 | 0.5 mg/kg |
| Cohort 2 | 1.0 mg/kg |
| Cohort 3 | 2.0 mg/kg |
| Cohort 4 | 3.0 mg/kg |
| Cohort 5 | 4.0 mg/kg |
| Cohort 6 | 5.0 mg/kg |

For Module A Dose Escalation, if the dose level in Cohort 1 exceeds the MTD, a de-escalation to Cohort -1 dose levels will be employed as summarized in **Table 3**.

**Table 4 MGC018 and MGA012 Dose Levels: Module B Dose Escalation Phase**

| Cohort | MGC018 Dose (Q3W) | MGA012 (Q3W) |
|---|---|---|
| Cohort -1 | MTD-3 (TBD) | 250 mg (TBD) |
| Cohort 1 | MTD -2 | 375 mg |
| Cohort 2 | MTD -1 | 375 mg |
| Cohort 3 | MTD | 375 mg |

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: MTD = maximum tolerated dose; Q3W = every 3 weeks; TBD = to be determined.

For Module B Dose Escalation Phase, if the dose level in Cohort 1 exceeds the MTD, a de-escalation to Cohort -1 dose levels will be employed as indicated in **Table 4**. Depending on the nature and timing of the observed toxicity, the MGC018 dose may be de-escalated to MTD-3, MGA012 may be decreased to 250 mg, or doses of both drugs may be adjusted to other levels at or below the Cohort 1 dose levels, as deemed most appropriate based on review of the cumulative data by the sponsor in consultation with the study investigators.

### 4.1.2 Cohort Expansion Phase

During the Cohort Expansion Phase, Module A, participants with relapsed/refractory, unresectable locally advanced or metastatic mCRPC, NSCLC, TNBC, SCCHN, and melanoma will receive MGC018 alone at the recommended phase II dose (RP2D) based on safety, PK, and antitumor activity from the Dose Escalation Phase of the study. The RP2D for the Cohort Expansion Phase of Module A was determined based on the review of the safety, tolerability, and PK data. Participants in Module A Cohort Expansion Phase will receive 3 mg/kg every 3 weeks. The MGC018 dose will be capped for participants with a body weight ≥ 100 kg.

During the Cohort Expansion Phase, Module B, cohorts of participants with unresectable, locally advanced or metastatic SCCHN or mCRPC, and a cohort of participants with tumor type TBD, based on the prior experience with Module A and Module B (including any evidence of emerging antitumor activity in a given tumor type) will be treated with MGC018 in combination with MGA012 at the MTD/MAD dose based on the safety, PK and antitumor activity from the Dose Escalation Phase of the study for Module B. See **Table 5** for an overview of the Expansion Cohort.

**Table 5 Expansion Cohorts**

| Expansion Cohort per Module | Tumor Type | Planned Enrollment |
|---|---|---|
| Module A | mCRPC | Up to 16 |
| Module A | NSCLC | Up to 16 |
| Module A | TNBC | Up to 16 |
| Module A | SCCHN | Up to 16 |
| Module A | Melanoma | Up to 16 |
| Module B | SCCHN | Up to 16 |
| Module B | mCRPC | Up to 16 |
| Module B | Tumor Type TBD | Up to 16 |

Abbreviations: mCRPC = metastatic castrate-resistant prostate carcinoma; NSCLC = non-small cell lung cancer; SCCHN = squamous cell cancer of the head and neck; TBD = to be determined; TNBC = triple negative breast cancer.

## 4.2 Dose Limiting Toxicity

For the purposes of guiding study decisions regarding dose escalation, DLTs will be based on study drug-related AEs or laboratory abnormalities that occur up to Study Day 21 of Cycle 1 in the Dose Escalation Phase only for Module A and Study Day 42 of Cycle 1 in the Dose Escalation Phase only for Module B. The severity of AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (NCI CTCAE v4.03). Dose-limiting toxicities will be defined separately for hematologic, non-hematologic, and hepatic non-hematologic events.

In general, for participants who experience toxicity that may meet the criteria for a DLT, subsequent administration of the study drugs should be held pending management and/or resolution of the event and assessment of attribution to the study drug. Criteria for discontinuation of therapy are outlined in **Section 5.4**.

### 4.2.1 Hematologic Dose Limiting Toxicity

Hematologic DLT is defined as follows:

- Grade 4 neutropenia lasting > 7 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 is defined as any ≥ Grade 3 non-hematologic event

- Skin toxicity that meets the definition of Stevens Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) regardless of duration will be considered a dose limiting toxicity. SJS and TEN are to be reported immediately to the sponsor as an Immediately Reportable Events (IRE) and Adverse Events of Special Interest (AESI) per **Section 12.2.2**.

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

- Grade 3 electrolyte abnormality that lasts < 72 hours, is not otherwise associated with clinical complications, and responds to medical intervention
- Grade 3 fever that lasts < 72 hours and is not associated with hemodynamic compromise
- Grade 3 nausea or vomiting that lasts < 72 hours and responds to medical intervention
- Grade 3 or greater amylase and/or lipase elevation that is not associated with clinical or radiographic evidence of pancreatitis requiring hospitalization
- Grade 3 gastrointestinal AEs of diarrhea, constipation, abdominal pain, cramping, dyspepsia, or dysphagia that resolves to ≤ Grade 1 or baseline within 72 hours with maximal supportive care
- Grade 3 fatigue that lasts < 72 hours
- Grade 3 infusion-related reaction (IRR) or cytokine release syndrome (CRS) that lasts < 12 hours and responds to medical intervention
- Grade 3 endocrinopathy that is adequately controlled with hormone supplementation
- Grade 3 skin toxicity that resolves to ≤ Grade 1 or baseline within 72 hours with maximal supportive care
- Grade 3 dry eye or Grade 3 photophobia that lasts ≤ to 72 hours
- 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 1 or baseline within 5 days

Note: The following Grade 2 non-hematologic AEs may also be considered as DLTs:

- Grade 2 AEs that are prolonged inordinately, based upon the medical judgment of the investigator, and/or lead to permanent discontinuation of study drugs due to participant intolerance
- Any hepatic laboratory abnormalities meeting all 3 Hy's law criteria (described within **Section 4.2.3**)
- Eye pain or reduction in visual acuity that does not respond to topical ophthalmic therapy and does not improve to Grade 1 within 14 days of the initiation of topical ophthalmic therapy, or that requires systemic treatment

### 4.2.3 Hepatic Non-hematologic Dose Limiting Toxicity

Hepatic Non-Hematologic DLT will be defined as follows:

- Any elevation of one or more transaminases > 8 × the institutional reference laboratory upper limit of normal (ULN) irrespective of duration
- Any Grade 3 elevation of one or more transaminases > 5.0 – 8.0 × ULN that does not resolve to Grade 2 (i.e., > 3.0 – 5.0 × ULN) within 7 days and Grade 1 (i.e., > ULN - 3.0 × ULN) within 14 days. In addition, steroids must be tapered to ≤ 10 mg of prednisone or equivalent per day, by Day 14. Please see **Section 7.2.2.1** for further management guidelines.
- A Grade 3 elevation of total bilirubin that is > 5 × the ULN irrespective of duration.
- Any Grade 3 elevation of total bilirubin > 3.0 – 5.0 × ULN that does not resolve to Grade 2 (i.e., > 1.5 – 3.0 × ULN) within 7 days and Grade 1 (i.e., > ULN – 1.5 × ULN) within 14 days. In addition, steroids must be tapered to ≤ 10 mg of prednisone or equivalent per day, by Day 14. Please see **Section 7.2.2.2** for further management guidelines.
- Any event meeting the criteria for Hy's law as follows (all 3 features):
    - Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 3 × ULN
    - Concurrent elevation of total bilirubin > 2 × ULN without initial evidence of cholestasis
    - No alternative etiology can be identified

## 4.3 Dose Escalation Rules

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

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

If 1 of the first 3 participants treated at a given dose level experiences a drug-related DLT, then 3 additional participants will be enrolled at that dose level (thus making a total of 6 participants in this cohort) to further assess the safety of MGC018 alone (Module A) or in combination with MGA012 (Module B).

- If ≥ 2 of these 3 additional participants (i.e., ≥ 3 of the 6 participants enrolled in the cohort) experience a DLT, it will be concluded that the MTD has been exceeded, and 3 participants will be enrolled and treated at the next lower dose level.
- If 1 of these 3 additional participants experiences a drug-related DLT, then another 3 additional participants (for a total of 9 participants in the cohort, 3 + 3 + 3) will be enrolled and treated at that dose level to further characterize the safety of MGC018 alone (Module A) or in combination with MGA012 (Module B).
- If 0 of the 3 additional participants experiences a DLT, then the dose will be escalated, and 3 participants will be enrolled at the next higher dose level.

If ≥ 2 participants out of the first 3 participants treated at a given dose level, or ≥ 3 of 6 participants treated at a given dose level, or ≥ 3 out of 9 participants treated at a given dose level experience a drug-related DLT, then it will be concluded that the MTD for MGC018 alone (Module A) or in combination with MGA012 (Module B) has been exceeded at that dose level, and all subsequent participants will be treated at the next lower dose level.

If ≥ 2 participants out of the first 6 participants 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 MGC018 alone (Module A) or in combination with MGA012 (Module B) has been exceeded and all subsequent participants will be treated at the next lower dose level. In categorizing DLTs, all related MedDRA Preferred Terms will be used to determine whether the same DLT has occurred in a given cohort.

If ≥ 2 participants out of the first 6 participants treated at a given dose level experience a Grade 4 DLT, then the enrollment in that cohort will stop, and it will be concluded that the MTD for MGC018 alone (Module A) or in combination with MGA012 (Module B) has been exceeded and all subsequent participants will be treated at the next lower dose level.

For participants being treated at a dose level subsequently determined to exceed the MTD for a given cohort of the study, the dose of MGC018 alone (Module A) or in combination with MGA012 (Module B) will be reduced to the next lower dose level as summarized in **Table 3** and **Table 4**. 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 participants enrolled in the current dose cohort have completed the DLT evaluation period and the safety data have been reviewed by the sponsor medical monitor, Independent Safety Monitor, and the investigators participating in the study. Evaluation of safety data from each cohort will include an assessment of the proportion of participants who receive planned doses, and the percentage of participants that require dose reductions or dose discontinuations for toxicity. The sponsor medical monitor, Independent Safety Monitor and investigators will consider all available data from participants both during and beyond the DLT evaluation period when making dose escalation decisions and in the determination of the recommended phase 2 dose to be evaluated in expansion cohorts. In particular, if a Grade 4 febrile neutropenia has been observed, the sponsor will review and evaluate the safety database for other events of any grade febrile neutropenia prior to making a decision to dose escalate.

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, pharmacodynamics, 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. In addition, if an MTD is established, the sponsor may decide to open the Cohort Expansion Phase at a dose lower than the MTD, based on the totality of the PK, pharmacodynamic, biomarker, safety, and response data.

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

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

## 4.4 Guidelines for Dose Modification

Dose modifications are allowed for toxicity related to study drug according to the guidelines in **Section 7**.

Modification of dose or schedule may be necessitated by the observation of suspected study drug-related AEs. The investigator should use their best medical judgment to safeguard the participant's welfare.

In general, observation of any study drug-related ≥ Grade 3 AE by CTCAE v4.03 should result in suspension of all study drug administration pending evaluation. Reinstitution of assigned study drug administration should be delayed until the study drug-related AE has resolved to ≤ Grade 1 or baseline for that participant (whichever is greater).

If the study drug-related ≥ Grade 3 AE fails to resolve to ≤ Grade 1 or baseline (whichever is greater), causing the participant to miss > 2 scheduled doses of study drug, the investigator should consider whether the participant should be withdrawn from further study drug administration unless there are extenuating circumstances and the investigator reviews the

situation with and receives permission to continue study drug from the medical monitor (refer to **Section 5.4**).

If the participant experiences a second (either similar or different) study drug-related ≥ Grade 3 AE after reinstituting assigned study drugs for a first occurrence of a study drug-related ≥ Grade 3 AE, study drug administration should be delayed. Reinstitution of study drug administration should be delayed until the AE has resolved to ≤ Grade 1 or baseline (from Cycle 1 Day 1, pre-dose) for that participant (whichever is greater), with exceptions noted under **Section 7**. If resolution occurs and the participant misses ≤ 2 scheduled dose(s), the investigator upon consultation with the medical monitor may reinstitute study drug.

If the second ≥ Grade 3 study drug-related AE fails to resolve to ≤ Grade 1 or baseline causing the participant to miss ≥ 2 scheduled doses of study drug, the investigator should consider whether the participant should be withdrawn from further study drug administration (refer to **Section 5.4**).

If a third possibly, probably, or definitely related ≥ Grade 3 AE occurs, the investigator in consultation with the sponsor's medical monitor should consider whether the participant should be withdrawn from further study drug administration.

### 4.4.1 Guidelines for Other Study Drug Related Toxicities

For all other study drug-related toxicity not listed in **Section 7** dose modifications of study drug may be allowed for participants (see **Table 6** for general guidelines). The investigator should contact the sponsor to discuss the appropriate dose of study drug based on the safety profile and evidence of antitumor activity. Sponsor approval must be obtained in advance of the dose modification of study drug.

For study drug-related ≥ Grade 3 toxicities except fatigue, local reaction, fluid retention, anemia, laboratory abnormalities without clinical significance, and toxicities without serious morbidity to participants, study drug should be held up to 21 days from the planned date of reinfusion until resolution to ≤ Grade 1 or baseline (from Cycle 1 Day 1, pre-dose) for that participant (whichever is greater), then reinstituted, if medically appropriate. Any measures such as frozen gloves or socks or scalp cooling cap to prevent cutaneous toxicity or alopecia are left to the investigator's judgment.

**Table 6 Guidelines for Other Study Drug Related Toxicities**

| Adverse Event Severity Grade | MGC018 Management Guidelines | Medical Care Guidelines |
|---|---|---|
| 1 | No dose modification necessary. Consider delaying dose of MGC018 until < Grade 1 or baseline (from Cycle 1 Day 1, pre-dose) for that participant (whichever is greater). Consider dose reduction of one dose level. | Consider clinical evaluation of the participant once weekly or every other week to monitor. Obtain clinical laboratory evaluations as indicated e.g., weekly CBC, chemistry. |
| 2 | Consider delaying dose of MGC018 until ≤ Grade 1 or baseline (from Cycle 1 Day 1, pre-dose) for that participant (whichever is greater). Consider dose reduction of one dose level. | Consider clinical evaluation of the participant once weekly or every other week to monitor. Obtain clinical laboratory evaluations as indicated e.g., weekly CBC, chemistry. |
| 3 | Delay dose of MGC018 until ≤ Grade 1 or baseline (from Cycle 1 Day 1, pre-dose) for that participant (whichever is greater). Consider dose reduction of one or two dose levels. If the same event ≥ Grade 3 recurs consider study drug discontinuation. | Consider hospitalization. Consider clinical evaluation of the participant ≥1 time per week or every week to monitor. Perform imaging and/or other evaluations to determine the etiology of the event. Obtain clinical laboratory evaluations as indicated e.g., weekly CBC, chemistry. |
| 4 | Delay dose of MGC018 until ≤ Grade 1 or baseline (from Cycle 1 Day 1, pre-dose) for that participant (whichever is greater). Consider dose reduction of one or two dose levels. Consider study drug discontinuation. If the same event ≥ Grade 3 recurs consider study drug discontinuation. | General guidance includes hospitalization and emergent medical care. Perform imaging and/or other evaluations to determine the etiology of the event. Consider clinical evaluation of the participant ≥ 1 time per week or every week to monitor. Obtain clinical laboratory evaluations as indicated e.g., weekly CBC, chemistry. |

Abbreviations: CBC: complete blood count.

### 4.4.2 Dose Delays

Participants who experience toxicity should have study drug held pending assessment, management, and resolution of the toxicity. Participants in whom the toxicity is assessed to be unrelated to study drug or for whom the toxicity does not meet the criteria for discontinuation, may reinstitute study drug as per guidelines outlined in **Section 4.4.1** and **Section 7**. Reinstitution of study drug shall be conducted as follows:

- For participants in whom the toxicity is assessed to be related to study drug, dose delays of up to 21 days are allowed.
- For participants in whom the toxicity is unrelated to study drug, dose delays of up to 21 days are allowed. Dose delays up to 4 weeks are allowed for participants who require palliative radiotherapy only in consultation with the medical monitor (see **Section 8.1.1**).

- The medical monitor must be consulted prior to the restart of study drug after a dose delay.

A participant with a dose delay > 21 days due to an AE, but who has otherwise experienced clinical benefit, in the judgement of the investigator in consultation with medical monitor, may continue to receive study drug.

#### 4.4.2.1 COVID-19/SARS-CoV-2 Infection or Vaccination

The following guidelines apply to participants with confirmed (positive by regulatory authority approved/authorized test) or presumed (test pending/clinical suspicion) coronavirus disease 2019 (COVID-19)/severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection:

- For participants with confirmed or presumed SARS-CoV-2 infection, study drug should be delayed for at least 14 days from the start of symptoms. Consideration for study treatment continuation will be made on a case-by-case basis with the medical monitor and the principal investigator.
- Prior to restarting study drug, participants should be afebrile for at least 72 hours and SARS-CoV-2–related symptoms should have recovered to ≤ Grade 1 or baseline for a minimum of 72 hours.
- The sponsor should be informed when resuming study drug.

The sponsor must be informed within 24 hours of awareness of a participant with confirmed or presumed COVID-19/ SARS-CoV-2 infection. Suspected cases of COVID-19/ SARS-CoV-2 should be tested per local practice/institutional guidelines with an approved/authorized test.

At the discretion of the investigator, non-live COVID-19 vaccines may be administered per local practice. Participants may have study drug held to allow for COVID-19 vaccination; delays of up to 5 days are allowed.

## 4.5 Study Duration

It is expected that enrollment of the Dose Escalation Phase of the study (including Module A and Module B) will occur over approximately 18 months and that enrollment of the cohort expansion portions of the study will take approximately 12 months from the time of initiation of the Cohort Expansion Phase for each Module A and Module B.

The total time for conduct of the trial is expected to be approximately 78 months (which includes 2 years of survival follow-up). These estimates of the timing for study conduct may vary from that observed in the actual conduct of the trial.

### 4.5.1 Participant Accrual

The maximum number of participants to be enrolled in this study will be approximately 182 participants. This number of participants does not take into account participants who may be replaced or the possibility of expanding the mCRPC cohort with an additional 24 participants at the discretion of the sponsor.

The number of participants enrolled in the Dose Escalation Phase cannot be precisely determined in advance and could range from 6 up to 54 participants depending on results in the course of the trial and the number of dose levels explored. This participant number does not take into account replacement of non-evaluable participants or the possibility of expanding an individual escalation cohort up to 15 participants to allow for further evaluation of safety, PK, and antitumor activity of the study drugs at the dose level in that cohort.

The Cohort Expansion Phase of the study will enroll up to 128 participants. Module A Cohort Expansion Phase will enroll up to 16 participants into each of 5 cohorts (mCRPC, NSCLC, TNBC, SCCHN, and melanoma) treated with MGC018 monotherapy. Module B will enroll up to 16 participants into each of 3 cohorts treated with the combination of MGC018 and MGA012: participants with unresectable, locally advanced or metastatic SCCHN, mCRPC, and participants with a tumor type TBD at a later date. During the Cohort Expansion Phase of the study, participants 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, additional participants may be enrolled. In addition, up to 4 participants may be added per cohort.

### 4.5.2 Definition of End of Study

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

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

## 4.6 Appropriateness of Measurements

Routine laboratory evaluations including hematology, chemistry, coagulation, endocrine tumor markers, 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 evaluate AEs.

# 5 SELECTION AND WITHDRAWAL OF PARTICIPANTS

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

The participant population to be enrolled in this study will consist of adult participants with histologically proven, relapsed or refractory, unresectable locally advanced or metastatic solid tumors.

## 5.1 Inclusion Criteria

1. Ability to provide informed consent and documentation of informed consent prior to initiation of any study-related tests or procedures that are not part of standard-of-care for the participant's disease. Participants must also be willing and able to comply with study procedures, including the acquisition of specified research specimens.
2. Age ≥ 18 years old.
3. Archival or formalin-fixed paraffin-embedded (FFPE) tissue must be available for determination of B7-H3 (Module A) and B7-H3 and PD-L1 expression (Module B). Participants may undergo a fresh tumor biopsy to obtain a specimen for testing if a tumor sample is not available; mCRPC with bone only disease not amenable to fresh biopsy may be eligible in consultation with the sponsor.
4. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2.
5. Life expectancy ≥ 12 weeks for Dose Escalation Phase and ≥ 24 weeks for Cohort Expansion Phase.
6. Measurable disease as per RECIST v1.1 criteria (**Appendix 5**). Participants with mCRPC without measurable disease may be enrolled. Cutaneous or subcutaneous lesions must be measurable by calipers. Note: Lesions to be used as measurable disease for the purpose of response assessment must not reside in a field that has been subjected to prior radiotherapy.
7. Tumor Histology Types

   **Dose Escalation Phase of the Study:**

   a. Participants with histologically proven, relapsed or refractory, unresectable locally advanced or metastatic solid tumors of any histology for whom no therapy with demonstrated clinical benefit is available.

   **Cohort Expansion Module A:**

   a. mCRPC that has progressed during or following one prior line of chemotherapy for metastatic disease, and if approved and available, no more than two prior lines of an anti-hormonal agent (e.g., abiraterone, enzalutamide) with a PSA value of at least 2 ng/mL and meeting at least one of the following:

      - Progression in measurable disease (RECIST v1.1).

- Appearance of 2 or more new bone lesions according to Prostate Cancer Working Group 2 (PCWG2).
- Rising PSA defined as at least two sequential rises in PSA (PSA obtained ≥ 1 week apart) over a reference value (the last PSA [PSA ≥ 2 ng/mL] measured before the first rise in PSA) (as defined by the PCWG2).

b. NSCLC

- Metastatic NSCLC who have failed standard cytotoxic, targeted, and biologic or checkpoint inhibitor therapy. No more than two prior lines of cytotoxic chemotherapy.

c. TNBC

- Locally advanced or metastatic TNBC that has progressed during or following at least one systemic therapy. American Society of Clinical Oncology (ASCO) College of American Pathologists (CAP) guidelines should be followed for establishing the diagnosis of TNBC (**76**).

d. SCCHN that has progressed during or following at least one systemic therapy for metastatic or recurrent unresectable disease. No more than 2 prior lines of cytotoxic chemotherapy are allowed.

e. Melanoma that has progressed during or following at least one systemic treatment for unresectable locally advanced or metastatic disease. Patients who are intolerant of or refused standard therapy are eligible.

**Cohort Expansion Module B:**

Participants with histologically proven, unresectable, locally advanced or metastatic solid tumors for whom no therapy with demonstrated clinical benefit is available as described below.

a. SCCHN that has progressed following treatment with platinum-based chemotherapy for metastatic or recurrent disease, or progression of disease within 6 months of completing prior platinum therapy used as part of neoadjuvant, concurrent chemoradiation, or adjuvant therapy.

- Participants with upper esophageal or salivary gland tumors will not be considered as SCCHN.
- Participants who refuse radical resection for recurrent disease are eligible.

b. mCRPC that has progressed during or following one prior line of chemotherapy for metastatic disease, and if approved and available, no more than two prior lines of anti-hormonal agent (e.g., abiraterone, enzalutamide) with a PSA value of at least 2 ng/mL and meeting at least one of the following:

- Progression in measurable disease (RECIST v1.1).
- Appearance of 2 or more new bone lesions according to Prostate Cancer Working Group 2 (PCWG2).
- Rising PSA defined as at least two sequential rises in PSA (PSA obtained ≥ 1 week apart) over a reference value (the last PSA [PSA ≥ 2 ng/mL] measured before the first rise in PSA) (as defined by the PCWG2).

c. Tumor type TBD at a later date; cancer will be required to have progressed or recurred despite prior standard therapy for that specific tumor.

8. Acceptable laboratory parameters as follows:
   a. Platelet count ≥ 100 × 103/µL without transfusion within 28 days prior to the initiation of study drug,
   b. Absolute neutrophil count ≥ 1.5 × $10^3$/µL in the absence of any growth factor support within 21 days prior to the initiation of study drug,
   c. ALT/AST ≤ 3.0 × ULN; for participants with hepatic metastases, ALT and AST ≤ 5 × ULN,
   d. Total bilirubin ≤ 1.5 × ULN, except participants with Gilbert's syndrome, who may enroll if the conjugated bilirubin is within normal limits,
   e. Creatinine < 2 mg/dL, or a calculated creatinine clearance (based on the Cockcroft-Gault formula) or measured creatinine clearance > 50 mL/min,
   f. Negative urine or serum pregnancy test for women of childbearing potential.
   g. Albumin ≥ 3.0 g/dL
   h. Hemoglobin ≥ 8.0 g/dL without transfusion within 28 days prior to initiation of study drug.
9. Female participants of childbearing potential, defined as not surgically sterilized (hysterectomy, bilateral salpingectomy, and bilateral oophorectomy) and between menarche and 1-year post menopause, must have a negative serum pregnancy test performed within 72 hours prior to the initiation of study drug administration. Female participants should abstain from egg donation during the study.
10. Female participants of childbearing potential and male participants with partners who are females of childbearing potential must agree to use highly-effective methods of contraception according to **Section 8.1.3** from the time of consent through 27 weeks after discontinuation of study drug administration. Male participants should abstain from sperm donation during the study.
11. The female of childbearing potential is not pregnant or breastfeeding or male participant is not expecting to father children within the projected duration of the study, starting with screening visit through 27 weeks after the last dose of study drug.

12. Module B only: Previous Checkpoint Inhibitor Therapy: Participants 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. Note that participants who experienced previous hypothyroidism toxicity on a checkpoint inhibitor are eligible to enter study regardless of Common Terminology Criteria for Adverse Events (CTCAE) grade resolution as long as the participant is well controlled on thyroid replacement hormones.

## 5.2 Exclusion Criteria

Participants who meet any of the following criteria will be excluded from the study.

1. Participants with history of prior central nervous system (CNS) metastasis must have been treated, must be asymptomatic, and must not have any of the following at the time of enrollment:
    a. Concurrent treatment for the CNS disease (e.g., surgery, radiation, corticosteroids > 10 mg prednisone/day or equivalent),
    b. Progression after primary treatment of CNS metastases on imaging with MRI, CT or positron emission tomography (PET)/CT within 6 months prior to screening,
    c. History of leptomeningeal disease or spinal cord compression.
2. Module B only: Participants 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 participants with a history of Grave's disease that are now euthyroid clinically and by laboratory testing.
3. Treatment with any investigational therapy within the 4 weeks prior to the initiation of study drug administration.
4. Module B only: Previous Checkpoint Inhibitor Therapy: Participants who experienced the following immune checkpoint inhibitor-related AEs make the participant 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,
    e. ≥ Grade 3 pneumonitis,
    f. ≥ Grade 3 renal toxicity,

g. ≥ Grade 3 skin toxicity.

5. Prior treatment with MGD009, enoblituzumab, or other B7-H3 targeted agents for cancer.
6. Treatment with any systemic anti-cancer therapy within the interval provided prior to study drug administration
    a. 4 weeks for cytotoxic chemotherapy for all tumor types or anti-hormonal therapy (e.g., enzalutamide, abiraterone) for mCRPC,
    b. 14 days or 5 half-lives, whichever is longer, for small molecule targeted or kinase inhibitors,
    c. 4 weeks prior for biologic agents,
    d. Prior radioligand (e.g., radium-223) within 6 months for mCRPC in the Cohort Expansion Phase.
7. Treatment with mediastinal or pelvic radiation therapy within 4 weeks prior to the initiation of study drug administration. Palliative, limited field radiation for symptom control to soft tissues, or bone lesions within 2 weeks prior to the initiation of study drug administration.
8. Module B only: Treatment with systemic corticosteroids (> 10 mg per day prednisone or equivalent) or other immune suppressive drugs within the 14 days prior to the initiation of study drug administration.
9. Clinically significant cardiovascular disease including but not limited to:
    a. Myocardial infarction or unstable angina within the 6 months prior to the initiation of study drug,
    b. Stroke or transient ischemic attack within 6 months prior to the initiation of study drug,
    c. Clinically significant cardiac arrhythmias, e.g., atrial fibrillation that are not well controlled with optimal medical intervention,
    d. Uncontrolled hypertension: systolic blood pressure > 180 mmHg, diastolic blood pressure > 100 mmHg,
    e. Congestive heart failure (New York Heart Association class I-IV),
    f. Pericarditis or pericardial effusion,
    g. Myocarditis,
    h. Participants with a baseline left ventricular ejection fraction (LVEF) of < 50%,
    i. Prolongation of QTcF > 480 milliseconds.
10. Clinically significant pulmonary compromise, including pneumonia, pneumonitis, or a requirement for supplemental oxygen use to maintain adequate oxygenation or history of ≥ Grade 3 drug-induced or radiation pneumonitis.

11. Evidence of active viral, bacterial, or systemic fungal infection requiring parenteral antibiotic, antiviral, or antifungal treatment within 7 days prior to the initiation of study drug. Participants 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.
12. Known history of positive testing for human immunodeficiency virus or history of acquired immune deficiency syndrome.
13. 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.
14. History of prior allogeneic bone marrow, stem-cell, or solid organ transplantation.
15. Second primary invasive malignancy that has not been in remission for greater than 2 years except non-melanoma skin cancer; cervical carcinoma in situ on biopsy; or squamous intraepithelial lesion on Pap smear; localized prostate cancer (Gleason score < 6); or resected melanoma in situ.
16. Major trauma or major surgery within 4 weeks prior to the initiation of study drug administration.
17. Any serious underlying medical or psychiatric condition that would impair the ability of the participants to receive or tolerate the planned treatment at the study site.
18. Known hypersensitivity to recombinant proteins, or any excipient contained in the drug formulation or custom vehicle (**Section 6.5**).
19. Vaccination with any live virus vaccine within 4 weeks prior to the initiation of study drug administration. Inactivated annual influenza vaccination is allowed.
20. Dementia or altered mental status that would preclude understanding and rendering of informed consent.
21. Prisoners or other individuals who are involuntarily detained.
22. Any investigative site personnel directly affiliated with this study.
23. Any issue that, in the opinion of the investigator in consultation with the sponsor, would contraindicate the participant's participation in the study or confound the results of the study.
24. Clinically significant venous insufficiency.
25. > Grade 1 peripheral neuropathy.
26. Evidence of pleural effusion.
27. Evidence of ascites.
28. Serum testosterone >50 ng/dl or >1.7 nmol/L in mCRPC in Module A Cohort Expansion Phase and Module B Cohort Expansion Phase.

29. Confirmed or presumed COVID-19/SARS-CoV-2 infection. While SARS-CoV-2 testing is not mandatory for study entry, testing should follow local clinical practice guidelines/standards. Participants with a positive test result for SARS-CoV-2 infection, known asymptomatic infection, or presumed infection are excluded.

## 5.3 Withdrawal of Participant from the Study

Participants who withdraw before Study Day 21 (Module A) or Study Day 42 (Module B) during the Dose Escalation Phase for a reason unrelated to drug toxicity may be considered to have inadequate data to support dose escalation. In this case, replacement participants may be enrolled in the same dose level. These participants will be followed for safety assessments (see **Section 12.2**).

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

## 5.4 Rules for Study Treatment Discontinuation

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

- Participant meets RECIST v1.1 criteria for disease progression
- Participant meets PCWG-2 criteria for radiographic progression
- Withdrawal of participant due to an AE or SAE
- Withdrawal of participant consent
- Completion of protocol-defined therapy
- Investigator discretion
- Pregnancy
- Occurrence of drug-related DLT or AEs that lead to discontinuation of study drug
- Dose delay > 21 days due to AEs unless approved by the sponsor.
- The sponsor, investigator, or regulatory agency terminates the study
- Death

For individual participants who meet these criteria, but who are otherwise considered to be experiencing clinical benefit in the judgment of the investigator, consideration may be given to continue therapy of MGC018 alone (Module A) or in combination with MGA012 (Module B), for up to maximum of total of 18 cycles (i.e. approximately 2 years), on a case-by-case basis in consultation with the sponsor. If the investigator decides that the participant 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 by completing the appropriate electronic case report forms (eCRFs) (**Section 12.2.2**).

## 5.5 Guidelines for Discontinuation of Participant from Study

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

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

# 6 STUDY TREATMENTS

## 6.1 Description of Treatments

For Module A, MGC018 will be administered on Days 1 and 22 of each 42-day cycle. For Module B, MGC018 will be administered on Days 1 and 22 of each 42-day cycle. In addition, for Module B, MGA012 will be administered on Day 22 of Cycle 1 and on Days 1 and 22 of every 42-day cycle thereafter. Each cycle is 42 days.

MGC018 will be administered as an IV infusion over 60 minutes. MGA012 will be administered by IV infusion 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. MGC018 and MGA012 will be administered as separate IV infusions.

## 6.2 Method of Assigning Participants to Treatment Groups

Participants will be assigned sequentially to the dose escalation cohorts and cohort expansion cohorts as specified in **Section 4.1.1** and **Section 4.1.2**, respectively. Participants in the Cohort Expansion Phase will receive doses of MGC018, alone (Module A) or in combination with MGA012 (Module B), at the MTD (or MAD if no MTD is defined) based on results from the Dose Escalation Phase of the respective modules. A predetermined number of participants will then be enrolled in each cohort.

## 6.3 Blinding

This is an open-label study.

## 6.4 Emergency Unblinding

Not applicable. This is an open-label study.

## 6.5 Study Drug and Supplies

### 6.5.1 MGC018

[redacted]

MGC018 must be diluted with sterile 0.9% Sodium Chloride Injection, USP (normal saline), prior to administration. MGC018 will be administered by IV infusion over 60 minutes. MGC018 must not be administered as an IV push or bolus.

### 6.5.2 MGA012

MGA012 must be diluted with sterile 0.9% Sodium Chloride Injection, USP (normal saline), prior to administration. MGA012 will be administered by IV infusion over 60 minutes. MGA012 must not be administered as an IV push or bolus.

**Table 8 MGA012 Drug Product Composition**

## 6.6 Study Infusion Preparation

### 6.6.1 General Guidelines and Precautions

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

#### 6.6.1.1 MGC018 (Module A and B)

The calculated dose of MGC018 will be administered based on the participant's actual weight at Cycle 1, Day 1 (or up to 24 hours prior to Cycle 1, Day 1). In the cohort expansion phase, the MGC018 dose will be capped for participants with a body weight ≥ 100 kg. Body weight will be measured at Screening and Days 1 and 22 of each cycle. Significant (≥ 10%) change in BW from baseline should prompt recalculation of dose using the most recent body weight. Refer to the pharmacy manual for further instructions on allowable parameters for dose rounding.

MGC018 should not be administered as an IV push or bolus. All doses of MGC018 will be diluted in normal saline and administered as an IV infusion over 60 minutes with a commercially available infusion pump or syringe pump. All infusion pumps must be calibrated in accordance with the institutional standards, policies, and procedures to ensure consistent, accurate delivery of MGC018.

Infusion or allergic reactions may occur with the infusion of monoclonal antibodies and other protein-based therapeutics. Precautions for anaphylaxis should be observed during administration. Supportive measures may include, but are not limited to, epinephrine, antihistamines, corticosteroids, IV fluids, vasopressors, oxygen, bronchodilators, diphenhydramine, and acetaminophen. Please refer to **Section 7.1** for specific guidelines

regarding the management of infusion reactions. Supportive care measures consistent with optimal participant care will be provided throughout the study according to institutional standards.

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.

Note: Participants should remain in the infusion center for 4 hours after the completion of administration of the first dose of **MGC018 alone** (**Module A**, Day 1 of Cycle 1). For **Module B**, participants should remain in the infusion center for 4 hours after the completion of administration of the first dose of **MGC018 alone** (Day 1 Cycle 1) and 4 hours after the completion of the first dose of combined administration of **MGC018 and MGA012** (Day 22, Cycle 1).

#### 6.6.1.2 MGA012 (Module B only)

MGA012 should not be administered as an IV push or bolus. All doses of MGA012 will be diluted in normal saline and administered as an IV infusion over 60 minutes with a commercially available infusion pump or syringe pump. All infusion pumps must be calibrated in accordance with the institutional standards, policies, and procedures to ensure consistent, accurate delivery of MGA012. Refer to the pharmacy manual for instructions on infusion preparation.

MGA012 dose will be administered as per **Table 4**.

Infusion or allergic reactions may occur with the infusion of monoclonal antibodies and other protein-based therapeutics. Precautions for anaphylaxis should be observed during MGA012 administration. Supportive measures may include, but are not limited to, epinephrine, antihistamines, corticosteroids, IV fluids, vasopressors, oxygen, bronchodilators, diphenhydramine, and acetaminophen. Please refer to **Section 7.1** for specific guidelines regarding the management of infusion reactions. Supportive care measures consistent with optimal participant care will be provided throughout the study according to institutional standards.

### 6.6.2 Study Drug Preparation and Administration

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

Instructions on the thawing and preparation of the study drugs (MGC018 and MGA012) for IV infusion are detailed in the pharmacy manual.

Do not mix the study drugs with, or administer as an infusion with, other medicinal products.

#### 6.6.2.1 MGC018

All doses of MGC018 must be diluted in sterile 0.9% Sodium Chloride Injection, USP (normal saline) prior to dose administration. MGC018 diluted in normal saline must be within the concentration range of 0.1 mg/mL to 6.0 mg/mL for syringe pump administration and 0.5 mg/mL to 2.9 mg/mL for infusion pump administration. Administer the diluted dosing solution over 60 minutes through an IV line with a commercially available infusion pump or syringe pump. Up to 10 additional minutes of infusion time (i.e. up to a total infusion time of 70 minutes) is permitted to allow for flushing the line. A sterile, non-pyrogenic, low protein binding PES 0.2 µm in-line filter administration set should be used for IV administration of MGC018. Do not administer as an IV push or bolus.

Because there is no preservative and drug loss may occur over time. The administration of study drug should begin immediately after preparation, but no later than 4 hours at room temperature after preparation. Alternatively, the dose-prepared IV bag or syringe may be stored for up to 24 hours at 2° to 8°C. If the dose solution is stored at 2° to 8°C, it should be removed from the refrigerator at least 30 to 60 minutes prior to administration, to allow solution to reach room temperature. If there is a delay in administration of study drug such that the drug will not be administered according to the above parameters, the medical monitor must be notified immediately, and instructions on how to proceed will be provided.

#### 6.6.2.2 MGA012

All doses of MGA012 must be diluted to a concentration range of 0.3 mg/mL to 12.0 mg/mL in sterile 0.9% Sodium Chloride Injection, USP (normal saline). Administer the diluted dosing solution over 60 minutes through an IV line with a commercially available infusion pump. A sterile, non-pyrogenic, low protein binding PES 0.2 µm in-line filter administration set must be used for IV administration of MGA012. MGA012 should not be administered as an IV push or bolus.

The administration of study drug should begin immediately after preparation. The administration should be no later than 4 hours and study drug kept at room temperature after preparation. Alternatively, the dose-prepared IV bag may be stored for up to 24 hours at 2° to 8°C. If the dose solution is stored at 2° to 8°C, it should be removed from the refrigerator at least 30 to 60 minutes prior to administration, to allow solution to reach room temperature. If there is a delay in administration of study drug such that the drug will not be administered according to the above parameters, the medical monitor must be notified immediately, and instructions on how to proceed will be provided.

### 6.6.3 Combination Therapy

When MGC018 and MGA012 are to be administered on the same day (Module B only), MGA012 should be given first, followed immediately thereafter by MGC018.

After MGA012 infusion, the IV line should be cleared with normal saline infusion given at the same rate as the MGA012 infusion.

**Do not manually push normal saline after MGA012 or MGC018 infusion.**

## 6.7 Treatment Compliance

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

## 6.8 Packaging and Labeling

MGC018 drug product is supplied as a single-use, packaged in a United States Pharmacopeia-National Formulary (USP-NF) and European Pharmacopoeia (Ph. Eur.) conforming Type 1 borosilicate, 20 cc clear glass vial with a 20 mm FluroTec® and B2-40® -coated 4023/50 gray butyl rubber serum stopper. The vial is sealed with a 20 mm aluminum closure with a plastic overseal. MGC018 is supplied in 93 mg/9.3 mL (10 mg/mL) single-use vials. MGC018 is labeled according to local regulatory health authority requirements. Please see the pharmacy manual for detailed information about the packaging of the study drug.

MGA012 drug product is supplied packaged in a USP and Ph. Eur. conforming Type I borosilicate, 10 mL glass vial with a 4432/50 gray butyl rubber stopper with B2-40® coating and FluroTec® coating on plug. The vial is sealed with a 20 mm aluminum closure with a plastic overseal. MGA012 is supplied as 10 mL (250 mg/vial) single-use vials. MGA012 is labeled according to local regulatory health authority requirements. Please see the pharmacy manual for detailed information about the packaging of the study drug.

Please see the MGC018 and MGA012 pharmacy manuals for detailed information about the packaging of the study drugs. All study drug will be labelled with a minimum of the protocol number, directions for use, and storage conditions; the statements “For clinical trial use only,” and/or “CAUTION: New Drug – Limited by Federal (United States) Law for Investigational Use”; and the sponsor’s name and address.

## 6.9 Storage and Accountability

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/her 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 15.1** of the protocol.

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. Additional details regarding storage, handling, and accountability can be found in the pharmacy manual.

### 6.9.1 MGC018

Vials containing study drug should be stored in an appropriate, locked room accessible only to pharmacy personnel, the investigator, or duly designated personnel. used for drug storage must be maintained at a temperature To ensure compliance with storage conditions, temperature logs should be maintained. Vials should be protected from light during storage and should not be shaken. Standard laboratory practices should be used for avoidance of contact with MGC018.

### 6.9.2 MGA012

Vials containing MGA012 must 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 with MGA012.

## 6.10 Investigational Product Disposition at End of Study

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

# 7 POTENTIAL ADVERSE EVENTS AND SUPPORTIVE CARE MEASURES

## 7.1 Infusion Related Reactions Including Cytokine Release Syndrome

Infusion reactions (including CRS) associated with the administration of mAb-based therapeutics 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).

Participants should be monitored closely for the development of infusion related reactions (IRRs) during 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 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 20 to 40 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 participant should be treated according to the best available local practices and procedures. All supportive measures consistent with optimal participant 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. Participants should be evaluated carefully for the presence of infection (including COVID-19), with the acquisition of cultures and/or implementation of empiric antibiotic therapy as appropriate based on the assessment of the investigator. Please refer to **Section 7.1.3** for guidance regarding the management of infusion reactions.

### 7.1.1 Grading and Management of Infusion Reactions

Infusion reactions will be categorized as follows:

- Grade 1: mild reaction; infusion interruption not indicated, intervention not indicated; Note: although interruption in infusion is not indicated, temporary rate reduction indicated before resuming original rate, as participant tolerates (see **Section 7.1.3**);
- 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);
- Grade 3: prolonged (e.g., not rapidly responsive to medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates);
- Grade 4: life-threatening consequences; pressor or ventilatory support indicated;

- Grade 5: death.

The above grading scale is the CTCAE v4.0.3 grading scale for CRS, which is nearly identical to the CTCAE v4.0.3 grading scale for infusion reaction and allergic reaction and is therefore considered appropriate for grading all infusion reactions in this study, irrespective of the underlying mechanism of the reaction. The sponsor's medical monitor or designee should be contacted immediately if questions arise concerning the grade of the reaction.

### 7.1.2 Premedication and Prophylaxis

The following are guidelines for the investigator regarding prophylactic pre-infusion measures to be followed to mitigate the occurrence or severity of potential infusion reactions.

At least 30 minutes prior to each infusion of MGC018 alone or the combination of MGC018 and MGA012:

- Acetaminophen 650 to 1000 mg orally (PO), or ibuprofen 400 mg PO
- Diphenhydramine 50 mg PO or IV or equivalent H1 antagonist
- Famotidine 40 mg PO or 20 mg IV, or equivalent H2 antagonist
- Corticosteroid eg. Dexamethasone 4 mg IV or equivalent

For subsequent administration of MGC018 alone or in combination with MGA012, participants who had infusion reactions that were not adequately or only moderately controlled, other medications may also be considered as a part of the pre-medication regimen for subsequent doses. Non-steroidal pre-medications may be administered prior to the subsequent infusion, if warranted.

For participants treated on Module B (combination of MGC018 and MGA012), if the administration of the MGC018 is delayed by more than 4 hours after completion of MGA012 administration, repeat dosing of pre-medications may be considered prior to administration of MGC018.

### 7.1.3 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 IRR:

Grade 1:

- Slow the infusion rate by 50%.
- Monitor the participant 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 subsequent infusions at 50% rate and increasing as tolerated.
- If a participant has an infusion reaction, prophylactic pre-infusion medications should be given prior to all subsequent infusions. The following prophylactic pre-infusion medications are recommended prior to future infusions of MGC018 alone or in combination with MGA012 for participants who experience Grade 1 infusion reactions: diphenhydramine 25 to 50 mg (or equivalent) PO/IV and acetaminophen 650 mg PO and/or ibuprofen 400 mg PO, with or without famotidine 40 mg PO or 20 mg IV (or equivalent H2-antagonist) at least 30 minutes before additional study drug administrations.

Grade 2:

- Stop the infusion.
- Administer diphenhydramine hydrochloride 25 to 50 mg IV.
- Acetaminophen 650 mg PO or ibuprofen 400 mg PO for fever.
- 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.
- Prophylactic pre-infusion medications should be given prior to subsequent infusions of MGC018 alone or in combination with MGA012. Participants who experience a Grade 2 infusion reaction, for subsequent doses of MGC018 alone or in combination with MGA012, pre-medicate with diphenhydramine hydrochloride 25 to 50 mg IV/PO, acetaminophen 650 mg PO and/or ibuprofen 400 mg PO, with or without famotidine 40 mg PO or 20 mg IV (or equivalent H2-antagonist) at least 30 minutes before additional study drug administrations. For these participants, corticosteroids (dexamethasone 10 mg IV or hydrocortisone 25 to 100 mg IV or higher) also may be added to the premedication regimen for subsequent dosing of MGC018 alone or in combination with MGA012.

Grade 3:

- STOP THE INFUSION AND DISCONNECT THE INFUSION TUBING FROM THE PARTICIPANT.

- TO AVOID EXACERBATION OF INFUSION REACTION OR CRS: DO NOT FLUSH THE TUBING – ASPIRATE RESIDUAL DRUG FROM THE VASCULAR ACCESS DEVICE.
- Administer diphenhydramine hydrochloride 25 to 50 mg IV, dexamethasone 20 mg IV (or equivalent), and other medications/treatment as medically indicated. Higher doses of corticosteroids (e.g., methylprednisolone 2 to 4 mg/kg IV or the equivalent) may also be considered for acute management.
- IV fluids, supplemental oxygen, and bronchodilators should be considered, as appropriate.
- If the Grade 3 infusion reaction occurs with administration of MGC018 alone or in combination with MGA012, it will be discontinued for that day. If symptoms have resolved to baseline within 12 hours, MGC018 alone or combination with MGA012 may be infused the next day. In addition, participants should be pre-medicated for this re-challenge and for any subsequent doses of MGC018 alone or in combination with MGA012 with the following: diphenhydramine hydrochloride 25 to 50 mg IV, acetaminophen 650 mg PO and/or ibuprofen 400 mg PO, with or without famotidine 40 mg PO or 20 mg IV (or equivalent H2-antagonist). Corticosteroids (dexamethasone 10 to 20 mg IV or hydrocortisone 50 to 100 mg IV or higher) should be considered as well.
- Participants who have a Grade 3 infusion reaction that does not resolve within 12 hours despite medical management should not receive further treatment with MGC018 alone or in combination with MGA012. Participants who experience a second Grade 3 infusion reaction at the time of re-challenge of MGC018 alone or in combination with MGA012 will permanently discontinue treatment with study drugs.
- Report as an IRE within 24 hours.
- Report the event as a SAE, if appropriate.

Grade 4:

- STOP THE INFUSION AND DISCONNECT THE INFUSION TUBING FROM THE PARTICIPANT.
- TO AVOID EXACERBATION OF INFUSION REACTION OR CRS: DO NOT FLUSH THE TUBING – ASPIRATE RESIDUAL DRUG FROM THE VASCULAR ACCESS DEVICE.
- Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 20 mg 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.
- Participants who have a Grade 4 infusion reaction will not receive further treatment with MGC018 alone or in combination with MGA012.

Grade 5:

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

All changes in the infusion of MGC018 and MGA012, including interruption of the infusion and its duration as well as reductions in infusion rate and duration, must be recorded.

## 7.2 Immune-Related Adverse Events

Blockade of immune checkpoints has been associated with several immune-mediated AEs that develop as a result of disruption of immune tolerance in normal tissues (**31**, **58**, **65**). These include, but are not limited to: pneumonitis, colitis, autoimmune hepatitis, arthritis, glomerulonephritis, myocarditis and cardiomyopathy, hypophysitis, thyroiditis, myositis, uveitis, neurotoxicity, pericarditis, autoimmune endocrinopathies (e.g., pancreatitis and diabetes), and dermatologic toxicity (including Stevens Johnson syndrome and toxic epidermal necrolysis). The occurrence of any of these may dictate delay and potentially discontinuation of study drug administration pending further evaluation and reporting them to the sponsor as adverse events of special interest (AESI). 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 high-dose corticosteroids.

General guidelines for specific toxicity regarding dosing and treatment are provided below. All toxicities will be graded according to NCI CTCAE v4.03. Refer to the National Comprehensive Cancer Network Guidelines for the Management of Immune-related Toxicities (https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf) for toxicities not specifically mentioned in this section. Unless otherwise specified, Grade 1 irAEs may be monitored without administering specific interventions. Guideline principles may be adapted to local standard of care at the investigator's discretion.

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

### 7.2.1 Diarrhea or Colitis

Diarrhea that develops in participants while receiving the study drugs may reflect immune reactivity against normal colonic epithelium, and careful monitoring for potential immune-related colitis should be instituted. Participants should be monitored closely for evidence of diarrhea or other change in bowel habits, as well as other signs and symptoms suggestive of colitis. Participants 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. For management of symptoms:
    - Loperamide/diphenoxylate
    - Low-dose steroids if clinically indicated
    - Consider management of prolonged Grade 2 event lasting more than 5 to 7 days or relapsed diarrhea as Grade 3 diarrhea (see below)
- Grade 3 diarrhea - Hold study drugs. Hospitalize participant promptly for further evaluation and management, including the following:
    - Bowel rest
    - Supplemental IV fluids with close monitoring of fluid and electrolyte status
    - Monitor frequency of bowel movements
    - Consider imaging to rule out bowel obstruction or perforation
    - Consideration of colonoscopy as appropriate
    - Implementation of initial empiric immune suppression consisting of IV corticosteroids using methylprednisolone at a dosage of 2 mg/kg/day (or equivalent) divided twice daily. As tolerated, participants may be converted to oral corticosteroids (i.e., prednisone 2 mg/kg/day divided twice daily) and tapered as appropriate guided by the participants' clinical status.
    - Taper corticosteroids as clinically indicated
    - For participants 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
    - It is determined there is no colitis and an alternative cause of diarrhea is found, consider restarting study drug(s) if:
        - Diarrhea resolves to ≤ Grade 1 within 21 days
- Grade 4 diarrhea - discontinue study drugs and treat as for Grade 3.

### 7.2.2 Hepatic Toxicity

#### 7.2.2.1 Elevations in Transaminases

Management guidelines for participants experiencing hepatic toxicity are as follows:

- Grade 1 elevations - No specific therapy required.
- Grade 2 elevations - For elevations in transaminases 3 to 5 × ULN, rule out viral and other etiologies. Consider imaging studies such as ultrasound or CT scan and liver biopsy to ascertain etiology of liver dysfunction. Consider starting oral prednisone 60 mg/day divided twice daily and hold study drugs.
    - 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 study drugs at the next scheduled dose if no more than one dose of MGC018 alone or in combination with MGA012 was missed.
    - If improvement to ≤ Grade 1 does not occur within 21 days, discontinue study drugs.
- Grade 3 elevations - Hold study drugs.
    - For elevations in transaminases > 8 × ULN, permanently discontinue study drugs.
        - Begin immediate IV steroids and,
        - If no response to corticosteroid therapy within 3 to 5 days is observed, consider adding immune suppression therapy with mycophenolate.
        - Monitor liver function tests at least twice weekly (or more frequently as clinically appropriate in the judgment of the investigator) until transaminases have returned to Grade 1 or baseline.
    - For elevations in transaminases > 5 but ≤ 8 × ULN:
        - Begin immediate IV steroids; suggest methylprednisolone at a dosage of 2 mg/kg/day divided twice daily.
        - Consider additional immune suppression as above for participants who do not respond to corticosteroid therapy within 3 to 5 days.
        - Monitor liver function tests at least twice weekly (or more frequently as clinically appropriate in the judgment of the investigator) until transaminases have returned to Grade 1 or baseline.

        - If the elevation does not improve to Grade 2 within 7 days and to Grade 1 within 21 days, discontinue study drugs.
    - Resume study drugs administration if following conditions are met:
        - Laboratory elevations improved to ≤ Grade 2 within 7 days and improve to ≤ Grade 1 or baseline within 21 days.
        - Steroids have been tapered to ≤ 10 mg per day of prednisone or equivalent.
        - On resuming study drugs, AST, ALT, and total and direct bilirubin laboratory test values will be evaluated at least once per week for 3 consecutive weeks.
    - Permanently discontinue study drug treatment in the case of a second increase of AST or ALT to ≥ Grade 3.
- Grade 4 elevation - Discontinue study drugs and treat as for Grade 3 elevation.

#### 7.2.2.2 Elevations in Total Bilirubin

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

- Grade 1 elevations - No specific therapy required.
- Grade 2 elevations - Hold study drugs until improvement to ≤ Grade 1.
    - Rule out viral and other etiologies. Consider imaging studies such as ultrasound or CT scan and liver biopsy to ascertain etiology of liver dysfunction. Consider oral steroids.
    - If improvement to ≤ Grade 1 does not occur within 21 days, discontinue study drugs and begin oral steroids.
- Grade 3 elevations - Hold study drugs.
    - For elevations in total bilirubin > 5 × ULN, permanently discontinue study drugs and initiate IV steroids, suggest methylprednisolone at a dosage of 2 mg/kg/day divided twice daily, and,
        - If no response to corticosteroid therapy within 3 to 5 days is observed, consider adding immune suppression therapy with mycophenolate.
        - Monitor liver function testing at least twice weekly (or more frequently as clinically appropriate in the judgment of the investigator) until total bilirubin has returned to Grade 1 or baseline.
    - For elevations in total bilirubin > 3.0 but ≤ 5 × ULN:
        - Begin immediate IV steroids, suggest methylprednisolone at a dosage of 2 mg/kg/day divided twice daily. Consider additional

immune suppression as above for participants who do not respond to corticosteroid therapy within 3 to 5 days.

- Monitor liver function including total bilirubin testing at least twice weekly (or more frequently as clinically appropriate in the judgment of the investigator) until total bilirubin has returned to Grade 1 or baseline.
- If the elevation does not improve to Grade 2 within 7 days and to Grade 1 within 21 days, discontinue study drugs.
- Resume study drugs administration if:
  - Laboratory elevations downgrade to ≤ Grade 2 within 7 days and improve to ≤ Grade 1 or baseline within 21 days.
  - Steroids have been tapered to ≤ 10 mg per day of prednisone or equivalent
  - On resuming study drugs, AST, ALT, and total bilirubin laboratory test values will be evaluated at least once per week for 3 consecutive weeks.
- Permanently discontinue study drugs in the case of a second increase of total bilirubin to ≥ Grade 3.

- Grade 4 elevations - Discontinue study drugs and treat as for Grade 3 elevation.

### 7.2.3 Pneumonitis

Management guidelines for participants experiencing pneumonitis are as follows:

- Grade 1 pneumonitis - No specific therapy required; close monitoring of lung function and imaging.
- Grade 2 pneumonitis - Hold study drugs.
  - Consider corticosteroids: 1 to 2 mg/kg of oral prednisone or equivalent per day divided twice daily.
  - Taper corticosteroids over 4 weeks or as clinically indicated.
  - Resume study drug administration at next scheduled dose if pneumonitis resolves to ≤ Grade 1 within 5 days with or without treatment.
- Grade 3 and 4 pneumonitis - Permanently discontinue study drugs.
  - Hospitalize.
  - Recommend a pulmonary consult/diagnostic evaluation including chest X-ray and CT scan.

- Initiate maximal supportive care including IV corticosteroids, suggest methylprednisolone at 2 to 4 mg/kg/day divided twice daily. Higher doses may be used in consultation with the sponsor's medical monitor.
- If no response to corticosteroid therapy is observed within 3 to 5 days, consider adding immune suppression therapy (i.e., infliximab, etc.).

An evaluation for infection including COVID-19 should be performed.

### 7.2.4 Dermatologic Toxicity

Management guidelines for participants experiencing dermatologic toxicity are as noted below. Participants should limit sun exposure and apply broad-spectrum sunscreen to exposed skin when outdoors.

- Grade 1 or 2 skin reactions:
  - For dry skin, consider application of moisturizers as needed to affected area.
  - Symptomatic treatment with low-dose topical corticosteroids (betamethasone 0.1% or hydrocortisone 1%) or antihistamines (diphenhydramine).
  - Persistent Grade 1 or 2 rash should be managed with higher dose topical corticosteroids and/or oral prednisone (1 to 2 mg/kg/day) if there is not improvement with topical therapies or the rash is associated with other dermal toxicities such as pruritus.
  - Evaluate participant use of concomitant medications and herbal supplements that may exacerbate skin toxicity.
- Grade 3 skin reactions – Hold study drugs.
  - Initiate oral corticosteroids (oral prednisone 1 to 2 mg/kg/day).
  - Evaluate participant use of concomitant medications and herbal supplements that may exacerbate skin toxicity.
  - Consider obtaining skin biopsy if SJS or TEN is suspected. If possible, refer to specialized care center for clinical management. Cyclosporine and/or IV immunoglobulin may be considered for management of SJS or TEN.
  - Resume study drug administration at next scheduled dose if:
    - Skin toxicity resolves to ≤ Grade 1 or baseline within 21 days with maximal supportive care.
  - Discontinue study drugs if skin toxicity does not resolve to ≤ Grade 1 or baseline within 21 days, or for any grade SJS or TEN of any duration.
- Grade 4 skin reactions – Permanently discontinue study drugs.
  - Initiate oral corticosteroids (oral prednisone 1 to 2 mg/kg/day).

- Evaluate participant use of concomitant medications and herbal supplements that may exacerbate skin toxicity.
- Consider obtaining a skin biopsy if a possible diagnosis of SJS or TEN. If possible, refer to specialized care center for clinical management. Cyclosporine and/or IV immunoglobulin may be considered for management of SJS or TEN.
- Consideration should be given to start IV corticosteroids (methylprednisolone 1 to 2 mg/kg/day) for Grade 4 dermatologic toxicities with tapering on resolution to < Grade 2 over 30 days.

### 7.2.5 Nephritis

Management guidelines for participants experiencing nephritis are as follows:

- Grade 1 nephritis - No specific therapy required; close monitoring of renal function.
- Grade 2 nephritis - Hold study drugs.
  - 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 corticosteroids over 4 weeks or as clinically indicated.
  - Resume study drug administration at next scheduled dose if:
    - Nephritis resolves to ≤ Grade 1 within 21 days with or without treatment
- Grade 3 and 4 nephritis - Permanently discontinue study drugs.
  - Consider hospitalization, nephrology consultation, and renal biopsy to confirm interstitial nephritis
  - Begin corticosteroids: 2 to 4 mg/kg of oral or IV methylprednisolone or equivalent per day divided twice daily. Taper corticosteroids over 4 weeks or as clinically indicated.

### 7.2.6 Immune-Mediated Hypophysitis

Management guidelines for participants experiencing hypophysitis are as follows:

- Grade 1 hypophysitis - No specific therapy required.
- Grade ≥ 2 hypophysitis - Hold study drugs.
  - Consult endocrinologist.

- Consider hospitalization.
- Consider short course of high dose IV corticosteroids: e.g., methylprednisolone 2 to 4 mg/kg IV (or equivalent) divided twice daily.
- Initiate hormonal replacement as indicated.
- Study drug administration may be resumed as allowed by protocol when:
  - Endocrinopathy is controlled with appropriate replacement therapy.
  - Corticosteroid dose reduced to ≤ 10 mg prednisone or equivalent per day.
- Brain MRI recommended.

### 7.2.7 Thyroid Toxicity

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

- Grade 1 hyperthyroidism - No specific therapy required.
- Grade 2 hyperthyroidism - Hold study drugs.
  - Consider starting oral corticosteroid therapy.
  - Short course of corticosteroid such as methylprednisolone 1 to 2 mg/kg IV (or equivalent) divided twice daily.
- Resume study drugs if corticosteroid dose is reduced to ≤ 10 mg prednisone or equivalent per day and stable on hormone replacement therapy (if necessary).
- Grade 3 or 4 hyperthyroidism - Hold study drugs.
  - Consider hospitalization and consulting endocrinologist.
  - Begin IV corticosteroids such as methylprednisolone 2 to 4 mg/kg IV (or equivalent) divided twice daily.
  - Initiate hormonal replacement as necessary.
  - Consider restarting study drugs with complete resolution or stable on hormone replacement therapy within 21 days and if corticosteroid dose is reduced to ≤ 10 mg prednisone or equivalent per day.

## 7.3 Ocular Toxicity

Ocular toxicity, including, but not limited to, dry eye, photophobia or blurry vision have been observed in participants treated with antibody drug conjugates, and could occur at any time during treatment with MGC018 administered alone or in combination with MGA012. Uveitis has been observed in participants treated with checkpoint inhibitors, including anti-PD-1 antibodies, and could be seen in participants treated with MGA012. Prophylactic eye drops (e.g., corticosteroid, antihistamine, artificial tears) are recommended for participants 3 times per day, or as needed. Participants are advised not to wear contact lenses or rub their eyes during treatment. Participants with dry eye, photophobia or blurry vision that persists for more than 72 hours or worsens, or signs/symptoms suggestive of keratitis, conjunctivitis, or uveitis irrespective of duration, should obtain a prompt ophthalmology evaluation for further assessment and management, including local topical care and/or immune suppression as appropriate.

### 7.3.1 Uveitis

- Grade 1 - Refer to Ophthalmology within 7 days. Apply lubricating eye drops.
- Grade 2 - Hold study drugs. Refer to Ophthalmology within 2 days.
    - Coordinate management with Ophthalmology. Evaluations, under the guidance of ophthalmology, including but not limited to, red reflex, pupil size, shape, and reactivity, fundoscopic examination, and inspection of anterior part of eye with penlight. Consider cycloplegic eye drops, topical/ocular and/or systemic corticosteroids.
    - Short course of corticosteroid such as methylprednisolone 1 to 2 mg/kg IV (or equivalent) divided twice daily.
    - Resume study drugs if resolved to ≤ Grade 1 within 7 days. Continued topical/ocular and/or systemic corticosteroids are permitted when resuming therapy to manage and minimize local toxicity.
- Grade 3 - Hold study drugs.
    - Consult Ophthalmology within 24 hours.
    - Coordinate management with Ophthalmology. Evaluations, under the guidance of ophthalmology, including but not limited to, red reflex, pupil size, shape, and reactivity, fundoscopic examination, and inspection of anterior part of eye with penlight. Consider cycloplegic eye drops, topical/ocular, intravitreal, periocular, and/or systemic corticosteroids.
    - Consider restarting study drugs with resolution to ≤ Grade 1 within 7 days and if corticosteroid dose is reduced to ≤ 10 mg prednisone or equivalent per day. Continued topical/ocular and/or systemic corticosteroids are permitted when resuming therapy to manage and minimize local toxicity.
- Grade 4 - Permanently discontinue study drugs.
    - Consult Ophthalmology within 24 hours.

- Coordinate management with Ophthalmology. Evaluations, under the guidance of ophthalmology, including but not limited to, red reflex, pupil size, shape, and reactivity, fundoscopic examination, and inspection of anterior part of eye with penlight. Consider cycloplegic eye drops, topical/ocular, intravitreal, periocular, and/or systemic corticosteroids.

### 7.3.2 Blepharitis

- Grade 1 - No specific therapy required. Daily cleansing with warm, clean cloth. Apply lubricating eye drops.
- Grade 2 - Hold study drugs
  - Consider topical/ocular corticosteroids, antihistamine, artificial tears.
  - Resume study drugs if resolved to ≤ Grade 1 within 7 days.
- Grade 3 - Hold study drugs.
  - Consider Ophthalmology consultation.
  - Consider topical/ocular and/or systemic corticosteroids.
  - Resume study drugs if resolved to ≤ Grade 1 within 7 days.
- Grade 4 - Permanently discontinue study drugs.
  - Consult Ophthalmology within 24 hours.
  - Treat as for Grade 3 and as appropriate for life-threatening symptoms.

## 7.4 Hematologic Toxicity

Blood counts should be monitored to determine if dose modification is needed. Consider monitoring CBC bi-weekly or weekly based on the participant's medical history and incidence of myelosuppressive AEs during study drug administration.

In Cohort Expansion Phase for Module A and Module B, use of granulocyte colony stimulating factor (G-CSF) is permitted after Cycle 1 Day 1. Blood counts will be performed in case of fever (a measured temperature of 100.4°F [38°C] or greater) or evidence of infection. Neutropenic complications should be managed promptly with antibiotic support and use of G-CSF according to current ASCO guidelines for use of white blood cell growth factors.

Consider transfusion of platelets for thrombocytopenia. Use of anticoagulants and platelet inhibitors (e.g., aspirin or nonsteroidal anti-inflammatory drugs, e.g., ibuprofen) should be held until thrombocytopenia resolves.

Anemia should be evaluated and treated for other underlying etiology e.g., iron or vitamin $B_{12}$ deficiency, bleeding, and renal insufficiency. Consider transfusion of red blood cells or whole

blood for anemia. Caution is recommended in participants with ≥ Grade 2 anemia, with appropriate measures taken as clinically indicated. Participants will be supported appropriately by the treating physician. The investigator should refer to current ASCO guidelines for management of cancer-associated anemia with erythropoiesis-stimulating agents.

No specific treatment or study drug holds are required for lymphopenia, regardless of CTCAE grade, unless associated with opportunistic infection. If the participant develops an opportunistic infection with concurrent lymphopenia, study drug should be delayed until resolution of lymphopenia and the opportunistic infection (see **Table 6**).

### 7.4.1 Neutropenia

- Grade 1 or Grade 2 - No specific therapy required. Study drug should not be given to participants with neutrophil counts ≤ 1,500 cells/$mm^3$. Consider dose reduction of study drug.
- Grade 3
    - Hold study drug until recovery to ≤ Grade 1
    - Monitor neutrophil counts weekly until recovery to ≤ Grade 1
    - Discontinue study drug if not recovered to ≤ Grade 1, within 21 days.
    - Restart study drug at one lower dose level if recovered to ≤ Grade 1 within 21 days.
- Grade 4
    - Hold study drug until recovery to ≤ Grade 1
    - Monitor neutrophil counts weekly until recovery to ≤ Grade 1
    - Discontinue study drug if not recovered to ≤ Grade 1 within 21 days.
    - Restart study drug with one or two level dose reduction if recovered to ≤ Grade 1.

### 7.4.2 Thrombocytopenia

- Grade 1 - No specific therapy required. Consider dose reduction of study drug.
- Grade 2 or Grade 3
    - Hold study drug until recovery to ≤ Grade 1
    - Monitor platelet counts weekly until recovery to ≤ Grade 1
    - Restart study drug with one level dose reduction if recovered to ≤ Grade 1
    - Discontinue study drug if not recovered to ≤ Grade 1 within 21 days.

- Grade 4
  - Hold study drug until recovery to ≤ Grade 1
  - Monitor platelet counts weekly until recovery to ≤ Grade 1
  - Restart study drug with one or two level dose reduction if recovered to ≤ Grade 1
  - Discontinue study drug if not recovered to ≤ Grade 1 within 21 days.

### 7.4.3 Anemia

- Grade 1 - No specific therapy required.
- Grade 2
  - Consider iron replacement therapy, erythropoiesis stimulating agent
- Grade 3
  - Consider iron replacement therapy, erythropoiesis stimulating agent
  - Consider transfusion if symptomatic
  - Consider hold study drug until recovery to ≤ Grade 2
  - Dose reduction of one dose level for ≥ 2 events of Grade 3 anemia
- Grade 4
  - Transfuse with whole blood or packed red blood cells
  - Permanently discontinue study drug for Grade 4 anemia that persists despite intervention.

## 7.5 Palmar-Plantar Erythrodysesthesia

Management guidelines for participants experiencing skin disorders due to study drug-related toxicity are documented in **Section 7.2.4**.

For palmar-plantar erythrodysesthesia (PPE), hold study drug until toxicity resolves to ≤ Grade 1. Study drug may be resumed with a study drug decrease of one dose level. Discontinue study drug if the participant does not recover to ≤ Grade 1 within 28 days.

## 7.6 Pleural and Pericardial Effusions

Supportive care per institutional practice should be used to manage pleural and pericardial effusions. For pleural and pericardial effusions consider a dose delay and/or dose reduction. The investigator should contact the sponsor to discuss the appropriate dose of study drug based on the safety profile and evidence of antitumor activity with study drug.

### 7.6.1 Pleural Effusion

- Grade 1 - No specific therapy required; close monitoring of cardiac and lung function and imaging.
    - Consider diuretics.
- Grade 2 - Hold study drugs.
    - Consider diuretics or limited therapeutic thoracentesis.
    - Consider corticosteroids: 1 to 2 mg/kg of oral prednisone or equivalent per day divided twice daily. Taper corticosteroids (e.g., 5 to 10 mg every 1 to 2 weeks from an initial dose above 40 mg prednisone per day) over 4 weeks or as clinically indicated.
    - Resume study drug administration with a one level dose reduction at next scheduled dose if pleural effusion resolves to ≤ Grade 1 within 21 days. If pleural effusion Grade 2 recurs further reduce dose by one dose level.
- Grade 3 - Hold study drugs.
    - Therapeutic thoracentesis
    - Consider corticosteroids: 1 to 2 mg/kg of oral prednisone or equivalent per day divided twice daily. Taper corticosteroids (e.g., 5 to 10 mg every 1 to 2 weeks from an initial dose above 40 mg prednisone per day) over 4 weeks or as clinically indicated.
    - Resume study drug administration with a one level dose reduction at next scheduled dose if pleural effusion resolves to ≤ Grade 1 within 21 days. If pleural effusion Grade 3 recurs further reduce dose by one dose level.
- Grade 4 - Permanently discontinue study drugs.
    - Hospitalize.
    - Recommend a pulmonary consult/diagnostic evaluation including chest X-ray and CT scan.
    - Initiate maximal supportive care including IV corticosteroids, suggest methylprednisolone at 2 to 4 mg/kg/day divided twice daily. Continue IV methylprednisolone 2 mg/kg/day for a total of 5 days then switch to oral prednisolone 1 mg/kg/day × 3 days, then reduce to 60 mg/day prednisolone. Reduce prednisolone dose by 10 mg every 7 days (as toxicity allows) until dose is 10 mg/day. Once steroid dose is 10 mg/day, reduce by 5 mg every 7 days then stop. Higher doses may be used in consultation with the sponsor's medical monitor.

### 7.6.2 Pericardial Effusion

- Grade 2 - Hold study drugs.
  - Consider diuretics.
  - Consider corticosteroids: 1 to 2 mg/kg of oral prednisone or equivalent per day divided twice daily. Taper corticosteroids (e.g., 5 to 10 mg every 1 to 2 weeks from an initial dose above 40 mg prednisone per day) over 4 weeks or as clinically indicated.
  - Resume study drug administration at next scheduled dose with a one level dose reduction if pericardial effusion resolves to ≤ Grade 1 within 21 days. If pericardial effusion Grade 2 recurs further reduce dose by one dose level.
- Grade 3 - Hold study drugs.
  - Consider pericardiocentesis.
  - Consider corticosteroids: 1 to 2 mg/kg of oral prednisone or equivalent per day divided twice daily. Taper corticosteroids (e.g., 5 to 10 mg every 1 to 2 weeks from an initial dose above 40 mg prednisone per day) over 4 weeks or as clinically indicated.
  - Resume study drug administration at next scheduled dose with a one level dose reduction if pericardial effusion resolves to ≤ Grade 1 within 21 days. If pericardial effusion Grade 3 recurs further reduce dose by one dose level.
- Grade 4 - Permanently discontinue study drugs.
  - Hospitalize. Consider pericardiocentesis
  - Recommend a cardiology consult/diagnostic evaluation including echocardiogram.
  - Initiate maximal supportive care including IV corticosteroids, suggest methylprednisolone at 2 to 4 mg/kg/day divided twice daily. Continue IV methylprednisolone 2 mg/kg/day for a total of 5 days then switch to oral prednisolone 1 mg/kg/day × 3 days, then reduce to 60 mg/day prednisolone. Reduce prednisolone dose by 10 mg every 7 days (as toxicity allows) until dose is 10 mg/day. Once steroid dose is 10 mg/day, reduce by 5 mg every 7 days then stop. Higher doses may be used in consultation with the sponsor's medical monitor.

## 7.7 Nervous System Toxicity

Consider discontinuation of **MGA012** for patients who experience Grade 2 myasthenia gravis, Grade 2 Guillain-Barre syndrome, and permanently discontinue study drugs for any grade transverse myelitis. Management guidelines for participants experiencing nervous system toxicity are as follows:

- Grade 1 - No specific therapy required; close monitoring of neuropathy.
- Grade 2 - Hold study drugs.
    - Consider neurology consultation.
    - Consider corticosteroids: 1 to 2 mg/kg of oral prednisone or equivalent per day divided twice daily. Taper corticosteroids over 4 weeks or as clinically indicated.
    - Resume study drug administration at next scheduled dose if:
        - Resolves to ≤ Grade 1 within 21 days with or without treatment
- Grade 3 and 4 - Permanently discontinue study drugs.
    - Consider hospitalization and neurology consultation
    - Begin corticosteroids: 2 to 4 mg/kg of oral or IV methylprednisolone or equivalent per day divided twice daily. Continue IV methylprednisolone 2 mg/kg/day for a total of 5 days then switch to oral prednisolone 1 mg/kg/day × 3 days, then reduce to 60 mg/day prednisolone. Reduce prednisolone dose by 10 mg every 7 days (as toxicity allows) until dose is 10 mg/day. Once steroid dose is 10 mg/day, reduce by 5 mg every 7 days then stop.

## 7.8 Cardiotoxicity

Management guidelines for participants experiencing cardiovascular toxicity are as follows:

- Grade 1 - No specific therapy required; close monitoring.
- Grade 2 - Permanently discontinue study drugs for patients who experience Grade 2 myocarditis.
    - Consider cardiology consultation. Evaluate cardiac biomarkers e.g., creatine kinase, troponin, and beta-natriuretic peptide. Echocardiogram and CT imaging if clinically indicated.
    - Consider corticosteroids: 1 to 2 mg/kg of oral prednisone or equivalent per day divided twice daily. Taper corticosteroids over 4 weeks or as clinically indicated.
- Grade 3 and 4 - Permanently discontinue study drugs.
    - Consider hospitalization and cardiology consultation

- Evaluate cardiac biomarkers e.g., creatine kinase, troponin, and beta-natriuretic peptide. Echocardiogram and CT imaging if clinically indicated.
- Begin corticosteroids: 2 to 4 mg/kg of oral or IV methylprednisolone or equivalent per day divided twice daily. Continue IV methylprednisolone 2 mg/kg/day for a total of 5 days then switch to oral prednisolone 1 mg/kg/day × 3 days, then reduce to 60 mg/day prednisolone. Reduce prednisolone dose by 10 mg every 7 days (as toxicity allows) until dose is 10 mg/day. Once steroid dose is 10 mg/day, reduce by 5 mg every 7 days then stop.
- Consider infliximab.

## 7.9 Musculoskeletal Toxicity

Management guidelines for participants experiencing musculoskeletal toxicity are as follows:

- Grade 1 - No specific therapy required; close monitoring. Consider nonsteroidal anti-inflammatory medication e.g., ibuprofen.
- Grade 2 - Hold study drugs.
  - Consider rheumatology consultation.
  - Consider corticosteroids: 1 to 2 mg/kg of oral prednisone or equivalent per day divided twice daily. Taper corticosteroids over 4 weeks or as clinically indicated.
  - Resume study drug administration at next scheduled dose if:
    - Resolves to ≤ Grade 1 within 21 days with or without treatment.
- Grade 3 and 4 - Hold or permanently discontinue study drugs.
  - Consider hospitalization and rheumatology consultation
  - Begin corticosteroids: 2 to 4 mg/kg of oral or IV methylprednisolone or equivalent per day divided twice daily. Continue IV methylprednisolone 2 mg/kg/day for a total of 5 days then switch to oral prednisolone 1 mg/kg/day × 3 days, then reduce to 60 mg/day prednisolone. Reduce prednisolone dose by 10 mg every 7 days (as toxicity allows) until dose is 10 mg/day. Once steroid dose is 10 mg/day, reduce by 5 mg every 7 days then stop.
  - Consider infliximab.
  - If not responding within 14 days consider use of disease modifying antirheumatic drugs, e.g., sulfasalazine, methotrexate.

# 8 CONCOMITANT THERAPY AND RESTRICTIONS

## 8.1 Concomitant Therapy

All concomitant medications, including prophylactic pre-infusion medications and IV fluids, and blood products administered during the participant's participation in the study until the End of Treatment Visit must be recorded in the source document and on the eCRF. All changes in infusions, including interruptions and their duration as well as reductions in rate and duration, must be recorded.

### 8.1.1 Prohibited Therapy

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

- Any other anti-neoplastic therapies are prohibited, including but not limited to, chemotherapy or other small molecules, vaccines, biologics, radiotherapy (including radioligands e.g., radium-223) for all tumor types or androgen receptor antagonists or androgen synthesis inhibitors (e.g., enzalutamide or abiraterone, respectively) for mCRPC.
    - For participants who require palliative radiotherapy (i.e., cumulative dose less than 3000 rads, limited field of distribution) for reasons other than disease progression, therapy may be interrupted for up to 4 weeks. Palliative radiotherapy may not be given concurrently with the study drug. Treatment with palliative therapy should be initiated at least 24 hours after receiving study drug, and re-initiation of MGC018 alone (Module A) or in combination with MGA012 (Module B) can begin 2 weeks after the completion of palliative radiotherapy as appropriate, if there were no complications associated with the radiotherapy. If palliative radiotherapy fields overlap tumor lesions that are designated target lesions, the participant may continue on study, but will no longer be evaluable for objective response from the time palliative radiotherapy is initiated.
- Participants may not receive other investigational drugs during the period of study participation.
- Module B only: Because MGA012 has 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 are prohibited other than for the management of drug-related adverse experiences. Steroids may be employed in the treatment of suspected 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 AE (including topical, otic, and ophthalmic corticosteroids).

- Prophylactic use of G-CSF, granulocyte-macrophage colony stimulating factor (GM-CSF), or other growth factors is prohibited during Dose Escalation Phase with the first cycle of treatment with MGC018 administered alone or in combination with MGA012.
- Participants should not receive vaccination with any live virus vaccine during the study and for 120 days following a participant's last dose of study drug. Inactivated annual influenza and non-live SARS-CoV-2 vaccinations are allowed.

### 8.1.2 Permitted Therapies

Participants 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.
- Use of bisphosphonates or receptor activator of nuclear factor kappa-B ligand (RANK-L) inhibitors is allowed.
- For participants with prostate cancer, testosterone suppression with human gonadotropin releasing hormone antagonists or agonists is allowed.
- The use of growth factors in Cohort Expansion Phase as prophylaxis in any cycle or with successive cycles of study drug is permitted. In Dose Escalation Phase growth factors may be considered on a case-by-case basis in consultation with the sponsor.

### 8.1.3 Contraception

Male and female participants are required to use highly-effective contraceptive measures as specified below. Male participants are required to use a condom regardless of his female of childbearing potential partner’s method of contraception.

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - Oral
    - Intravaginal
    - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
    - Oral
    - Injectable
    - Implantable

- Intrauterine device (IUD)
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner is a highly effective birth control method provided that the vasectomized partner is the sole sexual partner of the female of child bearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success.

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.

## 8.2 Restrictions

### 8.2.1 Fluid and Food Intake

There are no requirements for fasting and no restrictions for fluid and food intake by the participants during the study, although it is recommended that, to the extent possible, participants have an adequate fluid intake on days associated with PK sampling.

### 8.2.2 Participant Activity Restrictions

There are no restrictions on participant activities and no requirement for participant confinement during the study. However, participants are advised to limit direct sun exposure and to use a broad-spectrum sunscreen when outdoors. Participants are advised not to wear contact lenses or rub their eyes during treatment. Participants should be advised to avoid activities that promote skin chafing, prolonged or untoward skin pressure, occlusive skin dressings, or hot tub baths.

# 9 STUDY PROCEDURES

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

During the COVID-19 pandemic, alternative methods for conducting study assessments should be considered when compliance, feasibility, and safety can be assured. These methods may include:

- Telemedicine visits, e.g., via telephone/video (using compliant video-conference tools as permitted by health authority regulations)
- Use of primary care centers and local laboratories for blood draws and imaging/radiographs

If alternative methods are used, local laboratory reference ranges will be documented and submitted to the sponsor. Local laboratory test results, laboratory accreditation (if possible), and reports of tumor assessments should be retrieved and documented in the participant's study records.

## 9.1 Informed Consent

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

## 9.2 Screening Period

Participants may receive the first dose up to 28 days from signing the informed consent. This period is defined as the screening period. At the screening visit, participants 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 participant.

## 9.3 Registration

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

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

- Age
- Tumor type
- Date of signed informed consent
- Planned date of first administration

Instructions for the registration process are provided in the Slot Assignment Plan.

## 9.4 Medical History

A complete medical history will be obtained during the screening visit. All concurrent medical conditions and any past medical conditions in the medical record (e.g., hospitalizations, surgeries, chronic conditions, prior cancer history, etc.) will be collected. All PSA values in the medical record up to 12 months (mCRPC only), BRAF mutation status (melanoma only, if available), HPV status (SCCHN only, if available), and BRCA-1 and BRCA-2 results prior to enrollment will be collected (if available). Any untoward event that occurs prior to the first dose of study drug will be recorded as medical history and not as an AE, unless it is due to a protocol-related procedure.

## 9.5 Prior and Concomitant Medications

All concomitant medications and blood products administered to participants during screening and participation in the study until the End of Treatment Visit (EOTV) must be recorded in the source document and on the eCRF.

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

## 9.6 Physical Examination

The investigator will perform physical examination of all participants; the examinations will be conducted as specified in **Appendix 1**. A full physical examination will include height (screening only), weight, and examination of head, eyes, ears, nose, throat, lymph nodes, heart, chest, lungs, abdomen, extremities, neurologic system and total body skin examination (TBSE). If any visual signs or symptoms are noted at screening, an ophthalmologic examination will be performed.

A directed physical examination will be conducted as specified in **Appendix 1**. The examination will be based on review of participant symptoms, history, and as clinically indicated. Each examination should include a TBSE to detect muco-cutaneous AEs.

### 9.6.1 Vital Signs

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

## 9.7 ECOG Performance Status

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

## 9.8 Clinical Laboratory Tests

Blood and urine samples will be collected at the times specified in **Appendix 1**. Hematology, chemistry, pregnancy, urinalysis, coagulation time, and endocrine evaluation tests (as applicable) will be performed locally. Test results for pregnancy, chemistry, and hematology must be reviewed prior to all infusions of MGC018. On the dosing days, clinical laboratory tests should be collected prior to administration of prophylactic pre-medications. Local laboratory tests to be performed are presented in **Appendix 2**.

- A blood sample for local testing of the tumor marker PSA will be collected from participants with mCRPC. PSA measurements are performed at the times specified in **Appendix 1** and approximately every 12 weeks during the post-treatment follow-up period until disease progression, start of another cancer therapy, or the study cutoff date, whichever comes first.
- A blood sample for testosterone will be collected from participants with mCRPC in Cohort Expansion. Testosterone measurements are performed at the times specified in **Appendix 1** and approximately every 12 weeks during the post-treatment follow-up period until disease progression, start of another cancer therapy, or the study cutoff date, whichever comes first.

### 9.8.1 Central Laboratory Assays

Other laboratory tests (e.g., PK, anti-drug antibody [ADA] assays [**Appendix 1** and **Appendix 3**]) will be performed at sponsor-specified central laboratories. Additional details on collection, processing, storage, and shipping of central laboratory samples will be provided in the laboratory manual.

### 9.8.2 Pharmacokinetics

Blood samples for conjugated antibody, total antibody, and SYD986 and MGA012 PK will be collected at the time points shown in **Appendix 3**. Blood samples will be collected from the arm contralateral to the site of IV infusion. If an indwelling catheter is used, the fluid in the catheter will be removed and discarded prior to the collection of blood sample for PK assessment.

### 9.8.3 Pharmacodynamics/Biomarkers

Procedures for the acquisition, handling, and processing of pharmacodynamic biomarker specimens will be provided in the laboratory manual. These tests will be collected according to **Appendix 3**.

### 9.8.4 Sample Collection, Storage, and Shipping

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

## 9.9 Radiographic, CT, PET, MRI or Bone Assessments

Baseline tumor imaging consists of a CT (or PET/CT) and/or MRI scans of the chest, abdomen, and pelvis with contrast per RECIST v1.1 (unless medically contraindicated) for all participants to document tumor burden. The subsequent tumor assessments on treatment should use the same imaging modality as that for the baseline assessment. In addition, a bone scan will be used in the Cohort Expansion Phase for participants with mCRPC. For participants with equivocal new bone lesion(s) on bone scan consider obtaining additional imaging to evaluate new lesion(s) for tumor involvement e.g., x-ray, CT or MRI.

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

## 9.10 Electrocardiography

Twelve-lead electrocardiogram (ECGs) will be obtained according to the Time and Events Schedules (**Appendix 1**) in order to evaluate the potential cardiac effect, including QTc interval prolongation.

To account for intrinsic variability, all ECGs should be obtained in triplicate (3 ECGs per time point at approximately 1-minute intervals). Central interpretation of ECGs will be used for data analysis purposes. The actual time of the first of three ECGs per timepoint will be recorded as the actual time of the ECG.

## 9.11 Echocardiography/MUGA scan

An echocardiogram (or MUGA scan) to evaluate LVEF will be performed according to the schedule in **Appendix 1**. Echocardiogram/MUGA scan may be performed at the investigator's discretion as clinically indicated.

## 9.12 Ophthalmological Examination

Ophthalmic examination should be performed by an ophthalmologist, according to the schedule for Dose Escalation Phase Module A and Module B and Cohort Expansion Phase

Module B in **Appendix 1**. The examination will include visual acuity testing (with correction), fundoscopic examination, and tonometry. Other directed studies (e.g., optical coherence tomography) will be performed as clinically indicated. If clinically indicated, participants should obtain an ophthalmology evaluation for further assessment and management.

## 9.13 Archival Tissue

Participants to be enrolled on this study must have an identified archival tumor specimen block (FFPE) or at least 10 unstained slides from archival tumor specimen or contemporaneous biopsy for the determination of B7-H3 (Module A) and B7-H3 and PD-L1 (Module B) expression. Tumor specimens for determination of B7-H3 and PD-L1 expression via IHC staining will be collected during screening on all participants during both Dose Escalation Phase and Cohort Expansion Phase and will be assayed at a central laboratory designated by the sponsor. Determination of B7-H3 and PD-L1 IHC testing results will not be required prior to protocol enrollment. Prior B7-H3 testing results may be accepted at the discretion of the sponsor to satisfy this requirement. Participants may undergo a fresh tumor biopsy to obtain a specimen for testing if a suitable sample cannot be identified. The specimens will be analyzed retrospectively and will not be used to determine participant eligibility.

## 9.14 Tumor Biopsy Specimens

Tumor biopsies of accessible lesions, pre- and post-first cycle of treatment, are strongly encouraged for participants in the Cohort Expansion Phase of the study (Module A and B). Biopsy should be considered for any participant in the Cohort Expansion Phase with an accessible lesion and should be performed pre (baseline) and post the first Cohort Expansion Phase cycle (Day 42) of treatment. 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 v1.1 target lesions. 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 3 additional biopsy cores may be obtained if this can be performed with acceptable clinical risk in the judgment of the investigator. 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 at the time of acquisition. Additional instructions for the processing and storage of tumor biopsy specimens will be provided in the laboratory manual.

## 9.15 Patient-reported Outcome

Patient reported outcome (PRO) will be assessed using the BPI-sf (**Appendix 6**). 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. The participant will be asked to rate their “worst,” “least,” “average,” and “right now” (current) pain intensity on a

10-point scale ranging from zero (no pain) to 10 (pain as bad as you can imagine). Participants will also be asked to list their current treatments for pain and their perceived effectiveness (on a scale of 0% to 100%), and to rate the degree that pain interferes with 7 daily activities (general activity, mood, walking ability, normal work, relations with other persons, sleep, and enjoyment of life) on a 10 point scale ranging from zero (does not interfere) to 10 (completely interferes).

## 9.16 End of Treatment Visit

A list of evaluations to be performed for the EOTV is provided in **Appendix 1**. The EOTV should be performed after the participant has met study treatment discontinuation criteria specified in **Section 5.4**; the visit should be performed within 30 days following the last dose of study drug. It is recognized that certain participants (such as those experiencing progression of disease) may be cared for in facilities other than the participating study site, may proceed to receive other cancer therapy, and/or may elect not to return to the study site. Therefore, this visit is considered optional, but should be carried out whenever possible. All required procedures and tests should be performed if the visit is performed. Note: the tumor assessment will not be performed at the EOTV for participants who had a previous scan performed < 28 days of the EOTV.

## 9.17 Post-Treatment Follow-up Visit

The Post-Treatment Follow-up period includes the following:

- Survival follow-up for participants in the Cohort Expansion Phase of Module A or Module B: approximately a 2-year period for each participant following the last dose of MGC018; this period runs until the last participant in the study completes his/her survival follow-up period. Participants in Module A Dose Escalation will be followed for survival status until approval of Amendment 3, at which point they will be discontinued from follow up.
- During this time, participants will be followed via clinic visit, telephone, paper mail, or other electronic contact at 3-month (90 days) intervals for follow-up of OS.
- For mCRPC participants, serum testosterone and PSA will be collected approximately every 12 weeks during the follow-up period until disease progression, start of another cancer therapy, or the study cutoff date, whichever comes first.
- Response status: information regarding response status and/or the occurrence of disease progression may be collected every 3 months (90 days) on all participants who discontinued from study treatment due to reasons other than PD, if they have not initiated any other cancer-directed therapy. Tumor response results (e.g., CT imaging results) may be entered in the electronic data capture (EDC) system if available per standard of care procedures to document the date of progression.

Post-Treatment Follow-up is performed until the end of study for each participant. Survival follow-up will be discontinued for participants enrolled in Module A Dose Escalation Phase after the approval of Amendment 3.

# 10 ASSESSMENT OF PHARMACOKINETICS AND PHARMACODYNAMICS

## 10.1 Pharmacokinetics Assessments

Serum concentrations of conjugated antibody and total antibody following administration of MGC018 and serum concentrations of MGA012 will be monitored using quantitative bioanalytical methods. Plasma concentrations of SYD986 following administration of MGC018 will be monitored using a

Where applicable, single- and multiple-dose PK parameters, $C_{max}$, $T_{max}$, $AUC_{(0\text{-}T)}$, $AUC_{(TAU)}$, AUC from time 0 to infinity [$AUC_{(INF)}$], $C_{trough}$, CL, volume of distribution at steady state ($V_{ss}$), $t_{1/2}$, and accumulation index (AI), will be derived from serum or plasma concentration versus time data.

## 10.2 Immunogenicity Assessments

Blood samples for the immunogenicity assessments will be collected at the time points shown in **Appendix 3**. The anti-drug antibodies (ADA) against MGC018 and MGA012 will be detected using validated bridging assay methods.

## 10.3 Pharmacodynamic/Biomarker Assessments

### 10.3.1 Tests Performed for Both Dose Escalation and Cohort Expansion Participants

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

- Expression of B7-H3 (Module A) and B7-H3 and PD-L1 (Module B) by IHC on archival and on fresh pre-treatment harvested tumor specimens will be performed retrospectively
- Characterization of immune cell subset phenotype on peripheral blood mononuclear cells (PBMCs)
- Characterization of serum cytokine levels
- PD-1 receptor occupancy on PBMC in participants who receive MGA012 (Module B only).

### 10.3.2 Tests Performed for Cohort Expansion Phase Participants Only

Tests to be performed for pharmacodynamic/biomarker assessments may include, but are not limited to, the following:

- Characterization of ICD markers, immune infiltrate, PD-L1, and other markers, depending on tissue availability, within paired tumor biopsy specimens optional for participants that consent to biopsy (pre/on-treatment post Cycle 1 biopsies).
- Characterization of TCR repertoire using T-cell spectratyping on peripheral PBMCs and on immune-cellular infiltrate in the tumors done on paired tumor biopsy specimens (pre/on-treatment post Cycle 1 biopsies). Pre/on-treatment tumor biopsies are optional and will be carried out only during the Cohort Expansion Phase for participants that consent to biopsy.
- Characterization of IFNγ signature on paired tumor biopsy specimens (pre/on-treatment post Cycle 1 biopsies) via transcript profiling; and in circulation, pre/on-treatment tumor biopsies are optional and will be carried out only during the Cohort Expansion Phase for participants that consent to biopsy.
- Characterization of serum biomarkers, including, but not limited to, IFNγ signature, may be carried out depending on observed antitumor activity.

# 11 ASSESSMENT OF EFFICACY

## 11.1 Efficacy Assessments

### 11.1.1 Disease Response Assessments

Tumor assessments will be obtained using CT (or PET/CT) and/or MRI scans. For mCRPC participants a bone scan will be obtained in addition to CT and/or MRI scans at baseline and on study. Target and non-target lesions will be designated at screening and then evaluated at every 6 weeks (42 days) for the first four cycles, and every other cycle thereafter while the participant in Module A Dose Escalation and Module B is on study treatment; every 9 weeks (63 days) for Cohort Expansion Module A participants. For mCRPC a lymph node is to be ≥ 20 mm to be a target lesion. In situations where the bone scan findings are suggestive of a flare reaction or apparent new lesion(s) may represent trauma, additional imaging to confirm these results with other imaging modalities such as MRI or fine-cut CT should be obtained. At each tumor assessment time point, the overall response status will be determined based on assessment of target and non-target lesions as well as appearance of any new lesions. Radiographic disease progression in mCRPC is defined in **Section 14.6.4.1**. Participants who discontinued from study treatment due to reasons other than documented, confirmed progressive disease, will be contacted every 3 months (90 days) during the Post-Treatment Follow-up period about the response status and survival of these participants, as applicable.

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

### 11.1.2 Survival Assessments

Participants who are discontinued from study treatment in the Cohort Expansion Phase of Module A or Module B will be followed for survival status every 3 months (90 days) for a 2-year survival follow-up period following the last dose of MGC018 alone (Module A) or in combination with MGA012 (Module B), or until the event of death, they withdraw consent, or are lost to follow-up (see **Section 9.17**). Survival follow-up will be discontinued for participants enrolled in Module A Dose Escalation after the approval of Amendment 3.

# 12 ADVERSE EVENT REPORTING AND ASSESSMENT OF SAFETY

The safety assessment will be based on the evaluation of AEs that occur from the time of initiation of administration of study drug through 30 days following the last dose of study drug or until the start of a subsequent systemic anticancer therapy (whichever occurs first) and will be determined based on signs, symptoms, physical examination findings, procedure findings, and/or laboratory test results from enrolled participants, as appropriate.

Protocol-related AEs and 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 informed consent form (ICF) and the administration of the first dose of study drug will be captured as medical history unless the events are attributed to protocol-specified procedures that are not part of standard of care that occur during this time period, in which case the events will be collected on the Adverse Event CRFs.

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

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

## 12.1 Definitions

### 12.1.1 Adverse Event

Adverse event means 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 AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

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

### 12.1.2 Adverse Drug Reaction

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

### 12.1.3 Adverse Event of Special Interest

An adverse event of special interest (AESI) is an event of scientific and medical interest or concern to the sponsor's product or program, for which ongoing monitoring and rapid communication to the sponsor could be appropriate. It may be a serious or non-serious AE, which may require further investigation in order to characterize and understand it; refer to **Section 12.2.4** for full details.

### 12.1.4 Attribution/Assessment of Causality

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

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

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

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

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

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

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

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

*Possible:* There is an association between the event and the administration of the study drug and there is a plausible mechanism for the event to be related to study drug; but there may also be alternative etiology, such as characteristics of the participant's clinical status or underlying disease.

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

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

### 12.1.5 Serious Adverse Event

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

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

### 12.1.6 Severity Criteria

An assessment of severity grade will be made using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03 (v4.03). The CTCAE are published standardized definitions for AEs to describe the severity of laboratory and organ toxicity for participants receiving cancer therapy. The investigator should use clinical judgment in assessing the severity of events not directly experienced by the participant (e.g., laboratory abnormalities).

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

- Grade 1 = Mild; asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated.
- Grade 2 = Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
- Grade 3 = Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- Grade 4 = Life-threatening consequences; urgent intervention indicated.
- Grade 5 = Death related to AE.

## 12.2 Adverse Event Collection and Documentation

### 12.2.1 All Adverse Events

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

All adverse events whether serious or non-serious, will be reported from the time a signed and dated 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).

Both protocol-related AEs and 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.

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

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

Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g. cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). All treatment measures that are required for AE management must be recorded in the source document. The intensity (severity) of AEs will be assessed using NCI CTCAE v4.03 and serious events will be determined by the definition provided in **Section 12.1.5** above. Generally, all non-serious AEs should be entered into the eCRFs within 10 calendar days of the site's awareness.

Clinical Laboratory Changes: Safety laboratory assessments will be evaluated by the investigator to ensure participant safety. Laboratory tests will be graded according to NCI CTCAE v4.03. The investigator is responsible for reviewing the results of all laboratory tests as they become available:

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

**Section 12.2.6** summarizes AE (e.g., SAEs, pregnancy, IREs, etc.) reporting to the sponsor timeframes. The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also notify the investigator of regulatory submissions, as appropriate. The investigator is responsible for notifying the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol, unless otherwise required and documented by the IEC/IRB.

For this study, the participants must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Site number
- Participant number

### 12.2.2 Immediately Reportable Events

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

- All SAEs including any suspected transmission of an infectious agent via a medicinal product

- Pregnancy in a study participant or partner of a study participant
- ≥ Grade 3 infusion-related reactions or CRS
- Abnormal liver enzymes that meet the criteria for potential Hy's Law, which is defined as AST and/or ALT that is greater than 3 × ULN and total bilirubin that is greater than 2 × ULN and without any alternate etiology
- Immune-related AE of Grade 2 or greater; irAEs are defined in **Section 7.2**.
- SJS or TEN
- Ocular toxicity
    - ≥ Grade 3 keratoconjunctivitis sicca (dry eye)
    - ≥ Grade 3 conjunctivitis
    - ≥ Grade 3 keratitis
- Administration of a dose significantly greater (specifically, + 20% or higher) than the planned dose, and results in an event of clinical consequence
- AEs leading to permanent discontinuation of study drug in an individual participant
- Discontinuation of the participant from study drug administration for any reason other than disease progression
- Product quality issues with an associated clinical consequence
- Pleural effusion
- Pericardial effusion
- Confirmed or presumed COVID-19/SARS-CoV-2 infection

In those cases, in which the IRE is considered related to study drug, the study drug may be discontinued, and the participant will continue participation in the study for observational safety and efficacy analysis (except for cases where the participant is withdrawn from the study by the investigator or withdrew the consent).

### 12.2.3 Serious Adverse Events

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

After 30 days following the last dose of study drug administration, 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.

Within 24 hours of becoming aware of an SAE, the investigator should provide a completed SAE Report form, via email or fax, to the sponsor. Upon receipt of follow-up information pertaining to an SAE, a follow-up SAE Report form should be submitted to the sponsor within 24 hours of becoming aware of the follow-up information. All SAEs should be entered into the eCRFs within 5 calendar days of the site's awareness.

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

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

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

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to etiology other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

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

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

Adverse events related to disease progression should not be recorded as an AE or SAE term, as they will be collected as efficacy endpoints. However, if an AE or SAE occurs in a participant and it is unclear if the event is due to progressive disease, the AE or SAE should be reported.

### 12.2.4 Protocol-Specific Adverse Events of Special Interest

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

- All IRR or CRS events as defined in **Section 7.1.1**. Grade 3 IRR or CRS events are also considered an IRE, requiring notification to the sponsor within 24 hours.
- Abnormal liver enzymes that meet the criteria for potential Hy's law, which is defined as AST and/or ALT that is greater than 3 × ULN and total bilirubin that is greater than 2 × ULN and without any alternate etiology. This is also considered an IRE, requiring notification to the sponsor within 24 hours.
- Immune-related AE of Grade 2 or greater; irAEs are defined in **Section 7.2**. This is also considered an IRE, requiring notification to the sponsor within 24 hours.
- Skin toxicity that meets the definition of SJS or TEN.
- Pleural effusion
- Pericardial effusion
- PPE
- Ocular toxicity. This is also considered an IRE, requiring notification of the following to the sponsor within 24 hours:
    - ≥ Grade 3 keratoconjunctivitis sicca (dry eye)
    - ≥ Grade 3 conjunctivitis
    - ≥ Grade 3 keratitis

### 12.2.5 Pregnancy

All reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by study-site personnel within 24 hours of their knowledge of the event using the Pregnancy Exposure Form. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the SAE Report form. Any participant who becomes pregnant during the study must discontinue further study drug administration.

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

Upon confirmation of serum or urine pregnancy testing, the participant will be followed for the outcome of pregnancy. Follow-up information will be collected for all live newborns at

birth and 6 months after the birth. All necessary information will be collected to assess the effects of study drug on the newborn. If necessary, the follow-up period will be extended for the newborn.

### 12.2.6 Reporting of Adverse Events to the Sponsor

Throughout the study, the investigator must document all AEs, SAEs, and other IREs, as defined in **Section 12.2.2** in the eCRFs in a timely manner. See **Table 9**, Safety Reporting by Event Type, for details.

The investigator must immediately complete and transmit the SAE Report Form, within 24 hours of identifying the event, to MacroGenics Product Safety or designee. The SAE Report form and Completion Guidelines, and Contact Information for Reporting SAEs, are provided by the sponsor.

For reports of pregnancy, the MacroGenics Pregnancy Exposure Form must be completed and transmitted. The investigator must attempt to follow the pregnancy to term or termination in order to report the outcome and health status of the mother and child. The Pregnancy Exposure Form is provided by the sponsor.

Please refer to the **Table 9** for reporting timeframes to MacroGenics by event type.

**Table 9 Safety Reporting by Event Type**

| Type of Event: | Hard Copy Form/Timeline for reporting/Where to Report | eCRF Timeline for Data Entry |
|---|---|---|
| Serious Adverse Event (SAE) | Serious Adverse Event Form within 24 hours of awareness<br>Report Email to<br><br>Or fax to | Within 5 calendar days of awareness |
| Pregnancy | Pregnancy Exposure Form/<br>Within 24 hours of awareness/<br>Email to<br>Or fax to | Within 5 calendar days of awareness |
| Other IREs, as defined in **Section 12.2.2** | Not Applicable | Within 24 hours of awareness |
| Non-Serious Adverse Events (except for Pregnancy): | Not Applicable | Within 10 calendar days of awareness |

Abbreviations: eCRF = electronic case report form; IRE = immediately reportable event; SAE = serious adverse event.

## 12.3 Other Assessment of Safety

### 12.3.1 Symptomatic Skeletal Events

Symptomatic skeletal events (SSEs) are a clinical trial endpoint to describe skeletal morbidity defined as symptomatic fracture, surgery or radiation to bone, or spinal cord compression. Any of the following events must be recorded in the source document and on the SSE eCRF regardless of relationship to disease progression: symptomatic bone fracture, bone pain requiring surgery, bone pain requiring radiation, and/or spinal cord compression.

# 13 PRODUCT QUALITY COMPLAINT HANDLING

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

## 13.1 Procedure

All initial PQCs must be reported to the sponsor by the study-site personnel, after being made aware of the event, and those that are associated with clinical consequences must be reported within 24 hours.

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

## 13.2 Contacting sponsor Regarding Product Quality

Product quality issues should be reported via e-mail to:

# 14 STATISTICAL ANALYSIS

This section outlines the statistical methodology and principles which will be used for data analysis in this study. A separate statistical analysis plan (SAP) and statistical programming plan (SPP) will further describe the details regarding statistical methods and will govern the analysis. Analyses will be performed for MGC018 alone and in combination with MGA012 respectively.

## 14.1 Determination of 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, and 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 10** provides the 2-sided 95% confidence interval (CI) for a number of potential responses.

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

**Table 10 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.

## 14.2 Analysis Populations

The study analyses will be performed on the following populations:

- Safety Population: All participants who received at least one dose of 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 study drug, had baseline measurable or non-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 $\geq$ 2 ng/mL and at least 1 post baseline PSA measurement. This population will be used to calculate and summarize PSA response rates.

## 14.3 Demographics and Baseline Characteristics

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

## 14.4 Study Drug Exposures and Concomitant Medications

Study drug exposures and concomitant medications will be summarized by descriptive statistics. The summary of study drug exposure will include descriptive statistics as well as frequency counts for the number of doses or cycles received, the total dose 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.

## 14.5 Pharmacokinetic/Pharmacodynamic Analysis

### 14.5.1 Pharmacokinetic Analysis

Summary statistics will be tabulated separately for serum PK parameters by MGC018 and MGA012 dose. Where applicable, geometric means and percent coefficients of variation will be reported for $C_{max}$, $AUC_{(0\text{-}T)}$, $AUC_{(TAU)}$, $AUC_{(INF)}$, $C_{trough}$ and AI; arithmetic means and standard deviations will be reported for $t_{1/2}$, CL, and $V_{ss}$; and medians, minimum, and maximum will be reported for $T_{max}$. Separate scatter plots of $C_{max}$ and AUC will be provided versus dose to assess dose dependency. Dose proportionality may be assessed using a power model.

### 14.5.2 Immunogenicity Analysis

The proportion of participants who are negative for 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.

### 14.5.3 Pharmacodynamic Analysis

Summary statistics for pharmacodynamic parameters, such as, but not limited to, those listed under in **Section 10.3** 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.

## 14.6 Efficacy and Endpoint Analyses

### 14.6.1 Response Endpoints and Analyses

For RECIST v1.1, the best overall response (BOR) will be categorized as CR, PR, SD, PD, or NE. To be qualified as BOR, CR and PR requires 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.

The number and percent of participants with their BOR will be summarized. The 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.

### 14.6.2 Analysis of Tumor Size Change Over Time

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

### 14.6.3 Time-to-Event Endpoints and Analyses

Progression-free survival will be defined as the time from the first dose date of 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 objective assessment of disease per RECIST v1.1. For participants who are not known to be dead or progressed at the time of data cut-off for PFS analysis, the PFS will be censored at the date of the last tumor assessment. Specifically, the following censoring rules will be applied to analysis of PFS.

**Table 11 Censoring Rules for Primary Analysis of PFS**

| Situation | Date | Outcome |
|---|---|---|
| No baseline tumor assessments | First dose date | Censored |
| Death prior to first scheduled tumor assessment | Date of death | Progressed |
| No post-baseline tumor assessments in absence of death prior to first scheduled tumor assessment | First dose date | Censored |
| Documented progression | Date of progression | Progressed |
| Initiation of alternative anti-cancer treatments in absence of documented progression | Date of last tumor assessment on or prior to initiation of such treatment | Censored |
| Death or documented progression immediately after missing 2 or more consecutive scheduled tumor assessments | Date of last tumor assessment prior to missed assessments | Censored |

Abbreviation: PFS = progression-free survival

Duration of Response (DoR) is defined as the time from the date of initial response (CR or PR) to the date of first documented progression or death from any cause, whichever occurs first. The DoR is calculated only for the responders. For responders who are not known to be dead or progressed at the time of data cut-off for DoR analysis, the DoR will be censored at the date of the last tumor assessment. Specifically, the last 3 situations described in **Table 11** will be applied. The DoR analyses will be performed only if there are enough responders to render the analyses meaningful.

Overall survival (OS) is defined as the time from the first dose date of MGC018 treatment for Module A or MGC018 and MGA012 combination treatment for Module B to the date of death from any cause. For participants who are not known to be dead at the time of data cut-off for OS analysis, the OS will be censored at the time they are last known to be alive.

The Kaplan-Meier method will be applied to estimate PFS, DoR and OS curves; their median times; PFS rates at 3 and 6 months; and OS rates at 6 and 12 months, respectively. The method of Brookmeyer and Crowley **(8)** will be used to construct 95% CI for median time of each time-to-event endpoint. The 95% CIs for PFS and OS rates at each time point of interest will be calculated by normal approximation after log(-log) transformation.

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

### 14.6.4 Endpoints and Analyses in mCRPC

The analyses of ORR, DoR, and OS indicated above will be performed for participants with mCRPC. In addition, the following analyses will be performed in mCRPC.

#### 14.6.4.1 Radiographic Progression-free Survival

The rPFS will be defined as the time from the first dose of study drug to the first occurrence of the following events:

- Radiographic progression of soft tissue lesions using RECIST v1.1
- Radiographic progression of bone lesions: appearance of 2 or more new bone lesions
- Death from any cause

The censoring rules in **Table 11** will apply to rPFS with the radiographic progression defined for rPFS. The analysis of rPFS will be the same as that described for PFS.

#### 14.6.4.2 Prostate-specific Antigen

PSA response will be defined as a ≥ 50% decline from baseline in PSA with confirmation at least 3 weeks later. PSA response rate will be calculated for participants with a baseline PSA ≥ 2 ng/mL and at least 1 post-baseline value. 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 best PSA percent change from baseline will be presented by waterfall plot.

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 will be defined as the time from the first dose of study drug to the first documented PSA progression. Participants without PSA progression at the time of analysis will be censored to the date of their last PSA assessment. The Kaplan-Meier method will be applied to estimate time to PSA progression.

#### 14.6.4.3 Symptomatic Skeletal Events

SSEs include new symptomatic pathological fracture, use of external beam radiation to relieve bone pain, spinal cord compression, or tumor-related orthopedic surgical intervention. SSE rate will be summarized. Time to SSE is defined as the time from the first dose of study drug to the first occurrence of SSE. Participants without SSE at the time of analysis will be censored at the last assessment. The Kaplan-Meier method will be applied to estimate time to SSE.

### 14.6.5 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.

## 14.7 Safety Endpoints and Analyses

### 14.7.1 Adverse Events

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

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

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.

### 14.7.2 Laboratory Values

Summaries of laboratory values will display descriptive statistics for numerically quantified laboratory test results. Summaries will be grouped by laboratory panel (eg, 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.

### 14.7.3 Other Safety Endpoints

Twelve-lead 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 at which they are collected. Shift tables may be performed.

## 14.8 Other Assessments or Analyses

Additional analyses, if any, will be described in the SAP.

# 15 QUALITY CONTROL AND ASSURANCE

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

- Provide instructional material to the study sites, as appropriate.
- Sponsor a start-up training session (investigator meeting or study initiation visit) to instruct the investigators and study coordinators. This session will give instruction on the protocol, completion of the eCRFs, and study procedures.
- Monitor protocol and GCP compliance on a regular basis (on-site visits and/or remote monitoring).
- Be available for consultation and stay in contact with the study site personnel by mail, e-mail, telephone, and/or fax.
- Review and evaluate eCRF data and use standard computer checks to detect and query errors in data collection.
- Conduct a quality review of the database.

## 15.1 Monitoring, Auditing and Inspections

To ensure the safety of 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 participant medical records in the participant files as source documents for the study.

MacroGenics or its designee will monitor the study on a regular basis throughout the study period according to the study Monitoring Plan. The investigator will allocate adequate time for such monitoring activities. The study monitor periodically will conduct a cross-check of the participant data recorded on eCRFs against source documents at the study site and/or remote monitoring. 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 activities. Queries may be raised if any datum is unclear or contradictory. The investigator and study site personnel must address all queries in a timely manner.

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

## 15.2 Data Collection and Management

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

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

Site personnel record all data for each participant through eCRFs using the Medidata RAVE™, an EDC system provided and approved by the sponsor. Refer to the CRF Completion Guidelines for additional information regarding eCRFs, if any that will be used as source documentation. Study sites must complete eCRFs for each participant in a timely manner shortly after each participant visit. As the person ultimately responsible for the accuracy of all eCRF data, the investigator must sign the investigator's Statement in each participant's eCRF.

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

# 16 ADMINISTRATIVE CONSIDERATIONS

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

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

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

The investigator must, where required by local regulations, submit the following 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 participants or potential participants (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 participants or conduct of the study.
- At minimum, an annual update and/or request for re-approval of study, unless otherwise specified by IRB/IEC.
- Protocol deviations.
- Notification when the study has been completed.
- Proof of indemnity/liability insurance.
- Other documents required by the IRB/IEC.

## 16.2 Ethical Conduct of the Study

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

## 16.3 Participant Information and Consent

It is the responsibility of the investigator to obtain and document written informed consent from the participant. 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 participant in both oral and written form, and participants 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 participant's native language or language in which the participant has fluency) so as to be understood by the prospective participant. 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 participant and by the person who conducted the discussion of the informed consent.

All versions of each participant'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 participant should receive a copy of the signed and dated written ICF and any other written information provided to the participants.

## 16.4 Participant Confidentiality

To maintain confidentiality of participants, 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 participant or an individual with legal decision making authority for the participant or the participant's interests, except as necessary for monitoring by the relevant regulatory authorities, the sponsor of the clinical study, or the sponsor's representative. The investigator must also comply with all local applicable privacy regulations (e.g., US Health Insurance Portability and Accountability Act of 1996 [HIPAA]), on protection of individuals with regard to personal data.

## 16.5 Case Report Forms and Study Records

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

## 16.6 Access to Source Documentation

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

## 16.7 Retention of Data

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

## 16.8 Sample Retention and Further Testing

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

## 16.9 Financial Disclosure

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

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

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

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

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

## 16.10 Publication and Disclosure Policy

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

## 16.11 Discontinuation of the Study or Study Sites

### 16.11.1 Discontinuation of Study Sites

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

### 16.11.2 Discontinuation of the Study

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

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

## 16.12 Identification of the Coordinating Principal Investigator

A Coordinating Principal investigator will be appointed by the sponsor medical monitor prior to the end of the study.

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

# 17 REFERENCE LIST

***Note:*** *Newly added literature references are in colored text. Previously cited submitted literature references are in black text.*

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15. **Chen JT, Chen CH, Ku KL, Hsiao M, Chiang CP, Hsu TL, et al.** Glycoprotein B7-H3 overexpression and aberrant glycosylation in oral cancer and immune response. Proc Natl Acad Sci U S A. 2015;112(42):13057-62.

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# Appendix 1 Time and Events Schedules

**Module A Dose Escalation Phase**

| EVALUATION/ PROCEDURE | Screening [1] (Within 28 days) | Cycle 1 | | | | | | Cycle 2 and subsequent Cycles[3] | | | | EOTV [4] | Post TRT FUP [5] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 1 | Days 2 and 4 | Day 8 (±1d) | Day 15 (±1d) | Day 22 (±1d) | Day 42 [2] (± 3d) | Day 1 (±1d) | Day 22 (±1d) | Days 23, 25, 29, 36 (±1d) | Day 42 (± 3d) | | |
| **STUDY DRUG ADMINISTRATION** | | | | | | | | | | | | | |
| **Administer MGC018** | | X | | | | X | | X | X | | | | |
| **ELIGIBILITY** | | | | | | | | | | | | | |
| **Informed Consent** | X | | | | | | | | | | | | |
| **Baseline Tumor Imaging** | X | | | | | | | | | | | | |
| **Designate Target/ Non-Target Lesions** | X | | | | | | | | | | | | |
| See **Appendix 5** | | | | | | | | | | | | | |
| **Medical History** | X | | | | | | | | | | | | |
| **Archival Tumor Specimen** | X | | | | | | | | | | | | |
| All participants to be enrolled in the study must have an identified formalin-fixed, paraffin embedded tumor specimen and or tumor specimens sufficient for 10 slides; see **Section 9.13**. The specimens will be analyzed retrospectively and will not be used to determine participant eligibility. | | | | | | | | | | | | | |
| **Physical Exam** | X | X | | | | | | X | | | | X | |
| **Height** | X | | | | | | | | | | | | |
| **Body Weight** | X | X | | | | X | | X | X | | | X | |
| **Directed History/Physical** | | | | X | | X | | | X | | | | |
| **Concurrent Medications** | X | X | X | X | X | X | X | X | X | X | X | X | |
| **ECOG PS** | X | X | | | | | | X | | | | X | |
| **12-lead ECG** | X | X | | | | X | | X | | | | X | |
| To be performed in triplicate (approximately 1 minute apart).<br>*During non-treatment visits (Screening and EOTV)*, 12-lead ECG will be taken at 1 time point.<br>*Cycle 1 Day 1*: Pre-infusion (within -30 minutes), EOI (within 30 minutes after EOI), and Hour 4 after EOI (± 10 minutes).<br>*Cycle 1 Day 22*: Pre-infusion (within -30 minutes) and EOI (within 30 minutes of EOI).<br>*Cycle 2 and subsequent cycles*: Day 1: 12-lead ECG is recorded pre-infusion (within -30 minutes) and EOI (within 30 minutes of EOI). | | | | | | | | | | | | | |
| **Echocardiogram/MUGA** | X | | | | | | | | | | X | X | |
| Echocardiogram or MUGA scan performed at screening, approximately every 12 weeks [at the end of C2, C4, C6…(± 7 days)], at the end of treatment visit and at other time points if clinically indicated. See **Sections 9.11** | | | | | | | | | | | | | |

## Module A Dose Escalation Phase

| EVALUATION/ PROCEDURE | Screening [1] (Within 28 days) | Cycle 1 | | | | | | Cycle 2 and subsequent Cycles[3] | | | | EOTV [4] | Post TRT FUP [5] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 1 | Days 2 and 4 | Day 8 (±1d) | Day 15 (±1d) | Day 22 (±1d) | Day 42 [2] (± 3d) | Day 1 (±1d) | Day 22 (±1d) | Days 23, 25, 29, 36 (±1d) | Day 42 (± 3d) | | |
| **Ophthalmic Exam** | X | | | | | | | | | | X | X | |
| Ophthalmic examinations including visual acuity testing (with correction), fundoscopic examination, and tonometry are performed at screening, at Cycle 2 Day 42 (± 7 days), End of Treatment, and at other time points if clinically indicated. Other directed studies (e.g., optical coherence tomography) will be performed as clinically indicated. See **Section 9.12**. | | | | | | | | | | | | | |
| **Pregnancy Test (serum or urine)** | X | X | | | | | | X | | | | X | |
| Serum pregnancy test is required for eligibility. Subsequent pregnancy tests may use serum or urine. Test results must be reviewed before the study drug infusion on Day 1 of Cycle 1 and all subsequent cycles. If screening test is performed within 72 hours of 1st infusion, repeat of the test on Day 1 may be deferred. | | | | | | | | | | | | | |
| **Eligibility Checklist and Register Participant** | X | | | | | | | | | | | | |
| **SAFETY/PK/MECHANISTIC STUDIES** | | | | | | | | | | | | | |
| **Protocol Procedure Related AEs/SAEs** | X | | | | | | | | | | | | |
| **Assess for Adverse Events** | | Continuous | | | | | | | | | | | |
| **Vital Signs** | X | X | | X | | X | | X | X | | | X | |
| *During non-treatment visits (Screening, Day 8, and EOTV)*, vital signs will be taken once.<br>*Cycle 1*: Day 1 and Day 22: Pre-infusion (within -30 minutes); at 15 and 30 minutes after the start of the infusion (± 5 minutes), at EOI (± 10 minutes); and at 1- and 4-hours after EOI (± 10 minutes). Note: Cycle 1 Day 22, the 4-hour vital signs may be deferred based on the judgement of the investigator.<br>*Cycle 2 and Beyond:* Pre-infusion (within -30 min), at EOI (± 10 minutes), and at 1-hour after EOI (± 10 minutes). | | | | | | | | | | | | | |
| **CBC, PLTs, diff; Chemistry Panel** | X | X | | X | | X | | X | X | | | X | |
| To be collected pre-infusion and prior to prophylactic pre-medications on dosing days. Day 1 laboratory blood samples can be collected up to 3 days before infusion. See **Appendix 2** for list of assessments. | | | | | | | | | | | | | |
| **PT or INR** | X | X | | X | | X | | X | X | | | X | |
| PT is preferred. INR is acceptable based on local availability. To be collected pre-infusion and prior to prophylactic pre-medications on dosing days. Day 1 laboratory blood samples can be collected up to 3 days before infusion. See **Appendix 2** for list of assessments. | | | | | | | | | | | | | |
| **Free T4 and TSH** | X | | | | | | | | | | | X | |
| **Urinalysis** | X | X | | | | | | X | | | | X | |
| To be collected pre-infusion and prior to prophylactic pre-medications on dosing days. Day 1 urine samples can be collected up to 3 days before infusion. See **Appendix 2** for list of assessments. Collect urinalysis as scheduled and as clinically indicated. Reflex test for microscopic evaluation if abnormal. | | | | | | | | | | | | | |

## Module A Dose Escalation Phase

| EVALUATION/ PROCEDURE | Screening [1] (Within 28 days) | Cycle 1 | | | | | | Cycle 2 and subsequent Cycles[3] | | | | EOTV [4] | Post TRT FUP [5] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 1 | Days 2 and 4 | Day 8 (±1d) | Day 15 (±1d) | Day 22 (±1d) | Day 42 [2] (± 3d) | Day 1 (±1d) | Day 22 (±1d) | Days 23, 25, 29, 36 (±1d) | Day 42 (± 3d) | | |
| **PSA (mCRPC only)** | X | | | | | | | X | | | | | |
| PSA measurements to be performed at baseline and then repeated predose 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. | | | | | | | | | | | | | |
| **Pharmacokinetics** | See **Appendix 3** | | | | | | | | | | | | |
| **Serum Cytokines** | See **Appendix 3** | | | | | | | | | | | | |
| **Flow Cytometry (Subset)** | See **Appendix 3** | | | | | | | | | | | | |
| **Anti-Drug Antibody (ADA)** | See **Appendix 3** | | | | | | | | | | | | |
| **Tumor Assessment (CT/PET/MRI)** | | | | | | | X | | | | X | X | |
| Radiographic disease assessments will occur on Day 42 ± 3 days for the first four cycles, and every other cycle thereafter. Assessment will also be done at EOTV as per **Section 9.16**. | | | | | | | | | | | | | |
| **Survival Follow-up** | | | | | | | | | | | | | X |
| Participants in Module A Dose Escalation will be followed for survival status until approval of Amendment 3, at which point they will be discontinued from follow up: survival follow-up collected every 3 months (90 days ± 7 days) by clinic visit, telephone, paper mail, or other electronic contact; information regarding response status and/or the occurrence of disease progression may be collected approximately every 3 months in participants who discontinued from study treatment due to reasons other than progressive disease, if they have not initiated any other cancer directed therapy. See **Section 9.17** for details. | | | | | | | | | | | | | |

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

2 Cycle 1 Day 42 and Cycle 2 Day 1 may be combined. Whether or not the visits are combined, Cycle 1 Day 42 assessments should occur before Cycle 2 Day 1 assessments. The same applies to all consecutive cycles.

3 Evaluations/procedures performed on Days 23, 25, 29, and 36 apply to Cycle 2 only.

4 The EOTV should be performed within 30 days following the last dose of study drug.

5 Participants in Module A Dose Escalation Phase will be followed for survival status until approval of Amendment 3, after which they will be discontinued from follow up.

Abbreviations: CBC = complete blood cell; diff = differential; ECG = electrocardiography; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EOI = end of infusion; EOTV = End of Treatment Visit; FUP = follow-up; INR = international normalized ratio; PLTs = platelets; PT = prothrombin time; TRT = treatment; TSH = thyroid-stimulating hormone.

## Module A Cohort Expansion Phase

| EVALUATION/ PROCEDURE | Screening [1] (Within 28 days) | Cycle 1 | | | | | | Cycle 2 and Subsequent Cycles | | | EOTV [4] | Post TRT FUP |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 1 | Day 2 | Day 8 (±1d) | Day 15 (±1d) | Day 22 (±1d) | Day 42 (±5d) | Day 1 (±1d) | Day 22 (±1d) | Days 23, 29, 36 (±1d) [3] | | |
| **Study Day** | | **1** | **2** | **8** | **15** | **22** | **42** | **43** | **64** | **65, 71, 78** | | |
| **STUDY DRUG ADMINISTRATION** | | | | | | | | | | | | |
| **Administer MGC018** | | X | | | | X | | X | X | | | |
| **ELIGIBILITY** | | | | | | | | | | | | |
| **Informed Consent** | X | | | | | | | | | | | |
| **Baseline Tumor Imaging** | X | | | | | | | | | | | |
| **Designate Target/ Non-Target Lesions** | X | | | | | | | | | | | |
| See **Appendix 5** | | | | | | | | | | | | |
| **Medical History** | X | | | | | | | | | | | |
| **Archival Tumor Specimen** | X | | | | | | | | | | | |
| All participants to be enrolled in the study must have an identified formalin-fixed, paraffin embedded tumor specimen and or tumor specimens sufficient for 10 slides; see **Section 9.13**. The specimens will be analyzed retrospectively and will not be used to determine participant eligibility. | | | | | | | | | | | | |
| **Physical Exam** | X | X | | | | | | X | | | X | |
| If any visual signs or symptoms are noted at screening, an ophthalmologic examination will be performed. | | | | | | | | | | | | |
| **Height** | X | | | | | | | | | | | |
| **Body Weight** | X | X | | | | X | | X | X | | X | |
| **Directed History/Physical** | | | | | | X | | | X | | | |
| **SSE (mCRPC only)** | | X | | | | X | | X | X | | X | |
| For participants with mCRPC, complete eCRF documenting any SSEs predose of each treatment visit. | | | | | | | | | | | | |
| **Remote Telemedicine Contact** | | | X | X | X | | | | | X | | |
| Telemedicine contact may be by telephone or email. | | | | | | | | | | | | |
| **Optional tumor biopsies on study** | X | | | | | | X | | | | | |
| On-treatment tumor biopsy: Fresh tumor biopsy pre-treatment (after enrollment and prior to the Cycle 1 Day 1 dose) and in Cycle 1 Day 42 ± 5 days. Paired tumor biopsies if the tumor lesions are accessible for biopsy with acceptable clinical risk in the judgment of the investigator; see **Section 9.14**. Tumor biopsies of accessible lesions, pre- and post-first cycle of treatment, are strongly encouraged. | | | | | | | | | | | | |

## Module A Cohort Expansion Phase

| EVALUATION/ PROCEDURE | Screening [1] (Within 28 days) | Cycle 1 | | | | | | Cycle 2 and Subsequent Cycles | | | EOTV [4] | Post TRT FUP |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 1 | Day 2 | Day 8 (±1d) | Day 15 (±1d) | Day 22 (±1d) | Day 42 (±5d) | Day 1 (±1d) | Day 22 (±1d) | Days 23, 29, 36 (±1d) [3] | | |
| **Study Day** | | **1** | **2** | **8** | **15** | **22** | **42** | **43** | **64** | **65, 71, 78** | | |
| **Concurrent Medications** | X | X | X | X | X | X | | X | X | X | X | |
| **ECOG PS** | X | X | | | | | | X | | | X | |
| **12-lead ECG** | X | X | | | | X | | X | | | X | |
| To be performed in triplicate (approximately 1 minute apart). Assessed pre-infusion on dosing days. | | | | | | | | | | | | |
| **Echocardiogram/MUGA** | X | | | | | | | | | | | |
| Echocardiogram or MUGA scan performed at screening and other time points if clinically indicated. See **Section 9.11** | | | | | | | | | | | | |
| **Pregnancy Test (serum or urine)** | X | X | | | | | | X | | | X | |
| Serum pregnancy test is required for eligibility. Subsequent pregnancy tests may use serum or urine. Test results must be reviewed before the study drug infusion on Day 1 of Cycle 1 and all subsequent cycles. If screening test is performed within 72 hours of 1st infusion, repeat of the test on Day 1 may be deferred. | | | | | | | | | | | | |
| **SAFETY/PK/MECHANISTIC STUDIES** | | | | | | | | | | | | |
| **Protocol Procedure Related AEs/SAEs** | X | | | | | | | | | | | |
| **Assess for Adverse Events** | | Continuous | | | | | | | | | | |
| **Vital Signs** | X | X | | | | X | | X | X | | X | |
| *During non-treatment visits (Screening and EOTV)*, vital signs will be taken once. *Cycle 1*: Day 1 and Day 22: Pre-infusion; at 15 and 30 minutes after the start of the infusion (± 5 minutes), at EOI (± 10 minutes); and at 1- and 4-hours after EOI (± 10 minutes). Note: Cycle 1 Day 22, the 4-hours after EOI vital signs may be deferred based on the judgement of the investigator. *Cycle 2 and Beyond:* Pre-infusion, at EOI (± 10 minutes), and at 1-hour after EOI (± 10 minutes). | | | | | | | | | | | | |
| **CBC, PLTs, diff; Chemistry Panel** [2] | X | X | | | | X | | X | X | | X | |
| To be collected pre-infusion and prior to prophylactic pre-medications on dosing days. Day 1 laboratory blood samples can be collected up to 1 day before infusion. See **Appendix 2** for list of assessments. | | | | | | | | | | | | |
| **PT or INR and PTT** [2] | X | X | | | | X | | X | X | | X | |
| PT is preferred. INR is acceptable based on local availability. To be collected pre-infusion and prior to prophylactic pre-medications on dosing days. Day 1 laboratory blood samples can be collected up to 1 day before infusion. See **Appendix 2** for list of assessments. | | | | | | | | | | | | |

## Module A Cohort Expansion Phase

| EVALUATION/ PROCEDURE | Screening [1] (Within 28 days) | Cycle 1 | | | | | | Cycle 2 and Subsequent Cycles | | | EOTV [4] | Post TRT FUP |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 1 | Day 2 | Day 8 (±1d) | Day 15 (±1d) | Day 22 (±1d) | Day 42 (±5d) | Day 1 (±1d) | Day 22 (±1d) | Days 23, 29, 36 (±1d) [3] | | |
| **Study Day** | | **1** | **2** | **8** | **15** | **22** | **42** | **43** | **64** | **65, 71, 78** | | |
| **Urinalysis** [2] | X | X | | | | | | X | | | X | |
| To be collected pre-infusion and prior to prophylactic pre-medications on dosing days. Day 1 urine samples can be collected up to 1 day before infusion. See **Appendix 2** for list of assessments. Collect urinalysis as scheduled and as clinically indicated. Reflex test for microscopic evaluation if abnormal. | | | | | | | | | | | | |
| **PSA (mCRPC only)** [2] | X | X | | | | X | | X | X | | X | X |
| PSA measurements to be performed at baseline and then repeated predose 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 (per **Section 9.17**) until disease progression, start of another cancer therapy, or the study cutoff date, whichever comes first. | | | | | | | | | | | | |
| **Serum Testosterone (mCRPC only)** [2] | X | X | | | | X | | X | X | | X | X |
| **PRO** | X | X | | | | X | | X | X | | X | |
| Patient-reported outcome using the BPI-sf. On dosing days, assessments to be performed prior to infusion. | | | | | | | | | | | | |
| **Pharmacokinetics** | See **Appendix 3** | | | | | | | | | | | |
| **Serum Cytokines** | See **Appendix 3** | | | | | | | | | | | |
| **Flow Cytometry (Subset)** | See **Appendix 3** | | | | | | | | | | | |
| **TCR repertoire (TCR) (Cohort Expansion only)** | See **Appendix 3** | | | | | | | | | | | |
| **Serum Biomarkers (Cohort Expansion only)** | See **Appendix 3** | | | | | | | | | | | |
| **Anti-Drug Antibody (ADA)** | See **Appendix 3** | | | | | | | | | | | |
| **Tumor Assessment (CT/PET/MRI (bone scan for mCRPC)** | X | Every 9 weeks | | | | | | | | | X | |
| Radiographic disease assessments will occur every 9 weeks (63 days ± 3 days). Assessment will also be done at EOTV as per **Section 9.16**. | | | | | | | | | | | | |

## Module A Cohort Expansion Phase

| EVALUATION/ PROCEDURE | Screening [1] (Within 28 days) | Cycle 1 | | | | | | Cycle 2 and Subsequent Cycles | | | EOTV [4] | Post TRT FUP |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 1 | Day 2 | Day 8 (±1d) | Day 15 (±1d) | Day 22 (±1d) | Day 42 (±5d) | Day 1 (±1d) | Day 22 (±1d) | Days 23, 29, 36 (±1d) [3] | | |
| **Study Day** | | **1** | **2** | **8** | **15** | **22** | **42** | **43** | **64** | **65, 71, 78** | | |
| **Survival Follow-up** | | | | | | | | | | | | X |
| Survival follow-up collected every 3 months (90 days ± 7 days) by clinic visit, telephone, paper mail, or other electronic contact for 2 years; information regarding response status and/or the occurrence of disease progression may be collected approximately every 3 months in participants who discontinued from study treatment due to reasons other than progressive disease, if they have not initiated any other cancer directed therapy. See **Section 9.17** for details. | | | | | | | | | | | | |

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

2 All laboratory tests and body weight may be performed up to 24 hours prior to each treatment visit.

3 For ≥ Cycle 2 Visits on Days 23, 29, and 36 are remote telemedicine visits only.

4 The EOTV should be performed within 30 days following the last dose of study drug.

Abbreviations: ADA = anti-drug antibody; AE = adverse event; CBC = complete blood count; CT = computed tomography; diff = differential; ECG = electrocardiography; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EOI = end of infusion; EOTV = End of Treatment Visit; FUP = follow-up; INR = international normalized ratio; mCRPC = metastatic castration-resistant prostate carcinoma; MRI = magnetic resonance imaging; MUGA = multigated acquisition (scan); PET = positron emission tomography; PLTs = platelets; PRO = patient-reported outcome; PT = prothrombin time; PTT = partial thromboplastin time; SAE = serious adverse event; SSE = symptomatic skeletal event; TCR = T-cell repertoire; TRT = treatment.

## Module B Dose Escalation and Cohort Expansion Phases

| EVALUATION/ PROCEDURE | Screening [1] (Within 28 days) | Cycle 1 | | | | | | Cycle 2 and subsequent Cycles[3] | | | | End of Treatment Visit [4] | Post TRT FUP |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 1 | Days 2 and 4 | Day 8 (±1d) | Day 15 | Day 22 (±1d) | Day 42 [2] (±3d) | Day 1 (±1d) | Day 22 (±1d) | Days 23, 25, 29, 36 (±1d) | Day 42 (±3d) | | |
| **STUDY DRUG ADMINISTRATION** | | | | | | | | | | | | | |
| **Administer MGA012** | | | | | | X | | X | X | | | | |
| **Administer MGC018** | | X | | | | X | | X | X | | | | |
| **ELIGIBILITY** | | | | | | | | | | | | | |
| **Informed Consent** | X | | | | | | | | | | | | |
| **Baseline Tumor Imaging** | X | | | | | | | | | | | | |
| **Designate Target/ Non-Target Lesions** | X | | | | | | | | | | | | |
| See **Appendix 5** | | | | | | | | | | | | | |
| **Medical History** | X | | | | | | | | | | | | |
| **Archival Tumor Specimen** | X | | | | | | | | | | | | |
| All participants to be enrolled in the study must have an identified formalin-fixed, paraffin embedded tumor specimen and or tumor specimens sufficient for 10 slides; see **Section 9.13**. The specimens will be analyzed retrospectively and will not be used to determine participant eligibility. | | | | | | | | | | | | | |
| **Physical Exam** | X | X | | | | | | X | | | | X | |
| **Height** | X | | | | | | | | | | | | |
| **Body Weight** | X | X | | | | X | | X | X | | | X | |
| **Directed History/Physical** | | | | X | | X | | | X | | | | |
| **Optional tumor biopsies on study** | X | | | | | | X | | | | | | |
| On treatment tumor biopsy: Fresh tumor biopsy pre-treatment (after enrollment and prior to the Cycle 1 Day 1 dose) and at Cycle 1 D42 ± 5 days. Paired tumor biopsies if the tumor lesions are accessible for biopsy with acceptable clinical risk in the judgment of the investigator; see **Section 9.14**. Tumor biopsies of accessible lesions, pre- and post-first cycle of treatment, are strongly encouraged for participants in Cohort Expansion. | | | | | | | | | | | | | |
| **Concurrent Medications** | X | X | X | X | X | X | X | X | X | X | X | X | |
| **ECOG PS** | X | | | | | | | X | | | | X | |
| **12-lead ECG** | X | X | | | | X | | X | | | | X | |
| To be performed in triplicate (approximately 1 minute apart). *During non-treatment visits (Screening and EOTV)*, ECG will be taken at 1 time point. *Cycle 1 Day 1*: Pre-infusion of MGC018 (within -30 minutes), EOI of MGC018 (within 30 minutes after EOI), and Hour 4 after EOI (± 10 minutes). *Cycle 1 Day 22 and Day 1 of all subsequent cycles*: 12-lead ECG is recorded pre-infusion (within -30 minutes) and EOI (within 30 minutes after EOI). | | | | | | | | | | | | | |

## Module B Dose Escalation and Cohort Expansion Phases

| EVALUATION/ PROCEDURE | Screening [1] (Within 28 days) | Cycle 1 | | | | | | Cycle 2 and subsequent Cycles[3] | | | | End of Treatment Visit [4] | Post TRT FUP |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 1 | Days 2 and 4 | Day 8 (±1d) | Day 15 | Day 22 (±1d) | Day 42 [2] (±3d) | Day 1 (±1d) | Day 22 (±1d) | Days 23, 25, 29, 36 (±1d) | Day 42 (±3d) | | |
| **Echocardiogram/MUGA** | X | | | | | | | | | | X | X | |
| Echocardiogram or MUGA scan performed at screening, approximately every 12 weeks [at the end of C2, C4, C6…(± 7 days)], at the end of treatment visit and at other time points if clinically indicated See **Section 9.11** | | | | | | | | | | | | | |
| **Ophthalmic Exam** | X | | | | | | | | | | X | X | |
| Ophthalmic examinations including visual acuity testing (with correction), fundoscopic examination, and tonometry are performed at screening, at Cycle 2 Day 42 (± 7 days), End of Treatment, and at other time points if clinically indicated. Other directed studies (e.g., optical coherence tomography) will be performed as clinically indicated. See **Section 9.12** | | | | | | | | | | | | | |
| **Pregnancy Test (serum or urine)** | X | X | | | | | | X | | | | X | |
| Serum pregnancy test is required for eligibility. Subsequent pregnancy tests may use serum or urine. Test results must be reviewed before the study drug infusion on Day 1 of Cycle 1 and all subsequent cycles. If screening test is performed within 72 hours of 1st infusion, repeat of the test on Day 1 may be deferred. | | | | | | | | | | | | | |
| **Eligibility Checklist and Register Participant** | X | | | | | | | | | | | | |
| **SAFETY/PK/MECHANISTIC STUDIES** | | | | | | | | | | | | | |
| **Protocol Procedure Related AEs/SAEs** | X | | | | | | | | | | | | |
| **Assess for Adverse Events** | | Continuous | | | | | | | | | | | |
| **Vital Signs** | X | X | | X | | X | | X | X | | | X | |
| *During non-treatment visits (Screening, Day 8, and EOTV)*, vital signs will be taken once.<br>*Cycle 1:*<br>Day 1: Pre-infusion of MGC018 (within -30 minutes); at 15 and 30 minutes after the start of infusion (± 5 minutes), at EOI (± 10 minutes); and at 1- and 4-hours after EOI (± 10 minutes).<br>Day 22: Pre-infusion of MGA012 (within -30 minutes); at 15 and 30 minutes after the start of MGA012 infusion (± 5 minutes), at EOI of MGA012 (± 10 minutes); at EOI of MGC018 (± 10 minutes), and at 1 hour after MGC018 EOI (± 10 minutes).<br>*Cycle 2 and Beyond:* Pre-infusion of MGA012 (within -30 minutes); at EOI of MGA012 (± 10 minutes); at EOI of MGC018 (± 10 minutes), and at 1 hour after MGC018 EOI (± 10 minutes). | | | | | | | | | | | | | |

**Module B Dose Escalation and Cohort Expansion Phases**

| EVALUATION/ PROCEDURE | Screening [1] (Within 28 days) | Cycle 1 | | | | | | Cycle 2 and subsequent Cycles[3] | | | | End of Treatment Visit [4] | Post TRT FUP |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 1 | Days 2 and 4 | Day 8 (±1d) | Day 15 | Day 22 (±1d) | Day 42 [2] (±3d) | Day 1 (±1d) | Day 22 (±1d) | Days 23, 25, 29, 36 (±1d) | Day 42 (±3d) | | |
| **CBC, PLTs, diff; Chemistry Panel** | X | X | | X | | X | | X | X | | | X | |
| To be collected pre-infusion and prior to prophylactic pre-medications on dosing days. Day 1 laboratory blood samples can be collected up to 1 day before infusion. See **Appendix 2** for list of assessments. | | | | | | | | | | | | | |
| **PT or INR** | X | X | | X | | X | | X | X | | | X | |
| PT is preferred. INR is acceptable based on local availability. To be collected pre-infusion and prior to prophylactic pre-medications on dosing days. Day 1 laboratory blood samples can be collected up to 1 day before infusion. Collect as scheduled, and as clinically indicated. | | | | | | | | | | | | | |
| **Free T4 and TSH** | X | | | | | | | X | | | | X | |
| Sample to be drawn at Screening, Cycle 2 Day 1, and then on Day 1 every other cycle, i.e., Cycle 4, Cycle 6, etc. | | | | | | | | | | | | | |
| **Urinalysis** | X | X | | | | | | X | | | | X | |
| To be collected pre-infusion and prior to prophylactic pre-medications on dosing days. Day 1 urine samples can be collected up to 1 day before infusion. See **Appendix 2** for list of assessments. Collect as scheduled and as clinically indicated. Reflex test for microscopic evaluation if abnormal. | | | | | | | | | | | | | |
| **PSA (mCRPC only)** | X | | | | | | | X | | | | | |
| PSA measurements to be performed at baseline and then repeated predose on Day 1 of each cycle, 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. | | | | | | | | | | | | | |
| **Pharmacokinetics** | See **Appendix 3** | | | | | | | | | | | | |
| **Serum Cytokines** | See **Appendix 3** | | | | | | | | | | | | |
| **Flow Cytometry (Occupancy)** | See **Appendix 3** | | | | | | | | | | | | |
| **Flow Cytometry (Subset)** | See **Appendix 3** | | | | | | | | | | | | |
| **TCR repertoire (TCR) (Cohort Expansion only)** | See **Appendix 3** | | | | | | | | | | | | |
| **Serum Biomarkers (Cohort Expansion only)** | See **Appendix 3** | | | | | | | | | | | | |
| **Anti-Drug Antibody (ADA)** | See **Appendix 3** | | | | | | | | | | | | |

**Module B Dose Escalation and Cohort Expansion Phases**

| EVALUATION/ PROCEDURE | Screening [1] (Within 28 days) | Cycle 1 | | | | | | Cycle 2 and subsequent Cycles[3] | | | | End of Treatment Visit [4] | Post TRT FUP |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 1 | Days 2 and 4 | Day 8 (±1d) | Day 15 | Day 22 (±1d) | Day 42 [2] (±3d) | Day 1 (±1d) | Day 22 (±1d) | Days 23, 25, 29, 36 (±1d) | Day 42 (±3d) | | |
| **Tumor Assessment (CT/PET/MRI)** | X | | | | | | X | | | | X | X | |
| Radiographic disease assessments will occur on Day 42 ± 3 days for the first four cycles, and every other cycle thereafter. Assessment will also be done at EOTV. | | | | | | | | | | | | | |
| **Survival Follow-up** | | | | | | | | | | | | | X |
| Survival follow-up collected every 3 months (90 days ± 7 days) by clinic visit, telephone, paper mail, or other electronic contact for 2 years; information regarding response status and/or the occurrence of disease progression may be collected approximately every 3 months in participants who discontinued from study treatment due to reasons other than progressive disease, if they have not initiated any other cancer directed therapy. See **Section 9.17** for details. | | | | | | | | | | | | | |

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

2 Cycle 1 Day 42 and Cycle 2 Day 1 may be combined. Regardless if the visits are combined or not, Cycle 1 Day 42 assessments should occur before Cycle 2 Day 1 assessments. The same applies to all consecutive cycles.

3 Evaluations/procedures performed on Days 23, 25, 29, and 36 apply to Cycle 2 only.

4 The EOTV should be performed within 30 days following the last dose of study drug.

Abbreviations: ADA = anti-drug antibody; AE = adverse event; CBC = complete blood count; CT = computed tomography; diff = differential; ECG = electrocardiography; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EOI = end of infusion; EOTV = End of Treatment Visit; FUP = follow-up; INR = international normalized ratio; mCRPC = metastatic castration-resistant prostate carcinoma; MRI = magnetic resonance imaging; MUGA = multigated acquisition (scan); PET = positron emission tomography; PLTs = platelets; PSA = prostate-specific antigen; PT = prothrombin time; SAE = serious adverse event; SSE = symptomatic skeletal event; TCR = T-cell repertoire; TRT = treatment; TSH = thyroid stimulating hormone.

# Appendix 2 Clinical Laboratory Tests

| | |
|---|---|
| **Pregnancy test:**<br>Blood or Urine Human chorionic gonadotropin (hCG)<br><br>**Hematology (CBC with differential):**<br>Hemoglobin<br>Hematocrit<br>Platelet count<br>White blood cell count<br>Absolute neutrophils, lymphocytes, and eosinophils<br><br>**Serum chemistry:**<br>Albumin<br>Alkaline phosphatase<br>Alanine aminotransferase<br>Aspartate aminotransferase<br>Bicarbonate<br>Bilirubin (Total and Direct)<br>Blood urea nitrogen<br>Calcium<br>Chloride<br>Creatinine<br>Glucose<br>Magnesium<br>Phosphate<br>Potassium<br>Sodium<br>Uric acid | **Coagulation:**<br>Prothrombin time (PT) – preferred, or INR is acceptable<br>International normalised ratio (INR)<br>Partial thromboplastin time (PTT)<br><br>**Endocrine tests:**<br>Free thyroxine (Module A Dose Escalation and Module B Dose Escalation and Module B Cohort Expansion)<br>Thyroid-stimulating hormone (Module A Dose Escalation and Module B Dose Escalation and Module B Cohort Expansion)<br>Serum testosterone (mCRPC Module A Cohort Expansion and Module B Cohort Expansion)<br><br>**Urinalysis:**<br>Protein<br>Occult blood<br>If abnormal protein or occult blood, perform reflex test for microscopic evaluation<br><br>**Tumor marker:**<br>Prostate specific antigen (PSA) for mCRPC only |

# Appendix 3 Pharmacokinetics, Immunogenicity, and Pharmacodynamic Biomarkers Blood Sampling Schedule for Module A and B

Blood samples for PK, ADA, and pharmacodynamic biomarkers will be collected per **Table 12**, **Table 13**, and **Table 14**. Please note:

- 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 collection of the blood sample for immunogenicity assessment.
- Both planned and actual start and end of infusion date and times and blood sample collection date and times will be recorded on the eCRFs.

**Table 12 Module A: Pharmacokinetic, Immunogenicity, and Pharmacodynamic Biomarkers Blood Sampling Schedule: MGC018 Monotherapy Q3W Dose Escalation Phase**

| Cycle | Day | Window | Time Point | MGC018 PK (Total and ADC) Serum | MGC018 PK (SYD986) Plasma | ADA (for MGC018) | Cytokines | Flow Cytometry Subsets |
|---|---|---|---|---|---|---|---|---|
| Cycle 1 | 01 | N/A | Pre MGC018 Infusion | X | X | X | X | X |
| | | ± 5 min | EOI MGC018 Infusion | X | X | | X | |
| | | ± 10 min | 1 h after EOI MGC018 | X | X | | X | |
| | | ± 10 min | 4 h after EOI MGC018 | X | X | | X | |
| | 02 | N/A | Day 02 | X | X | | X | X |
| | 04 | N/A | Day 04 | X | X | | X | |
| | 08 | N/A | Day 08 | X | X | | | X |
| | 15 | N/A | Day 15 | X | X | | | |
| | 22 | N/A | Pre MGC018 Infusion | X | X | X | | X |
| | | ± 5 min | EOI MGC018 Infusion | X | X | | | |
| Cycle 2 | 01 | N/A | Pre MGC018 Infusion | X | X | X | | X |
| | | ± 5 min | EOI MGC018 Infusion | X | X | | | |
| | 22 | N/A | Pre MGC018 Infusion | X | X | | | X |
| | | ± 5 min | EOI MGC018 Infusion | X | X | | | |
| | | ± 10 min | 1 h after EOI MGC018 | X | X | | | |
| | | ± 10 min | 4 h after EOI MGC018 | X | X | | | |
| | 23 | N/A | Day 23 | X | X | | | X |
| | 25 | N/A | Day 25 | X | X | | | |
| | 29 | N/A | Day 29 | X | X | | | X |
| | 36 | N/A | Day 36 | X | X | | | X |

**Table 12 Module A: Pharmacokinetic, Immunogenicity, and Pharmacodynamic Biomarkers Blood Sampling Schedule: MGC018 Monotherapy Q3W Dose Escalation Phase**

| Cycle | Day | Window | Time Point | MGC018 PK (Total and ADC) Serum | MGC018 PK (SYD986) Plasma | ADA (for MGC018) | Cytokines | Flow Cytometry Subsets |
|---|---|---|---|---|---|---|---|---|
| Cycle 3 | 01 | N/A | Pre MGC018 Infusion | X | X | X | | X |
| | | ± 5 min | EOI MGC018 Infusion | X | X | | | |
| Cycle 4 and Beyond | 01 | N/A | Pre MGC018 Infusion | X | X | X | | |
| | | ± 5 min | EOI MGC018 Infusion | X | X | | | |
| IRR/ CRS | | N/A | IRR/CRS | X | X | | X | |
| EOTV | | N/A | EOTV | X | X | X | | X |

Abbreviations: ADA = anti-drug antibody; ADC = antibody-drug conjugate; CRS = cytokine release syndrome; EOI = end of infusion; EOTV = End of Treatment Visit; NA = not applicable; IRR = infusion-related reaction.

**Table 13 Module A: Pharmacokinetic, Immunogenicity, and Pharmacodynamic Biomarkers Blood Sampling Schedule: MGC018 Monotherapy Q3W Cohort Expansion Phase**

| Cycle | Day | Window | Time Point | MGC018 PK (Total and ADC) Serum | MGC018 PK (SYD986) Plasma | ADA (for MGC018) | Cytokines | Flow Cytometry Subsets | Serum Biomarkers | T-cell Repertoire |
|---|---|---|---|---|---|---|---|---|---|---|
| Cycle 1 | 01 | N/A | Pre MGC018 Infusion | X | X | X | X | X | X | X |
| | | + 5 min | EOI MGC018 Infusion | X | X | | X | | | |
| | | ± 10 min | 1 h after EOI MGC018 | X | X | | X | | | |
| | | ± 10 min | 4 h after EOI MGC018 | X | X | | X | | | |
| | 22 | N/A | Pre MGC018 Infusion | X | X | X | X | X | X | |
| | | + 5 min | EOI MGC018 Infusion | X | X | | X | | | |
| | 42 | ± 5 Days | Biopsy | | | | | X [a] | X [a] | X [a] |
| Cycle 2 | 01 | N/A | Pre MGC018 Infusion | X | X | X | X | X | X | X |
| | | + 5 min | EOI MGC018 Infusion | X | X | | X | | | |
| | 22 | N/A | Pre MGC018 Infusion | X | X | | X | X | X | |
| | | +5 min | EOI MGC018 Infusion | X | X | | X | | | |
| Cycle 3 | 01 | N/A | Pre MGC018 Infusion | X | X | X | X | X | X | X |
| | | + 5 min | EOI MGC018 Infusion | X | X | | X | | | |
| Cycle 4 | 01 | N/A | Pre MGC018 Infusion | X | X | X | X | | | |
| | | + 5 min | EOI MGC018 Infusion | X | X | | X | | | |

**Table 13 Module A: Pharmacokinetic, Immunogenicity, and Pharmacodynamic Biomarkers Blood Sampling Schedule: MGC018 Monotherapy Q3W Cohort Expansion Phase**

| Cycle | Day | Window | Time Point | MGC018 PK (Total and ADC) Serum | MGC018 PK (SYD986) Plasma | ADA (for MGC018) | Cytokines | Flow Cytometry Subsets | Serum Biomarkers | T-cell Repertoire |
|---|---|---|---|---|---|---|---|---|---|---|
| Cycle 5 and Beyond | 01 | N/A | Pre MGC018 Infusion | X | X | X | | | | |
| | | + 5 min | EOI MGC018 Infusion | X | X | | | | | |
| IRR/ CRS | | N/A | IRR/CRS | X | X | | X | | | |
| EOTV | | N/A | EOTV | X | X | X | X | X | | |

Abbreviations: ADA = anti-drug antibody; ADC = antibody-drug conjugate; CRS = cytokine release syndrome; EOI = end of infusion; EOTV = End of Treatment Visit; NA = not applicable; IRR = infusion-related reaction

a Blood sample drawn from participants that consent to undergo a biopsy.

**Table 14 Module B: Pharmacokinetic, Immunogenicity, and Pharmacodynamic Biomarkers Blood Sampling Schedule: MGC018 and MGA012 Combination Therapy Q3W**

| Cycle | Day | Window | Time Point | MGC018 PK (Total and ADC) Serum | MGC018 PK (SYD986) Plasma | MGA012 PK Serum | ADA (for MGA012 and MGC018) | Cytokines | Flow Cytometry Occupancy | Flow Cytometry Subsets | Serum Biomarkers (Expansion only) | T-Cell Repertoire (Expansion only) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cycle 1 | 01 | N/A | Pre MGC018 Infusion | X | X | | X | X | X | X | X | X |
| | | ± 5 min | EOI MGC018 Infusion | X | X | | | X | | | | |
| | | ± 10 min | 1 h after EOI MGC018 | X | X | | | X | | | | |
| | | ± 10 min | 4 h after EOI MGC018 | X | X | | | X | | | | |
| | 02 | N/A | Day 02 | X | X | | | X | | X | | |
| | 04 | N/A | Day 04 | X | X | | | X | | | | |
| | 08 | N/A | Day 08 | X | X | | | | | X | X | |
| | 15 | N/A | Day 15 | X | X | | | | | | | |
| | 22 | N/A | Pre MGA012 Infusion | | | X | X | | X | X | X | |
| | | ± 5 min | EOI MGA012 Infusion | X | X | X | | | X | X | | |
| | | ± 5 min | EOI MGC018 Infusion | X | X | | | | | | | |
| | 42 | ± 5 Days | Biopsy (SCCHN only) | | | | | | | X [a] | X [a] | X [a] |
| Cycle 2 | 01 | N/A | Pre MGA012 Infusion | | | X | X | | X | X | X | X |
| | | ± 5 min | EOI MGA012 Infusion | X | X | X | | | X | | | |
| | | ± 5 min | EOI MGC018 Infusion | X | X | | | | | | | |
| | 22 | N/A | Pre MGA012 Infusion | | | X | | | X | X | X | |
| | | ± 5 min | EOI MGA012 Infusion | X | X | X | | | X | | | |
| | | ± 5 min | EOI MGC018 Infusion | X | X | | | | | | | |

**Table 14 Module B: Pharmacokinetic, Immunogenicity, and Pharmacodynamic Biomarkers Blood Sampling Schedule: MGC018 and MGA012 Combination Therapy Q3W**

| Cycle | Day | Window | Time Point | MGC018 PK (Total and ADC) Serum | MGC018 PK (SYD986) Plasma | MGA012 PK Serum | ADA (for MGA012 and MGC018) | Cytokines | Flow Cytometry Occupancy | Flow Cytometry Subsets | Serum Biomarkers (Expansion only) | T-Cell Repertoire (Expansion only) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | ± 10 min | 1 h after EOI MGC018 | X | X | | | | | | | |
| | | ± 10 min | 4 h after EOI MGC018 | X | X | | | | | | | |
| | 23 | N/A | Day 23 | X | X | | | | | X | | |
| | 25 | N/A | Day 25 | X | X | | | | | | | |
| | 29 | N/A | Day 29 | X | X | | | | | X | | |
| | 36 | N/A | Day 36 | X | X | | | | X | X | | |
| Cycle 3 | 01 | N/A | Pre MGA012 Infusion | | | X | X | | X | X | X | X |
| | | ± 5 min | EOI MGA012 Infusion | X | X | X | | | X | | | |
| | | ± 5 min | EOI MGC018 Infusion | X | X | | | | | | | |
| Cycle 4 and Beyond | 01 | N/A | Pre MGA012 Infusion | | | X | X | | | | | |
| | | ± 5 min | EOI MGA012 Infusion | X | X | X | | | | | | |
| | | ± 5 min | EOI MGC018 Infusion | X | X | | | | | | | |
| **IRR/CRS** | | N/A | IRR/CRS | X | X | X | | X | | | | |
| **EOTV** | | N/A | EOTV | X | X | X | X | | | X | | |

Abbreviations: ADA = anti-drug antibody; ADC = antibody-drug conjugate; CRS = Cytokine Release Syndrome; EOI = end of infusion; EOTV = End of Treatment Visit; N/A = not applicable; IRR = infusion-related reaction.

a Blood sample drawn from participants in the Cohort Expansion Phase that consent to and undergo a biopsy.

# 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 v1.1 Guidelines

Adapted from Eisenhauer 2009 (**22**).

All participants 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.

## 1 Measurability of Tumor at Baseline

### 1.1 Definitions

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

#### 1.1.1 Measurable

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

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

#### 1.1.2 Non-measurable

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

#### 1.1.3 Special considerations regarding lesion measurability

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

Bone lesions:

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

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither 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 participant, these are preferred for selection as target lesions.

Lesions with prior local treatment:

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

## 1.2 Specifications by methods of measurements

### 1.2.1 Measurement of lesions

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

### 1.2.2 Method of assessment

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

*Clinical lesions:* Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). For the case of skin

lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

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

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

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

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

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

# 2 Tumor Response Evaluation

## 2.1 Assessment of overall tumor burden and measurable disease

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

## 2.2 Baseline documentation of ‘target’ and ‘non-target’ lesions

Where more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as *target lesions* and will be recorded and measured at baseline. For example, in instances where patients have only one or two organ sites involved, a maximum of two and four lesions respectively will be recorded). Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. It may be

the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesions which can be measured reproducibly should be selected.

*Lymph nodes* merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. As noted 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 x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

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

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

## 2.3 Response criteria

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

### 2.3.1 Evaluation of target lesions

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

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

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

absolute increase of at least 5 mm. (*Note:* the appearance of one or more new lesions is also considered progression).

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

### 2.3.2 Special notes on the assessment of target lesions

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

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

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

### 2.3.3 Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be 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 (< 10 mm 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).

### 2.3.4 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.

### 2.3.5 New Lesions

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

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

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

## 2.4 Evaluation of best overall response

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

### 2.4.1 Time point response

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

### 2.4.2 Missing assessments and inevaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements is made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

### 2.4.3 Best overall response: all time points

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

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

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

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

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

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

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

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

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.

## 2.5 Confirmation/Duration of response

### 2.5.1 Confirmation

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

### 2.5.2 Duration of overall response

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

### 2.5.3 Duration of stable disease

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

# Appendix 6 Brief Pain Inventory-Short Form (BPI-sf)

# Appendix 7 Principal Investigator's Agreement

**Study Title:** 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

**Study Number:** CP-MGC018-01

I have read the protocol described above.

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

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

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

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

**Signed:** _____

**Date:** _____

**Name (printed):** _____

**Title:** _____

**Affiliation:** _____

**Address:** _____

**Phone Number:** _____

CP-MGC018-01 Protocol Amendment 6 (16-Aug-2021)
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