PROTOCOL

TITLE:	**A PHASE II STUDY OF VOBRAMITAMAB DUOCARMAZINE (MGC018) IN PATIENTS WITH RELAPSED OR REFRACTORY EXTENSIVE-STAGE SMALL-CELL LUNG CANCER (ES-SCLC)**
STUDY NUMBER:	STUDY00007316
Version Date:	September 24, 2024
VERSION NUMBER:	Version 2.0
IRB NUMBER	STUDY00007316
NCT NUMBER	NCT06227546
TEST PRODUCTS:	MGC018
INDICATION:	ES-SCLC
INVESTIGATOR:	Chul Kim, MD, MPH 3800 Reservoir Road NW Lombardi Comprehensive Cancer Center Washington, DC 20007 Telephone: [redacted] E-mail: [redacted]
SUB-INVESTIGATORS:	Stephen V. Liu, MD Joshua E. Reuss, MD Jillian Thompson, MSN, ANP-BC, AOCNP Vincent Yeung, MD Irina Veytsman, MD Martin Gutierrez, MD Kevin Chen, MD Brinda Gupta, MD Jaeil Ahn, PhD (study statistician)
SUPPORT PROVIDED BY:	Macrogenics, Inc.

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Declaration of Sponsor or Responsible Medical Officer

Title: A Phase II Study of Vobramitamab duocarmazine (MGC018) in Patients with Relapsed or Refractory Extensive-Stage Small-Cell Lung Cancer (ES-SCLC)

This study protocol was subjected to critical review and has been approved by the Sponsor. The information it contains is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on Good Clinical Practice.

Signed by Chul Kim, MD

I approve this document
30-Oct-2024 | 11:48 PDT

30-Oct-2024 | 11:48 PDT

Chul Kim, MD, MPH

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Date

Lombardi Comprehensive Cancer Center

Georgetown University Medical Center

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ADA	Anti-drug antibody
ADC	Antibody-drug conjugate
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AESI	Adverse event of special interest
ANC	Absolute neutrophil count
B7-H3	B7 homolog 3 protein
CFR	Code of Federal Regulations
CNS	Central nervous system
CTCAE	Common terminology criteria for adverse effects
DOR	Duration of response
DSMC	Data safety monitoring committee
ECOG	Eastern Cooperative Oncology Group
EBV	Epstein Barr Virus
ES-SCLC	Extensive stage small cell lung cancer
EOTV	End of treatment visit
FFPE	Formalin fixed paraffin-embedded
GCP	Good clinical practice
HIPAA	Health Insurance Portability and Accountability
HTSR	Histopathology & Tissue Shared Resource
IB	Investigator's brochure
ICF	Informed consent form
IMP	Investigational medicinal product
IRB	Institutional review board
IRR	Infusion related reaction
LCCC	Lombardi comprehensive cancer center
LPLV	Last patient, last visit
mCRPC	Metastatic castration resistant prostate cancer
MGUH	MedStar Georgetown University Hospital
mIg	Membrane bound immunoglobulin
MRI	Magnetic resonance imaging

NGS	Next generation sequencing
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PET	Positron emission tomography
PFS	Progression free survival
PI	Principal investigator
PK	Pharmacokinetic
RECIST	Response evaluation criteria in solid tumors
SAE	Severe adverse event
SBRT	Stereotactic body radiation therapy
SCLC	Small cell lung cancer
SRS	Stereotactic radiosurgery
STIAMP	Suspected transmission of an infectious agent by the study drug
T3	Free triiodothyronine
T4	Free thyroxine
TcR	T-cell antigen receptor
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
VAF	Variant allele frequency
WGS	Whole genome sequencing
WES	Whole exome sequencing
WTS	Whole transcriptome sequencing

1. BACKGROUND

1.1 BACKGROUND ON SMALL CELL LUNG CANCER (SCLC)

Small cell lung cancer (SCLC) an exceptionally aggressive subtype of lung cancer; it accounts for 10-15% of all lung cancers (Gazdar et al. 2017). SCLC is characterized by early metastases along with rapid growth and resistance to treatment. In 2018, there was an estimated 29,514 new cases of SCLC with a 5-year survival rate of just 6.9%. About 75% of patients with newly diagnosed SCLC present with disseminated disease, with a 5-year survival of only about 3% (Surveillance Research Program, National Cancer Institute).

1.2 BACKGROUND ON THE TREATMENT OF EXTENSIVE STAGE SMALL CELL LUNG CANCER (ES-SCLC)

For extensive stage small cell lung cancer (ES-SCLC), the standard of care frontline treatment has generally involved platinum-based chemotherapy with etoposide for several decades. Despite high initial response rates of about 65%, patients will predictably experience relapse after chemotherapy alone, with median overall survival (OS) of only about 10 months (Rossi et al. 2012). In the last several years, immunotherapy has demonstrated clinical activity in ES-SCLC. The phase III IMpower133 trial demonstrated that in patients with ES-SCLC, the addition of atezolizumab to standard first-line platinum-based chemotherapy improved both PFS (5.2 months vs 4.3 months) and OS (12.9 months vs 10.3 months) when compared to platinum-based chemotherapy alone (Horn et al. 2018). The CASPIAN trial showed similar modest improvements in OS with the addition of the programmed cell death ligand-1 (PD-L1) inhibitor durvalumab to platinum-based chemotherapy (Paz-Ares et al. 2019).

Despite these improvements in therapy, the majority of patients will relapse. Outcomes in patients with relapsed or refractory ES-SCLC remain poor, with median OS of less than six months. Camptothecins such as topotecan are used as second-line therapy, however objective response rates (ORRs) are low at about 15% (Garst et al. 2007). The alkylating agent lurbinectedin obtained accelerated FDA approval in 2020 for patients with ES-SCLC who had disease progression on or after platinum-based chemotherapy. The overall response rate was 33% with median duration of response (DOR) of 5.1 months (Trigo et al. 2020). For patients with chemotherapy free interval ≥ 90 days, the response rates were even greater with ORR of 45% and median PFS of 4.5 months. In patients with chemotherapy free interval < 90 days, the ORR was 22% and median PFS of 2.6 months. Despite these recent advances, outcomes remain poor, and there is need to develop novel therapeutics for relapsed or refractory ES-SCLC.

1.3 BACKGROUND ON B7-H3

B7 homolog 3 protein (B7-H3), which is also known as CD276, is a type I transmembrane protein encoded on chromosome 15 and is a member of the B7 family of immune check points (Seaman et al. 2017). The B7 family of cell surface molecules consist 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 (Collins et al. 2005). The B7-H3 pathway is involved in the immune response in various ways, including blocking NK mediated lysis and augmenting proinflammatory cytokines. Although B7-H3 mRNA is widely distributed, B7-H3 protein expression in normal human tissue is limited, presumably thought to be from the negative regulation of B7-H3 protein expression by the microRNA miR-29 (Xu et al. 2009). B7-H3 has been implicated in the delivery of both co-stimulatory and co-inhibitory signals (Hofmeyer et al. 2008).

B7-H3 is an appealing therapeutic target due to its overexpression in many malignant tumors and limited expression in normal tissues (**Figure 1**). Additionally, B7-H3 upregulation is associated with a worse prognosis.

Figure 1. Summary of B7-H3 expression in human cancer

Potential Indications:	IHC Summary of >1,400 Tumor Tissue Samples Screened			
	B7-H3 Positive[a]		2+ or Above	
Head and Neck	19/19	100%	19/19	100%
Kidney Cancer	77/78	99%	75/78	96%
Glioblastoma	65/66	98%	63/66	95%
Thyroid Cancer	34/35	97%	33/35	94%
Mesothelioma	41/44	93%	39/44	89%
Melanoma	132/146	90%	94/146	64%
Prostate Cancer	88/99	89%	51/99	52%
Pancreas Cancer	69/78	88%	45/78	58%
Bladder	134/156	86%	123/156	79%
Lung Cancer	324/379	85%	300/379	79%
Breast Cancer	189/249	76%	156/249	63%
Ovarian Cancer	59/79	75%	36/79	46%

1.4 BACKGROUND ON VOBRAMITAMAB DUOCARMAZINE (MGC018)

Figure 2. Schematic representation of MGC018 and mechanisms of release of prodrug from MGC018 and conversion to the active duocarmycin drug DUBA

[redacted]

1.5 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

1.5.1 Study rationale for MGC018 in ES-SCLC with progression after prior platinum-based chemotherapy

[redacted]

[redacted]

Table 1. [redacted]

[redacted]		

[redacted]

2. OBJECTIVES AND ENDPOINTS

2.1 PRIMARY OBJECTIVE

- To determine the efficacy of MGC018 in patients with relapsed or refractory ES-SCLC as defined by investigator-assessed ORR according to RECIST v1.1

2.2 SECONDARY OBJECTIVES

- To evaluate the safety profile of MGC018 in patients with relapsed or refractory ES-SCLC
- To examine duration of response (DOR), progression-free survival (median PFS and 6-month PFS), and overall survival

2.3 EXPLORATORY OBJECTIVES

- To assess efficacy of MGC018 according to the expression of B7-H3 on tumor tissue
- To assess the role of blood-based biomarkers in predicting response and resistance to MGC018

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

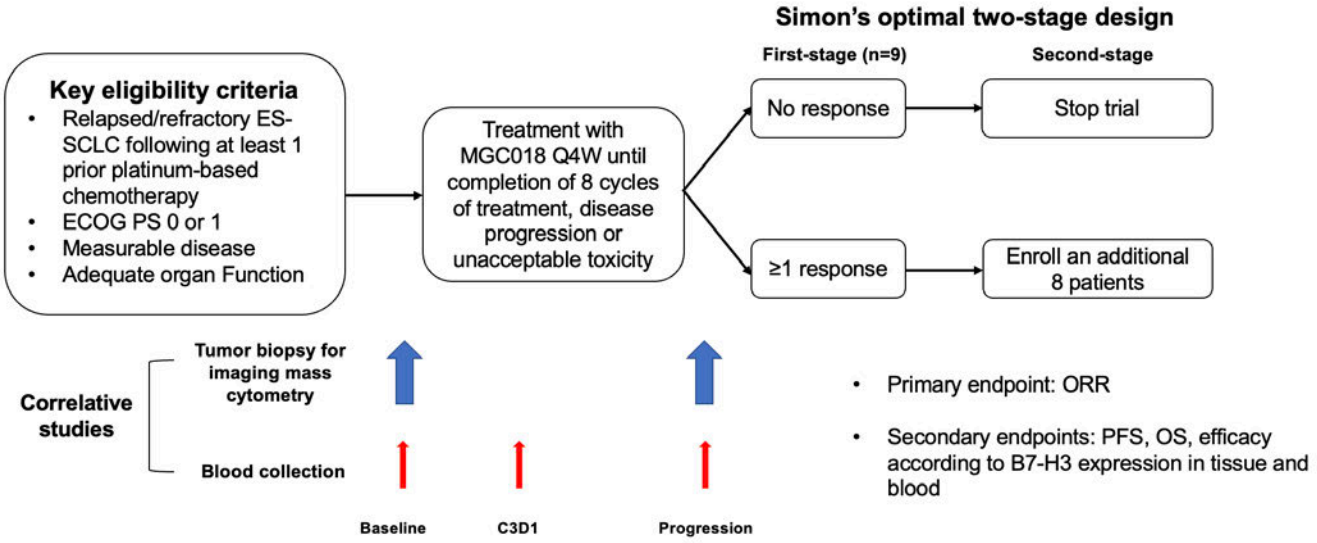
3.1.1 Study schema & overview of study design

This is an open label phase 2, multi-center, single arm study evaluating the efficacy of MGC018 in patients with relapsed or refractory ES-SCLC. Our cohort will enroll patients with ES-SCLC who experience progression during or following treatment with platinum-based chemotherapy. For full detailed inclusion/exclusion criteria, see section 4.1.

Patients enrolled will receive MGC018 at 2.0 mg/kg every 28 days continuously until completion of 8 cycles, disease progression, or unacceptable toxicity. Tumor assessment will be done every 2 cycles. The primary endpoint of the study will be assessed by ORR utilizing RECIST v1.1.

Key secondary endpoints will include incidence of adverse events per CTCAE v5.0, DOR, PFS, and OS. In an exploratory fashion, we plan to evaluate efficacy according to expression of B7-H3 on tumor tissue and blood-based biomarkers. Pre-treatment biopsy will be obtained to assess expression of B7-H3 on tumor tissue. If biopsy is not considered safe and medically feasible by the investigator, the patient may be approved for enrollment after consultation the principal investigator. In this case, we will obtain archival tissue if available. Expression of B7-H3 and other immune markers on tumor tissue will be assess using Imaging Mass Cytometry (Fluidigm platform) and correlated with treatment outcomes such as ORR, PFS, and OS. Blood samples will be obtained for biomarker analysis at day 1 of cycle 1, on day 1 of cycle 3, and at time of progression.

Figure 3 – Study Schema (N=17)



3.1.2 Hypothesis

Administration of MGC018 will achieve a clinically meaningful response rate of 25% in patients with relapsed or refractory ES-SCLC.

3.1.3 Summary of sample size calculation, study accrual and duration

Using the Simon's optimal two-stage design (Simon, Controlled clinical trials, 1989), we plan to enroll up to 17 patients. The null hypothesis that the true response rate is 5% will be tested against a one-sided alternative. In the first stage, 9 patients will be accrued. If there is no response in these 9 patients, the study will be stopped. If there is at least one response (including unconfirmed partial response) in the first 9 patients, 8 additional patients will be accrued for a total of 17. The null hypothesis will be rejected if 3 or more responses are observed in 17 patients. This design yields a type I error rate of 4.7% and power of 81.2%, when the true response rate is 25%. Time-to-event data, such as DOR, PFS, and OS, will be estimated using the Kaplan-Meier method. Cox proportional hazards models will be used to estimate hazard ratios. Safety data will be summarized descriptively. Adverse events will be summarized by severity, seriousness, and relationship to the study drug.

Patients will be enrolled at Georgetown Lombardi Comprehensive Cancer Center (LCCC), Washington Hospital Center, John Theurer Cancer Center, and Rutgers Cancer Institute of New Jersey at University Hospital. Other sites may be added to the study. Combined expected accrual is 1-2 patients per month. With expected required accrual period of 12 months duration. Patients will be followed with imaging tumor assessments every 2 cycles assess ORR. Upon progressive disease of unacceptable toxicity, patients will be taken off study and monitored every 6 months for two years for survival data.

3.1.4 PK and ADA data

Blood samples will be regularly collected and submitted for PK and anti-drug antibody (ADA) assays. Support for these assays will be provided by MacroGenics. Total and ADC PK assays as well as ADA assays will be performed on the serum. Samples for PK data will be collected pre- and post-infusion as

well as on day 15 of cycles 1 and 2 then pre- and post-infusion for cycles 3 through 5 as well as every 3 cycles for cycles 6 through 12. ADA assays will be performed on samples collected pre-infusion as well as on day 15 of cycle 1 then pre-infusion for cycles 2 through 5 and every 3 cycles for cycles 6 through 12. PK and ADA testing will be obtained at the EOTV. PK and ADA testing may be performed at the time of any IRR.

Table 2. PK and ADA collection schedule

Cycle	Day	Timepoint	Window	PK: Total and ADC (serum)	ADA: (serum)
1	1	Pre-infusion	N/A	X	X
1	1	End of infusion	+10 min	X	
1	15	Day 15	N/A	X	X
2	1	Pre-infusion	N/A	X	X
2	1	End of infusion	+10 min	X	
2	15	Day 15	N/A	X	
3, 4, and 5	1	Pre-infusion	N/A	X	X
3, 4, and 5	1	End of infusion	+10 min	X	
6, 9, and 12	1	Pre-infusion	N/A	X	X
6, 9, and 12	1	End of infusion	+10 min	X	
IRR[a]	N/A	N/A	N/A	X	X
EOTV	N/A	EOTV	N/A	X	X

Note: Actual start of infusion times, EOI times, and PK/ADA sample collection times will be recorded on the eCRFs. Do not collect PK samples from infusion port. Pre-infusion PK samples may be collected before start of infusion on visit day (dosing day) or day before infusion. When collecting multiple samples, collect the PK sample first.

[a]PK and ADA samples may be obtained at additional time points in participants who experience signs and symptoms of IRR. Samples should be obtained as soon as possible after onset of IRR, if feasible.

3.1.5 Tumor biopsies

A tissue biopsy will be obtained prior to initiation of study treatment with an optional biopsy at the time of progression. If biopsy is not considered safe and medically feasible by the investigator, the patient may be approved for enrollment after consultation the principal investigator. In this case, we will obtain archival tissue if available. Expression of B7-H3 and other immune markers on tumor tissue will be assessed using Imaging Mass Cytometry (IMC; Fluidigm platform) and correlated with treatment outcomes such as ORR, PFS, and OS. Imaging Mass Cytometry platform is capable of simultaneous detection of up to 40 protein markers including B7-H3 at subcellular resolution in fixed tissues sections. Imaging Mass Cytometry is available through the Histopathology & Tissue Shared Resource (HTSR) at Georgetown Lombardi Comprehensive Cancer Center. Samples are analyzed using ilastik and Cell Profiler software (**Figure 4**) for cell mask segmentation, allowing to identify individual cells in the tissue based on staining of the nuclei (DAPI staining) and plasma membrane. This analysis is followed by evaluating the expression of the markers using HistoCAT software. An optional tumor biopsy at the time of disease progression will be obtained after radiographic progression prior to start of new anti-cancer treatment, if any. These samples will enable analysis of tumor tissue biomarkers related to resistance, disease progression, and clinical benefit of the study treatment. If sufficient tissue is available after IMC analysis, next generation sequencing (NGS) may be performed to understand the correlation between genomic findings and response to treatment. Please refer to the lab manual for full details.

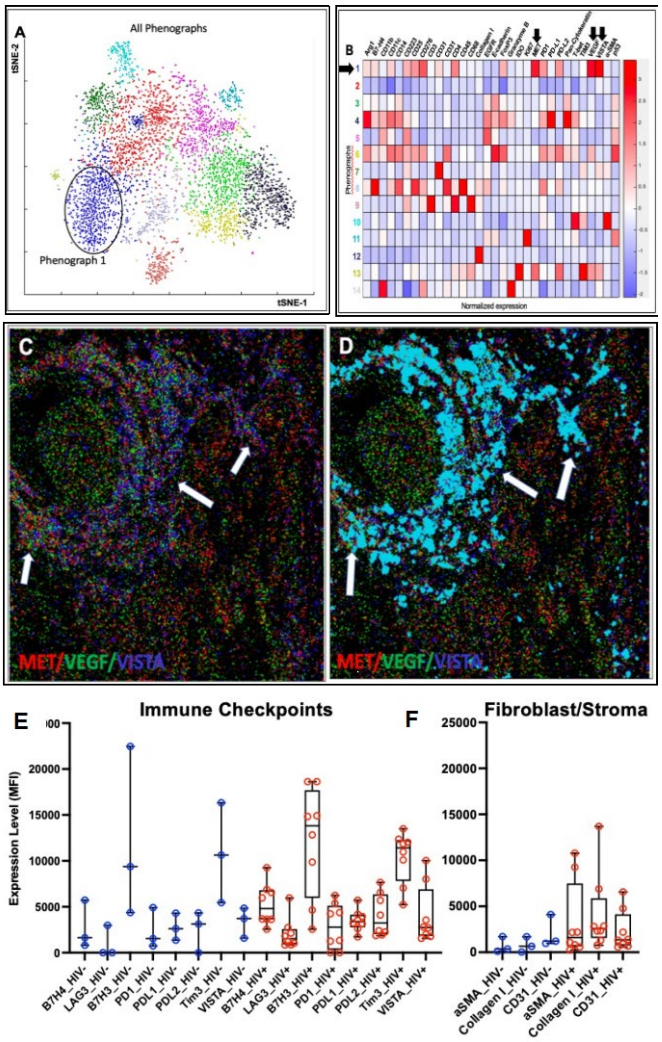


Figure 4. High dimensional data analysis of images of NSCLC tissue sample. (A) tSNE (t-distributed stochastic neighbor embedding) plot showing multidimensional data. (B) Phenograph clustering analysis representing phenotypic similarities between cells. (C) Overlay images of MET, VEGF and VISTA on histoCAT. (D) Overlay of the markers highlighting phenograph cluster 1 (turquoise). Immune checkpoints including B7-H3 (E), and fibroblast/stroma (F).

3.1.6 Blood based correlative studies

In collaboration with Dr. Christian Rolfo at the Tisch Cancer Institute at Mount Sinai Health System, we plan to analyze extracellular vesicle (EV) B7-H3 expression on day 1 of cycle 1, on day 1 of cycle 3, and at the time of progression. Peripheral blood will be collected into EDTA Vacutainer® tubes. Blood samples will be centrifuged at 2,000 × g for 15 minutes, and plasma will be isolated and frozen at -80 °C. Blood samples will be analyzed in a batch. Following the last recommendations of the International Society of Extracellular Vesicles (ISEV), EVs will be characterized by nanoparticle tracking analysis (NTA), transmission electron microscopy (TEM), and western blot following standardized

methodology established at Dr. Rolfo's laboratory (de Miguel-Perez et al. 2022). The baseline EV expression of B7-H3 and the EV B7-H3 dynamics will be correlated with treatment outcomes. Please refer to the lab manual for full details.

3.1.7 Safety assessment

Safety will be closely monitored by assessing for the frequency of severe adverse events and unexpected adverse events, including adverse events of special interest (AESIs). Georgetown University institutional review board (IRB) and data safety monitoring committee (DSMC), in conjunction with the study Principal Investigator (PI), will be responsible for monitoring the safe conduct of this study in real time. Regular DSMC meetings will take place approximately every 3 months or more frequently and resulting recommendations will be forwarded to the IRB, in addition to the PI (as study sponsor). If the DSMC recommends a study change for patient safety or efficacy reasons, it is the responsibility of the PI to implement said changes expeditiously. In the unlikely event of disagreement, the trial PI, DSMC Chair and LCCC Deputy Director will be responsible for determining a mutually agreed upon decision. Should the DSMC recommend trial closure for any reason, the recommendation will be reviewed by the LCCC Deputy Director. Authority to close a trial for safety concerns lies with the IRB in concert with DSMC and LCCC Deputy Director input. No interim analyses specifically for safety are planned as part of this study.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the required number of events for the final analysis of ORR has occurred or all patients meet one of the following criteria: patient has experienced a PFS event, patient has become lost to follow-up, patient has withdrawn consent, or patient has completed at least 24 months of follow-up after study treatment initiation. The end of the study is expected to occur approximately 1 year after the last patient is enrolled. In addition, the principal investigator may decide to terminate the study at any time. The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 3 years.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for MGC018 dose and schedule

MGC018 will be administered at a dose of 2.0 mg/kg every 28 days continuously until completion of 8 cycles, disease progression, or unacceptable toxicity. The dose was selected on the basis of available clinical pharmacokinetics, efficacy, and safety data from the open label, dose escalation CP-MGC018-01 phase I study. Specifically, the dosing was 3.0 mg/kg every 21 days in the prior phase 1 dose escalation study of MGC018 (Shenderov et al. 2021). However, there has been subsequent evidence of increased neutropenia and hand-foot syndrome at this dose, and doses of 2.0 mg/kg every 28 days and 2.7 mg/kg every 28 days are being investigated in the phase 2 and 3 MGC018 trials. For patients who require a dose-reduction, the first reduction would be to 1.5 mg/kg every 28 days and a second reduction to 1.0 mg/kg as needed. Please refer to the MGC018 IB for details.

3.3.2 Rationale for ORR as primary endpoint

In this study, the primary endpoint of efficacy will be investigator-assessed ORR as determined by RECIST v1.1 with tumor imaging assessments obtained every 2 cycles. As this is a small phase 2 study to evaluate the efficacy of a novel therapy in a treatment refractory patient population, ORR was chosen in order to make an early determination for signal of efficacy that could then be used to warrant larger scale clinical trials powered for OS/PFS or, given the modified Simon 2-stage design, early study closure for futility if no efficacy signal is observed. Given the low historical ORR to chemotherapy in relapsed or refractory patients with ES-SCLC, a rapid estimation of response utilizing ORR will also be important as it will enable patients with robust functional status who experience disease progression on this trial seek additional treatments either in a clinical trial or standard of care setting.

3.3.3 Rationale for PK and ADA assessments

The optimal dosing of MGC018 is still being determined. While the dose 3.0 mg/kg every 21 days was used in the phase 1 trial, this dose was subsequently found to be associated with increased rates of neutropenia and hand-foot syndrome. The use of 2.0 mg/kg every 28 days are currently being investigated in phase 2 and 3 trials. Collection of PK and ADA data for patients receiving 2.7 mg/kg every 28 days, as well as for those who require a dose-reduction to 2.0 mg/kg every 28 days, will be useful in elucidating the optimal regimen.

3.3.4 Rationale for biomarker assessments

Early clinical studies have shown that efficacy of MGC018 in patients with non-small cell lung cancer (NSCLC) and metastatic castration resistant prostate cancer (mCRPC) can be seen across varying levels of B7-H3 expression (Shenderov et al. 2021). This is suspected to be likely from bystander killing of neighboring tumor cells which has been demonstrated *in vivo* (Scribner et al. 2020). However, this has not been studied in ES-SCLC, and current clinical data regarding correlation between MGC018 efficacy and B7-H3 expression is still early. In this study, we will assess expression of B7-H3 on tumor tissue obtained prior to study initiation and correlate with treatment outcomes. Furthermore, blood-based biomarkers including exosome analysis in collaboration with Dr. Christian Rolfo at the Tisch Cancer Institute at Mount Sinai Health System will be analyzed and correlated with treatment outcomes.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 17 patients with relapse or refractory ES-SCLC will be enrolled in this study.

4.1.1 Inclusion criteria

Patients must meet the following criteria for study entry:

1) Age $\geq$ 18 years at time of signing ICF
2) Ability to comply with the study protocol, in the investigator's judgment.

3) Histologically or cytologically confirmed advanced small cell lung cancer that is not amenable to definitive therapy. Patients with *EGFR*-mutant NSCLC that has transformed to SCLC will be allowed.
4) Disease progression during or following treatment with platinum-based chemotherapy.
    a) Patients could have received any number of therapies for relapsed or progressive disease.
5) Measurable disease per RECIST v1.1
6) ECOG Performance Status of 0-2
7) Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:
    a) ANC $\geq 1.0 \times 10^9$/L (1000/μL) without granulocyte colony-stimulating factor support
    b) Platelet count $\geq 100 \times 10^9$/L (100,000/μL) without transfusion
    c) Hemoglobin ≥ 80 g/L (8 g/dL)
        (1) Patients may be transfused to meet this criterion.
    d) AST, ALT, and alkaline phosphatase (ALP) $\leq 2.5 \times$ upper limit of normal (ULN), with the following exceptions:
        (1) Patients with documented liver metastases: AST and ALT $\leq 5 \times$ ULN
        (2) Patients with documented liver or bone metastases: ALP $\leq 5 \times$ ULN
    e) Serum bilirubin $\leq 1.5 \times$ ULN with the following exception:
        (1) Patients with known Gilbert disease: serum bilirubin $\leq 3 \times$ ULN
    f) Creatinine clearance ≥ 30 mL/min (calculated using the Cockcroft-Gault formula, see Appendix 2)
    g) For patients not receiving therapeutic anticoagulation: INR and aPTT $\leq 1.5 \times$ ULN

NOTE: Screening labs that are performed outside the 14-day window for eligibility criteria may be repeated on C1D1 to verify the subject meets eligibility requirements.

8) Ability to understand and the willingness to sign a written informed consent document.
9) Availability of pre-treatment tumor tissue via a biopsy. If biopsy is not considered safe and medically feasible by the Investigator, the patient may be approved for enrollment after consultation with the Principal Investigator.
10) For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, and agreement to refrain from donating eggs, as defined below:
    (1) Women must remain abstinent or use contraceptive methods with a failure rate of $< 1\%$ per year during the treatment period and for 6 months after the final dose of study treatment. Women must refrain from donating eggs during this same period.
    (2) A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state ($\geq$ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

(3) Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

(4) The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception.

11) For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:

(1) With a female partner of childbearing potential who is not pregnant, men who are not surgically sterile must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for 90 days after the final dose of MGC018. Men must refrain from donating sperm during this this same period.

(2) With a pregnant female partner, men must remain abstinent or use a condom during the treatment period and 90 days after the final dose of MGC018 to avoid potential exposure to the embryo.

(3) The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception.

ii) Exclusion criteria

Patients who meet any of the following criteria will be excluded from study entry:

1) Patients with treated CNS metastases are eligible if they are symptomatically stable while off steroid therapy for a minimum of 7 days
2) Symptomatic leptomeningeal disease. Patients with asymptomatic treated or untreated leptomeningeal disease could be enrolled provided that all other protocol-defined criteria are met.
3) Patient who are receiving any other investigational agents
4) Major surgical procedure, other than for diagnosis, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study
5) Diagnosis of another malignancy. However, patients with prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.
6) Evidence of pleural and/or pericardial effusion. A small and/or asymptomatic effusion is not exclusionary.
7) Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that, in the view of the investigator, contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications.
8) Pregnancy or breastfeeding, or intention of becoming pregnant during study treatment or within 6 months after the final dose of study treatment.

4.2 STUDY TREATMENT

The investigational medicinal product (IMP) for this study is MGC018.

4.2.1 Study treatment formulation, packaging, and handling

4.2.1.1 MGC018

MGC018 will be supplied by Macrogenics as sterile liquid at a nominal protein concentration of 10 mg/mL in a single-use glass vial containing 93 mg/9.3mL MGC018. The drug product is formulated in a solution of 0.46.mg/mL L-histidine, 1.47 mg/mL L-histidine hydrochloride monohydrate, 90 mg/mL sucrose, and 0.1 mg/mL polysorbate 80, pH 5.7. For further information on the MGC018 formulation, refer to the MGC018 investigator's brochure (IB).

4.2.2 Study treatment dosage, administration, and compliance

The treatment regimens are summarized in Section 3.1.1.

Any overdose or incorrect administration of MGC018 should be noted in the patient's medical records and reported according to Sections 5.4 and 5.5. Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded in the patient's medical records and appropriate eCRF.

Guidelines for dosage modification, treatment interruption or discontinuation for patients who experience adverse events are provided in Section 4.3.3 and Appendix 4. Dose modification of all study drugs (MGC018) will not be permitted.

4.2.2.1 MGC018

MGC018 will be administered by IV infusion at a dose of 2.0 mg/kg on Day 1 of each 28-day cycle until completion of cycle 8, unacceptable toxicity, or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (see Section 3.1.1 for details). For subjects weighing $\geqslant$ 100 kg the doses will be based on 100 kg for these subjects. To decrease the frequency and severity of palmar-plantar erythrodysesthesia (PPE) and effusions, prednisone 40 mg will be given twice daily for three days of each cycle starting the evening after each infusion for a total of 6 doses. In addition, patients will be provided with a strong or moderate-strength topical steroid cream to be applied as prescribed to the hands and soles prophylactically for the first 12 weeks of therapy.

Administration of MGC018 will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 3. MGC018 infusions will be administered per the instructions outlined in Table 3.

Table 3. Administration of first and subsequent MGC018 infusions

Study Drug	First Infusion	Subsequent Infusions
MGC018 infusion	• Premedication with acetaminophen (650mg to 1000 mg), diphenhydramine 50 mg PO or IV, famotidine 40 mg PO or 20 mg IV, and corticosteroid (e.g	• If the patient experienced an infusion-related reaction (IRR) with any previous infusion, additional premedication may also be considered.

	dexamethasone 4 mg IV or equivalent) • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be measured within 60 minutes prior to the infusion. • MGC018 should be infused over 60 minutes. Up to 10 additional minutes of infusion time is permitted to allow for flushing the IV line. • If clinically indicated, vital signs should be measured every 15 (± 5) minutes during the infusion. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• Vital signs should be measured within 60 minutes prior to the infusion. • MGC018 should be infused over 60 minutes (± 10 minutes) if the previous infusion was tolerated without an IRR, or 60 (± 15) minutes if the patient experienced an IRR with the previous infusion. • If clinically indicated, vital signs should be measured during the infusion and at 30 (± 10) minutes after the infusion.
Observation period after infusion of MGC018	• After the infusion of MGC018, the patient begins a 60-minute observation period. • Vital signs should be recorded at 30 +/-10) minutes after the infusion of MGC018. • Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient tolerated the previous MGC018 infusion well without infusion-associated adverse events, no observation period is needed. • If the patient experienced infusion-associated adverse events in the previous infusion, an observation period of 60 minutes should occur. • If clinically indicated, vital signs should be recorded at 30 (+/-10) minutes after the infusion of MGC018.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

4.2.3 Dose modification and management of adverse events

4.2.3.1 General notes regarding dose modifications & delays

Reasons for dose delays, supportive measures taken, and subsequent outcome will be documented in the patient's chart and recorded on the eCRF. The severity of adverse events will be graded according to the NCI CTCAE v5.0 grading system.

- When several toxicities with different grades of severity occur at the same time, appropriate action should be made according to the highest grade observed.
- If, in the opinion of the investigator, a toxicity is considered to be due solely to MGC018 and is of sufficient grade to warrant treatment delay, therapy should be delayed and omitted until resolution of toxicity.
- If, in the opinion of the investigator, a toxicity attributed to MGC018 is of sufficient grade to warrant permanent discontinuation of therapy, therapy should be permanently discontinued.

For patients who require a dose-reduction, the first reduction would be to 1.5 mg/kg every 28 days with a second reduction to 1.0 mg/kg every 28 days, as needed (**Table 4**).

Table 4. Dose levels of MGC018

Dose levels	**MGC018**
Level 1 (starting dose)	2.0 mg/kg Q4W
Level -1	1.5 mg/kg Q4W
Level -2	1.0 mg/kg Q4W

4.2.3.2 Guidelines for management of suspected MGC018-related toxicities

Criteria for treatment modification and guidelines for the management of toxicities are summarized below. Generally, temporary suspension of MGC018 must occur if a patient experiences a serious adverse event or a grade 3 or 4 non-serious adverse event assessed by the investigator as related to MGC018. If the event resolves to grade ≤ 1, MGC018 may be restarted at the same dose level. If MGC018 is delayed due to toxicity for $>$ 8 weeks beyond when the next dose should have been given, the patient must be permanently discontinued from MGC018.

PULMONARY EVENTS

Immune-mediated pulmonary events are a potential risk with MGC018. Patients will be assessed for pulmonary signs and symptoms throughout the study and will have computed tomography (CT) scans of the chest performed at every tumor assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events are provided in Table 5.

Table 5. Management Guidelines for Pneumonitis

Event	Management
Grade 1	• Continue MGC018 and monitor closely. • Re-evaluate on serial imaging. • No specific therapy required
Grade 2	• Hold MGC018 • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone or equivalent divided twice daily • Taper corticosteroids over 4 weeks or as clinically indicated • Resume MGC018 administration at next scheduled dose if pneumonitis resolves to grade 1 or baseline within 5 days with or without treatment. On resuming MGC018, reduce dose by one dose level. • Discontinue MGC018 after second occurrence
Grade 3 or 4	• Permanently discontinue MGC018 • Hospitalize • Referral for pulmonary consult with diagnostic evaluation with chest X-ray and CT scan. • Initiate treatment with 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 event does not improve within 3 to 5 days after initiating corticosteroids, consider adding an immunomodulatory agent.

HEPATIC EVENTS

Immune-mediated hepatic events are a potential risk with MGC018.

Immune-related hepatitis has been associated with the administration of MGC018. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment.

Patients with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests (LFTs) performed immediately and reviewed before administration of the next dose of study drug.

For patients with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

Table 6. Management Guidelines for Elevations in Transaminases

Event	Management

Grade 1	• Continue MGC018. • No specific therapy required • Monitor LFTs until values resolve to within normal limits or to baseline values.
Grade 2	• Rule out viral and other etiologies • Consider imaging such as ultrasound, or CT scan • Hold MGC018 • Consider starting oral prednisone 1 mg/kg per day • If improvement to grade 1 or baseline does not occur within 72 hours with oral steroids, consider IV steroids (i.e methylprednisolone 1-2 mg/kg/day divided twice daily) • Resume MGC018 at next scheduled dose if no more than one dose of MGC018 was missed • If improvement to grade 1 or baseline does not occur within 21 days, discontinue MGC018 • No dose reduction required after first occurrence • On resuming MGC018, reduce dose by one dose level after second and third occurrences • Discontinue MGC018 after fourth occurrence
Grade 3	• Hold MGC018 • Begin IV steroids methylprednisolone 2 mg/kg/day divided twice daily and if no response within 3 to 5 days, consider adding additional immune suppression therapy (e.g. mycophenolate). • Monitor liver functions tests at least twice weekly (or more frequently as clinically appropriate) until transaminases have returned to grade 1. • For elevations in transaminases >8 x ULN, permanently discontinue MGC018. • If elevation does not improve to grade 2 within 10 days and to grade 1 within 21 days, discontinue MGC018. • Resume MGC018 if following conditions are met: o Lab elevations improve to grade 2 within 10 days and to grade 1 within 21 days o Steroids have been tapered to ≤10 mg per day or prednisone or equivalent o On resuming MGC018, LFT's will be evaluated at least once per week for 3 consecutive weeks • On resuming MGC018, reduce dose by one dose level after first and second occurrences

	• Discontinue MGC018 after third occurrence
Grade 4	• Treat as grade 3 as above • On resuming MGC018 reduce dose by two dose levels after first occurrence • Discontinue MGC018 after second occurrence

Table 7. Management Guidelines for Elevations in Total Bilirubin

Event	Management
Grade 1	• Continue MGC018 • No specific therapy required
Grade 2	• Hold MGC018 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 prednisone 1 mg/kg • If improvement to ≤ grade 1 does not occur within 21 days, discontinue MGC018 and begin oral steroids • No dose reduction required after first occurrence • On resuming MGC018, reduce dose by one dose level after second and third occurrences • Discontinue MGC018 after fourth occurrence
Grade 3	• Hold MGC018 • For elevations in total bilirubin >5 x ULN o Permanently discontinue MGC018 and initiate IV steroids, i.e methylprednisolone 2 mg/kg/day divided twice daily o If no response to corticosteroids within 3 to 5 days, consider adding additional immune suppression therapy (e.g. mycophenolate) o Monitor liver function testing at least twice weekly (or more frequently as clinically appropriate) until total bilirubin has returned to grade 1 or baseline • For elevation in total bilirubin >3 but ≤ 5 times ULN o Begin IV steroids, i.e methylprednisolone at 2 mg/kg/day divided twice daily. o Consider additional immune suppression as above if no response to corticosteroids within 3 to 5 days

	○ Monitor liver function testing at least twice weekly (or more frequently as clinically appropriate) until total bilirubin has returned to grade 1 or baseline. • Resume MGC018 if: ○ Total bilirubin elevations improve 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 MGC018, monitor liver function testing at least once per week for 3 consecutive weeks • On resuming MGC018, reduce dose by one dose level after first and second occurrences • Discontinue MGC018 after third occurrence
Grade 4	• Treat as grade 3 elevation • On resuming MGC018 reduce dose by two dose levels after first occurrence • Discontinue MGC018 after second occurrence

GASTROINTESTINAL EVENTS

Immune-mediated colitis has been associated with administration of MGC018.

Management guidelines for diarrhea or colitis are provided in Table 8.

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased C-reactive protein, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy.

Table 8. Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	Management
Diarrhea or colitis, Grade 1	• Continue MGC018 • Initiate symptomatic treatment. • Closely monitor the diarrhea until resolution
Diarrhea or colitis, Grade 2	• Hold MGC018 • On resolution to grade 1 or baseline, resume MGC018 without dose reduction • Increase frequency of monitoring until resolution • Initiate symptomatic treatment.

	○ Loperamide and or diphenoxylate/atropine ○ Low dose steroids, if clinically indicated ○ Consider management or prolonged grade 2 event lasting more than 5 to 7 days or relapsed diarrhea as grade 3 diarrhea (below)
Diarrhea or colitis, Grade 3	• Hold MGC018. Hospitalize patient promptly for further evaluation and management including the following: ○ Bowel rest ○ IV fluid with close monitoring of fluid and electrolyte status ○ Consider imaging to rule out bowel obstruction or perforation ○ Consideration of colonoscopy as appropriate ○ Empiric immune suppression with IV corticosteroids using methylprednisolone at 2 mg/kg/day (or equivalent) divided twice daily. As tolerated steroids may be converted to oral corticosteroids and tapered as appropriate guided by patient's clinical status ○ For patients who do not respond to corticosteroids, additional immunosuppression with anti-TNF alpha antibodies (i.e infliximab) should be considered. • If it is determined there is no colitis and an alternative cause of diarrhea is found, consider restarting MGC018 if diarrhea resolves to ≤ grade 1 within 21 days • On resuming MGC018, reduce dose by one dose level after first and second occurrences • Discontinue MGC018 after third occurrence
Diarrhea or colitis, Grade 4	• Treat as grade 3 • On resuming MGC018 reduce dose by two dose levels after first occurrence • Discontinue MGC018 after second occurrence

DERMATOLOGIC EVENTS

Immune-related dermatologic events are a potential risk with MGC018. Management guidelines for dermatologic events are provided in Table 9. Patients should limit sun exposure and apply broad spectrum sunscreen to exposed skin when outdoors.

For palmar-plantar erythrodysesthesia, hold MGC018 until toxicity resolves to ≤ grade 1. MGC018 may be resumed with MGC018 decrease of one dose level. Discontinue MGC018 if patient does not recover to ≤ grade 1 within 28 days.

Table 9. Management Guidelines for Dermatologic Events

Event	Management

Dermatologic event, Grade 1	• 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 • 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 pruritis. • Evaluate for use of concomitant medications and herbal supplements that may exacerbate skin toxicity.
Dermatologic event, Grade 2	• Treat as grade 1 • No dose reduction required after first occurrence • On resuming MGC018, reduce dose by one dose level after second and third occurrences • Discontinue MGC018 after fourth occurrence
Dermatologic event, Grade 3	• Hold MGC018 • 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 MGC018 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. • On resuming MGC018, reduce dose by one dose level after first and second occurrences • Discontinue MGC018 after third occurrence
Dermatologic event, Grade 4	• Initiate oral corticosteroids (oral prednisone 1 to 2 mg/kg/day) • Evaluate patient for use of concomitant medications or herbal supplements that may exacerbate skin toxicity • Consider obtaining a skin biopsy if 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. • If SJS or TEN are confirmed, permanently discontinue MGC018 • On resuming MGC018 reduce dose by two dose levels after first occurrence • Discontinue MGC018 after second occurrence

SJS=Stevens-Johnson Syndrome, TEN=toxic epidermal necrolysis

RENAL EVENTS

Immune-related nephritis is a potential risk with MGC018. Eligible patients must have adequate renal function. Renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs).

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 10.

Table 10. Management Guidelines for Nephritis

Event	Management
Nephritis, Grade 1	• Continue MGC018 • No specific therapy required • Close monitoring of renal function
Nephritis, Grade 2	• Hold MGC018 • Consider nephrology consultation and renal biopsy to confirm interstitial nephritis. • Consider initiating treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone per day, dose divided twice daily. • Taper corticosteroids over 4 weeks or as clinically indicated. • Resume MGC018 at next scheduled dose if nephritis resolves to ≤ grade 1 within 21 days with or without treatment • No dose reduction required after first occurrence • On resuming MGC018, reduce dose by one dose level after second and third occurrences • Discontinue MGC018 after fourth occurrence

Nephritis, Grade 3	• Consider hospitalization, nephrology consultation, and renal biopsy to confirm interstitial nephritis. • Initiate treatment with corticosteroids equivalent to 2–4 mg/kg/day IV methylprednisolone divided twice daily. Taper corticosteroids over 4 weeks or as clinically indicated. • On resuming MGC018, reduce dose by one dose level after first and second occurrences • Discontinue MGC018 after third occurrence
Nephritis, Grade 4	• Treat as grade 3 • On resuming MGC018 reduce dose by two dose levels after first occurrence • Discontinue MGC018 after second occurrence

ENDOCRINE EVENTS

Endocrine events are a potential risk with MGC018.

Thyroid disorders may occur at any time during treatment with MGC018. 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.

Management guidelines for endocrine events are provided in Table 11.

Table 11. Management Guidelines for Endocrine Events

Event	Management
Hyperthyroidism, Grade1	• Continue MGC018 • No specific therapy required
Hyperthyroidism, Grade 2	• Hold MGC018 • Consider starting oral corticosteroid therapy. • Short course of corticosteroid such as methylprednisolone 1 to 2 mg/kg IV (or equivalent) divided twice daily. • Resume MGC018 if corticosteroid if corticosteroid dose is reduced to ≤ 10 mg prednisone or equivalent per day and stable on hormone replacement therapy (if necessary). • No dose reduction required after first occurrence • On resuming MGC018, reduce dose by one dose level after second and third occurrences • Discontinue MGC018 after fourth occurrence
Hyperthyroidism, Grade 3	• Hold MGC018 • 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 therapy as necessary • Consider restarting MGC018 with complete resolution or stable on hormone replacement therapy within 28 days and if corticosteroid dose is reduced to ≤ 10 mg prednisone or equivalent per day. • On resuming MGC018, reduce dose by one dose level after first and second occurrences • Discontinue MGC018 after third occurrence
Hyperthyroidism, Grade 4	• Treat as grade 3 • On resuming MGC018 reduce dose by two dose levels after first occurrence • Discontinue MGC018 after second occurrence

Event	Management
Hypophysitis, Grade 1	• No specific therapy required • Continue MGC018
Hypophysitis,	• Hold MGC018

Grade ≥ 2	• Consult endocrinologist
	• Consider hospitalization
	• Consider short course of high dose IV corticosteroids e.g. methylprednisolone 2 to 4 mg/kg/day or equivalent divided twice daily.
	• Initiate hormonal replacement as indicated
	• Study drug 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

MRI = magnetic resonance imaging

OCULAR EVENTS

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. Management guidelines for ocular events are provided in Table 12.

Table 12. Management Guidelines for Blepharitis

Event	Management
Blepharitis, Grade 1	• No specific therapy required. • Daily cleansing with warm, clean cloth. Apply lubricating eye drops • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Blepharitis, Grade 2	• Hold MGC018 • Consider topical/ocular corticosteroids, antihistamine, artificial tears • Resume MGC018 if resolved to ≤ grade 1 within 28 days and discontinue MGC018 if symptoms last > 28 days • On resuming MGC018, if symptoms lasted > 14 days, reduce dose by one dose level
Blepharitis, Grade 3	• Hold MGC018 • Consider referral to ophthalmologist. • Consider topical/ocular and/or systemic corticosteroids • Resume MGC018 if resolved to ≤ grade 1 within 28 days and discontinue MGC018 if symptoms last > 28 days • On resuming MGC018, reduce dose by one dose level
Blepharitis, Grade 4	• Permanently discontinue MGC018 • Consult ophthalmology within 24 hours • Treat as for grade 3 and as appropriate for life-threatening symptoms

HEMATOLOGIC EVENTS

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 AE's during study drug administration.

Blood counts will be performed in case of fever (a measured temperature of 100.4 F 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 should be held until thrombocytopenia resolves.

Anemia should be evaluated and treated for other underlying etiology e.g. iron or vitamin B12 deficiency, bleeding, and renal insufficiency. Consider transfusion of red blood cells or whole blood for

anemia. Caution is recommended in patients with ≥ grade 2 anemia, with appropriate measures taken as clinically indicated. Patients will be supported appropriately by the treating physician.

No specific treatment or drug holds are required for lymphopenia, regardless of CTCAE grade, unless associated with opportunistic infection. If the patient develops an opportunistic infection with concurrent lymphopenia, MGC018 should be delayed until resolution of lymphopenia and the opportunistic infection

Management guidelines for hematologic events are provided in Table 13.

Table 13. Management Guidelines for Hematologic Events

Event	Management
Neutropenia, Grade 1 or 2	• No specific therapy required • MGC018 should not be given to participants with neutrophil counts ≤ 1500 cells/mm^3 • Consider dose reduction of MGC018
Neutropenia, Grade 3	• Hold MGC018 until recovery to ≤ grade 1 • Monitor neutrophil counts weekly until recovery to ≤ grade 1 • Discontinue MGC018 if not recovered to ≤ grade 1, within 21 days • Restart MGC018 if recovered to ≤ grade 1 within 21 days. • On resuming MGC018, reduce dose by one dose level after first and second occurrences • Discontinue MGC018 after third occurrence
Neutropenia, Grade 4	• Hold MGC018 until recovery to ≤ grade 1 • Monitor neutrophil counts weekly until recovery to ≤ grade 1 • Discontinue MGC018 if not recovered to ≤ grade 1, within 21 days • Restart MGC018 at one or two level dose reduction if recovered to ≤ grade 1 within 21 days. • On resuming MGC018 reduce dose by two dose levels after first occurrence • Discontinue MGC018 after second occurrence
Thrombocytopenia, Grade 1	• No specific therapy required • Consider dose reduction of MGC018

Thrombocytopenia, Grade 2 or 3	• Hold MGC018 until recovery to ≤ grade 1 • Monitor platelet counts weekly until recovery to ≤ grade 1 • Restart MGC018 with one level dose reduction if recovered to ≤ grade 1 • Reduce dose by one dose level on resumption after second and third occurrences • Discontinue MGC018 after fourth occurrence • Discontinue MGC018 if not recovered to ≤ grade 1 within 21 days.
Thrombocytopenia, Grade 4	• Hold MGC018 until recovery to ≤ grade 1 • Monitor platelet counts weekly until recovery to ≤ grade 1 • Restart MGC018 with one or two level dose reduction if recovered to ≤ grade 1 • Discontinue MGC018 if not recovered to ≤ grade 1 within 21 days. • On resuming MGC018 reduce dose by two dose levels after first occurrence • Discontinue MGC018 after second occurrence
Anemia, Grade 1	• No specific therapy required
Anemia, Grade 2	• Consider iron replacement therapy, erythropoiesis stimulating agent
Anemia, Grade 3	• Consider iron replacement therapy, erythropoiesis stimulating agent • Consider transfusion if symptomatic • Consider holding MGC018 until recovery to ≤ grade 2 • Dose reduction of one dose level for ≥ 2 events of grade 3 anemia • Discontinue MGC018 after fourth occurrence
Anemia, Grade 4	• Transfuse with whole blood or packed red blood cells • Permanently discontinue MGC018 for grade 4 anemia that persists despite intervention.

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.

Management guidelines for pleural effusions are provided in Table 14. Management guidelines for pericardial effusions are provided in Table 15.

Table 14. Management Guidelines for Pleural Effusions

Event	Management
Pleural effusion, Grade 1	• No specific therapy required • Close monitoring of cardiac and lung function and imaging • Consider diuretics
Pleural Effusion, Grade 2	• Hold MGC018 • Consider diuretics or therapeutic thoracentesis • Consider corticosteroids: 1 to 2 mg/kg or oral prednisone or equivalent per day divided twice daily. Taper corticosteroids over 4 weeks or as clinically indicated • Resume MGC018 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.
Pleural Effusion, Grade 3	• Hold MGC 018 • Therapeutic thoracentesis • Consider corticosteroids: 1 to 2 mg/kg or oral prednisone or equivalent per day divided twice daily. Taper corticosteroids over 4 weeks or as clinically indicated. • Resume MGC018 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.
Pleural Effusion, Grade 4	• Permanently discontinue MGC018 • Recommend hospitalization with pulmonary consultation and diagnostic evaluation including chest X-ray and CT scan. • Initiate maximal supportive care including IV corticosteroids. Continue IV methylprednisolone 2 mg/kg/day for 5 days then switch to oral prednisolone 1 mg/kg/day x 3 days, then reduce to 60 mg/day prednisolone. Reduce prednisolone dose by 10 mg every 5-7 days (as toxicity allows) until dose is 10 mg/day. Once steroid dose is 10 mg/day, reduce by 5 mg every 5-7 days then stop. High doses may be used in consultation with the sponsor's medical monitor.

Table 15. Management Guidelines for Pericardial Effusions

Event	Management
Pericardial Effusion, Grade 1	• No specific therapy required • Continue MGC018
Pericardial Effusion, Grade 2	• Hold MGC018 • Consider diuretics • 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 MGC018 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 dose reduce by one level.
Pericardial Effusion, Grade 3	• Hold MGC018 • Consider pericardiocentesis. • 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 MGC018 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.
Pericardial Effusion, Grade 4	• Permanently discontinue MGC018 • Hospitalize, consider pericardiocentesis • Recommend cardiology consult/diagnostic evaluation including echocardiogram • Initiate maximal supportive care including IV corticosteroids. Continue IV methylprednisolone 2 mg/kg/day for 5 days then switch to oral prednisolone 1 mg/kg/day x 3 days, then reduce to 60 mg/day prednisolone. Reduce prednisolone dose by 10 mg every 5-7 days (as toxicity allows) until dose is 10 mg/day. Once steroid dose is 10 mg/day, reduce by 5 mg every 5-7 days then stop. High doses may be used in consultation with the sponsor's medical monitor.

NERVOUS SYSTEM EVENTS

Management guidelines for patients experiencing nervous system toxicity are provided in Table 16.

Table 16. Management Guidelines for Nervous System Events

Event	Management
Grade 1	• No specific therapy required, close monitoring of neuropathy
Grade 2	• Hold MGC018 • 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 MGC018 at next scheduled dose if symptoms resolve to ≤ grade 1 within 21 days with or without treatment.
Grade 3 or 4	• Permanently discontinue MGC018 • 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 x 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 5-7 days then stop

CARDIOVASCULAR EVENTS

Management guidelines for patients experiencing cardiovascular toxicity are provided in Table 17.

Table 17. Management Guidelines for Cardiovascular System Events

Event	Management
Grade 1	• No specific therapy required; close monitoring
Grade 2	• Permanently discontinue MGC018 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 or 4	• Permanently discontinue MGC018 • Consider hospitalization and cardiology consultation • Condier obtaining 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 x 3 days, then reduce to 60 mg/day prednisolone. Reduce prednisolone dose by 10 mg every 5-7 days (as toxicity allows) until dose is 10 mg/day. Once steroid dose is 10 mg/day, reduce by 5 mg every 5-7 days then stop. • Consider infliximab

MUSCULOSKELETAL TOXICITY

Management guidelines for patients experiencing musculoskeletal toxicity are provided in Table 18.

Table 18. Management Guidelines for Musculoskeletal Events

Event	Management
Grade 1	• No specific therapy required, close monitoring • Consider anti-inflammatory medication e.g. ibuprofen
Grade 2	• Hold MGC018 • 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 MGC018 at next scheduled dose if symptoms resolve to ≤ grade 1 within 21 days with or without treatment. • No dose reduction required after first occurrence • On resuming MGC018, reduce dose by one dose level after second and third occurrences • Discontinue MGC018 after fourth occurrence
Grade 3	• Hold or permanently discontinue MGC018 • 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 x 3 days, then reduce to 60 mg/day prednisolone. Reduce prednisolone dose by 10 mg every 5-7 days (as toxicity allows) until dose is 10 mg/day. Once steroid dose is 10 mg/day, reduce by 5 mg every 5-7 days then stop. • Consider infliximab • If not responding within 14 days, consider use of disease modifying antirheumatic drugs e.g. sulfazine, methotrexate. • On resuming MGC018, reduce dose by one dose level after first and second occurrences • Discontinue MGC018 after third occurrence
Grade 4	• Treat as grade 3 • On resuming MGC018 reduce dose by two dose levels after first occurrence • Discontinue MGC018 after second occurrence

INFUSION-RELATED REACTIONS

Premedications at least 30 minutes prior to each infusion of MGC018 include: acetaminophen 650 to 1000 mg 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 (e.g dexamethasone 4 mg IV or equivalent).

For subsequent administration of MGC018, participants who had infusion reactions that were not adequately or only moderately controlled, other medications may also be considered as part of the pre-medication regimen for subsequent doses.

Guidelines for medical management of IRRs during Cycle 1 are provided in Table 19. For subsequent cycles, IRRs should be managed according to institutional guidelines.

Table 19. Management Guidelines for Infusion-Related Reactions

Event	Management
IRR, Grade 1	• Reduce infusion rate to half the rate being given at the time of event onset. • Monitor the participant for worsening of condition • After the event has resolved, the sponsor-investigator should wait for 30 minutes while delivering the infusion at the reduced rate. • If the infusion is tolerated at the reduced rate for 30 minutes after symptoms have resolved, the infusion rate may be increased to the original rate. • Prophylactic premedication with antipyretics, antihistamines, and/or analgesics should be given prior to all subsequent infusions
IRR, Grade 2	• Interrupt infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen, IV fluids). • After symptoms have resolved to baseline or deceased to grade 1, resume infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at reduced rate for 30 minutes, rate may be escalated to original rate after 30 minutes as tolerated • For subsequent infusions, prophylactic administration of premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs. Corticosteroids may also be added (dexamethasone 10 mg IV or hydrocortisone 25 to 100 mg IV or higher)
IRR, Grade 3 or 4	• Stop infusion. Do not flush tubing. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen, IV fluids). • If grade 3 infusion reaction occurs, discontinue treatment for that day. If symptoms have resolved to baseline within 12 hours, MGC018 may be infused the next day with premedication and for any subsequent doses with antipyretics, antihistamines, and corticosteroids. • Participants who have a grade 3 infusion reaction that does not resolve within 12 hours should not receive further treatment with MGC018. • Participants who experience a second grade 3 infusion reaction at time of rechallenge with MGC018 will permanently discontinue treatment with study drugs. • Participants who have a grade 4 infusion reaction will not receive further treatment with MGC018 • Reports as an IRE within 24 hours and event as SAE

IRR = infusion-related reaction, IRE=infusion related event, SAE=serious adverse event

4.2.4 IMP handling and accountability

All IMPs required for completion of this study will be provided by Macrogenics. The study site (i.e., investigator or other authorized personnel [e.g., pharmacist]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by Macrogenics, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only patients enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to Macrogenics with the appropriate documentation. The site's method of destroying Macrogenics-supplied IMPs must be agreed to by Macrogenics. The site must obtain written authorization from Macrogenics before any Macrogenics-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the pharmacy manual and the MGC018 IB for information on IMP handling, including preparation and storage, and accountability.

4.3 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded in the patient’s medical records as well as on the Concomitant Medications eCRF.

4.3.1 Prohibited therapy

Use of the following concomitant therapies is prohibited as described below:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, is prohibited during study treatment, until disease progression is documented and the patient has discontinued study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during study treatment, and for 5 months after the last dose of study treatment.

- Available vaccines for COVID-19 will be permitted at any time while a patient is enrolled on study but preferably not administered on same day as study drug infusion to avoid potential for overlapping immune-related reactions.

4.4 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities must be performed and documented for each patient. Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

All treatment visits must occur ±3 days from the scheduled date unless otherwise noted (see Appendix 1). All assessments should be performed on the day of the specified visit unless a time window is specified. Patients must be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable. Assessments scheduled on the day of study treatment administration should be performed prior to dosing, unless otherwise specified.

Laboratory tests performed within 14 days of Day 1 of Cycle 1 and within 3 days of Day 1 of subsequent cycles do not need to be repeated prior to therapy administration.

If a holiday, weekend, or other event precludes scheduled dosing, dosing may be postponed to the soonest following date, with subsequent dosing continuing on a 28-day schedule. If treatment is postponed for fewer than 3 days, the patient can resume the original schedule.

4.4.1 Informed consent forms (ICFs)

Written informed consent for participation in the study must be obtained before performing any study-related procedures. ICFs for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

4.4.2 Medical history, concomitant medication, and demographic data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded. Demographic data will include age, sex, and self–reported race/ethnicity.

4.4.3 ECOG performance status

Performance status will be measured using the ECOG Performance Status scale at the timepoints specified in the schedule of activities in Appendix 1.

4.4.4 Physical examinations

A physical examination performed at screening, should include an evaluation of the dermatologic, cardiovascular, respiratory, and neurologic systems. Other systems should be examined as clinically indicated. Any abnormality identified at baseline should be recorded in the patient's medical records.

Limited, symptom-directed physical examinations should be performed as clinically indicated during subsequent visits. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.4.5 Tumor response evaluations

Any evaluable or measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening. Measurable disease is a requirement for study inclusion and response will be assessed by the investigator per RECIST v1.1 at baseline. Patients will undergo tumor assessments every 2 cycles while on study until radiographic disease progression per RECIST v1.1 or loss of clinical benefit as determined by the investigator. Tumor assessments should be performed during the last week of the cycle and before the start of treatment in the next cycle (see Appendix 1). At the investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected.

Screening assessments must include CT or magnetic resonance imaging (MRI) scans (with IV contrast unless contraindicated) of the chest, abdomen, and pelvis. If a positron emission tomography (PET)/CT scan is performed, the CT portion of the study must be consistent with the standards of a full-contrast diagnostic CT scan unless IV contrast is contraindicated. A CT scan with contrast or MRI scan of the head must be done at screening to evaluate for the presence of CNS metastases in all patients (MRI preferred). An MRI scan of the head is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal CT scan. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

All measurable and evaluable lesions identified at baseline should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans). Stable brain metastases must be evaluated with each subsequent tumor assessment with the same radiographic procedure as the baseline study. Patients without brain metastases do not need brain scans for subsequent on-treatment tumor assessment unless clinically warranted or part of standard-of-care treatment.

4.4.6 Laboratory, biomarker, and other biological samples

Samples for the following laboratory tests must be reviewed prior to dosing. See Appendix 1 for specifics related to which lab tests are required at specific time points during study ("screening" vs "on treatment", etc.):

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).
- Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, ALT, and AST.
- Coagulation: INR, and aPTT (screening only).
- Thyroid function testing: thyroid-stimulating hormone (TSH), free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), and free thyroxine (also known as T4) at screening only. Repeat thyroid function testing as clinically indicated.

- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test at screening, and during the study, urine pregnancy tests will be performed at every cycle and after study treatment is discontinued. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

The following samples will be sent to the PI or a designee for analysis or banked for subsequent analysis:

- Peripheral blood to be obtained on day 1 of cycle 1, day 1 of cycle 3, and at progression
- Prior to treatment initiation, tumor tissue will be obtained following progression on most-recent therapy for determination of biomarker status including exploratory correlative analyses. Please refer to the lab manual for details. **If a biopsy is not feasible and/or safe, it may be waived after discussion with the principal investigator.** In this case, we will obtain archival tissue if available.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Should a patient withdraw from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Personnel performing laboratory analysis or biostatistics will only have access to random specimen codes and/or study subject ID numbers and not specific identifiers.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to patients unless required by law and may be disclosed to third parties only as permitted by the ICF (or separate authorization for use and disclosure of personal health information) signed by the patient. The aggregate results of any conducted research will be available in accordance with the effective investigator policy on study data publication.

4.5 TREATMENT, PATIENT, AND STUDY DISCONTINUATION

4.5.1 Treatment discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Intolerable toxicity related to study treatment, determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment
- Investigator determines it is in the best interest of the patient
- Use of another non-protocol anti-cancer therapy
- Pregnancy

- Loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease)
- Radiographic disease progression per RECIST v1.1 or symptomatic deterioration attributed to disease progression

In select scenarios, patients may continue therapy in setting of radiographic progression and ongoing clinical benefit, as assessed by investigator. In this scenario, medical interventions such as stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT) to isolated sites of disease progression in the setting of otherwise ongoing treatment response will be allowed on a case-by-case basis with PI approval.

The primary reason for study treatment discontinuation should be documented in the patient's medical records and on the appropriate eCRF. Patients who have received ≥1 cycle of study therapy and discontinue study treatment prematurely will not be replaced. Patients will return to the clinic for a treatment discontinuation visit $\leq$30 days after the last dose of study treatment. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit. After the end of treatment visit, all adverse events (including serious adverse events [see Section 5.2.2], regardless of attribution, will be recorded until 60 days after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first. Protocol-defined events of special interest [see Section 5.2.3]) will be recorded until 60 days after the last dose of study treatment regardless of whether or not subsequent anti-cancer therapy is initiated. Ongoing adverse events thought to be related to study treatment will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anti-tumor treatment is initiated, the patient is lost to follow up, the patient withdraws consent, or it has been determined that the study treatment or participation is not the cause of the adverse event.

Patients who discontinue study treatment for any reason other than progressive disease or loss of clinical benefit will continue to undergo tumor response assessments as outlined in the schedule of activities (see Appendix 1).

After treatment discontinuation, information on survival follow-up and new anti-cancer therapy will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 6 months for 2 years (unless the patient withdraws consent or the PI terminates the study).

4.5.2 Patient discontinuation from study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Withdrawal of consent
- Study termination or site closure
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the Investigator

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented in the patient's medical records and on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced. Study withdrawal will not prohibit the analysis of clinical data and samples collected prior to withdrawal of study consent.

If a patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

4.5.3 Study discontinuation

The investigator has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

4.6 MULTI-INSTITUTIONAL TRIAL MANAGEMENT

4.6.1 Personnel

At each site, personnel dedicated to this protocol will be:

- A study PI
- A research coordinator
- A data manager

In addition, the Georgetown University Lombardi Comprehensive Cancer Center (LCCC) Consortium Investigator Initiated Trial (IIT) Office will play the primary role in coordinating the trial between Lombardi-Georgetown and additional sites. The Georgetown University Lombardi Comprehensive Cancer Center (LCCC) Consortium Investigator Initiated Trial (IIT) Office will be the main point of contact for Dr. Kim (study Principal Investigator) and the other site PIs for any study related concerns, and to confirm eligibility of each patient being considered for enrollment (including “remote” confirmation of eligibility for the patients being screened at other sites). The Georgetown University Lombardi Comprehensive Cancer Center (LCCC) Consortium Investigator Initiated Trial (IIT) Office will also be the point of contact for the data managers for data entry questions. Finally, the Georgetown LCCC Consortium IIT Office will play a major role in regulatory coordination of the study, specifically by: 1) reviewing and confirming all study-related adverse events; 2) ensuring that sites are submitting all severe adverse event (SAE) reports to the site IRB per local IRB policy; 3) gathering and preparing all necessary primary source data for review/audit.

4.6.2 Patient enrollment

If a patient is being screened for enrollment, the local research coordinator must send an email within 24 hours containing the patient’s initials to the local PI, to Dr. Kim, and to the Georgetown University Lombardi Comprehensive Cancer Center (LCCC) Consortium Investigator Initiated Trial (IIT) Office. If a patient is successfully screened, the local research coordinator must send all supporting source documentation used to verify eligibility to the Georgetown University Lombardi Comprehensive Cancer Center (LCCC) Consortium Investigator Initiated Trial (IIT) Office (by secure email) for review, to [redacted]

Patients should not start therapy until Dr. Kim and the LCCC Consortium IIT Office have reviewed the patient’s records and confirmed that the patient is indeed eligible for enrollment. Once eligibility is confirmed, a unique study ID will be assigned/confirmed by the LCCC Consortium IIT Office. Study IDs will denote study site, and patient number enrolled in cohort. For example, if the first patient enrolled is

enrolled at Georgetown University and the second patient enrolled is enrolled at Washington Hospital Center the unique IDs for these patients would be GUH-001 and WHC-002, respectively.

4.6.3 Data collection and management

Patient data will be entered into the online accessible database. This database is housed at Lombardi-Georgetown but is accessible anywhere there is internet access. The data manager and research coordinator at each site will attend an online training session so that they may learn how to enroll data into the database. All screening data should be entered prior to starting therapy, and all ongoing patient data should be entered within 10 business days of each patient visit.

4.6.4 Conference calls

A bimonthly conference call will be held between Lombardi-Georgetown and the other sites. Georgetown University will conduct the bimonthly conference call to review screening and enrollment metrics, patient milestone dates, troubleshoot study challenges, and answer site questions. Site PI, participating investigators, study coordinators and data managers may attend. At least one site representative should attend each call.

4.6.5 Trial monitoring

The LCCC Consortium IIT Office will request primary source documents for the patients to be monitored. This will include collecting copies of the primary source data for any patients treated at other sites and/or reviewing Electronic Health Records when accessible. Trial monitoring may be conducted in person or remotely by the LCCC Consortium IIT Office.

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety plan for patients in this study is based on clinical experience with MGC018 in completed and ongoing studies.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of all study therapies will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Guidelines for managing patients who experience anticipated adverse events, including criteria for treatment interruption or discontinuation, are provided in Section 4.2.3.

Refer to Sections 5.2–5.6 for details on safety reporting (e.g., adverse events, pregnancies) for this study.

5.1.1 Risks associated with MGC018

MGC 018 has been associated with risks such as the following: infusion-related reactions, pneumonitis, myelosuppression, peripheral edema, severe cutaneous adverse reactions, pericardial effusion, pleural effusion, ocular toxicity, arthritis, and colitis. Please refer to the MGC018 IB for a detailed description of anticipated safety risks for MGC018.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and reporting adverse events including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

5.2.1 Adverse events (AEs)

According to the ICH guideline for Good Clinical Practice (GCP), an AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An AE can be an unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP or other protocol-imposed intervention, regardless of attribution. This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with SCLC that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as tumor biopsy).
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment.
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

5.2.2 Serious adverse events (SAEs)

An AE should be classified as an SAE if any of the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires hospitalization ≥ 24 hours or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE); the event itself may be of relatively minor medical significance (such as severe headache without any further findings). Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF. SAEs are required to be reported by the investigator to the sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4. and 5.5 for reporting instructions).

5.2.3 Adverse events of special interest (AESIs)

AESIs are a subset of events to monitor of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the study sponsor is required (no more than 24 hours after learning of the event). Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., Regulatory Authorities; Macrogenics) may also be warranted.

AESIs for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law:

  Treatment-emergent ALT or AST $> 3 \times$ ULN in combination with total bilirubin $> 2 \times$ ULN

  Treatment-emergent ALT or AST $> 3 \times$ ULN in combination with clinical jaundice
- Grade 3 or higher pneumonitis
- Grade 3 or higher pleural and/or pericardial effusion
- Grade 3 or higher ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

5.3 METHODS AND TIMING FOR ASSESSING AND RECORDING SAFETY VARIABLES

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are recorded on the AE eCRF and reported to the FDA, appropriate IRB, and Macrogenics Inc. in accordance with Code of Federal Regulations (CFR) 312.32 (IND Safety Reports).

For each adverse event recorded on the AE eCRF, the investigator will assess seriousness (see 5.2.2), severity (see 5.3.1.3) and causality (5.3.1).

All communication regarding AEs, SAEs, AESIs and/or protocol deviations from sub-site investigators and co-investigators should be directed to Chul Kim, MD (Study PI) at [redacted]

5.3.1 Assessment of adverse event

All AEs and SAEs whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to study therapies (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes

There is a plausible temporal relationship between the onset of the AE and administration of study drug, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response MGC018; and/or the AE abates or resolves upon discontinuation of study drug and, if applicable, reappears upon re-challenge.

No

Evidence exists that the AE has an etiology other than study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to study drug administration.

Expected adverse events are those adverse events that are listed or characterized in the current MGC018 IB.

Unexpected adverse events are those not listed in the current IB or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the IB.

5.3.1.1 Diagnosis vs. signs and symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

5.3.1.2 Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 5.3.2), that are attributed by the investigator solely to progression of SCLC should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study treatment, must be recorded on the AE eCRF and immediately reported to the study sponsor. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death". The DSMC will monitor the frequency of deaths from all causes.

5.3.1.3 Preexisting medical conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.1.4 Hospitalizations for medical or surgical procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting as an AE or SAE:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study
- Hospitalization solely due to progression of the underlying cancer
- Hospitalization for respite care
- Hospitalization for a pre-existing condition, provided that all of the following are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.

  The patient has not experienced an adverse event

An event that leads to hospitalization under the following circumstances is not considered to be a SAE, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.1.5 Assessment of severity of AEs

The adverse event severity grading scale for the NCI CTCAE v 5.0 will be used for assessing adverse event severity. Table 21 should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 20. Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

• Grade	• Severity
• 1	• Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
• 2	• Moderate; minimal, local, or non-invasive intervention indicated; or limiting age–appropriate instrumental activities of daily living [a]
• 3	• Severe or medically significant, but not immediately life–threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
• 4	• Life-threatening consequences or urgent intervention indicated d

• 5	• Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a SAE

[d] Grade 4 and 5 events must be reported as SAEs

5.3.1.6 Pregnancies

5.3.1.6.1 Pregnancies in female patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 6 months after the final dose of study treatment. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any SAEs associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF.

Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported to the sponsor as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to study treatment should be reported to the study sponsor as an SAE.

5.3.1.6.2 Pregnancies in female partners of male patients

Male patients will be instructed through the ICF to immediately inform the investigator if their partner becomes pregnant during the study treatment, or within 90 days after the final dose of MGC018. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.3.1.7 Other special Situations reports

The following other Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Macrogenics:

- Data related to the Product usage during breastfeeding
- Data related to overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors)

- In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population

5.3.1.8 Product complaints

A product complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

5.3.2 Adverse event reporting period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record.

After informed consent has been obtained but prior to initiation of study treatment, only SAEs caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported.

After initiation of study treatment, all AEs will be reported until 30 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and SAEs will continue to be reported until 60 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. AESIs will continue to be reported until 60 days after the final dose of study treatment, regardless of initiation of new anti-cancer therapy.

Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the AE eCRF and sent to Macrogenics contact specified above in section 5.4. All SAE and AESIs should be sent within 1 business day of date of SAE/AESI identification.

5.3.2.1 Post-study adverse events

After the end of the adverse event reporting period (defined as 30 days after last dose of study drug for all adverse events and 60 days for adverse events of special interest), the investigator should report all deaths (regardless of cause), and any SAE including development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study (including pregnancy occurring in the partner of a male study subject) that is believed to be related to prior exposure to study drug through a long-term survival follow-up eCRF.

Case Transmission Verification will be performed by both parties during this period twice per year to ensure successful transmission of Single case reports

5.3.3 MedWatch 3500A reporting guidelines

Events requiring reporting to the Sponsor-Investigator may be reported using the provided Macrogenics forms (SAE Report form, Pregnancy Exposure form) or a Medwatch form. If a MedWatch form 3500A is used to report an event, then in addition to completing appropriate patient demographic (Section A) and

suspect medication information (Section C and D), the report should include the following information within the Event Description (Section B.5) of the MedWatch 3500A form:

- Protocol number and title description
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics (Section B.6)
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

5.3.4 Follow-up after adverse events

5.3.4.1 Investigator follow-up

The investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all SAEs considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

During the study period, resolution of AEs (with dates) should be documented on the AE eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.3.4.2 Sponsor follow-up

For SAEs, AESIs and pregnancies, the sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.3.4.3 Follow-up information

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e., D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

MedWatch 3500A (Mandatory Reporting) form is available at:
https://www.fda.gov/media/69876/download

5.3.5 Reporting to regulatory authorities, ethics committees and investigators

The investigator, as the sponsor of the study, will be responsible for the expedited reporting of safety reports originating from the study to the regulatory authorities (FDA) where it has filed a clinical trial approval, in compliance with local regulations.

The study PI, as the sponsor of the study, will be responsible for the expedited reporting of safety reports originating from the study.

The study PI will be responsible for the expedited reporting of safety reports originating from the study to the IRB and DSMC, where applicable.

The study PI will be responsible for the distribution of safety information to its own investigators, where relevant, in accordance with local regulations.

Additional reporting requirements for IND holders:

For Investigator-Initiated IND Studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR § 600.80.

Events meeting the following criteria need to be submitted to the FDA as expedited IND safety reports according to the following guidance and timelines:

7 calendar day telephone or fax report

The investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of MGC018. An unexpected adverse event is one that is not already described in the MGC018 IBs. Such reports are to be telephoned or faxed to the FDA within 7 calendar days of first learning of the event.

15 calendar day written report

The investigator is also required to notify the FDA and all participating investigators, in a written IND safety report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of MGC018. An unexpected adverse event is one that is not already described in the MGC018 IBs.

Written IND safety reports should include an analysis of similar events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with analysis of similar events are to be submitted to the FDA, Macrogenics, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 form, but alternative formats are acceptable (e.g., summary letter).

FDA fax number for IND Safety Reports:

Fax: 1 (800) FDA 0178

All written IND Safety Reports submitted to the FDA by the investigator must also be sent to Macrogenics:

[redacted]

And the investigator will be responsible for the distribution of safety information to the site IRB per local IRB reporting guidelines:

[redacted]

5.4 ADVERSE EVENT REPORTING TO MACROGENICS

The investigator will be responsible for collecting all protocol-defined AE/SAE data, pregnancy reports (including pregnancy occurring in the partner of a male study subject), other special situation reports, AESIs, product complaints with an AE where the patient has been exposed to the product. The completed MedWatch form should be sent to the Georgetown University Lombardi Comprehensive Cancer Center (LCCC) Consortium Investigator Initiated Trial (IIT) Office and Macrogenics contact specified below. Transmission of these reports (initial and follow-up) will be either electronically via email or by fax and within the timelines specified below:

Email: [redacted]

Investigators must report all the above mentioned single case reports adequately to the LCCC Consortium IIT Office and Macrogenics on a MedWatch or CIOMS I or on Macrogenics approved SAE form within one (1) business day of the awareness date

The investigator will forward quarterly listings of non-serious AEs originating from the study to Macrogenics.

5.4.1 Case transmission verification of single case reports

The study PI agrees to conduct the case transmission verification to ensure that all single case reports have been adequately received by Macrogenics via PI emailing Macrogenics a quarterly line-listing documenting single case reports in the preceding time period.

The periodic line-listing will be exchanged within seven (7) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon.

If discrepancies are identified, the Study PI as sponsor and Macrogenics will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The sponsor shall receive reconciliation guidance documents within the 'Activation Package'.

Following case transmission verification, single case reports which have not been received by Macrogenics shall be forwarded by the study PI to Macrogenics within five (5) calendar days from request by Macrogenics.

At the end of the study, a final cumulative case transmission verification report will be sent to Macrogenics.

5.5 AGGREGATE REPORTS

Development safety update report

As study sponsor, the PI, in conjunction with Georgetown University IRB and DSMC, will be responsible for the preparation of their own Development Safety Update Report (DSUR) for the study and for the submission of the report to the regulatory authorities and other bodies such as ethics committees, where applicable. The study PI agrees to share a copy of their own DSUR with Macrogenics as soon as reasonably possible after completion.

Macrogenics agrees to forward to the study PI an executive summary of the Macrogenics DSUR upon request. Furthermore, Macrogenics agrees that the study PI may cross-reference the executive summary of the Macrogenics DSUR, as applicable.

Other reports

The PI will forward a copy of the Final Study Report to Macrogenics upon completion of the study.

5.6 STUDY CLOSE-OUT

Any study report submitted to the FDA by the investigator should be copied to Macrogenics. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Macrogenics. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study.

5.7 QUERIES

Queries related to the study will be answered by the PI and Georgetown University. However, responses to all safety queries from regulatory authorities or for publications will be discussed and coordinated between all parties, including Macrogenics. The study PI agrees that it shall not address such queries from regulatory authorities and other sources relating to the study therapy independently but shall involve Macrogenics in such queries.

All parties will use all reasonable effort to ensure that deadlines for responses to urgent requests for information or review of data are met. The parties will clearly indicate on the request the reason for urgency and the date by which a response is required.

5.8 SIGNAL & RISK MANAGEMENT

Macrogenics is responsible for safety signal management (signal detection and/or evaluation) for their own products. However, it is agreed that study PI**,** as sponsor of the study, will be primarily responsible for assessment of the benefit-risk balance of the study.

If study PI issues a safety communication relevant for Macrogenics (i.e., a safety issue that notably impacts the benefit-risk balance of the study and / or triggers any changes to the study) this will be sent to Macrogenics within five (5) business days of its internal approval.

As needed, Macrogenics will reasonably assist study PI with signal and risk management activities related to the product within the study. Macrogenics will also provide study PI with any new relevant information that may modify or supplement known data regarding the Product (e.g., relevant Dear Investigator Letter).

5.9 COMPLIANCE WITH PHARMACOVIGILANCE AGREEMENT/AUDIT

The parties shall follow their own procedures for adherence to AE reporting timelines. Each party shall monitor and, as applicable, request feedback from the other party regarding AE report timeliness in accordance with its own procedures. The parties agree to provide written responses in a timely manner to inquiries from the other party regarding AE reports received outside the agreed upon agreement timelines. If there is any detection of trends of increasing or persistent non-compliance to transmission timelines stipulated in this agreement, both parties agree to conduct ad hoc or institute a regular joint meeting to address the issue.

In case of concerns related to non-compliance of processes, other than exchange timelines, with this agreement, the parties will jointly discuss and collaborate on clarifying and resolving the issues causing non-compliance. Every effort will be made by the non-compliant party to solve the non-compliance issues and inform the other party of the corrective and preventative actions taken.

Upon justified request, given sufficient notice of no less than sixty (60) calendar days, an audit under the provisions of this agreement can be requested by either party. The parties will then discuss and agree in good faith upon the audit scope, agenda and execution of the audit. The requesting party will bear the cost of the audit.

6. STATISTICAL CONSIDERATIONS

6.1 DETERMINATION OF SAMPLE SIZE

The primary efficacy endpoint of this study is to evaluate the ORR of the study drug MGC018 in patients with ES-SCLC. Simon's two-stage optimal design is used for sample size calculation.

We plan to enroll up to 17 patients. The null hypothesis that the true response rate is 5% will be tested against a one-sided alternative. This design yields a type I error rate of 4.7% and power of 81.2% when the true response rate is 25%.

6.2 PLANNED PRIMARY EFFICACY EVALUATION & VARIABLE

ORR will be the planned primary efficacy variable assessed by RECIST v1.1 (the planned efficacy evaluation). All patients who receive at least one dose of study treatment will be included in the primary efficacy analysis.

6.3 SECONDARY EFFICACY VARIABLES

Secondary efficacy variables include:

- PFS: Defined as the time from study drug initiation until progression event or death as assessed using the Kaplan-Meier method.
- OS: Defined as time from study drug initiation to death as assessed using the Kaplan-Meier method.
- DOR: Defined as the time from response to disease progression or death in patients who achieve complete or partial response.

6.4 METHOD OF ANALYSIS

The analysis of ORR will be performed according to the Simon two stage design using the prespecified stage-2 boundaries described in the Section 6.1 (Simon 1989). The null hypothesis that the true response rate is 5% will be tested against a one-sided alternative. In the first stage, 9 patients will be accrued. If there is no response in these 9 patients, the study will be stopped. Otherwise, 8 additional patients will be accrued for a total of 17. This design yields a type I error rate of 4.7% and power of 81.2% when the true response rate is 25%.

The analysis of time to event data, such as PFS and OS, will be performed using the all treated population with the Kaplan-Meier methodology. Safety data will be summarized descriptively. Adverse events will be summarized by severity, and relationship to study drug. The treatment outcomes of patients with EGFR-mutant non-small cell lung cancer (NSCLC) that has transformed into small cell lung cancer (SCLC) will be evaluated both as part of the overall data analysis and as a separate subgroup analysis.

6.5 ANALYSIS OF EXPLORATORY BIOMARKERS

Exploratory analyses will be descriptive/graphical in nature and are designed to generate new hypotheses to be tested in future clinical studies. Continuous variables will be summarized with means and standard deviations. Dichotomous and categorical variables will be summarized using proportions with exact 95% confidence intervals and counts, respectively. These summaries will be computed for each treated patient at multiple time points before and initiation of study treatment as indicated on the study schema and study calendar. For each patient, comparisons in the pre- and post-study treatment responses will be compared using paired t-tests (or Wilcoxon signed rank tests if appropriate) for continuous variables and McNemar's test for dichotomous or categorical variables. Associations between immune responses will be explored graphically (e.g. scatterplots, boxplots) and numerically (e.g. correlations, $\chi 2$ tests).

7. INVESTIGATOR REQUIREMENTS

7.1 RETENTION OF RECORDS

FDA regulations (21 CFR §312.62[c]) and the ICH Guideline for GCP (see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of clinical trials and the distribution of investigational drug, patient records, consent forms, laboratory test results, and medication inventory records, must be retained for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply.

7.2 STUDY MEDICAL MONITORING REQUIREMENTS

This clinical research study will be monitored both internally by the PI and externally by the Georgetown University IRB. In terms of internal review, the PI will continuously monitor and tabulate AEs. Appropriate reporting to the Georgetown University IRB will be made. The PI of this study will also continuously monitor the conduct, data, and safety of this study to ensure that:

- Interim analyses occur as scheduled,

- Stopping rules for toxicity and/or response are met,
- Risk/benefit ratio is not altered to the detriment of the subjects,
- Appropriate internal monitoring of AEs and outcomes is done,
- Over-accrual does not occur,
- Under-accrual is addressed with appropriate amendments or actions,
- Data are being appropriately collected in a reasonably timely manner.

Routine monitoring will be carried out via a periodic team conference among investigators during which toxicity data, including all SAEs, will be reviewed and other issues relevant to the study such as interim assessment of accrual, outcome, and compliance with study guidelines, will be discussed. Monitoring will be carried out on an ongoing basis. The severity, relatedness, and whether or not the event is expected will be reviewed.

7.2.1 IRB

GCP requires that the clinical protocol, any protocol amendments, the IB, the ICF and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents must be reviewed by an IRB. Georgetown IRB approval of the protocol, ICF and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site. Any amendments to the protocol will require IRB approval prior to implementation of any changes made to the study design. Any SAEs that meet the reporting criteria, as dictated by local regulations, will be reported to the IRB. During the conduct of the study, the investigator should promptly provide written reports to the IRB of any changes that affect the conduct of the study and/or increase the risk to subjects.

7.2.2 Data management and monitoring/auditing

The Georgetown LCCC will be responsible for the data and safety monitoring of this trial. As this study is an investigator-initiated Phase 2 study, it is considered a high-risk study which requires real-time monitoring by the PI and study team, and regular reviews by the LCCC DSMC.

All SAEs are required to be reported to Dr. Kim and the Georgetown University Lombardi Comprehensive Cancer Center (LCCC) Consortium Investigator Initiated Trial (IIT) Office. In additions, SAEs should be reported to the local and/or to the Georgetown IRB per local IRB policy. Based on SAEs, the IRB retains the authority to suspend further accrual pending more detailed reporting and/or modifications to further reduce risk and maximize the safety of participating patients.

Progress on the trial and the toxicities experienced will be reviewed by the LCCC DSMC on a quarterly basis from the time the first patient is enrolled on the study. Results of the DSMC meetings will be forwarded to the IRB and Macrogenics with recommendations regarding need for study closure.

DSMC recommendations should be based not only on results for the trial being monitored, but also on data available to the DSMC from other studies (if applicable). It is the responsibility of the PI to ensure that the DSMC is kept apprised of non-confidential results from related studies that become available. It is the responsibility of the DSMC to determine the extent to which this information is relevant to its decisions related to the specific trial being monitored.

A written copy of the DSMC recommendations will be given to the trial PI and the IRB, and will be forwarded to representatives at Macrogenics. If the DSMC recommends a study change for patient safety or efficacy reasons, the PI must act to implement the change as expeditiously as possible. In the unlikely event that the PI and study team does not concur with the DSMC recommendations, then the LCCC Associate Director of Clinical Research must be informed of the reason for the disagreement. The PI, DSMC Chair, and the LCCC AD for Clinical Research will be responsible for reaching a mutually acceptable decision about the study and providing details of that decision to the IRB. Confidentiality must be preserved during these discussions. However, in some cases, relevant data may be shared with other selected trial investigators and staff to seek advice to assist in reaching a mutually acceptable decision.

If a recommendation is made to change a trial for reasons other than patient safety or efficacy, the DSMC will provide an adequate rationale for its decision. If the DSMC recommends that the trial be closed for any reason, the recommendation will be reviewed by the Associate Director for Clinical Research at Georgetown University LCCC. Authority to close a trial for safety reasons lies with the IRB, with the above described input from DSMC and the AD for Clinical Research.

Of note, if applicable, the DSMC will also review the safety data of the patients enrolled outside of Georgetown University. The data managers at each site will be entering data into the Georgetown database, so that all data will be available for the DSMC at Georgetown to review. De-identified source records should be sent via secure email to the Georgetown University Lombardi Comprehensive Cancer Center (LCCC) Consortium Investigator Initiated Trial (IIT) Office, as requested, and Dr. Chul Kim to confirm receipt of those records.

7.3 STUDY MEDICATION ACCOUNTABILITY

The PI, as study sponsor, will ensure maintenance of complete and accurate records of the receipt, dispensation, and disposal or return of all study drug in accordance with 21 CFR, Part 312.57 and 312.62 and Macrogenics requirements.

All unused remaining product at the end of the study should be disposed of at the study site according to institutional standard operating procedure. If there is no standard operating procedure at the site for drug destruction, study drug will be returned to Macrogenics as directed.

7.4 DATA COLLECTION

The study coordinator and investigators are responsible for ensuring that the eligibility checklist is completed in a legible and timely manner for every patient enrolled in the study, and that data are recorded on the appropriate forms and in a timely manner. Any errors on source data should be lined through, but not obliterated, with the correction inserted, initialed, and dated by the study coordinator or PI. All source documents will be available for inspection by the FDA and the Georgetown University IRB.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

Patients who comply with the requirements of the protocol, are tolerating study treatment, and may be receiving benefit will be offered dosing beyond Cycle 1 at the investigator’s discretion after a careful assessment and thorough discussion of the potential risks and benefits of continued treatment with the patient. Such patients may have the option to receive treatment as long as they continue to experience clinical benefit in the opinion of the investigator until the occurrence of unacceptable toxicity,

symptomatic deterioration attributed to disease progression, or any of the other reasons for treatment discontinuation.

8.2 INFORMED CONSENT

The informed consent document must be signed by the subject or the subject's legally authorized representative before his or her participation in the study. The case history for each subject shall document that informed consent was obtained prior to participation in the study. A copy of the informed consent document must be provided to the subject or the subject's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

Signed consent forms must remain in each subject's study file and must be available for verification by study monitors at any time.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

The PI is responsible for keeping the IRB apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case, the IRB must be updated at least once a year. The PI must also keep the IRB informed of any significant AEs.

Investigators are required to promptly notify their respective IRB of all adverse drug reactions that are both serious and unexpected. This generally refers to SAEs that are not already identified in the study therapy IB and that are considered possibly or probably related to the molecule or study drug by the investigator. Investigators must immediately forward to their IRB any written safety report or update provided by Macrogenics (e.g., IND safety report, IB, safety amendments and updates, etc.).

8.4 CONFIDENTIALITY

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the ICF (or separate authorization to use and disclose personal health information) signed by the patient or unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the FDA and other regulatory agencies, national and local health authorities, Macrogenics representatives and collaborators, and the study site IRB if appropriate.

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, ICFs and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the study sponsor (study PI) and to the IRB in accordance with established IRB policies and procedures. Please reference section 5.3 for submission of Protocol Deviations to the study sponsor (study PI). The sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 PROTOCOL AMENDMENTS

As study sponsor, any protocol amendments will be prepared by the PI. Protocol amendments will be submitted to the IRB and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in contact information).

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Appendix 1
Study Flowcharts

Table 1: Screening Procedural Outline

Procedure	Screening Visit (D-28 to D1)	Notes
Eligibility Assessments		
Informed Consent	X	Must be documented before any study-specific screening procedures are performed, and may be obtained >28 days prior to treatment initiation
Inclusion/Exclusion Criteria	X	
Medical History	X	
Demographic Data	X	
Baseline Assessments		
Con Medication Review	X	Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit
Vital Signs	X	Includes: temperature, heart rate, respiratory rate, blood pressure
Weight	X	
Height	X	
Physical Exam	X	Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Record abnormalities observed at baseline in the patient's medical records
ECOG Performance Status	X	

Laboratory Tests[a]	X	CBC with differential, serum chemistry (bicarbonate/total carbon dioxide, sodium, potassium, chloride, glucose, BUN, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, ALT, AST), thyroid function (TSH, free/total T3, free T4)
Pregnancy Test	X	Serum pregnancy test at screening for women of child-bearing potential only[b]
Tumor Biopsy[c]	X	Mandatory for study entry
Imaging Assessments[d]	X	CT (preferred) or MRI with contrast (unless contraindicated) of chest, abdomen and pelvis MRI (preferred) or CT of head with contrast (unless contraindicated) to assess for presence of CNS metastases

[a]Screening laboratory test results must be obtained within 14 days of treatment initiation. Screening labs that are performed outside the 14-day window for eligibility criteria may be repeated on C1D1, prior to treatment, to verify the subject continues to meet eligibility requirements.
[b]a woman is defined as "of childbearing potential" if she is postmenarchal and has not reached post-menopausal state (≥12 continuous months of amenorrhea without identified cause other than menarche), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

[c]Must be performed ≥5 days prior to study treatment administration. If a biopsy is not feasible and/or safe, it may be waived after discussion with the principal investigator. In this case, we will obtain archival tissue if available.

[d]imaging assessments performed as standard-of-care prior to obtaining study informed consent and within 28 days of study treatment initiation do not have to be repeated at screening.

[e]MRI brain is required to confirm or refute diagnosis of CNS metastases in the event of equivocal CT scan.

Table 2 – Study Calendar

Procedure	**Treatment Cycles** (28-day cycle)			**Treatment Discontinuation**	**Follow-up**
	Cycle 1 D1 and D15 (±3 days)	**Cycle 2 D1 and D15** (±3 days)	**Subsequent Cycles D1** (±3 days)	**≤30 days after last treatment**	
Clinical Assessment					
ECOG PS	X	X	X	X	
Vital Signs[a]	X	X	X	X	

Weight	X	X	X	X	
Laboratory Tests[b]					
CBC w/ diff	X	X	X	X	
Chemistries[c]	X	X	X	X	
Imaging Response Assessments[d]			X		
Correlative Studies					
Peripheral blood[e]	X (only on C1D1)		X (only on C3D1)	X	
Tumor biopsy[f]				X	
Other Assessments					
Con Meds[h]	X	X	X	X	
Adverse Events[i]	X	X	X	X	X
Study Treatment administration	X	X	X		
Survival follow-up and anti-cancer treatment[j]					X

[a]includes temperature, respiratory rate, heart rate, and blood pressure. For the first infusion, vital signs should be measured within 60 minutes prior to the infusion of MGC018, every 15 (± 5) minutes during MGC018 infusion if clinically indicated, and 30 (± 10) minutes after the infusion. For subsequent infusions, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during and 30 (± 10) minutes after the infusion.

[b]pre-treatment lab assessments do not have to be repeated if performed within 14 days of Cycle 1 D1, and within 3 days of D1 of all subsequent cycles.

[c]chemistry includes: bicarbonate/total carbon dioxide, sodium, potassium, chloride, glucose, BUN, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, ALT, AST.

[d]Imaging assessments should be performed every two cycles within a -7 day window (i.e. imaging performed within 7 days of next scheduled treatment is acceptable) until radiographic disease progression per RECIST v1.1 or loss of clinical benefit. Tumor assessments should continue according to this schedule for patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit. The same radiographic procedures used to assess disease sites at screening should be used for subsequent assessments (same contrast protocol for CT scans). CNS imaging only required if CNS metastases identified on screening imaging. If needed, CNS imaging should occur according to the same schedule as chest/abdomen/pelvis (CAP) imaging assessment.

[e]peripheral blood for correlative analyses will be drawn on day 1 of cycle 1, on day 1 of cycle 3, and upon disease progression/treatment discontinuation

[f]optional biopsy upon progression of disease. Should be performed within 30 days of documented progression or prior to next anti-cancer therapy, whichever is sooner.

[h]medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit.

[i]after informed consent has been obtained but prior to initiation of study treatment, only SAEs caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. SAEs will continue to be reported until 60 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. Adverse events of special interest will be reported until 60 days after last dose of study treatment regardless of initiation of new systemic anti-cancer therapy. After this period, all deaths, regardless of cause, should be reported. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all SAEs considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

[j]after treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 6 months (unless the patient withdraws consent or the Investigator terminates the study) for 2 years. If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

Table 3 – Calendar of Biopsy and Peripheral Blood draws for correlative analyses

Study Interval	Time	Sample
Tumor Biopsy[a]		
Pre-treatment	≥5 days prior to C1	Tumor tissue
Disease progression (optional)	≤30 days following documented disease progression	Tumor tissue
Peripheral blood		
Day 1 of Cycle 1	Predose	10 mL peripheral blood
Day 1 of Cycle 3	Predose	10 mL peripheral blood
Disease progression	At visit	10 mL peripheral blood

[a]See lab manual for information regarding tissue biopsy processing

Table 4 – Calendar of Peripheral Blood draws for PK and ADA testing

Cycle	Day	Timepoint	Window	PK: Total and ADC (serum)	ADA: (serum)
1	1	Pre-infusion	N/A	X	X
1	1	End of infusion	+10 min	X	
1	15	Day 15	N/A	X	X
2	1	Pre-infusion	N/A	X	X
2	1	End of infusion	+10 min	X	
2	15	Day 15	N/A	X	
3, 4, and 5	1	Pre-infusion	N/A	X	X
3, 4, and 5	1	End of infusion	+10 min	X	
6, 9, and 12	1	Pre-infusion	N/A	X	X
6, 9, and 12	1	End of infusion	+10 min	X	
IRR[a]	N/A	N/A	N/A	X	X
EOTV	N/A	EOTV	N/A	X	X

Note: Actual start of infusion times, EOI times, and PK/ADA sample collection times will be recorded on the eCRFs. Do not collect PK samples from infusion port. Pre-infusion PK samples may be collected before start of infusion on visit day (dosing day) or day before infusion. When collecting multiple samples, collect the PK sample first.

[a]PK and ADA samples may be obtained at additional time points in participants who experience signs and symptoms of IRR. Samples should be obtained as soon as possible after onset of IRR, if feasible.

Appendix 1
Calculation of Creatinine Clearance Using the Cockcroft-Gault Formula

$$\text{Creatinine Clearance (men)} = (140\text{-Age}) \times \text{Lean Body Weight [kilograms]}$$

$$\text{Serum Creatinine (mg/dL)} \times 72$$

$$\text{Creatinine Clearance (women)} = 0.85 \times (140\text{-Age}) \times \text{Lean Body Weight [kilograms]}$$

$$\text{Serum Creatinine (mg/dL)} \times 72$$

Source: Gault MH, Longerich LL, Harnett JD, et al. Predicting glomerular function from adjusted serum creatinine (editorial). Nephron 1992;62:249.

Appendix 3
Anaphylaxis Precautions

EQUIPMENT NEEDED

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for intravenous, intramuscular, and endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment infusion, the following procedures should be performed:

1. Stop the study treatment infusion.
2. Call for additional medical assistance.
3. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring, if possible.
4. Administer antihistamines, epinephrine, or other medications as required by participant status and as directed by the physician in charge.
5. Continue to observe the participant and document observations.
6. Draw serum/plasma samples for immunogenicity testing.
7. Ask participant to return for washout immunogenicity sample if appropriate