CLINICAL STUDY PROTOCOL: CP-MGA271-06
PROTOCOL AMENDMENT 1

Study Title:	A Phase 2 Open-Label Trial to Evaluate Enoblituzumab in Combination with Retifanlimab or Tebotelimab in the First-Line Treatment of Patients with Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck
Study Number:	CP-MGA271-06
Study Phase:	Phase 2
Product Name:	Enoblituzumab (also known as MGA271) Retifanlimab (also known as MGA012 or INCMGA00012) Tebotelimab (also known as MGD013)
IND Number:	
EudraCT Number:	NA
Indication:	First-line treatment of patients with recurrent or metastatic SCCHN (squamous cell carcinoma of the head and neck) not curable by local therapy
Coordinating Principal Investigator:	TBD
Sponsor:	MacroGenics, Inc. 9704 Medical Center Drive Rockville, MD 20850 301-251-5172
Sponsor's Medical Monitor:	Refer to study contact list

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

SPONSOR SIGNATURES

Study Title:	A Phase 2 Open-Label Trial to Evaluate Enoblituzumab in Combination with Retifanlimab or Tebotelimab in the First-Line Treatment of Patients with Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck
Study Number:	CP-MGA271-06

This clinical study protocol has been approved by the Sponsor:

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

Executive Director, Clinical Development
MacroGenics, Inc.

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

Director, Biostatistics
MacroGenics, Inc.

LIST OF ABBREVIATIONS

The list of abbreviations of specialist terms does not include general scientific abbreviations of temperature, weight and volume.

ADA	anti-drug antibodies
ADCC	antibody-dependent cell-mediated cytotoxicity
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase (SGPT)
AST	aspartate aminotransferase (SGOT)
B7-H3	B7 homolog 3
BOR	best overall response
CFR	Code of Federal Regulations
CI	confidence interval
CNS	central nervous system
CPS	combined positive score
CR	complete response
CRS	cytokine release syndrome
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DLT	dose limiting toxicity
DoR	duration of response
DSM	Data Safety Monitor
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOTV	End of Treatment Visit

FACS	fluorescence activated cell sorting
Fc	fragment crystallizable
FcγR	Fc gamma receptor
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FU	fluorouracil
GC	gastric cancer
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBV	hepatitis B virus
HPV	human papilloma virus
HR	hazard ratio
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IFN	interferon
IHC	immunohistochemistry
IL	interleukin
IgG	immunoglobulin G
irAE	immune-related adverse event
IRB	Institutional Review Board
IRR	infusion related reaction
IRT	interactive response technology
IV	intravenous
LAG-3	lymphocyte-activation gene 3
LTFU	lost to follow up
mAb	monoclonal antibody
MAD	maximum administered dose
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging

MTD	maximum tolerated dose
NE	not evaluable
NCI	National Cancer Institute
NK	natural killer
NSCLC	non-small-cell lung cancer
NT-proBNP	N-terminal pro b-type natriuretic peptide
ORR	objective response rate
OS	overall survival
Pap	Papanicolaou
PBMC	peripheral blood mononuclear cells
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed death ligand 1
PD-L2	programmed death ligand 2
PFS	progression free survival
PK	pharmacokinetics
PO	orally
PPK	population pharmacokinetics
PQC	product quality complaint
PR	partial response
PT	Preferred Term
QW	weekly
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
RECIST	response evaluation criteria in solid tumors
RES242	MGA271 with wild-type Fc
R/M	recurrent/metastatic
SAE	serious adverse event
SAP	statistical analysis plan

SC	subcutaneous
SCC	squamous cell cancer
SCCHN	squamous cell cancer of the head and neck
SD	stable disease
SOC	System Organ Class
SPP	statistical programming plan
TCR	T-cell receptor
TEAE	treatment-emergent adverse event
TNBC	triple negative breast cancer
TRAE	treatment-related adverse event
TPS	tumor proportion score
ULN	upper limit of normal
US	United States
USP	United States Pharmacopeia
WOCBP	women of child-bearing potential

1 SYNOPSIS

Sponsor: MacroGenics, Inc.	**IND Number:** 143772
Name of Products: Enoblituzumab (also known as MGA271) Retifanlimab (also known as MGA012 or INCMGA00012) Tebotelimab (also known as MGD013)	
Study Title: A Phase 2 Open-Label Trial to Evaluate Enoblituzumab in Combination with Retifanlimab or Tebotelimab in the First-Line Treatment of Patients with Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck	
Study Number: CP-MGA271-06	
Study Phase: Phase 2	
Investigator(s)/Centers: The study will be conducted at approximately 35 centers in approximately 5 countries.	
Primary Objective(s): <u>Retifanlimab Cohort:</u> • To assess the efficacy of the combination of enoblituzumab + retifanlimab, based primarily upon evaluation of Investigator-assessed objective response rate (ORR) in the response evaluable patient population, in patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) not curable by local therapy, with no prior systemic therapy for SCCHN in the recurrent or metastatic setting (with the exception of systemic therapy completed > 6 months prior if given as part of multimodal treatment for locally advanced disease). <u>Tebotelimab Cohort:</u> • To assess the safety, tolerability, and preliminary efficacy of the combination of enoblituzumab + tebotelimab, based primarily upon evaluation of Investigator-assessed ORR in the response evaluable patient population, in patients with recurrent or metastatic SCCHN not curable by local therapy, with no prior systemic therapy for SCCHN in the recurrent or metastatic setting (with the exception of systemic therapy completed > 6 months prior if given as part of multimodal treatment for locally advanced disease).	
Secondary Objective(s): <u>Retifanlimab Cohort:</u> • To evaluate the Investigator-assessed progression free survival (PFS), disease control rate (DCR), duration of response (DoR), and overall survival (OS). • To evaluate safety and tolerability. • To assess the pharmacokinetics (PK) of enoblituzumab + retifanlimab. • To evaluate the immunogenicity of enoblituzumab + retifanlimab.	

Tebotelimab Cohort:

- To evaluate the Investigator-assessed PFS, DCR, DoR, and OS.
- To assess the PK of enoblituzumab + tebotelimab.
- To evaluate the immunogenicity of enoblituzumab + tebotelimab.

Study Drug:

- Enoblituzumab is a humanized IgG1κ monoclonal antibody (mAb) that binds B7 homolog 3 (B7-H3), a member of the B7 family of ligands that bind to receptors on lymphocytes and regulate immune responses.
- Retifanlimab is a humanized, hinge-stabilized, IgG4κ mAb that recognizes human PD-1.
- Tebotelimab is an Fc-bearing bispecific tetravalent (bivalent for each antigen) DART® protein engineered as a hinge stabilized immunoglobulin G_4 (IgG_4) molecule designed to concomitantly bind programmed cell death protein 1 (PD-1) and lymphocyte-activation gene 3 (LAG-3)

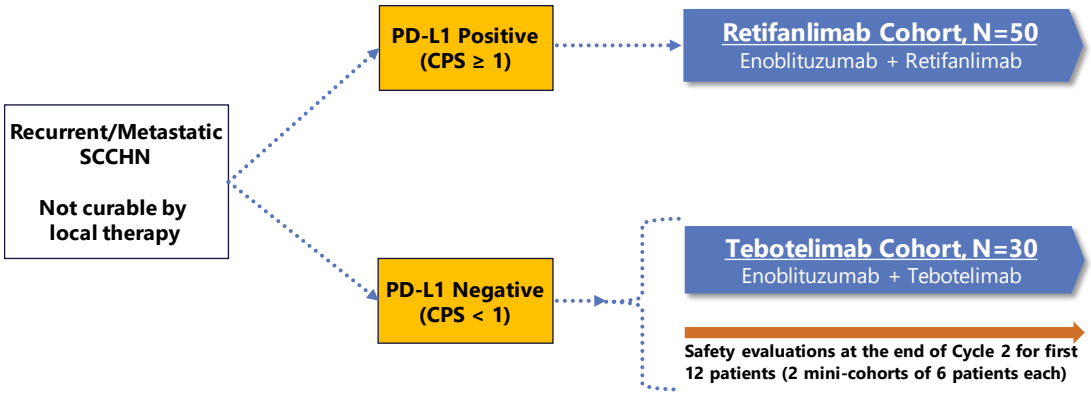
Study Design:

This is a Phase 2, open label, non-randomized study in the first-line treatment of patients with recurrent or metastatic SCCHN not curable by local therapy, with no prior systemic therapy for SCCHN in the recurrent or metastatic setting (with the exception of systemic therapy completed > 6 months prior if given as part of multimodal treatment for locally advanced disease). The study will be conducted at approximately 35 centers in approximately 5 countries.

Approximately 80 patients will be enrolled in 2 cohorts, to receive enoblituzumab in combination with either retifanlimab (Retifanlimab Cohort, programmed cell death ligand 1 [PD-L1] positive [combined positive score (CPS) ≥ 1] patients, N=50) or tebotelimab (Tebotelimab Cohort, PD-L1 negative [CPS < 1] patients, N=30; see figure below). Enrollment into each cohort will occur independently in a non-randomized fashion. Patients may not crossover between cohorts. PD-L1 expression will be prospectively collected and prospectively analyzed based on IHC staining using the FDA-approved 22C3 pharmDx assay. B7-H3 and LAG-3 expression will be prospectively collected and retrospectively analyzed.

An independent Data Safety Monitor (DSM), the Sponsor, and Investigators will maintain regular oversight of patient safety throughout the trial. In the Tebotelimab Cohort, toxicity will be evaluated by monitoring the occurrence and severity of dose limiting toxicities (DLTs) in the first 12 patients (2 mini-cohorts of 6 patients each) through Cycle 2 Day 7. If warranted, enrollment in the Tebotelimab Cohort will be paused and ad hoc meetings with the Principal Investigators (or designee), the Medical Monitor, and the independent DSM will be held to consider dose reduction of tebotelimab to 300 mg, Tebotelimab Cohort termination, or continuation at the pre-established 600 mg dose.

Study Schema



Enrollment in the 2 study cohorts will occur independently in a non-randomized fashion

Dosing Regimens:
Enoblituzumab: 15 mg/kg Q3W
Retifanlimab: 375 mg Q3W
Tebotelimab: 600 mg Q3W

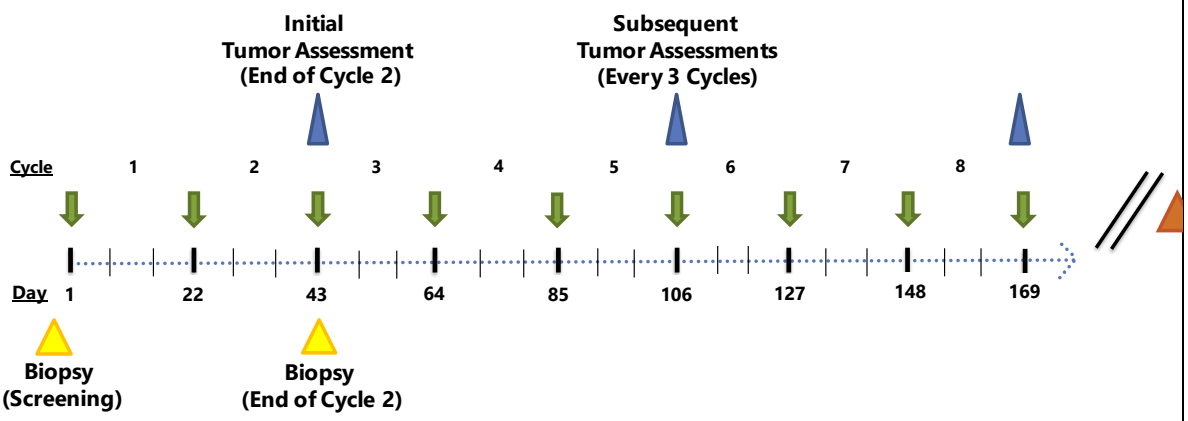
Efficacy Outcomes

Primary: ORR
Secondary: PFS, DCR, DoR, OS

The data for each of the Retifanlimab and Tebotelimab Cohorts will be analyzed upon completion of enrollment of each cohort, and after all patients in the applicable cohort have at least one tumor assessment, to inform whether to proceed with the study and to determine any modifications to the trial design.

Patients will receive the assigned study drugs (enoblituzumab 15 mg/kg and either retifanlimab 375 mg or tebotelimab 600 mg) on an every 3 week (Q3W) basis, in cycles of 3 weeks duration (see figure below). The initial tumor assessment will occur at the end of Cycle 2 (i.e., after approximately 6 weeks), and at the end of every 3 cycles thereafter (i.e., approximately every 9 weeks). After receipt of the last dose of study treatment, patients will enter an Efficacy Follow-up Period and will be followed for survival.

Treatment Cycles



Retifanlimab Cohort: enoblituzumab 15 mg/kg + retifanlimab 375 mg
Tebotelimab Cohort: enoblituzumab 15 mg/kg + tebotelimab 600 mg

Tumor Assessment

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

The Principal Investigator, in consultation with the Sponsor, will waive requirement for biopsies depending on individual patient circumstances. This requirement will expire after an adequate number of samples have been collected, as determined by the Sponsor

Dose Limiting Toxicity (Tebotelimab Cohort):

For the purposes of safety management and defining DLTs, the combination of enoblituzumab + tebotelimab will be treated as one entity. If a DLT is considered related to study treatment, no distinction will be made as to which agent is the causative agent and administration of both agents will be stopped.

Dose limiting toxicities will be based on treatment-emergent drug-related AEs (or laboratory abnormalities) occurring through Cycle 2 Day 7.

Patients in the Tebotelimab Cohort who experience DLT will discontinue study treatment.

Number of Patients Enrolled:

The total sample size is planned to be approximately 80 patients, with approximately 50 and approximately 30 patients in the Retifanlimab and Tebotelimab Cohorts, respectively.

Patient Population/Key Entry Criteria:

The patient population to be enrolled in this study will consist of adult patients with histologically proven, recurrent or metastatic SCCHN not curable by local therapy, and with no prior systemic therapy for SCCHN in the recurrent or metastatic setting (with the exception of systemic therapy completed > 6 months prior if given as part of multimodal treatment for locally advanced disease). Patients must have good performance status, adequate end organ function, radiographic evidence of measurable disease suitable for response monitoring, and no serious concurrent illnesses that would increase the risk to the patient or confound the study data.

Duration of Treatment and Study Duration:

Study treatment will continue in cycles of 3 weeks duration until confirmed complete response (CR; except as noted below), disease progression, unacceptable toxicity, withdrawal of consent, physician recommendation to

discontinue therapy, death, or the maximum allowed treatment duration has been reached. The maximum allowed treatment duration is 35 cycles for each study drug.

Discontinuation of study treatment may be considered for patients who have attained a confirmed CR. However, until Cycle 33, 2 additional cycles of study treatment may be completed beyond the date of confirmed CR (the total number of cycles of study treatment must not exceed 35).

Patients who have radiographic progression may remain on study treatment until the next scheduled radiographic evaluation if the following conditions are met: absence of clinical symptoms or signs indicating clinically significant disease progression; no decline in ECOG performance status; absence of rapid disease progression or threat to vital organs or critical anatomical sites (e.g., central nervous system [CNS] metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention; and no significant, unacceptable, or irreversible toxicities related to study treatment.

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

End of study for each patient is defined as follows: Patient is lost to follow-up (LTFU) or discontinues from the study due to any reason.

Criteria for Evaluation:

Safety Assessments:

The safety assessment will be based on the evaluation of adverse events (AEs) that occur from the time of initiation of administration of study drug until 30 days following the last dose of study drug or until the start of a subsequent systemic anticancer therapy, if earlier, and will be determined based on signs, symptoms, physical examination findings, and/or laboratory test results from enrolled patients as appropriate. The severity of AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0.

Disease progression or events deemed related to disease progression (including events resulting in hospitalization or death without other serious adverse event [SAE] criteria) will be documented as an antitumor activity outcome, **not reported** as an AE or SAE; they will be collected as efficacy endpoints. **Conversely,** AEs and SAEs should be reported if it is unclear if the event is due to PD.

Response Assessments:

Tumor assessments will be obtained using computed tomography (CT) and/or magnetic resonance imaging (MRI) scans and tumor response evaluated according to response evaluable criteria in solid tumors (RECIST) v1.1. Target and non-target lesions will be designated at screening and assessed at the end of Cycle 2 (i.e., after approximately 6 weeks, with a window of -3 days in relation to the beginning of the next cycle), and at the end of every 3 cycles thereafter (i.e., approximately every 9 weeks, with a window of -7 days in relation to the beginning of the next applicable cycle) until discontinuation of treatment. After receipt of the last dose of study treatment, all patients will enter an Efficacy Follow-up Period, during which tumor assessments will be obtained every 12 weeks (± 1 week) after the end of treatment visit (EOTV; or, if no EOTV is conducted, after the decision to end treatment), until evidence of disease progression, initiation of another anticancer therapy, withdrawal of consent, LTFU, death, or 36 weeks after the last patient's EOTV. EOTV tumor assessment does not need to be conducted if prior tumor assessment was performed within 28 days of the EOTV and results are available for RECIST assessments. Patients who discontinue study treatment due to AEs are followed by radiographic evaluation until PD by RECIST v1.1, if the patients' condition allows. If not, patients will be followed for OS without radiographic evaluation upon the discussion with the Sponsor's Medical Monitor.

The overall responses will be categorized as Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD), or Not Evaluable (NE). At each on-treatment tumor assessment time point, the objective response status will be determined. In the context of the statistical analysis for this trial, objective response determination and the assessment of best overall response (BOR) will be defined using RECIST v1.1.

Survival Assessments:

After discontinuation of treatment, patients will be followed for survival via telephone or other electronic contact at approximately 12-week (± 1 week) intervals after the EOTV (or, if no EOTV is conducted, after the decision to end treatment) until LTFU, withdrawal of consent, or death, or until 36 weeks after the last patient's EOTV. Prior to the database lock for final OS analysis, all current survival data will be requested regardless of interval from the prior assessment to collect the most up-to-date survival information for the final OS analysis.

Pharmacokinetic Assessments:

Serum concentrations of enoblituzumab, retifanlimab, and tebotelimab will be analyzed using validated assay methods that will be carried out in the Sponsor's designated central laboratory. Analysis of PK data will be carried out using industry standard software. Single and multiple dose PK parameters, including but not limited to C_{max} and C_{trough}, will be derived from serum concentration versus time data. Population PK (PPK) and exposure-response analyses will be conducted, using data from this study alone or combined with data from other studies.

Immunogenicity Assessments:

The generation of anti-drug antibodies (ADA) for enoblituzumab, retifanlimab, and tebotelimab will be monitored using validated analytical methods carried out in the Sponsor's designated central laboratory.

Analysis Populations:

Safety Population: All patients who received at least one dose of any study drug. This population will be used for analyses of safety, PK, pharmacodynamics, and immunogenicity. It will also be used for summary of baseline data and analyses of PFS and OS.

Response Evaluable Population: All patients who received at least one dose of any study drug and had baseline radiographic tumor assessment. This population will be used for summary of tumor assessment data and analyses of responses.

Statistical Methods:

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

Sample Size:

The total sample size is planned to be approximately 80 patients, with approximately 50 and approximately 30 patients in the Retifanlimab and Tebotelimab Cohorts, respectively. The sample size for each cohort is primarily based on providing preliminary estimation of ORR. In the Retifanlimab Cohort, 50 patients will distinguish a favorable true ORR of 36% from an unfavorable rate of 19% with 91% power and a 1-sided type 1 error rate of 0.079. In the Tebotelimab Cohort, 3 responses out of 30 patients will have 80% confidence that the true ORR is > 5%.

Safety:

Adverse events (AEs) will be summarized in tables and in listings. AEs will be summarized by System Organ Class (SOC) and Preferred Term (PT), by relationship to study drugs, and by highest severity. Summaries of laboratory values will display descriptive statistics for numerically quantified labs.

Efficacy:

The primary efficacy endpoint is the Investigator-assessed ORR per RECIST v1.1, defined as the proportion of patients in the response evaluable population who achieve the BOR of CR or PR per RECIST v1.1. The BOR will be categorized as CR, PR, SD, PD, or NE. Number and percent of patients with their BOR will be summarized. The ORR and its 2-sided 95% exact binomial CI will be calculated for each cohort.

DCR and its 2-sided 95% exact binomial CI will be calculated. Kaplan-Meier method will be applied to estimate PFS, DoR, and OS.

2 BACKGROUND INFORMATION

2.1 Disease Background

Head and neck cancer accounts for over 500,000 new cases and nearly 300,000 deaths annually worldwide as of 2012 **(40, 72)**. Treatment options for patients with this disease vary according to the disease setting as well as other clinical characteristics. Patients with localized squamous cell carcinoma of the head and neck (SCCHN; American Joint Committee on Cancer stages I-IVB) are treated with potentially curative therapy using ≥ 1 treatment modality (surgery, radiation therapy, chemotherapy, and biologic therapy). However, many patients' disease recurs; the recurrence rate in early-stage SCCHN is ≈ 10–20% **(90)**, whereas the recurrence rate in locally advanced SCCHN is ≈ 50% with a predominance of locoregional failure **(5, 9, 23)**. Patients with recurrent or metastatic (R/M) SCCHN have a poor prognosis with median overall survival (OS) of under 1 year **(62)**. Thus, there remains a medical need for improved treatment in advanced cases.

This population includes patients whose disease recurred locally or who developed distant metastasis after initial treatment for localized disease and patients with distant metastasis at first presentation. A small percentage of patients with localized recurrence can be treated with curative intent, but the vast majority receive palliative treatment with systemic therapy.

Cancers of the head and neck constitute a collection of tumors that begin in the squamous cells lining the mucosal surfaces of the head and neck, referred to as SCCHN, and are categorized by the area of the head or neck in which they begin: oral cavity, pharynx (includes nasopharynx, oropharynx, and hypopharynx), paranasal sinuses, nasal cavity, and salivary glands. Although cancers originating in the salivary glands are usually classified as part of head and neck cancers, salivary gland cancers can arise from multiple types of cells within a gland and therefore have a heterogeneous histological pathology compared to the other head and neck cancers arising from a squamous cell lining. Therefore, patients with salivary gland cancers will not be evaluated in this planned study.

Infection with human papilloma virus (HPV), specifically the cancer causing type, HPV-16, is considered a risk factor for certain head and neck cancers, particularly oropharyngeal cancers involving the tonsils or the base of the tongue **(20, 39)**. In the US the incidence of oropharyngeal cancers caused by HPV infection is increasing, while the incidence of oropharyngeal cancers related to other causes is falling **(20)**.

2.2 Rationale for Study

The proposed study design will allow the assessment of the efficacy, safety, and tolerability of the combinations of enoblituzumab + retifanlimab and enoblituzumab + tebotelimab in patients with relapsed/metastatic SCCHN not curable by local therapy, with no prior systemic therapy for SCCHN in the recurrent or metastatic setting (with the exception of systemic therapy completed > 6 months prior if given as part of multimodal treatment for locally advanced disease). In this study, the enoblituzumab + retifanlimab combination will be given to programmed death ligand 1 (PD-L1) positive patients, and the enoblituzumab + tebotelimab combination will be given to PD-L1 negative patients.

According to National Comprehensive Cancer Network [NCCN] guidelines, relapsed metastatic PD-L1 positive SCCHN can be treated with single agent pembrolizumab, while PD-L1 negative patients should be treated with pembrolizumab + chemotherapy. However, most patients do not get cured and there is still an unmet need. Previous data for enoblituzumab monotherapy from MacroGenics study CP-MGA271-01 (NCT01391143; see **Section 2.3.2.2**), taken into consideration with results of the KEYNOTE-048 trial (see below in this section), indicate that modulation of B7 homolog 3 (B7-H3) with enoblituzumab might improve the response to programmed cell death protein 1 (PD-1) inhibitors such as retifanlimab, a drug with very similar characteristics to pembrolizumab and nivolumab (see below in this section). Preliminary data on enoblituzumab and other Fc-optimized antibodies (such as margetuximab) suggest elicitation of a coordinated engagement of both the innate and adaptive immune response, which could in turn enhance anti-tumor response. In PD-L1 negative patients chemotherapy toxicity is not trivial, and many patients and practitioners choose not to administer chemotherapy upfront to preserve quality of life. Providing not only PD-L1 inhibition but also lymphocyte-activation gene 3 (LAG-3) inhibition in addition to B7-H3 modulation (i.e., enoblituzumab + tebotelimab) might offer an efficacious therapeutic option to those patients who are not willing or not able to receive cytotoxic chemotherapy.

The simultaneous targeting of PD-1 and B7-H3, and PD-1, LAG-3 and B7-H3 through the described combination strategies is supported by the complementary biology of these three molecules in modulating the immune response against tumor cells **(63)**.

Simultaneous targeting of LAG-3 and PD-L1 with monoclonal antibodies is a promising strategy in a number of solid tumors. Preclinical and early-phase trial data suggest that concomitant inhibition of these pathways works synergistically to reactivate T-cells **(60)**. Notably, a Phase 3 registrational trial of the anti-PD-1 antibody nivolumab (Opdivo®, Bristol-Myers Squibb) and the anti-LAG-3 antibody relatlimab (Bristol-Meyers Squibb) is currently ongoing in patients with advanced melanoma (NCT03470922). Early phase data of this combination shows activity in heavily pretreated patients, particularly in those with positive LAG-3 expression **(6)**.

The simultaneous targeting of B7-H3 and PD-1 through combined enoblituzumab and retifanlimab administration potentially enhances the antitumor response compared to treatment with either molecule alone. The biology of B7-H3 and PD-1 (also called B7-H1) might be complementary in mediating tumor evasion. Enoblituzumab and retifanlimab have the ability to potentially engage adaptive and innate immunity, thus optimizing the anti-cancer response. Non-clinical and clinical observations to date supporting this are summarized below.

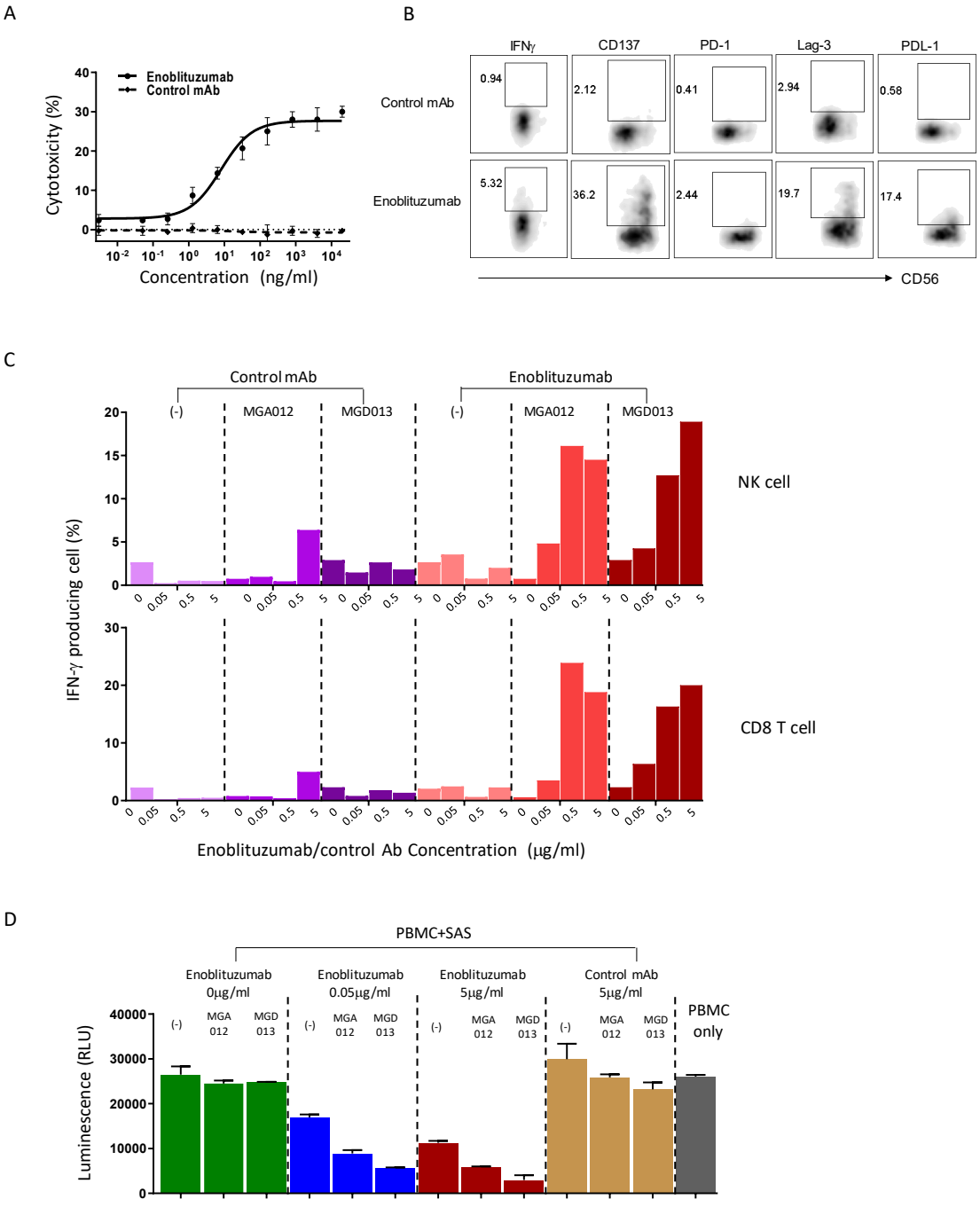
Non-clinical studies have demonstrated that targeting B7-H3 through administration of an anti-B7-H3 antibody mediates anti-tumor activity in syngeneic mouse models including models of melanoma **(50)**, SCCHN **(52)**, pancreatic cancer and lung cancer **(87)**. The anti-tumor activity supported by anti-B7-H3 in these immune competent models appears dependent on immune mechanisms distinct from those mediated by PD-1 pathway blockade with dependence on natural killer (NK)-cells and CD8 T-cell infiltration **(50, 87)**. Consistent with distinct mechanisms of immune-mediated tumor evasion, combined blockade of B7-H3 and PD-1 through administration of anti-B7-H3 with either an anti-PD1 monoclonal antibody

(mAb) **(50)** or anti-PD-L1 mAb **(87)** provides more robust mouse tumor control than treatment with anti-B7-H3 or mAbs targeting the PD-1 axis alone.

Clinically, it is well documented that therapeutic antibody blockade of the PD-1/PD-L1 checkpoint pathway overcomes T-cell exhaustion resulting in anti-tumor responses; these responses however appear limited to CD8 T-cell infiltrated tumors **(82)**. While preliminary, immunohistochemistry (IHC) analyses of post-treatment prostate cancer biopsies revealed that enoblituzumab (anti-B7-H3 mAb) mediates an increase in tumor T-cell infiltrate **(71)**, providing a potential complementary immune mediated mechanism to overcome limitations to PD-1 intervention. Examination of peripheral T-cell receptor (TCR) repertoire demonstrates that administration of enoblituzumab also enhances peripheral T-cell clonality and clone abundance **(61)**. While it is unclear whether this clonal expansion is also occurring in tumors, it is notable that PD-1 inhibitors have been reported to be more effective against tumors bearing increased tumor T-cell clonality, providing a possible additional mechanism by which enoblituzumab could enhance anti-PD-1 therapeutic response **(4, 45, 59)**. The potential for B7-H3 targeting to overcome limitation to PD-1 blockade is also supported by the apparent inverse relationship of B7-H3 tumor expression and response to PD-1 inhibitors observed in a cohort of non-small-cell lung cancer (NSCLC) patients, where it has been demonstrated that responses to anti-PD-1 therapy are statistically greater in patients absent B7-H3 tumor expression **(87)**.

In addition to its potential T-cell modulatory properties, enoblituzumab is an Fc-enhanced monoclonal antibody modified to increase its Fc stimulatory activity by virtue of increased affinity for the activating receptor CD16A and reduced affinity for the inhibitory receptor CD32B **(51)**. Biologically this supports enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) directed against B7-H3 expressing tumor cells, which has been demonstrated in vitro (**Section 2.3.2.1**) and has yielded enhanced anti-tumor activity in mouse xenograft models **(51)**. As shown in **Figure 1**, enoblituzumab mediated ADCC activity (in this example directed against a B7-H3 expressing head and neck cancer cell line) is accompanied with increased interferon (IFN)-γ expression and the upregulation of both co-stimulatory and co-inhibitory molecules, including CD137, LAG-3, and PDL-1 (**Figure 1**, panels A and B). Notably, combination of enoblituzumab with retifanlimab (anti-PD-1) or tebotelimab (PD-1 x LAG-3 bispecific DART molecule) sustained the ability of NK cells and CD8 T cells from peripheral blood mononuclear cells (PBMC) co-cultured with tumor cells to produce IFN-γ upon re-stimulation (**Figure 1**, panel C). Furthermore, both retifanlimab and tebotelimab enhanced enoblituzumab dependent cytotoxicity targeting B7-H3 expressing tumor cells (**Figure 1**, panel D). These in vitro data suggest that both retifanlimab and tebotelimab have potential to sustain enoblituzumab-mediated immune activation and anti-tumor activity.

Figure 1 **Retifanlimab and Tebotelimab Sustain Enoblituzumab Mediated Immune Activation in Vitro**



Retifanlimab (MGA012 or INCMGA00012) and tebotelimab (MGD013) sustain enoblituzumab mediated immune activation in vitro. Enoblituzumab mediated a dose dependent ADCC targeting SAS (B7-H3 expressing head and neck cancer cell line) at E:T ratio of 30:1 (A), and upregulation of costimulatory and co-inhibitory molecules on NK cells from PBMCs co-cultured with SAS cells (B). The values in fluorescence activated cell sorting (FACS) plots represent the percent of positive cells within NK cell (CD3-CD56+) gate. (C, D) Both retifanlimab and tebotelimab promote the sustained enoblituzumab dependent immune activation. PBMCs were co-cultured with SAS tumor cells in the presence of

enoblituzumab alone, or in combination with retifanlimab or tebotelimab for 6 days. (C) Cells were collected and re-stimulated with PMA/Ionomycin in the presence of Golgistop. Levels of NK cell and CD8 cell specific intracellular IFN-γ were measured by FACS. (D) Alternatively, cells were collected and used as effector cells to measure the cytotoxicity targeting B7-H3 expressing tumor cell line (NCI H1975-luc) at E:T ratio of 15:1. The loss of luminescence signal was used to measure the target cell lysis.

The potentially coordinated engagement of innate and adaptive immune responses is related to the polymorphisms observed in the Fcγ receptors (FcγR). CD16A and CD32A are activating receptors with ITAM signaling motifs. CD32B is an inhibitory receptor with an ITIM signaling motif. CD16 is GPI-linked decoy receptor homologous to CD16A. Polymorphisms at position 158 of CD16A and position 131 of CD32A influence their Fc binding properties. Homozygotes for the high-binding alleles of these receptors occur in a minority of the population (~15% in USA and Europe). Improved responses of breast cancer patients to trastuzumab are associated with homozygosity for CD16A-158V and, to a lesser extent, homozygosity for CD32A-131H **(57)**.

Monocytes, macrophages, and dendritic cells (DC) express all 3 FcγRs, while other circulating blood cells express a more limited repertoire of receptors. NK cells express only CD16A. Neutrophils express CD32A and CD16B, a GPI-linked decoy receptor homologous to CD16A. Platelets express CD32A, while B cells express only CD32B. Several pieces of evidence suggest that all these blood elements contribute to the antitumor activity of antibodies. An important role, however, is exerted by monocytes and macrophages, as indicated by experimental evidence in the mouse **(83)**. Because these cells express the inhibitory receptor, these data support the notion that CD32B negatively impacts the in vivo therapeutic activity of monoclonal antibodies **(24)**.

There is evidence that tumor cell breakdown components may be delivered by therapeutic antibodies to antigen-presenting cells. Antigen delivery via immune complexes that bind both activating and inhibitory receptors has limited immune activating properties compared with delivery under condition of CD32B blockade **(13, 30, 31)**. Therefore, exploitation of this phenomenon by Fc optimization may further contribute to the ability of immunotherapy to break tolerance in cancer and induce an adaptive response. Enoblituzumab comprises an engineered human immunoglobulin G1 (IgG1) fragment crystallizable (Fc) domain that imparts increased affinity for the human activating Fcγ receptor (FcγR) IIIA (CD16A) and decreased affinity for the human inhibitory FcγRIIB (CD32B) **(74, 75)**. The engineered Fc domain imparted enoblituzumab with enhanced tumor-specific antibody-dependent cell cytotoxicity.

When enoblituzumab is combined with single checkpoint blockade using anti-PD-1 antibody, both innate and adaptive immunity appear to mediate antitumor activity that substantially exceeds historical experience with either therapy alone. Enhanced ADCC activity and engagement with FcγRIII on antigen presenting cells may also result in increased tumor antigen presentation and an improved adaptive immune response. Furthermore, as shown above (**Figure 1**), retifanlimab (anti-PD-1 mAb) or tebotelimab (PD-1 x LAG-3 DART molecule) can sustain enoblituzumab mediated NK-cell and CD8 T-cell activation and NK cell mediated anti-tumor cell cytolytic activity.

Preliminary clinical data evaluating the combination of tebotelimab and margetuximab (Fc-optimized anti-HER2 antibody containing an identical Fc region to enoblituzumab) in the Phase 1 CP-MGD013-01 (NCT03219268) study suggest that the combination of this Fc-optimized mAb with tebotelimab has acceptable tolerability, with early signs of activity. Notably PD-L1 expression in archival tumor biopsies collected was low (combined positive score [CPS] ≤ 1) in all patients responding to Fc-optimized margetuximab in combination with tebotelimab. Taken together these observations support the concept of evaluating enoblituzumab in combination with tebotelimab in PD-L1 negative SCCHN patients.

The Phase 1 CP-MGA271-03 (NCT02475213) clinical study, evaluating enoblituzumab in combination with pembrolizumab in patients with advanced B7-H3-expressing solid tumors, has provided clinical data demonstrating an acceptable safety profile and significant efficacy, including long-term responses, in patients with PD-1-naïve SCCHN and NSCLC. In addition, this trial has provided data demonstrating that the safety and tolerability profile of enoblituzumab in combination with retifanlimab is highly comparable to the data yielded by the combination of pembrolizumab and enoblituzumab. Summaries of clinical safety and efficacy in CP-MGA271-03 are included in **Section 2.3.2.2**.

The Phase 1 INCMGA 0012-101 (NCT03059823) clinical study, evaluating retifanlimab (INCMGA00012) in patients with advanced solid tumors, has provided clinical data demonstrating an acceptable safety profile and is comparable to other anti-PD-1 molecules, including pembrolizumab and nivolumab. Retifanlimab has been administered to approximately 200 patients in the ongoing trial, and data to date has demonstrated evidence of antitumor activity in several different tumor types, and an acceptable safety profile. See **Section 2.3.3.2** for further details regarding the clinical experience with retifanlimab. Collectively, the evolving experience to date suggests that retifanlimab has comparable binding affinity, functional properties, receptor occupancy, pharmacokinetics (PK), clinical safety and patterns of clinical activity comparable to other anti-PD-1 molecules, including pembrolizumab and nivolumab (see also retifanlimab Investigator Brochure).

First-line treatment of recurrent/metastatic SCCHN has been the combination of platinum chemotherapy, fluorouracil (5-FU), and cetuximab followed by cetuximab maintenance, commonly known as the EXTREME regimen. This regimen is associated with an OS of about 10 months. While EXTREME incurs substantial toxicity, it is tolerable for fit patients. Immunotherapy with PD-1 inhibitors nivolumab and pembrolizumab has recently become standard of care for recurrent/metastatic disease after failure on platinum-based therapy based on durable responses, improved survival, favorable toxicity profile, and improved quality of life.

The randomized Phase 3 KEYNOTE-048 trial compared first-line pembrolizumab as both monotherapy and in combination with platinum chemotherapy plus 5-FU to the current standard of care (EXTREME) in patients with recurrent/metastatic SCCHN **(16, 65)**. Patients were randomized (1:1:1) to receive one of the following treatments: pembrolizumab as a single agent; pembrolizumab, carboplatin or cisplatin, and FU (pembrolizumab + platinum + 5-FU); or cetuximab, carboplatin or cisplatin, and FU (EXTREME). Randomization was stratified by tumor PD-L1 expression (Tumor Proportion Score [TPS] ≥ 50% or < 50%), HPV status according to p16 IHC (positive or negative), and ECOG PS (0 vs. 1). PD-L1 expression

(TPS and CPS) was determined using the PD-L1 IHC 22C3 pharmDx kit. Overall survival (OS), sequentially tested in the subgroup of patients with CPS ≥ 20 SCCHN, the subgroup of patients with CPS ≥ 1 SCCHN and the overall population, was the major efficacy measure.

Pembrolizumab + platinum + 5-FU significantly improved OS vs. EXTREME in the CPS ≥ 20 (hazard ratio [HR] 0.60, 95% confidence interval [CI] 0.45-0.82, p = .0004; median 14.7 vs. 11.0 months) and CPS ≥ 1 (HR 0.65, 95% CI 0.53-0.80, p < .0001; median 13.6 vs. 10.4 months) populations. HR (95% CI) for progression free survival (PFS) was 0.76 (0.58-1.01) for CPS ≥ 20 and 0.84 (0.69-1.02) for CPS ≥ 1. Objective response rate (ORR) (pembrolizumab + platinum + 5-FU vs. EXTREME) was 42.9% vs. 38.2% for CPS ≥ 20 and 36.4% vs. 35.7% for CPS ≥ 1; median duration of response (DoR) was 7.1 vs. 4.2 months and 6.7 vs. 4.3 months, respectively. Pembrolizumab did not significantly improve OS vs. EXTREME in the total population (HR 0.83, 95% CI 0.70-0.99, p = .0199; median 11.5 vs. 10.7 months). HR (95% CI) for PFS was 1.29 (1.09-1.53). ORR (pembrolizumab vs. EXTREME) was 16.9% vs. 36.0%; median DoR was 22.6 vs. 4.5 months. Pembrolizumab monotherapy significantly improved OS vs. EXTREME in the CPS ≥ 1 population (HR 0.78, 95% CI 0.64-0.96, p=.0086; median 12.3 vs. 10.3 months; HR (95% CI) for PFS was 1.16 (0.96-1.39), median 3.2 vs. 5.0 months; ORR was 19% vs. 35%, median DoR 23.4 vs. 4.5 months. ORR in pembrolizumab monotherapy for CPS < 1 was 5%.

All-cause Grade 3-5 adverse event (AE) rates were 54.7% for pembrolizumab, 85.1% for pembrolizumab + platinum + 5-FU, and 83.3% for EXTREME. The most common adverse reactions reported in ≥ 20% of patients who received pembrolizumab in combination with chemotherapy in KEYNOTE-048 were nausea, fatigue, constipation, vomiting, mucosal inflammation, diarrhea, decreased appetite, stomatitis, and cough.

Based on these results, pembrolizumab was approved for use in combination with platinum and FU for all patients and as a single agent for patients whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test.

2.3 Background on Study Drugs

2.3.1 Background on Study Drug Targets

2.3.1.1 Background on B7-H3

The B7 family of cell surface molecules consists of structurally related protein ligands that bind to receptors on lymphocytes and regulate immune responses. Activation of T and B lymphocytes is initiated by engagement of antigen-specific receptors, T cell antigen receptor (TcR) and membrane-bound immunoglobulin (mIg) respectively, but additional signals delivered simultaneously to members of the CD28 family of receptors by B7 ligands determine the ultimate immune response **(26)**. B7 homolog 3 (B7-H3) is a novel member of the B7 family. B7-H3 has been implicated in the delivery of both co-stimulatory and co-inhibitory signals **(44)**. The apparent contrasting activities of B7-H3 may be attributed to multiple factors. While the murine B7-H3 molecule exists as a 2-Ig form, the human counterpart has undergone gene duplication and exists primarily as a 4-Ig molecule **(77)**.

Further, as with other members of the B7 family, B7-H3 may bind, on different cells, to multiple receptors that remain to be identified.

B7-H3 is an attractive target for tumor immunotherapy without regard to its immunological properties. Tissue expression studies have demonstrated that B7-H3 protein is not expressed in most normal tissues, rather its expression is inducible on certain antigen presenting cells **(19, 78)** and vasculature, exists on certain endocrine tissues (most notably in the cytoplasm of epithelial cells of the adrenal cortex), and is over-expressed in a wide range of cancers (including cultured cancer stem-like cells). B7-H3 is broadly over-expressed on many malignant neoplasms, including SCCHN (MacroGenics unpublished observation); bladder cancer **(11)**; prostate cancer **(21, 81, 88)**, where expression of B7-H3 is associated with metastatic behavior and poor outcome; renal cell carcinoma **(28)**, where B7-H3 is broadly expressed in tumor vasculature; ovarian cancer **(89)**; colorectal cancer **(78)**; gastric cancer **(86)**; non-small cell lung cancer **(68, 79)** (MacroGenics unpublished observation); glioblastoma **(56)**; melanoma (MacroGenics unpublished observation); and certain small round blue cell tumors of childhood, including neuroblastoma and rhabdomyosarcoma **(18, 41)**.

B7-H3 has also been found to be expressed on a high percentage of SCCHN tumors (**enoblituzumab Investigator's Brochure**) **(46, 58)**. Based on IHC evaluation of SCCHN patient samples enrolled in the clinical program to date and complemented by an evaluation of SCCHN samples obtained outside the clinical program, MacroGenics has observed a B7-H3 positivity rate of 90.3% (65/72). Furthermore, independent published studies evaluating primary tumor tissue samples obtained from either 165 SCCHN patients **(52)** or 37 hypopharyngeal squamous cell carcinoma (SCC) patients **(46)** revealed a high percentage of B7-H3 positive specimens by IHC. In addition to the high percentage of SCCHN tumors expressing membranous B7-H3, the level of B7-H3 expression as determined by IHC staining on the tumor was inversely correlated with the number of tumor infiltrating CD8 + T-cells **(46)** and directly proportional to the development of distal metastases and decreased survival **(46, 52)**.

2.3.1.2 Background on PD-1

PD-1 is an immune-modulatory receptor expressed on activated T-cells. The physiological role of PD-1 is to limit the inflammatory response to infection and prevent autoimmunity by limiting the activity of T cells in the periphery **(8, 36, 47)**.

The basis for this physiology is that the ligands for PD-1, namely PD-L1 (B7-H1) and PD-L2 (B7-DC), are up-regulated on many cell types — hematopoietic, endothelial, and epithelial — in response to pro-inflammatory cytokines, notably interferon gamma. In addition, B7-DC/programmed death ligand 2 (PD-L2) is up-regulated on dendritic cells and macrophages in response to different pro-inflammatory cytokines such as IL-4 **(76, 85)**.

To avoid antitumor response, cancer cells co-opt the normal physiology of the PD-1 pathway used to prevent collateral normal tissue damage that would occur in an unchecked inflammatory immune response. Expression of B7-H1/ PD-L1 as an adaptive response to

antitumor immunity likely occurs because this ligand is induced on most epithelial cancers in response to interferon-gamma, similarly to epithelial and stromal cells in normal tissues **(81)**.

In addition, PD-1 is highly expressed on induced regulatory T-cells (T-regs), and PD-1: PD-L1 interactions appear to promote the induction, conversion and maintenance of T-regs, suggesting an additional mechanism for immunosuppression in a tumor microenvironment rich in PD-1 ligands **(3, 35)**.

Monoclonal antibodies targeting the T-cell immune checkpoint inhibitors PD-1 and PD-L1 have recently demonstrated antitumor activity in patients with advanced SCCHN. Pembrolizumab was evaluated in a cohort of 60 patients with both HPV-positive and HPV-negative SCCHN **(70)**. Of the 56 evaluable patients, 51% had a reduction in tumor volume, with 19.6% having either a partial response (PR) or complete response (CR) that was equally distributed between the HPV-positive and negative patients. In addition, MEDI4736, a humanized monoclonal antibody targeting PD-L1, demonstrated a 32% objective response rate (ORR) in a cohort of 22 patients with advanced SCCHN **(69)**.

More recently, pembrolizumab was approved for use in the US in combination with platinum and fluorouracil (FU) for all patients, and as a single agent for patients whose tumors express PD-L1 (Combined Positive Score [CPS] ≥ 1) as determined by an FDA-approved test. Approval was based on KEYNOTE-048, a randomized, multicenter, 3-arm, open-label, active-controlled trial conducted in 882 patients with metastatic SCCHN, who had not previously received systemic therapy for metastatic disease, or with recurrent disease who were considered incurable by local therapies **(65)**. Overall, KEYNOTE-048 showed that compared with the combination of platinum chemotherapy, 5-FU, and cetuximab followed by cetuximab maintenance (commonly known as the EXTREME regimen), pembrolizumab + platinum + 5-FU had superior OS in the PD-L1 CPS ≥ 20, CPS ≥ 1, and total populations with comparable safety, and pembrolizumab had superior OS in the CPS ≥ 20 and ≥ 1 populations, noninferior OS in the total population, and favorable safety. These results support pembrolizumab and pembrolizumab + platinum + 5-FU as new first line standards of care for R/M SCCHN in the US.

2.3.1.3 Background on LAG-3

In addition to PD-1, another immune checkpoint molecule of growing interest is lymphocyte-activation gene 3 (LAG-3), a membrane protein that belongs to the immunoglobulin (Ig) superfamily and binds to major histocompatibility complex class II (MHC-II). LAG-3 engagement enhances regulatory T-cell activity and negatively regulates T-cell proliferation and differentiation **(7)**. LAG-3 has been shown to be expressed on dysfunctional, “exhausted” T cells and is a marker for regulatory T cells, suggesting an immune suppressive role **(73)**. Blockade of PD-1 and LAG-3 in animal tumor models generated enhanced antitumor immunity via distinct, nonredundant signaling pathways that fostered the accumulation of functionally competent CD8+ T cells in mice **(42, 85)**.

In gastric cancer (GC), several intrinsic factors, including LAG-3 and PD-1 have been recognized as negative regulatory proteins that block the expansion and suppress the effector function of antigen-specific CD8+ T cells **(80)**. An IHC analysis conducted by the Sponsor of

tumor specimens from 39 SCCHN patients revealed the majority (34/39) contained lymphocyte infiltrates with detectable LAG-3 expression (**Table 1**). LAG-3 is believed to confer poor prognosis in SCCHN, and its blockade may reshape antitumor response **(29)**.

Table 1 LAG-3+ Tumor Infiltrating Lymphocyte Profile Across SCCHN

Any detectable LAG-3$^+$ TIL	Moderate or above LAG-3$^+$ TIL	Heavy LAG-3$^+$ TIL
34/39 (87.2%)	28/39 (71.8%)	22/39 (56.4%)

LAG-3–positive tumor infiltrating lymphocyte prevalence rate determined by IHC analyses across 39 independent SCCHN patient specimens. IHC was performed with anti–LAG-3 antibody EPR4392 (Abcam) using the Ventana Discovery Ultra Platform and the following scoring criteria applied within the area of highest observed density LAG-3 expressing lymphocytes by 40x magnification: negative scoring < 1 LAG-3$^+$ lymphocyte; light: 1-5 LAG-3$^+$ lymphocytes; moderate: 6-15 LAG-3$^+$ lymphocytes; and heavy: > 15 LAG-3$^+$ lymphocytes.

Laboratory studies suggest a role of LAG-3 in squamous cell carcinoma (SCC). Studies on mouse models with SCC derived from injection of tumor cells from SCC have shown that CD8+ tumor-infiltrating lymphocytes (TILs) exhibit phenotypes of chronic activation and exhaustion, including overexpression of activation markers, co-expression of PD-1 and LAG-3, as well as TCRβ downregulation. Dual blockade of PD-1 and LAG-3 inhibited tumor growth of SCC in these mice **(55)**. Tebotelimab can achieve dual blockade of PD-1 and LAG-3 and may benefit patients with SCC.

2.3.2 Background on Enoblituzumab

2.3.2.1 General Information on Enoblituzumab

Enoblituzumab (also known as MGA271) is a humanized IgG1κ monoclonal antibody (mAb) that binds the B7-H3 immunoligand with high affinity **(51)**. The antibody has been engineered to have enhanced binding to the activating FcγR, CD16A, and especially the low affinity allele of CD16A, CD16A-158F. The rationale for the incorporation of an engineered Fc domain in enoblituzumab stems from observations that the clinical outcome of immunotherapy with rituximab **(17, 24, 67)**, cetuximab **(10)** and trastuzumab **(57)** can be predicted by the FcγR polymorphic variant expressed on the patient's immune cells. Patients homozygous for the high-binding alleles of CD16A (158 V/V) or CD32A (131 H/H) demonstrate improved survival as compared to those carrying the low-binding alleles (131-F and 131-R carriers). Although homozygosity for either FcγR allele is an independent predictor of outcome, CD16A polymorphism is by far the stronger factor. These data indicated that FcγR-dependent events, such as ADCC, play an important role in the mechanisms of action for these monoclonal antibodies.

Only approximately 15% of the patients are homozygous for the high-binding allele of CD16A; therefore, the Fc domain of enoblituzumab has been engineered to enhance the affinity for either CD16A allele but preferentially the low-binding form in order to enhance the overall activity and expand the benefit to the entire patient population. This approach has

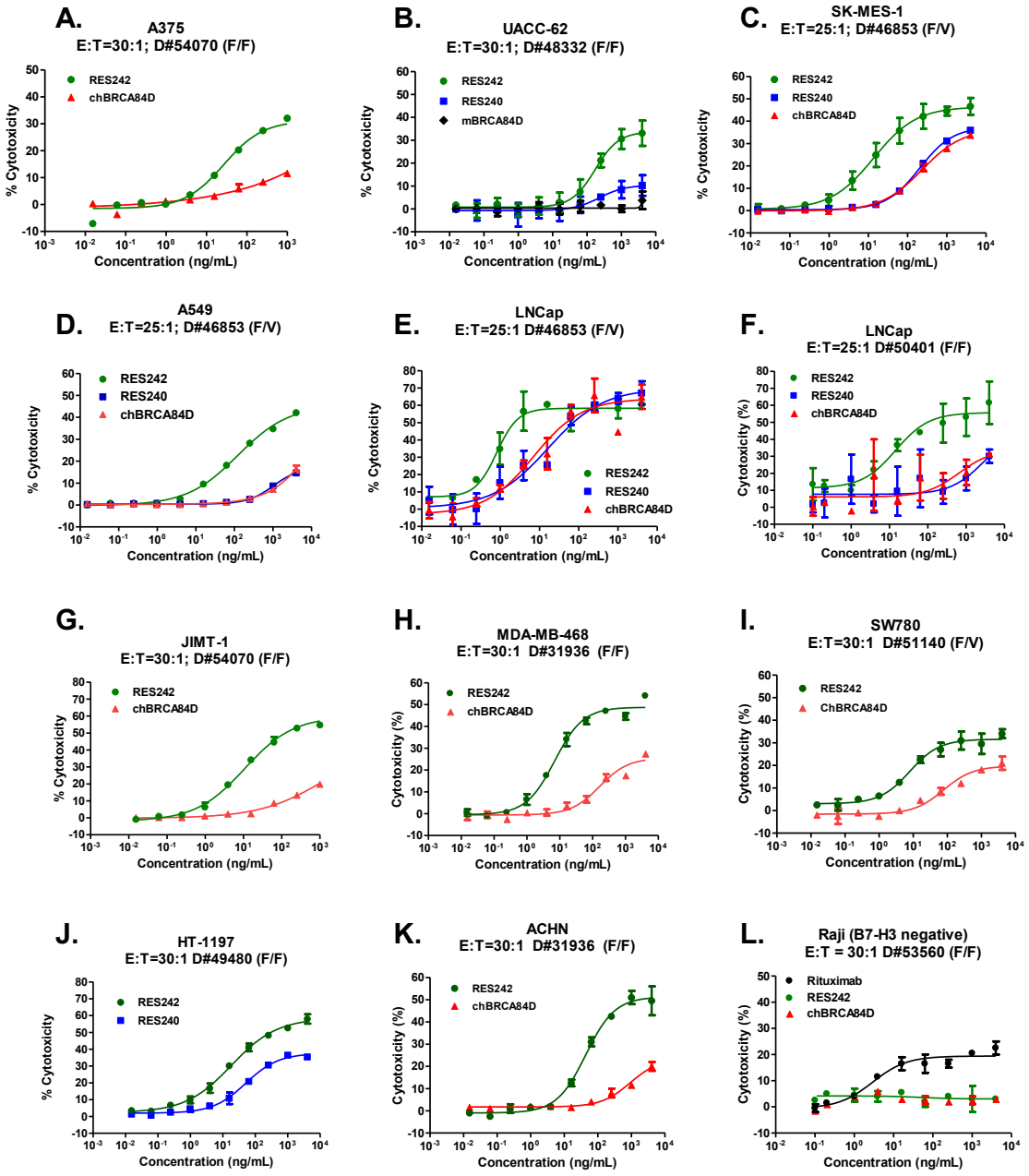
resulted in enhanced tumor-specific ADCC in vitro (including activity against low-antigen density expressing cells) and improved anti-tumor activity in mice with a variety of cancer-specific human IgG1 mAb, including enoblituzumab. Since most patients carry the low-affinity allele of CD16A, the enhanced binding of the Fc-optimized version is expected to impart binding improvement that benefits the whole patient population, not just those patients who are homozygous for the high-binding allele of CD16A (valine/valine [V/V] genotype, approximately 15% of the population). Enoblituzumab Fc domain also exhibits reduced binding to the low-affinity inhibitory receptor, CD32B, a property that is expected to further enhance its anti-tumor activity based on evidence of improved responses to human IgG1 immunotherapy in CD32B-deficient mice **(24)**.

ADCC has been shown to be an important mechanism of action for several monoclonal antibodies, including rituximab **(24, 84)** and trastuzumab **(24, 57)** and is likely an important mechanism of action for enoblituzumab.

The ability of enoblituzumab to mediate ADCC activity was evaluated across multiple cancer types expressing varying levels of B7-H3 as determined by flow cytometry. The cancer types tested included: melanoma (A375, UACC-62), lung cancer (SK-MES-1, A549), prostate cancer (LnCAP), breast cancer (JIMT-1, MDA-MB-468), bladder cancer (SW780, HT-1197), and renal cancer (ACHN) cell lines **(51)**.

Enoblituzumab mediated ADCC activity against all tumor lines that express B7-H3 at detectable levels. Furthermore, enoblituzumab showed enhanced ADCC potency compared to the related version of the antibody with wild type Fc domains, chBRCA84D or RES240, against all the tumor cell lines examined (see **Figure 2**). Consistent with the studies described above, the greatest enhancement in ADCC activity against the B7-H3 expressing prostate cancer cell line LnCAP was observed with effector populations obtained from individuals homozygous for the weak binding allele of CD16A (phenylalanine/phenylalanine [F/F]). In contrast, enoblituzumab did not mediate ADCC against Raji B-cell lymphoma cells, which do not express detectable cell surface B7-H3.

Figure 2 **Enoblituzumab (RES242) Mediates ADCC Activity Across a Spectrum of Cancer Types**



The ability of enoblituzumab (referred to as RES242 in the figure keys) to mediate ADCC was evaluated on B7-H3 positive melanoma (A&B), lung (C&D), prostate (E&F), breast (G&H), bladder (I&J), and renal cancer (K) cell lines, as well as the B7-H3 negative Raji B cell lymphoma line (L). Enoblituzumab activity was compared to the indicated control molecules: humanized BRCA84D (hBRCA84D); chimeric BRCA84D (chBRCA84D), and mouse BRCA84D (mBRCA84D). Resting human PBMC from independent healthy donor were utilized and the effector cell to target cell (E:T) ratio is indicated in each panel. The percent cytotoxicity, as determined by lactate dehydrogenase (LDH) release, was calculated.

A series of in vivo xenograft tumor efficacy studies were conducted to identify tumor cell lines that are sensitive to enoblituzumab as a single agent, establish dose response profiles for the antitumor activity of enoblituzumab, and identify cancer types that exhibit sensitivity to enoblituzumab. Weekly intravenous (IV) administration of enoblituzumab resulted in significant inhibition of growth of a variety of human tumor xenografts representing bladder, gastric, lung, melanoma, prostate, and kidney cancer. Enoblituzumab exhibited antitumor activity when administered approximately 1 week after tumor cell implantation or after tumors were allowed to become fully established (approximately 3 weeks after implantation when tumors were ~300 mm^3 in volume). See **enoblituzumab Investigator's Brochure** for additional details.

2.3.2.2 Clinical Trial Experience with Enoblituzumab

Enoblituzumab is currently being evaluated in patients with cancer in 4 (1 ongoing fully enrolled, and 3 completed), Phase 1, MacroGenics-sponsored clinical studies. Clinical trial experience is presented for enoblituzumab + pembrolizumab combination therapy, and enoblituzumab + retifanlimab combination therapy, for study CP-MGA271-03 **(1)**, and enoblituzumab monotherapy for study CP-MGA271-01 (NCT01391143). Data from the remaining 2 studies are not included, as 1 explores enoblituzumab treatment in a pediatric population and the other explores combination enoblituzumab and ipilimumab treatment.

Safety of Enoblituzumab

Safety data are available for 133 patients exposed to enoblituzumab + pembrolizumab in ongoing study CP-MGA271-03 (as of the cut-off date of 13 April 2020), and for 179 patients exposed to enoblituzumab in completed study CP-MGA271-01. In addition, safety data are available for 12 patients exposed to enoblituzumab + retifanlimab in ongoing study CP-MGA271-03 (as of the cut-off date of 13 April 2020). A discussion of safety for each study is presented below.

Study CP-MGA271-03 – Enoblituzumab + Pembrolizumab Combination Therapy

This open-label study is evaluating the safety, tolerability, dose limiting toxicities (DLTs), and maximum tolerated dose (MTD) or maximum administered dose (MAD) of enoblituzumab (3, 10, or 15 mg/kg) administered IV weekly (QW) in combination with 2 mg/kg pembrolizumab administered IV every 3 weeks (Q3W) to patients with unresectable, locally advanced, or metastatic melanoma, SCCHN, NSCLC, urothelial cancer, and other cancers. Enrollment in the enoblituzumab + pembrolizumab cohorts is complete (N=133). Patients enrolled in the combination enoblituzumab and pembrolizumab dose escalation and expansion cohorts have completed combination treatment; no MTD was defined.

Adverse events irrespective of grade and considered related to enoblituzumab + pembrolizumab treatment were reported in 117 patients (88.0%). The most common treatment-related adverse events (TRAEs) reported in ≥ 5% of patients exposed to enoblituzumab + pembrolizumab in decreasing order of frequency were as follows: infusion related reaction (IRR, 55.6%); fatigue (27.8%); nausea (9.8%); pyrexia (9.0%); lipase increased (8.3%); arthralgia (7.5%); events of diarrhea, hypothyroidism, rash maculo-papular,

and decreased appetite, pneumonitis (6.8%, each); lymphocyte count decreased (6.0%); and events of chills, anemia, and pruritus (5.3% each). Greater than or equal to Grade 3 TRAEs were reported in 38 patients (28.6%). Of these, the most commonly reported in ≥ 5% of patients were IRR (7.5%) and lipase increased (6.0%). The majority of ≥ Grade 3 AEs of lipase increased were isolated, reversible, and asymptomatic. The majority of IRR were Grade 1 or 2 in severity. Observed IRR to date have been manageable and have resolved without sequelae. Patients who experienced Grade 3 IRR have fully recovered following brief interruption in dosing and after receiving treatment based upon symptomatology. Typically, these IRR occurred only with the first dose of enoblituzumab and did not recur with subsequent dosing.

Twenty-three patients (17.3%) experienced serious adverse events (SAEs) considered related to enoblituzumab + pembrolizumab; for the majority of these patients (20/23, 87%), the events were ≤ Grade 3 in severity. The most common SAEs considered related were IRR (7.5%) and pneumonitis (4.5%). Fourteen patients (10.5%) experienced at least 1 ≥ Grade 3 SAE that was considered related to enoblituzumab + pembrolizumab; with the exception of IRR (7 patients, 5.3%) and pneumonitis (3 patients, 2.3%), the events were singularly reported.

Myocarditis and pneumonitis have been identified as important potential risks associated with enoblituzumab/pembrolizumab combination treatment. The cumulative safety data reviewed to date suggest the combination with enoblituzumab does not increase the risk of myocarditis or pneumonitis compared to anti-PD-1 inhibitors alone. Notably, both important potential risks are recognized, yet rare, adverse effects associated with the administration of PD-1 inhibitors. Furthermore, pneumonitis and myocarditis have not been observed in MacroGenics-sponsored monotherapy trials of enoblituzumab to date.

Study CP-MGA271-03 – Enoblituzumab + Retifanlimab Combination Therapy

This open-label study is evaluating the safety, tolerability, and DLT of 15 mg/kg enoblituzumab in combination with a flat dose of 375 mg of retifanlimab, each administered IV Q3W. Enrollment in the enoblituzumab + retifanlimab cohort is complete (N=12).

Adverse events irrespective of grade and considered related to enoblituzumab + retifanlimab treatment were reported in 10 (83.3%) patients. The most common TRAE reported in patients exposed to enoblituzumab + retifanlimab was IRR (50.0%). The remaining TRAEs of anemia, contusion, dysgeusia, eye irritation, fatigue, granulomatous lymphadenitis, influenza like illness, lipase increased, nausea, pruritus, pyrexia, rash maculo-papular, tumor pain, and weight increased were each reported in 1 (8.3%) patient.

Greater than or equal to Grade 3 TRAEs were reported in 2 (16.7%) patients: granulomatous lymphadenitis, IRR, lipase increased, and weight increased, each in 1 (8.3%) patient, all of which were Grade 3. The majority of IRR were Grade 1 or 2 in severity, manageable, and resolved without sequelae. For the 1 patient with Grade 3 IRR, the event, was manageable and resolved within 2 days. IRR occurred only with the first dose of enoblituzumab and did not recur with subsequent dosing. One (8.3%) patient experienced SAEs considered related to

enoblituzumab + retifanlimab. These SAEs (granulomatous lymphadenitis and IRR) were both Grade 3 in severity.

Study CP-MGA271-01 – Enoblituzumab Monotherapy

This Phase 1, open-label study evaluated the safety, tolerability, DLTs, and MTD or MAD of enoblituzumab (from 0.01 to 15 mg/kg) administered IV QW to patients with unresectable or metastatic B7-H3-expressing neoplasms or neoplasms whose vasculature expresses B7-H3 for whom no standard therapy is available.

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

Eleven patients (6.1%) experienced SAEs considered related to enoblituzumab treatment. The most common SAEs considered related were IRR (6, 3.4%) and pyrexia (2, 1.1%). The SAEs considered related to enoblituzumab treatment were generally mild (Grade 1) or moderate (Grade 2) in severity; few patients (5, 2.8%) experienced at least 1 ≥ Grade 3 SAE considered to be related, with the most commonly reported as IRR (1.7%).

Overall, enoblituzumab administration as a monotherapy was generally well tolerated, with IRR reactions, typically mild or moderate, being the primary safety concern. No MTD was identified, and the MAD was 15 mg/kg. Observed IRR were manageable, resolving without sequelae. Patients who experienced Grade 3 IRR fully recovered following brief interruption in dosing and after receiving treatment based upon symptomatology. Typically, these IRR occurred only with the first dose of enoblituzumab and did not recur with subsequent dosing.

Safety Summary

In conclusion, the data from the clinical studies CP-MGA271-03 and CP-MGA271-01 suggest that enoblituzumab, at doses up to 15 mg/kg combined with 2 mg/kg pembrolizumab weekly by IV and enoblituzumab monotherapy at doses up to 15 mg/kg administered weekly by IV, is generally well tolerated with toxicities manageable by standard medical therapy for patients with advanced cancer. See current **enoblituzumab Investigator's Brochure** for more detailed safety information. In addition, the safety and tolerability profile of 15 mg/kg enoblituzumab in combination with a flat dose of 375 mg of retifanlimab, each administered IV Q3W, is highly comparable to the data yielded by enoblituzumab monotherapy.

Efficacy of Enoblituzumab

Study CP-MGA271-03 – Enoblituzumab + Pembrolizumab Combination Therapy

Objective efficacy responses have been observed in study CP-MGA271-03 in the following expansion cohorts, receiving enoblituzumab in combination with pembrolizumab:

- melanoma (post PD-1/PD-L1 inhibitor),
- urothelial cancer (post PD-1/PD-L1 inhibitor),
- SCCHN without prior PD-1/PD-L1 inhibitor, and
- NSCLC with and without prior PD-1/PD-L1 inhibitor. Patients with NSCLC who had no prior PD-1/PD-L1 inhibitor had tumors whose PD-L1 expression level was negative (< 1%).

Durable objective responses were seen in PD-1/PD-L1 inhibitor-naïve SCCHN and NSCLC patients **(1)**. The overall response rate of PD-1/PD-L1 inhibitor-naïve SCCHN patients (post platinum chemotherapy) was 33% (6 of 18 patients) including 1 confirmed complete response and 5 confirmed partial responses. The overall response rate of PD-1/PD-L1 inhibitor-naïve NSCLC patients (PD-L1 < 1%) was 36% with 5/14 PRs. In both instances, the observed response rate for patients treated with the combination of enoblituzumab and pembrolizumab represent increases of 2 to 3-fold over what would be expected in similar patients treated with checkpoint inhibitors alone (**Table 2**).

Table 2 **Enoblituzumab + Pembrolizumab Combination Data in SCCHN and NSCLC**

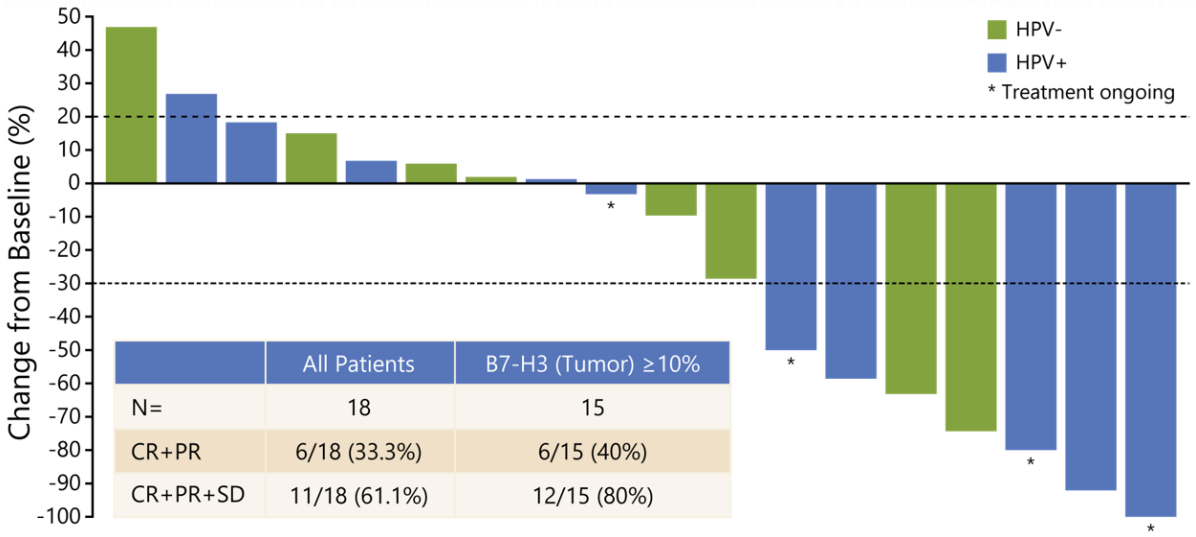
SCCHN	Study Results			
Agent (Study)	Enoblituzumab +Pembrolizumab	Nivolumab (CM-141)[a]	Pembrolizumab (KN-012)[b]	Pembrolizumab (KN-040)[c]
N	18	240	174	247
ORR	33.3%	13%	16%	15%

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

a Ferris et al, 2016 **(34)**.
b Keytruda® package insert **(33)**.
c Cohen et al, 2017 **(25)**.
d Borghaei et al, 2015 **(12)**.
e Brahmer et al. 2015 **(14)**.
f Garon et al. 2015 **(38)**.

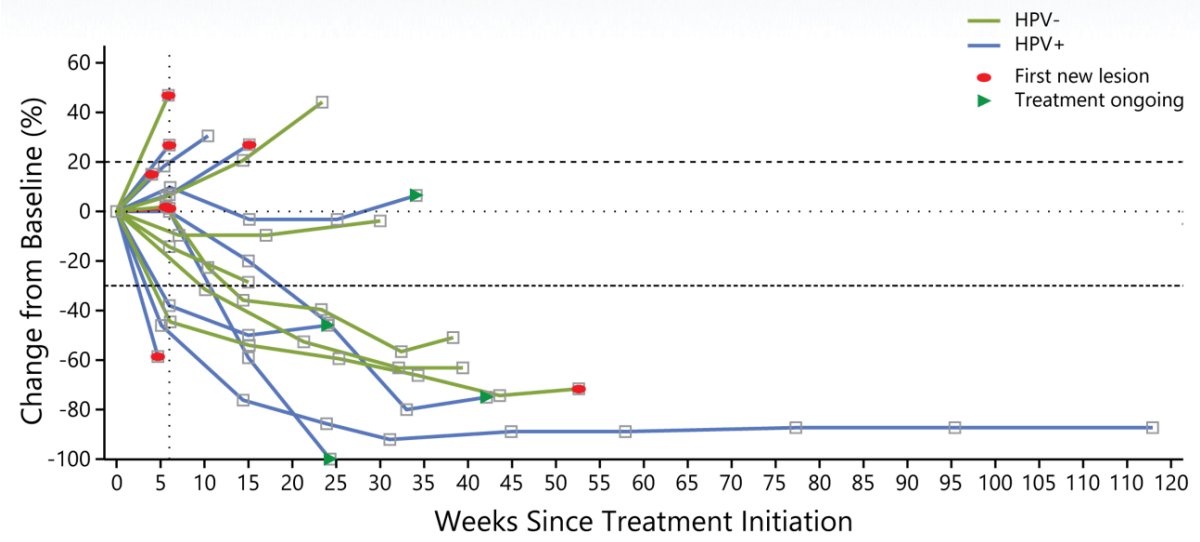
The degree of tumor regression and the durability of objective responses of anti-PD1-naïve SCCHN patients treated on CP-MGA271-03 as of November 2018 are demonstrated on the waterfall and spider plots in **Figure 3** and **Figure 4**, respectively.

Figure 3 **CP-MGA271-03 Anti-PD-1-Naïve SCCHN Waterfall Plot**



Note that the waterfall plot shows target lesions only, while overall patient response is represented in the table.

Figure 4 CP-MGA271-03 Anti-PD-1-Naïve SCCHN Spider Plot



2.3.2.3 Nonclinical Data for Enoblituzumab

A repeat dose Good Laboratory Practice (GLP) toxicology study was conducted in cynomolgus monkeys to determine the potential toxicity and toxicokinetics of enoblituzumab when administered weekly for 4 weeks via IV infusion at doses of 1, 10, 30, or 150 mg/kg and to evaluate recovery from any effects of the enoblituzumab over a dose-free period of at least 8 weeks. In this study, enoblituzumab was well tolerated at all dose levels evaluated. There were no test article-related mortalities and no test article-related changes in clinical observations, food consumption, body weight, clinical pathology parameters, gross pathology, and organ weights. The no observed adverse effect level (NOAEL) was considered to be 150 mg/kg. A detailed summary of pathology, laboratory and IHC findings in the cynomolgus monkeys from the repeat-dose GLP toxicology study can be found in the **enoblituzumab Investigator's Brochure**.

The potential cross reactivity of enoblituzumab with cryosections of normal human tissues was evaluated in the GLP-MGA271-03 study. The observed staining was generally consistent with reported sites of B7-H3 expression. Membrane staining was only present in rare conjunctival epithelium, esophageal epithelium, prostate epithelium, mononuclear cells (including rare Kupffer cells and rare alveolar macrophages), and placental decidual cells. The remainder of the staining in this study was cytoplasmic in nature, and it is unlikely that cytoplasm and cytoplasm structures would be accessible to enoblituzumab following IV administration (**enoblituzumab Investigator's Brochure**).

In IHC studies, enoblituzumab was shown to recognize epithelial elements in the normal human adrenal cortex, and in tissue distribution studies enoblituzumab was found to distribute to the adrenal cortex in cynomolgus monkeys treated with a 150 mg/kg dose. However, no changes in hormone parameters were observed in cynomolgus monkeys treated with enoblituzumab.

A comprehensive immunohistochemical study using the 8H9 antibody (with specificity against B7-H3) was performed in frozen tumors from 330 patients with neuroectodermal, mesenchymal, and epithelial neoplasia; in addition to 15 normal human tissue samples and 8 normal cynomolgus monkey tissue samples. This study clearly shows that the anti B7-H3 antibody 8H9 recognizes this antigen in a tumor-specific manner, with broad distribution across a spectrum of tumors of varying lineage (neuroectodermal, mesenchymal, and epithelial), with restricted expression in normal tissues **(2, 56)**.

2.3.3 Background on Retifanlimab

2.3.3.1 General Information on Retifanlimab

Retifanlimab (also known as INCMGA00012 or MGA012) is a humanized, hinge-stabilized, IgG4κ mAb that recognizes human PD-1. Retifanlimab contains a hinge-stabilized human IgG4 Fc domain to limit effector function, while retaining neonatal FcR (FcRn) binding to extend circulating half-life. Retifanlimab binds to PD-1 expressing cells in a dose-dependent manner. Consistent with its specific binding properties and designed mechanism of action, retifanlimab blocks the binding of the ligands PD-L1 and programmed death ligand 2 (PD-L2) to cell surface-expressed PD-1 in a dose-dependent manner.

2.3.3.2 Clinical Trial Experience with Retifanlimab

Retifanlimab is currently under development as a therapeutic candidate for the treatment of multiple solid tumors, both as a monotherapy and in combination with other agents. As of the data cutoff date of 23 September 2019, 382 unique participants with advanced malignancies have been exposed to retifanlimab as monotherapy (N = 322) or in combination with other agents (epacadostat in 31 participants, INCB050465 [also known as parsaclisib] in 22 participants, and pemigatinib in 7 participants).

Safety of Retifanlimab

Phase 1 (Study INCMGA 0012-101) dose-finding results in participants with advanced solid tumors (N = 37) have been presented **(49)**. Retifanlimab demonstrated acceptable tolerability with no dose-limiting toxicity observed at doses ranging from 1 to 10 mg/kg every 2 weeks (Q2W). Administration every 4 weeks (Q4W) was also studied. A maximum tolerated dose was not reached. A dose of 3 mg/kg Q2W was selected for further expansion in non-small-cell lung carcinoma (NSCLC), endometrial cancer, cervical cancer, and sarcoma cohorts, with subsequent evaluation of flat dosing in tumor-agnostic and microsatellite instability (MSI) high uterine cancer cohorts.

As of 23 September 2019, 230 participants have been exposed to any dose of retifanlimab monotherapy in Study INCMGA0012-101. As of the data cutoff date, 11.7% of participants have received ≥ 1 year of continuous treatment with retifanlimab. Treatment-emergent adverse events (TEAEs) were reported in 212 participants (92.2%). TEAEs reported for ≥ 10% of participants included fatigue, anemia, diarrhea, nausea, and vomiting. The most frequently reported TEAEs (≥ 10%) in the 29 patients receiving the fixed dose of 500 mg Q4W were fatigue, blood alkaline phosphatase increased, anemia, back pain, diarrhea, and rash. Adverse

events of special interest (AESI) included ≥ Grade 2 immune-related adverse events (irAEs), ≥ Grade 3 IRR or cytokine release syndrome (CRS), and abnormal liver enzymes that met the criteria for potential Hy's law (defined as aspartate aminotransferase [AST] and/or alanine aminotransferase [ALT] > 3 × upper limit of normal [ULN] and total bilirubin > 2 × ULN and without any alternate etiology). A total of 32 participants (13.9%) experienced ≥ 1 AESI in Study INCMGA 0012-101. The most common AESI (> 1 participant) were IRR, hypothyroidism, hyperthyroidism, colitis, rash, and diarrhea. There were no fatal irAEs. Further details of clinical data can be found in the retifanlimab Investigator's Brochure.

Efficacy of Retifanlimab

Preliminary efficacy in terms of confirmed response evaluation criteria in solid tumors (RECIST) overall response has been demonstrated in multiple tumor types in Study INCMGA 0012-101, and is consistent with previous experience with other PD-(L)1 inhibitors. Specifically, Investigator-assessed ORR was 17.1% with partial responses observed in 6 of 35 participants in the cervical cancer cohort **(54)**, and Investigator-assessed responses were observed in 6/28 evaluable participants with NSCLC and 4/23 evaluable participants with endometrial cancer **(53)**. Preliminary activity has also been demonstrated against squamous carcinoma of the anal canal **(64)**. Early evidence of activity has also been seen in Study INCMGA 0012-201 (NCT03599713; Merkel cell carcinoma) and the soft tissue sarcoma cohort of Study INCMGA 0012-101.

2.3.3.3 Nonclinical Data for Retifanlimab

In a single-dose PK study, administration of retifanlimab by intravenous (IV) infusion was well tolerated in cynomolgus monkeys at a dose level of 10 mg/kg. There were no changes in circulating immune cell subsets and no evidence of cytokine release. Binding profiles of retifanlimab to PD-1 on CD4+ and CD8+ T cells were similar to those exhibited by pembrolizumab but more durable than those exhibited by the nivolumab replica.

In repeat-dose GLP toxicology studies, retifanlimab was administered at dose levels of 0 to 150 mg/kg to cynomolgus monkeys. All the infusions were well tolerated. There were no deaths prior to study termination nor treatment-related toxicities. The only findings related to retifanlimab were modest decreases in lymphocytes after the first infusion, a mild-to-moderate increase in fibrinogen on Day 2 with no clear dose-response, and microscopic changes at the IV administration site consistent with effects of repeated injections. Further details of nonclinical data can be found in the retifanlimab Investigator's Brochure.

Consistent with its specific binding properties and designed mechanism of action, retifanlimab blocks the binding of the ligands PD-L1 and PD-L2 to cell surface-expressed PD-1 in a dose-dependent manner. These properties of retifanlimab are comparable to those observed with replicas of the approved anti-PD-1 mAbs, nivolumab and pembrolizumab. Retifanlimab functionally blocks the PD-1/PD-L1 inhibitory axis in a dose-dependent manner in various cellular assays, including enhancement of antigen-driven cytokine secretion (SEB re-stimulation), blockade of PD-L1 induced SHP-2 activation and reversal of PD-1 pathway blockade of T-cell receptor (TCR)-induced nuclear factor of activated T cells (NFAT) activation with activity that is again comparable to those observed with the nivolumab and

pembrolizumab replicas **(48)**. **Table 3** presents the in vitro potency of Retifanlimab in comparison to nivolumab and pembrolizumab replicas.

Table 3 Comparison of In Vitro Potencies of Retifanlimab and Nivolumab and Pembrolizumab Replicas

Property	EC_{50} (or IC_{50}) Values (µg/mL) [a] Mean ± SEM		
	Retifanlimab	Nivolumab replica	Pembrolizumab replica
Binding to PD-1-expressing NS0/PDCD1 cells	0.138 ± 0.046	0.158 ± 0.058	0.140 ± 0.048
Inhibition of sPD-L1 binding to PD-1 expressing NS0/PDCD1 cells	0.010 ± 0.001	0.016 ± 0.005	0.014 ± 0.001
Inhibition of sPD-L2 binding to PD-1 expressing NS0/PDCD1 cells	0.021 ± 0.001	0.028 ± 0.004	0.028 ± 0.003
Inhibition of PD-1/PD-L1 Signaling in luciferase reporter assay	0.090 ± 0.008	0.171 ± 0.017	0.103 ± 0.016

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

2.3.4 Background on Tebotelimab

2.3.4.1 General Information on Tebotelimab

Tebotelimab (also known as MGD013) is an Fc-bearing bispecific tetravalent (bivalent for each antigen) DART® protein engineered as a hinge stabilized immunoglobulin G_4 (IgG_4) molecule designed to concomitantly bind programmed cell death protein 1 (PD-1) and lymphocyte-activation gene 3 (LAG-3), 2 checkpoint molecules expressed by T lymphocytes following antigen-induced activation. See **tebotelimab Investigator's Brochure** for additional details.

2.3.4.2 Clinical Trial Experience with Tebotelimab

The first-in-human Phase 1 Study CP-MGD013-01 is ongoing in patients with unresectable or metastatic neoplasms. This trial characterizes safety, tolerability, PK, pharmacodynamic, immunogenicity, and preliminary antitumor activity of tebotelimab given by IV infusion on a Q2W or Q3W schedule, either as monotherapy or in combination with margetuximab.

Safety of Tebotelimab Monotherapy

As of the cut-off date of 16 May 2020, safety data are available for 263 patients exposed to tebotelimab monotherapy and 24 patients exposed to tebotelimab + margetuximab combination therapy in ongoing study CP-MGD013-01. A discussion of safety for monotherapy and combination therapy is presented below.

Study CP-MGD013-01 – Tebotelimab Monotherapy – Dose Escalation

A total of 53 patients with diverse solid tumor types have been treated in Dose Escalation with tebotelimab at flat doses ranging from 1 mg to 1200 mg given Q2W. Patients were treated at escalating dose levels as follows: 1 patient at 1 mg, 1 patient at 3 mg, 4 patients at 10 mg, 5 patients at 30 mg, 4 patients at 120 mg, 10 patients at 400 mg, 8 patients at 800 mg, and 7 patients at 1200 mg. Patients who were not safety evaluable were replaced at various dose levels, and additional patients were enrolled in the 400 mg and 800 mg cohorts to gain additional clinical experience. Separately, escalating doses of tebotelimab (120 mg, 400 mg, and 600 mg) have been evaluated specifically in patients with advanced hepatocellular carcinoma (n = 13).

All 53 (100%) patients treated with tebotelimab monotherapy in Dose Escalation experienced at least one AE, irrespective of attribution. Common AEs, reported in ≥ 15% of patients, include fatigue (28.3%); nausea (26.4%); abdominal pain (24.5%); pyrexia and vomiting (22.6% each); pruritus (20.8%); constipation and diarrhea (18.9%); hypothyroidism (17.0%); and aspartate aminotransferase increased, hyponatremia, and back pain (15.1% each).

TRAEs have been reported in 43 of 53 (81.1%) patients treated in Dose Escalation. Common TRAEs, reported in ≥ 10% of patients, include fatigue (22.6%); nausea (18.9%); pruritus (15.1%); IRR and pyrexia (13.2%); and diarrhea and hypothyroidism (11.3%). Potential irAEs observed less commonly (in ≥ 5% of patients) include lipase increased and amylase increased (7.5% each); and AST increased (5.7% each).

The majority of TRAEs observed in Dose Escalation have been mild-to-moderate in severity (i.e., Grade 1 or Grade 2). A total of 14 (26.4%) patients treated in Dose Escalation have had at least one ≥ Grade 3 TRAE. These events include lipase increased (n=3); fatigue and IRR (n = 2 each); and adrenal insufficiency, amylase increased, arthritis, colitis, diarrhea, hypophosphatemia, immune-mediated hepatitis, myalgia, pancreatitis, pruritus, rash, transaminases increased, and vomiting (n = 1 each). Additionally, 1 patient treated in the limited hepatocellular carcinoma dose escalation at 120 mg experienced Grade 4 asymptomatic events of amylase and lipase increased with no clinical or radiographic evidence of pancreatitis. No patients have experienced a Grade 5 TRAE.

A total of 13 (24.5%) patients experienced SAEs in Dose Escalation. Seven (13.2%) patients had at least 1 treatment-related SAE, including immune-mediated hepatitis (n = 2, 400 mg and 1200 mg); adrenal insufficiency with resultant hypotension (n = 1, 400 mg), anemia (n = 1, 400 mg), colitis (n = 1, 800 mg), hypophosphatemia (n = 1, 400 mg), pancreatitis (n=1, 1200 mg), and thyroiditis (n=1, 600 mg). SAEs assessed not to be related to tebotelimab include abdominal pain, clostridium difficile colitis, diarrhea, dyspnea, hemobilia, hyponatremia, inappropriate antidiuretic hormone secretion, pneumonia, pulmonary hemorrhage, pyrexia, small intestinal obstruction, and urinary tract infection. These events were related to the respective patient's underlying malignancy or comorbid condition(s).

The dose of 600 mg, given Q2W or Q3W, was chosen for further development in the Cohort Expansion Phase. This decision was based on the totality of clinical, PK, and receptor occupancy data. Within Dose Escalation, tebotelimab demonstrated acceptable tolerability.

The MTD was not defined or exceeded, and 1200 mg represents the maximum dose level to be administered in Study CP-MGD013-01.

Study CP-MGD013-01 – Tebotelimab Monotherapy – Cohort Expansion

A total of 210 patients with advanced cancer have been treated with tebotelimab 600 mg Q2W or Q3W. Of these patients, 187 (89.0%) experienced at least one AE, irrespective of attribution. Common AEs, reported in ≥ 15% of patients, include fatigue (26.7%), anemia (15.7%), and nausea (15.2%).

TRAEs have been observed in 125 (59.5%) patients treated with tebotelimab monotherapy in Cohort Expansion. The only TRAE occurring in ≥ 10% of patients is fatigue (16.2%). Potential irAEs observed less commonly (in ≥ 5% of patients.) include hypothyroidism (7.6%); AST increased (6.7%); ALT increased (5.7%); and amylase increased and lipase increased (5.2% each). The majority of irAEs were mild to moderate in severity. The majority of TRAEs have been mild to moderate in severity (i.e., Grade 1 or Grade 2). A total of 39 (18.6%) patients had at least one Grade ≥ 3 TRAE.

A total of 67 (31.9%) patients experienced SAEs in Cohort Expansion. Of these, 19 (9.0%) experienced a treatment-related SAE, including the following events: IRR (n=5); pyrexia (n=2); and colitis, confusional state, CRS, diarrhea, headache, hepatitis, hyperthyroidism, immune-mediated hepatitis, immune-mediated pneumonitis, pancytopenia, peripheral neuropathy, small intestinal hemorrhage, and transaminases increased (n = 1 each)

Safety Summary – Tebotelimab Monotherapy

Overall, the cumulative safety data continue to support an acceptable safety profile for the treatment of patients with unresectable or metastatic neoplasms. The safety observations are consistent with the mechanism of action of tebotelimab, and irAEs have been manageable with proactive surveillance to identify early symptoms, prompt and aggressive management with systemic immune-modulating agents, and adherence to protocol guidelines on treatment interruption or discontinuation. The safety profile has not clearly demonstrated synergistic toxicity between the blockade of the anti-PD-1 and anti-LAG-3 arms and is largely consistent with the safety demonstrated with established anti-PD-L1 monoclonal antibodies.

Efficacy of Tebotelimab Monotherapy

Although it is premature for definitive conclusions regarding the efficacy of tebotelimab in the multiple tumor types being evaluated, early signs of antitumor activity have been observed. Within Dose Escalation, 3 patients (triple negative breast cancer [TNBC], mesothelioma, and GC) experienced confirmed PRs, while 18 other patients with various tumor types (including 1 patient with SCCHN) had stable disease (SD) as a best response. In Cohort Expansion, objective responses, including those unconfirmed at data cut, have been reported in 17 (10.4%) response evaluable patients: epithelial ovarian cancer (n = 2), SCCHN (n=2), NSCLC (n = 5), TNBC (n = 4), cholangiocarcinoma (n=1), cervical cancer (n=1), and DLBCL (n = 2), and 61 (37.4%) response evaluable patients have experienced a best overall response of SD.

2.3.4.3 Nonclinical Data for Tebotelimab

Single- and multiple-dose studies with selected toxicological endpoints were conducted in cynomolgus monkeys. Tebotelimab was administered at 0 to 150 mg/kg by a 1-hour IV infusion. All the infusions were well tolerated. There were no deaths prior to study termination. Infusion of Tebotelimab did not induce an increase in serum concentrations of IFN-γ, IL-2, IL-4, IL-5, or TNF-α. Transient increases in IL-6 levels were observed. Tebotelimab occupancy is detectable in circulating T cells that express PD-1.

Tebotelimab-related changes were limited to transient decline with subsequent rebound in circulating immune cell populations between 23 and 71 hours post end of infusion (EOI) at 150 mg/kg. Clinical signs of emesis or vomitus and watery and/or green feces in males at ≥ 40 mg/kg and watery and/or green feces in females at 100 mg/kg that occurred sporadically during the dosing phase. Microscopic observations of increased frequencies of minimal mononuclear cell infiltrates in several organs in males at ≥ 10 mg/kg and females at ≥ 40 mg/kg at the end of the dosing phase. The observations showed a trend towards reversibility at the end of the 10-week recovery period.

2.4 Dose Selection

2.4.1 Dose Selection for Enoblituzumab

Enoblituzumab will be administered at a dose of 15 mg/kg Q3W.

Data from clinical studies CP-MGA271-03 and CP-MGA271-01 suggest that enoblituzumab at doses up to 15 mg/kg IV weekly in combination with pembrolizumab 2 mg/kg IV Q3W and enoblituzumab monotherapy at doses up to 15 mg/kg administered weekly by IV, is generally well tolerated with toxicities manageable by standard medical therapy for patients with advanced cancer (see **Section 2.3.2.2** and current **enoblituzumab Investigator's Brochure** for more detailed safety information).

Based on population PK modeling and simulation of enoblituzumab, the estimated $t_{1/2}$ was 18.7 days and average C_{min_SS} for the 15 mg/kg dose was 787.6 µg/mL (276.8-1548.1 µg/mL) when the doses were administered QW and 160.5 µg/mL (26.9-412.2 µg/mL) when the dose was administered Q3W. As expected, the decrease in dosing frequency would decrease the average C_{min_SS} in subjects; however, based on preclinical PK-pharmacodynamic analysis, this concentration remains higher than the therapeutically active plasma concentration estimated in xenograft mouse models. As per the multi-dose anti-tumor activity studies of enoblituzumab against B7-H3-expressing tumors in mCD16-/-, hCD16A+ FOXN1 mice, in general, a 5 mg/kg weekly dose was observed as the highest efficacious dose in mice. At the 5 mg/kg weekly dose of enoblituzumab, C_{min_SS} was estimated as 35 µg/mL. Furthermore, based on PK-pharmacodynamic modeling of tumor growth inhibition data, the threshold concentration for tumor growth inhibition in mice was estimated between 2.6 to 45 µg/mL. These data indicate that at the clinical dose of 15 mg/kg Q3W, C_{min_SS} would be at least ~4 fold higher than the tumor growth inhibitory concentrations in mice and ~160 fold higher than the concentrations corresponding to maximal in vitro ADCC activity (see **Section 2.3.2.1**).

2.4.2 Dose Selection for Retifanlimab

Retifanlimab will be administered as a flat dose of 375 mg, Q3W.

Retifanlimab was administered in Study INCMGA 00012-101 as both a weight-based dose (ranging from 1 mg/kg to 10 mg/kg) and at fixed doses of 500 mg and 750 mg. Treatment has been well tolerated over the entire dosing range and a maximum tolerated dose has not been reached **(49)**.

The monotherapy recommended Phase 2 dose of 500 mg Q4W is based on clinical data from the ongoing first-in-human monotherapy study (INCMGA 00012-101). This dose-escalation study of retifanlimab was performed and evaluated in 37 patients at the following doses: 1, 3, and 10 mg/kg Q2W, and 3 and 10 mg/kg Q4W. While more than dose proportional increases were observed for area under the curve (AUC) and C_{max} for the first dose over the dose range of 1 to 10 mg/kg, linear PK was shown from 3 to 10 mg/kg.

A population PK (PPK) analysis was performed on patients in the INCMGA 00012-101 study to characterize the effect of body weight on the PK of retifanlimab. The plasma concentrations of retifanlimab were adequately described by a 2-compartment model with first-order elimination. Higher clearance of retifanlimab was estimated for the 1 mg/kg dose than for other dose groups. Body weight dependence of clearance was characterized by a power relationship with an exponent of 0.911.

A simulation was conducted to investigate the use of weight-based dosing and flat dosing for retifanlimab, with the aim of targeting a steady-state trough concentration of approximately 21 µg/mL, the median trough concentration for pembrolizumab **(37)** providing flexibility for combinations with different schedules. The median retifanlimab exposure and its distribution around the median at 500 mg Q4W were similar to 7 mg/kg Q4W in the simulated population, which justified clinical exploration in an expansion cohort of the study. The median steady-state concentration at 500 mg Q4W was 24.8 µg/mL, and 54% of participants had trough concentrations greater than the target concentration. The median steady-state concentration at 350 mg Q3W was 27.6 µg/mL. The 375 mg Q3W dose was selected based on the trough concentration.

Fifteen patients are enrolled in an additional expansion cohort of Study INCMGA 00012-101 to test the 375 mg Q3W regimen. Preliminary safety experience with this dosing regimen is also favorable (Incyte Corporation, data on file). Pharmacokinetic data were obtained from 14 participants who received retifanlimab 375 mg Q3W in the cohort expansion portion of Study INCMGA 0012-101. Following a first dose of 375 mg Q3W, retifanlimab had $t_{½}$ (276 hours [11.5 days]) and CL (14.8 mL/min) values comparable to those of the 500 mg Q4W and 750 mg Q4W doses. Furthermore, simulated C_{min} at steady-state PK following a 375 mg Q3W infusion was 24.3 µg/mL with the accumulation ratio at approximately 1.4, making this a comparable dose to 500 mg Q4W. Based on these observations, a flat dose regimen of retifanlimab 375 mg Q3W is considered an acceptable alternative where flexibility in dosing is needed. Receptor occupancy analysis for patients dosed with retifanlimab demonstrated full occupancy in all cohorts assessed, with average receptor occupancy for both CD4+ and CD8+ T cells above 90% at all time points assessed (retifanlimab Investigator's Brochure). In

addition, population PK and modeling and simulation analyses indicate that a retifanlimab dose of 375 mg administered by IV Q3W is appropriate based on PK and receptor occupancy findings from the INCMGA 0012-101 study **(22)**.

The Q3W recommended dose of retifanlimab is 375 mg, based on population PK and modeling, and a demonstration of clinical safety and favorable pharmacology in the dose-finding INCMGA 00012-101 study **(22, 27, 53)**.

2.4.3 Dose Selection for Tebotelimab

Tebotelimab will be administered as a flat dose of 600 mg, Q3W.

Within Dose Escalation in the MacroGenics-sponsored trial CP-MGD013-01 in patients with unresectable or metastatic neoplasms, tebotelimab monotherapy demonstrated antitumor activity with acceptable tolerability up to a dose of 1200 mg without exceeding the MTD. Based on receptor occupancy data, a dose of 600 mg Q2W was selected for further study in monotherapy; and a dose of 600 mg Q3W was selected for further study in combination with margetuximab, an anti HER2 Fc-optimized mAb. Mean $t_{1/2}$ was 8.5 days, and peripheral blood flow cytometry analyses confirmed full and sustained on-target binding during treatment at doses ≥ 120 mg.

PK simulations were performed for different dose regimens (600 mg Q2W, Q3W, Q4W; and 800 mg Q2W) (Huang L, Liu L, Sun Q, Kaul S, and Sumrow B, unpublished data, 2020). Tebotelimab PK after IV infusion in cancer patients was nonlinear and was described by a two-compartment PK model with parallel linear and MM (target-mediated non-linear) elimination. Typical values of central volume and peripheral volume were 3.54 L and 4.07 L, respectively. The clearance and inter-compartment clearance were 7.99 mL/hr and 15.6 mL/hr, respectively. The maximum target-mediated elimination rate and MM constant were estimated at 88.0 µg/hr and 0.327 µg/mL, respectively. The CVs of all estimated PK parameters were no more than 30%. Based on simulation results using the final model, the PK curves of all tested dose regimens were above the pembrolizumab efficacious threshold (23.1 µg/mL).

Based on the PK modeling results, tebotelimab has a PK profile similar to other immune checkpoint inhibitors, and a dose regimen of 600 mg administered Q2W or Q3W maintains sufficient exposure. These data support the selection of a 600 mg Q3W dose in the present study. See **tebotelimab Investigator's Brochure** for additional details.

3 STUDY PURPOSE AND OBJECTIVES

3.1 Primary Objective

Retifanlimab Cohort

- To assess the efficacy of the combination of enoblituzumab + retifanlimab, based primarily upon evaluation of Investigator-assessed ORR in the response evaluable patient population, in patients with recurrent or metastatic SCCHN not curable by local therapy, with no prior systemic therapy for SCCHN in the recurrent or metastatic setting (with the exception of systemic therapy completed > 6 months prior if given as part of multimodal treatment for locally advanced disease).

Tebotelimab Cohort

- To assess the safety, tolerability, and preliminary efficacy of the combination of enoblituzumab + tebotelimab, based primarily upon evaluation of Investigator-assessed ORR in the response evaluable patient population, in patients with recurrent or metastatic SCCHN not curable by local therapy, with no prior systemic therapy for SCCHN in the recurrent or metastatic setting (with the exception of systemic therapy completed > 6 months prior if given as part of multimodal treatment for locally advanced disease).

3.2 Secondary Objectives

Retifanlimab Cohort

- To evaluate the Investigator-assessed PFS, disease control rate (DCR), DoR, and OS.
- To evaluate safety and tolerability.
- To assess the PK of enoblituzumab + retifanlimab.
- To evaluate the immunogenicity of enoblituzumab + retifanlimab.

Tebotelimab Cohort

- To evaluate the Investigator-assessed PFS, DCR, DoR, and OS.
- To assess the PK of enoblituzumab + tebotelimab.
- To evaluate the immunogenicity of enoblituzumab + tebotelimab.

3.3 Exploratory Objectives

Retifanlimab and Tebotelimab Cohorts

- To explore the relationships between PK, pharmacodynamics, patient safety, and antitumor activity.
- To explore PPK and exposure-response analyses.
- To explore the relationships between PD-1, PD-L1, B7-H3, and LAG-3 expression on tumor cells and response.
- To investigate the immune-regulatory activity in vivo, including various measures of T-cell and NK-cell activation/exhaustion in peripheral blood and/or tumor biopsy specimens.
- To assess circulating immune cells and effect of treatment.
- To evaluate peripheral biomarkers and correlate with potential clinical response.
- To explore gene expression profiles and Fc receptor polymorphism in PBMCs and/or pre-treatment tumor biopsies and correlate with clinical response (when applicable).

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

4 STUDY DESIGN

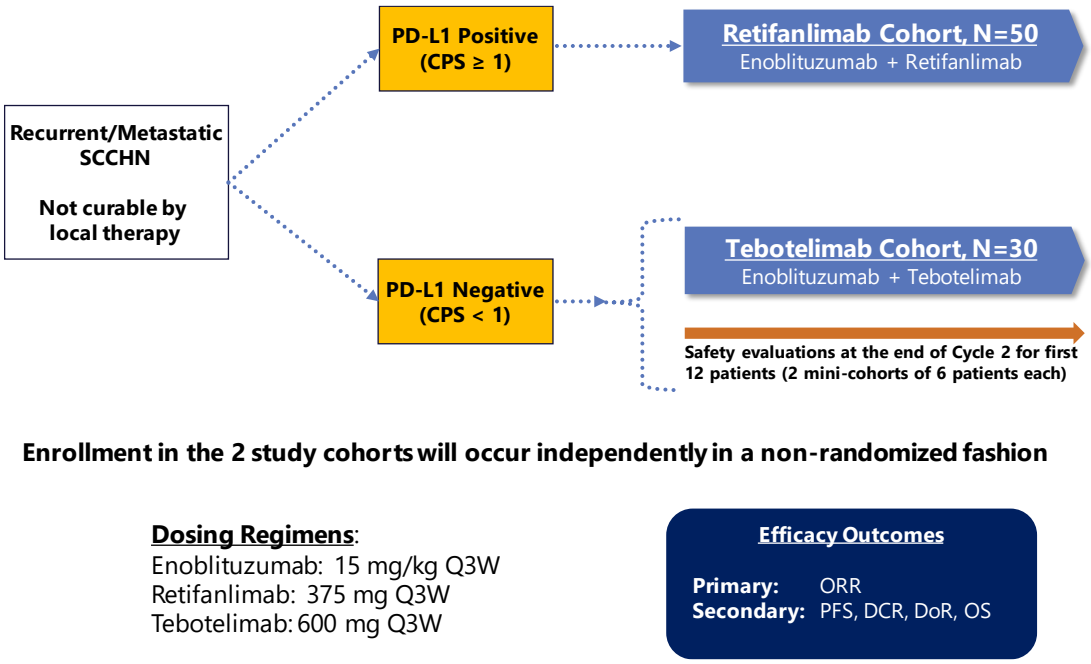
4.1 Overall Study Design

This is a Phase 2, open label, non-randomized study in the first-line treatment of patients with recurrent or metastatic SCCHN not curable by local therapy, with no prior systemic therapy for SCCHN in the recurrent or metastatic setting (with the exception of systemic therapy completed > 6 months prior if given as part of multimodal treatment for locally advanced disease). The study will be conducted at approximately 35 centers in approximately 5 countries.

Approximately 80 patients will be enrolled in 2 cohorts, to receive enoblituzumab in combination with either retifanlimab (Retifanlimab Cohort, PD-L1 positive [CPS ≥ 1] patients, N=50) or tebotelimab (Tebotelimab Cohort, PD-L1 negative [CPS < 1] patients, N=30; see **Figure 5**). Enrollment into each cohort will occur independently in a non-randomized fashion. Patients may not crossover between cohorts. PD-L1 expression will be prospectively collected and prospectively analyzed as described in **Section 10.2.1**. B7-H3 and LAG-3 expression will be prospectively collected and retrospectively analyzed.

An independent Data Safety Monitor (DSM), the Sponsor, and Investigators will maintain regular oversight of patient safety throughout the trial. In the Tebotelimab Cohort, toxicity will be evaluated by monitoring the occurrence and severity of DLTs (see **Section 4.2**) in the first 12 patients (2 mini-cohorts of 6 patients each) through Cycle 2 Day 7. If warranted, enrollment in the Tebotelimab Cohort will be paused and ad hoc meetings with the Principal Investigators (or designee), the Medical Monitor, and the independent DSM will be held to consider dose reduction of tebotelimab to 300 mg, Tebotelimab Cohort termination, or continuation at the pre-established 600 mg dose.

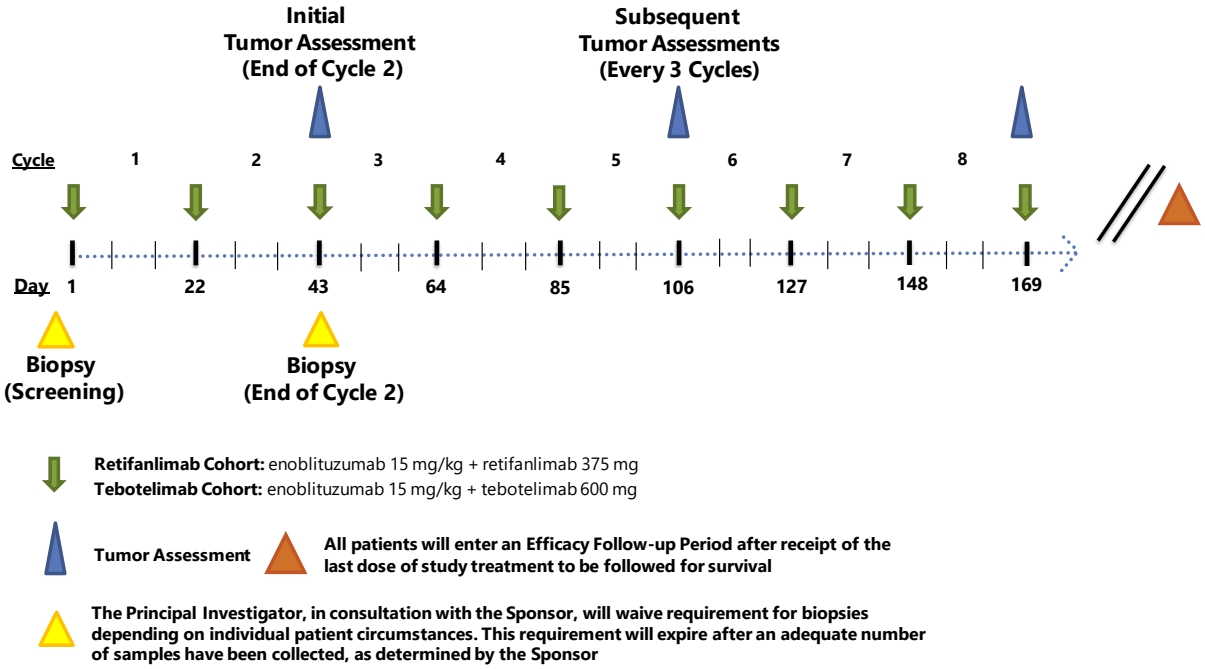
Figure 5 Study Schema



The data for each of the Retifanlimab and Tebotelimab Cohorts will be analyzed upon completion of enrollment of each cohort, and after all patients in the applicable cohort have at least one tumor assessment, to inform whether to proceed with the study and to determine any modifications to the trial design.

Patients will receive the assigned study drugs (enoblituzumab 15 mg/kg and either retifanlimab 375 mg or tebotelimab 600 mg) on a Q3W basis, in cycles of 3 weeks duration (see **Figure 6**). The initial tumor assessment will occur at the end of Cycle 2 (i.e., after approximately 6 weeks), and at the end of every 3 cycles thereafter (i.e., approximately every 9 weeks). After receipt of the last dose of study treatment, patients will enter an Efficacy Follow-up Period and will be followed for survival.

Figure 6 Treatment Cycles



Study treatment will continue in cycles of 3 weeks duration until confirmed CR (except as noted below), disease progression, unacceptable toxicity, withdrawal of consent, physician recommendation to discontinue therapy, death, or the maximum allowed treatment duration has been reached (see **Section 4.4** for a complete list of reasons for discontinuation of treatment). The maximum allowed treatment duration is 35 cycles for each study drug.

Discontinuation of study treatment may be considered for patients who have attained a confirmed CR. However, until Cycle 33, 2 additional cycles of study treatment may be completed beyond the date of confirmed CR (the total number of cycles of study treatment must not exceed 35).

Patients who have radiographic progression may remain on study treatment until the next scheduled radiographic evaluation if the following conditions are met: absence of clinical symptoms or signs indicating clinically significant disease progression; no decline in ECOG performance status; absence of rapid disease progression or threat to vital organs or critical anatomical sites (e.g., central nervous system [CNS] metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention; and no significant, unacceptable, or irreversible toxicities related to study treatment.

4.2 Dose Limiting Toxicity (Tebotelimab Cohort)

For the purposes of safety management and defining DLTs, the combination of enoblituzumab + tebotelimab will be treated as one entity. If a DLT is considered related to study treatment, no distinction will be made as to which agent is the causative agent and administration of both agents will be stopped.

Dose limiting toxicities will be based on treatment-emergent drug-related AEs (or laboratory abnormalities) occurring through Cycle 2 Day 7.

Patients in the Tebotelimab Cohort who experience DLT will discontinue study treatment.

4.2.1 Hematologic Dose Limiting Toxicity

Hematologic DLT is defined as follows:

- Grade 4 neutropenia lasting > 5 days
- ≥ Grade 3 febrile neutropenia
- Grade 4 thrombocytopenia, irrespective of duration
- Grade 3 thrombocytopenia associated with clinically significant bleeding
- ≥ Grade 3 hemolysis

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

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

4.2.2 Non-hematologic Dose Limiting Toxicity

- Any intolerable Grade 2 toxicity that results in dose interruption lasting more than 20 days, or requires drug withdrawal.
- Non-hematologic DLT is defined as any ≥ Grade 3 non-hematologic event with the following exceptions:
    - Grade 3 electrolyte abnormality that lasts less than 72 hours, that is not otherwise associated with clinical complications, and responds to medical intervention
    - Grade 3 fever that lasts < 72 hours and is not associated with hemodynamic compromise
    - Grade 3 nausea or vomiting that lasts < 72 hours and responds to medical intervention
    - Grade 3 amylase and/or lipase elevation that is not associated with either clinical or radiographic evidence suggestive of pancreatitis.
    - Grade 3 gastrointestinal AEs of diarrhea, constipation, abdominal pain, cramping, dyspepsia or dysphagia that resolves to ≤ Grade 1 within 14 days with medical therapy

- Grade 3 fatigue that lasts < 7 days
- Grade 3 infusion related reaction or cytokine release syndrome that lasts < 12 hours and responds to medical intervention.
- Grade 3 or 4 endocrinopathy that is adequately controlled with hormone supplementation
- Grade 3 skin toxicity that resolves to ≤ Grade 2 within 14 days of initiation of corticosteroids
- Grade 3 inflammatory reaction (e.g., with associated pain, swelling) attributed to a local antitumor response (e.g., inflammatory reaction at sites of metastatic disease, lymph nodes, etc.) that resolves to ≤ Grade 2 within 7 days.

4.2.3 Hepatic Non-hematologic Dose Limiting Toxicity

Hepatic non-hematologic DLT will be defined as follows:

- Any elevation of one or more transaminases > 8 × the institutional upper limit of normal (ULN) irrespective of duration.
- Any Grade 3 elevation of one or more transaminases > 5.0 – 8.0 × the ULN that does not resolve to Grade 2 within 7 days, and Grade 1 or baseline within 14 days. If steroids are administered, they must be tapered to ≤ 10 mg of prednisone or equivalent per day by Day 14. Please see **Section 7.2.2** for further management guidelines.
  - For patients with Grade 1 or 2 elevations of transaminases at baseline, a doubling of transaminases will be considered dose limiting, if not resolved to baseline within 14 days.
- Any Grade 3 elevation of total bilirubin that is > 5 × the ULN irrespective of duration.
- Any elevation of total bilirubin > 3.0 – 5.0 × ULN that does not resolve to Grade 2 within 7 days and Grade 1 or baseline within 14 days. If steroids are administered, they must be tapered to ≤ 10 mg of prednisone or equivalent per day by Day 14. Please see **Section 7.2.2** for further management guidelines.
- Any event meeting the criteria for Hy's law as follows (all three features):
  - Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 3 × ULN, or doubling of AST and/or ALT for patient having Grade 2 transaminase levels at baseline.
  - Concurrent elevation of total bilirubin > 2 × ULN without initial evidence of cholestasis
  - No alternative etiology can be identified.

4.3 Guidelines for Dose Modification

No intrapatient reductions in the dose of enoblituzumab, retifanlimab, or tebotelimab are allowed. Dose interruption or discontinuation should be used for the management of drug-related toxicity. The management of IRR is specified in **Section 7.1.3**. The management of immune-related AEs (irAEs) is specified in **Section 7.2**.

4.3.1 Dose Delays

Tebotelimab Cohort

Patients who experience a Grade 2 to 4 AE that is potentially dose-limiting should have study drug held pending assessment, management, and resolution of the AE. If the AE is assessed as unrelated to study drug or does not meet DLT criteria, therapy may be restarted at the previous dose and schedule, after appropriate recovery.

Retifanlimab and Tebotelimab Cohorts

A dose delay of up to 20 days is allowed for patients experiencing AEs. In the case of abnormal troponins or N-terminal pro b-type natriuretic peptide (NT-proBNP) values, study drug must be withheld and a thorough cardiac assessment performed promptly to diagnose myocarditis or other cardiovascular diseases; the patient may resume study drugs if myocarditis is not confirmed. Refer to **Section 7** for specific guidance on restarting study therapy for IRR and irAEs. A dose delay of up to 20 days may also be permitted for reasons other than AEs. All procedures at the missed dosing visit should be performed and treatment reinstituted as if the delay had not occurred.

Patients with infusion delays > 20 days will discontinue the study drug, complete the End of Treatment visit, and then enter the Post-treatment Follow-up Period.

4.4 Study Treatment Discontinuation

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

- Adverse Event Requiring Treatment Discontinuation
    - Patients who discontinue study treatment due to AEs are followed by radiographic evaluation until disease progression by RECIST v1.1, if the patients' condition allows. If not, patients will be followed for OS without radiographic evaluation upon the discussion with the Sponsor's Medical Monitor.
- Completed Treatment per Protocol
- Death
- Physician Decision (should occur only after discussion with the Sponsor's Medical Monitor)

- Lost to Follow-up
- Pregnancy
- Progressive Disease-Clinical Progression
- Progressive Disease-Objective Progression
    - Patients who have radiographic progression according to RECIST v1.1 may remain on study treatment until the next scheduled radiographic evaluation if the following conditions are met:
        - Absence of clinical symptoms or signs indicating clinically significant disease progression.
        - No decline in ECOG performance status.
        - Absence of rapid disease progression or threat to vital organs or critical anatomical sites (e.g., CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention.
        - No significant, unacceptable, or irreversible toxicities related to study treatment.
- Major Protocol Deviation Requiring Treatment Discontinuation
- Study Terminated (patients might be offered enrollment in a follow-up/roll over protocol if in place at the time of study termination)
- Patient Decision
- Patient Withdrew Consent for Study

If the Investigator decides that the patient should be withdrawn from the study or from dosing for any reason other than disease progression, the Sponsor or its designee must be alerted within 24 hours).

A patient may be determined to be lost to follow up (LTFU) after there have been 3 documented phone contact attempts. If this fails, a certified letter should be sent to the patient. Only after these attempts have failed can a patient be determined to be LTFU.

4.5 Study Discontinuation

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

- Completed Protocol-Defined Follow-up Period
- Death

- Lost to Follow-up
- Study Terminated by Sponsor
- Patient withdrew from Study

4.6 Definition of End of Study

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

End of study for each patient is defined as follows: Patient is LTFU or discontinues from the study due to any reason. Each patient's end of study status will be recorded in the End of Study CRF page.

5 ELIGIBILITY CRITERIA

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

5.1 Inclusion Criteria

1. Ability to provide informed consent and documentation of informed consent prior to initiation of any study-related tests or procedures that are not part of standard of care for the patient's disease.
2. Age ≥ 18 years old.
3. Histologically proven, recurrent or metastatic SCCHN not curable by local therapy.
4. No prior systemic therapy for SCCHN in the recurrent or metastatic setting (with the exception of systemic therapy completed > 6 months prior if given as part of multimodal treatment for locally advanced disease).
5. Primary tumor locations of oropharynx, oral cavity, hypopharynx, or larynx. Patients may not have a primary tumor site of upper esophagus, salivary gland, or nasopharynx (any histology).
6. All patients enrolled in this study must have an identified formalin-fixed, paraffin embedded (FFPE) tumor specimen for immunohistochemical evaluation of pharmacodynamic markers of interest. If no archival specimen is available, tissue from a contemporaneous core or excisional biopsy is acceptable (fine needle aspirate is not sufficient; refer to **Section 9.9.3** for details).

   Patients must also be willing to provide consent for a baseline and on-treatment tumor biopsy, if tumor lesions are accessible for biopsy with acceptable risk in the judgment of the Investigator and after discussion with the Sponsor (refer to **Section 9.9.3** for details). This requirement will expire after an adequate number of samples have been collected, as determined by the Sponsor.
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, verified within 3 days before Day 1.
8. Life expectancy ≥ 6 months.
9. Has adequate end organ function as determined by the site Investigator.
10. Has at least one radiographically measurable lesion (target lesion), as defined in RECIST v1.1 and documented by computed tomography (CT) or magnetic resonance imaging (MRI), suitable for response monitoring.
11. Has PD-L1 expression level that is either:
    a. Positive (CPS ≥ 1) for the **Retifanlimab Cohort**, or
    b. Negative (CPS < 1) for the **Tebotelimab Cohort**
12. Has results from testing of HPV p16 status for oropharyngeal cancer.

13. Acceptable laboratory parameters as follows:
    a. Platelet count ≥ 100 × 10^3/μL without transfusion within 28 days prior to the initiation of study drug.
    b. Absolute neutrophil count ≥ 1.5 × 10^3/μL in the absence of any growth factor support within 28 days prior to the initiation of study drug.
    c. ALT/AST ≤ 2.5 × ULN; for patients with hepatic metastases, ALT and AST ≤ 5 × ULN.
    d. Total bilirubin < 1.5 × ULN, except patients with Gilbert's syndrome, who may enroll if the conjugated bilirubin is within normal limits.
    e. Creatinine < 2 mg/dL, or a calculated or measured creatinine clearance > 50 mL/min.
    f. Negative serum pregnancy test, if applicable.
14. Women patients of child-bearing potential (WOCBP), defined as not surgically sterilized (hysterectomy, bilateral salpingectomy, and bilateral oophorectomy) and between menarche and 1-year post menopause, must have a negative serum pregnancy test performed within 72 hours prior to the initiation of study drug administration. Female patients must agree to abstain from egg donation during the course of the study.
15. WOCBP and male patients with partners of WOCBP must agree to use highly effective methods of contraception according to **Section 8.1.3** from the time of consent through 120 days after discontinuation of study drug administration. Male patients must agree to abstain from sperm donation during the course of the study.
16. WOCBP is not pregnant or breastfeeding or male patient is not expecting to father children within the projected duration of the study, starting with screening visit through 120 days after the last dose of study drug.

5.2 Exclusion Criteria

1. Disease suitable for local therapy administered with curative intent.
2. Has progressive disease within 6 months of completion of curatively intended systemic treatment for locoregionally advanced SCCHN.
3. Radiation therapy (or other non-systemic therapy) within 2 weeks prior to the first dose of study drug. Patients must have recovered from all radiation-related toxicities, not require corticosteroids for this purpose, and not have had radiation pneumonitis.
4. Toxicity of prior therapy that has not recovered to ≤ Grade 1 or baseline, with the exception of any grade of alopecia and anemia not requiring transfusion support.

5. Diagnosis of immunodeficiency or receiving systemic steroid therapy corticosteroids (≥ 10 mg per day prednisone or equivalent) or any other form of immunosuppressive therapy within 14 days prior to the first dose of study medication (physiologic doses of corticosteroids may be approved after consultation with the Sponsor).
6. Currently participating in a study of an investigational agent and receiving study therapy, participated in a study of an investigational agent and received study therapy, or used an investigational drug or device within 4 weeks of the first dose of study drug administration.
7. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or is not in the best interest of the patient, in the opinion of the treating Investigator and/or the Sponsor, including:
    a. Participants who are known to be HIV-positive, unless all the following criteria are met:
        - CD4+ count ≥ 300/μL,
        - Undetectable viral load, and
        - Receiving highly active antiretroviral therapy.
    b. Known history of or current acute or chronic hepatitis B virus (HBV) infection (as evidenced by detectable HBV surface antigen and HBV DNA ≥ 500 IU/ml).
    c. Patients with a history of hepatitis C virus (HCV) infection, unless the infection has been treated and cured.
    d. Has had an allogeneic stem cell or tissue/solid organ transplant.
    e. Patients with central nervous system metastases and/or carcinomatous meningitis.
    f. Patients with a history of psoriatic arthritis.
    g. Patients with any history of known or suspected autoimmune disease with the specific exceptions of vitiligo, resolved childhood atopic dermatitis, psoriasis not requiring systemic treatment within the past 2 years and patients with a history of autoimmune disease who are now clinically stable with replacement therapy and by laboratory testing.
    h. Evidence of active viral, bacterial, or systemic fungal infection requiring systemic treatment within 7 days prior to the initiation of study treatment. Patients requiring any systemic antiviral, antifungal, or antibacterial therapy for active infection must have completed treatment no less than 1 week prior to the initiation of study treatment.
    i. Known hypersensitivity to recombinant proteins, , or any excipient contained in the enoblituzumab, retifanlimab, or tebotelimab drug formulation (**Section 6.4**).

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

k. History of uncontrolled seizures within 6 months prior to the first dose of study drug.

l. Active or history of alcohol or other substance abuse within 1 year prior to the first dose of study drug.

8. Clinically significant cardiovascular disease including but not limited to:

   a. Myocardial infarction or unstable angina within the 6 months prior to the initiation of study drug.

   b. Stroke or transient ischemic attack within 6 months prior to the initiation of study drug.

   c. Clinically significant cardiac arrhythmias.

   d. Uncontrolled hypertension: systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg.

   e. Congestive heart failure (New York Heart Association class III-IV).

   f. Pericarditis or clinically significant pericardial effusion.

   g. Myocarditis.

   h. QTcF > 480 milliseconds as the average of 3 repeat examinations.

9. Clinically significant gastrointestinal disorders including but not limited to:

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

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

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

   d. Diverticulitis that is clinically significant in the opinion of the Investigator based on the extent or severity of known disease and/or the occurrence of clinically significant disease flares within 4 weeks prior to the initiation of study drug administration.

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

    a. If an immunization strategy for SARS-CoV-2 was available prior to enrollment, potential exclusion from the study based on history of receipt of SARS-CoV-2 prophylaxis will be discussed with the Sponsor.

11. Major surgical procedure or trauma within the 4 weeks prior to the initiation of study treatment.

12. A history of (non-infectious) pneumonitis or interstitial lung disease that required steroids, or current pneumonitis or interstitial lung disease.
13. Prior therapy with an anti-B7-H3, anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-LAG-3 agent.
14. Severe dyspnea at rest due to complications of advanced malignancy or requiring supplemental oxygen therapy.
15. Clinically significant pulmonary compromise, including but not limited to pneumonia or a requirement for supplemental oxygen use to maintain adequate oxygenation.
16. Second primary invasive malignancy that has not been in remission for greater than 2 years; except non-melanoma skin cancer; cervical carcinoma in situ on biopsy; or squamous intraepithelial lesion on Pap smear; localized prostate cancer (Gleason score < 6); or resected melanoma in situ.
17. Known psychiatric or substance abuse disorders, including but not limited to dementia or altered mental status that would preclude understanding and rendering of informed consent and cooperation with the requirements of the trial.
18. Employees of MacroGenics, Inc., or Incyte Corporation, unless approved by institutional review board (IRB) and principal Investigator.
19. Prisoners or other individuals who are involuntarily detained.
20. Any investigative site personnel directly affiliated with this study.
21. Any issue that in the opinion of the Investigator or the Sponsor would contraindicate the patient's participation in the study or confound the results of the study.

6 STUDY TREATMENTS

6.1 Description of Treatments

Patients in the Retifanlimab Cohort will receive enoblituzumab at a dose of 15 mg/kg and retifanlimab at a dose of 375 mg.

Patients in the Tebotelimab Cohort will receive enoblituzumab at a dose of 15 mg/kg and tebotelimab at a dose of 600 mg.

Patients in both cohorts will receive each study drug on a Q3W basis, in cycles of 3 weeks duration, for a maximum of 35 cycles.

All changes in study drug infusions, including interruptions and their duration, as well as reductions in rate and duration, must be recorded. The actual date, and infusion start time and end time will be recorded on the electronic case report form (eCRF).

6.2 Blinding

Not applicable. This is an open-label study.

6.3 Emergency Unblinding

Not applicable. This is an open-label study.

6.4 Study Drug and Supplies

Requests for additional study drug should be made to MacroGenics, Inc., via interactive response technology (IRT) at least 2 weeks in advance.

6.4.1 Supply of Enoblituzumab

Enoblituzumab (MGA271) drug product is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow or pale brown solution

Some visible, proteinaceous enoblituzumab particles may be present.

6.4.2 Supply of Retifanlimab

Retifanlimab (INCMGA00012 or MGA012) drug product is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution, practically free from visible particles.

6.4.3 Supply of Tebotelimab

Tebotelimab (MGD013) drug product is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow or pale brown solution, essentially free from foreign visible particles.

6.5 Study Infusion Preparation

6.5.1 General Guidelines and Precautions

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

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

Visual inspection of drug product vials for solution clarity, foreign particulate matter, and discoloration is required prior to use. If solution cloudiness or foreign particulate matter or pronounced discoloration (noting that a pale yellow or pale brown color is acceptable for enoblituzumab and tebotelimab, and a pale yellow color is acceptable for retifanlimab) is observed, the drug product should not be used for dose preparation. Enoblituzumab, retifanlimab, and tebotelimab drug product vials are single-dose containers. Any partially used vials or unused diluted dosing solutions should be discarded using appropriate drug disposal procedures (see Pharmacy Manual).

Instructions on the preparation of each study drug are detailed in the Pharmacy Manual. Standard laboratory practices should be used for avoidance of contact.

All IV infusions of study-agents must be administered separately. Do not mix enoblituzumab, retifanlimab, or tebotelimab in the same infusion with each other or with other medicinal products. Do not infuse enoblituzumab, retifanlimab, or tebotelimab as an IV push or bolus. A sterile, non-pyrogenic, low protein binding polyethersulfone

0.2 micron in-line filter administration set must always be used for IV administration of enoblituzumab, retifanlimab, and tebotelimab. **Study treatments are administered Q3W ± 3 days. An interval of at least 18 days should occur since the previous administration.**

Enoblituzumab, retifanlimab, and tebotelimab do not contain preservatives; once diluted in normal saline, the dose solution contained in the IV bag is stable up to 4 hours at room temperature or 24 hours refrigerated at 2° to 8°C with minimal exposure to light. If the dose solution is stored at 2° to 8°C, it should be removed from the refrigerator at least 30 to 60 minutes prior to administration, to allow the dose solution to reach room temperature. Precautions should be taken to minimize the time between dose preparation and IV infusion administration.

If there is a delay in administration of study drug such that it will not be administered on the day of preparation, the Medical Monitor should be notified immediately. Instructions on how to proceed will be provided.

Study treatments are administered in the following order:

- **Retifanlimab Cohort: (1) retifanlimab and (2) enoblituzumab.**
- **Tebotelimab Cohort: (1) tebotelimab and (2) enoblituzumab.**

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

6.5.2 Preparation and Administration of Enoblituzumab

Enoblituzumab will be administered at a dose of 15 mg/kg, initially calculated based on the patient's actual weight at Cycle 1 Day 1 (baseline) measurement. Significant (≥ 10%) change in body weight from baseline should prompt recalculation of the dose. Refer to the Pharmacy Manual for further instructions on allowable parameters for dose rounding of enoblituzumab.

Only in patients with body mass index (BMI) greater than or equal to 30 kg/m^2, the enoblituzumab dose will be calculated using ideal body weight (IBW). Refer to the Pharmacy Manual for further instructions on calculation of the enoblituzumab dose to be administered.

The desired amount of enoblituzumab should be withdrawn from the vial(s) and diluted to the appropriate final concentration with 0.9% Sodium Chloride Injection, USP (normal saline), according to the instructions provided in the Pharmacy Manual. The infusion bag containing enoblituzumab should be gently inverted to mix the solution. The dose solution should be administered via IV infusion over 120 minutes with a commercially available infusion pump. Up to 10 additional minutes of infusion time (i.e., up to a total of 130 minutes) are permitted to allow for flushing the line.

6.5.3 Preparation and Administration of Retifanlimab

Retifanlimab will be administered at a flat dose of 375 mg, regardless of body weight or body surface area.

Retifanlimab must be diluted in 0.9% Sodium Chloride Injection, USP (normal saline), prior to dose administration. Retifanlimab dose solution diluted in normal saline must be at a final concentration range of 0.3 mg/mL to 12 mg/mL. The infusion bag containing retifanlimab should be gently inverted to mix the solution. The dose solution should be administered via IV infusion over 60 minutes with a commercially available infusion pump. Up to 10 additional minutes of infusion time (i.e., up to a total of 70 minutes) are permitted to allow for flushing the line.

6.5.4 Preparation and Administration of Tebotelimab

Tebotelimab will be administered initially at a flat dose of 600 mg, regardless of body weight or body surface area.

Tebotelimab must be diluted in 0.9% Sodium Chloride Injection, USP (normal saline), prior to dose administration. Tebotelimab dose solution diluted in normal saline must be at a final concentration range of 0.12 mg/mL to 6.4 mg/mL. The dose solution should be administered via infusion over 60 minutes with a commercially available infusion pump. Up to 10 additional minutes of infusion time (i.e., up to a total of 70 minutes) are permitted to allow for flushing the line.

6.6 Placebo or Active Comparator

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

6.7 Treatment Compliance

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

6.8 Packaging and Labeling

All study drugs will be labeled according to local regulatory health authority requirements. Please see the Pharmacy Manual for detailed information about packaging and labeling.

6.8.1 Packaging and Labeling for Enoblituzumab

Enoblituzumab is supplied in a USP and Ph. Eur. conforming Type I borosilicate, 20 mL clear glass vial with a 20 mm FluroTec-coated 4432/50 gray butyl rubber serum stopper. The vial is sealed with a 20 mm TruEdge aluminum closure with a plastic overseal.

6.8.2 Packaging and Labeling for Retifanlimab

Retifanlimab is supplied in a single-dose vial packaged in a USP and Ph. Eur. conforming Type I borosilicate, 10 mL clear glass vial with a 20 mm FluroTec-coated 4432/50 gray butyl rubber serum stopper. The vial is sealed with a 20 mm aluminum closure with a plastic overseal.

6.8.3 Packaging and Labeling for Tebotelimab

Tebotelimab is supplied in a single-dose vial packaged in a USP and Ph. Eur. conforming Type I borosilicate, 20 mL clear glass vial with a 20 mm FluroTec-coated 4023/50 gray butyl rubber serum stopper. The vial is sealed with a 20 mm aluminum closure with a plastic overseal.

6.9 Storage and Accountability

Vials containing enoblituzumab, retifanlimab, or tebotelimab should be stored upright under monitored refrigeration at 2°–8°C (36°–46°F) in a room accessible only to pharmacy personnel, the Investigator, or duly designated personnel. Vials should be protected from light during storage and should not be shaken or frozen.

Accurate accounting of all study drug must be maintained. The Investigator agrees to keep an inventory of study drugs using the institution's drug accountability logs or logs provided by MacroGenics. The Investigator will maintain records of temperature monitoring of study drug. Drug disposition records must be kept in compliance with applicable guidelines and regulations.

A Pharmacy Manual will be provided to the Investigator or designee. When the study is completed, copies of all study drug accountability records must be provided to the Sponsor. Original drug accountability records must be maintained with the rest of the documentation for inspection by the study monitors.

6.10 Investigational Product Disposition at End of Study

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

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

7 POTENTIAL ADVERSE EVENTS AND SUPPORTIVE CARE MEASURES

7.1 Infusion Related Reactions Including Cytokine Release Syndrome

Infusion reactions (including cytokine release syndrome [CRS]) associated with study drugs administration should be managed according to the standard practice of medicine. General guidelines for the management of such reactions are provided in this section. However, severe reactions may require more intensive interventions (e.g., steroids, anti-TNFα antibodies, and/or IL-6 inhibitors).

Patients should be monitored closely for the development of infusion related reactions during infusions. Medications and supportive measures for the treatment of severe hypersensitivity reactions should be available for immediate use for an infusion reaction during study drug administration and may include, but are not limited to: subcutaneous (SC) epinephrine (0.3 to 0.5 mL of a 1:1000 solution), antihistamines (e.g., diphenhydramine 25 to 50 mg IV), corticosteroids (e.g., hydrocortisone 20-40 mg IV push or equivalent), IV fluids, vasopressors, oxygen, bronchodilators, and antipyretics. Resuscitation equipment and other supplies for the emergency management of an allergic/toxic reaction must be available. The patient should be treated according to the best available local practices and procedures. All supportive measures consistent with optimal patient care will be provided throughout the study according to institutional standards.

Should symptoms of fever or chills develop, it may be difficult to distinguish among potential causes including emerging infection, and infusion reaction. Patients should be evaluated carefully for presence of infection, with acquisition of cultures and/or implementation of empiric antibiotic therapy as appropriate based on the Investigator's assessment. Please refer to **Section 7.1.3** for guidance regarding the management of infusion reactions.

7.1.1 Grading and Management of Infusion Reactions

IRR, CRS and allergic reactions should be graded according to the criteria in **Table 4**.

Table 4 NCI CTCAE Version 5.0 Grading of Infusion-Related Reactions

System Organ Class	Injury, poisoning and procedural complications	Immune System Disorders	
Preferred Term	**Infusion–related Reaction**	**Allergic Reaction**	**Cytokine Release Syndrome**
Grade 1	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Systemic intervention not indicated	Fever with or without constitutional symptoms
Grade 2	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, non-steroidal anti-inflammatory drugs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs.	Oral intervention indicated	Hypotension responding to fluids; hypoxia responding to <40% O_2
Grade 3	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Bronchospasm; hospitalization indicated for clinical sequelae; intravenous intervention indicated	Hypotension managed with one pressor; hypoxia requiring ≥ 40% O_2
Grade 4	Life-threatening consequences; urgent intervention indicated		
Grade 5	Death due to AE		

7.1.2 Premedication and Prophylaxis

The following are suggested guidelines for the Investigator regarding prophylactic pre-infusion measures to be followed to mitigate the occurrence or severity of potential infusion reactions. Equivalent medications may be substituted based on the local practice of medicine and availability.

Cycle 1, Day 1: required prior to first infusion of study treatment:

- Acetaminophen 650-1000 mg orally (PO) or ibuprofen 400 mg PO
- H1 antagonist: Diphenhydramine 50 mg PO or IV
- H2 antagonist: Famotidine 40 mg PO or 20 mg IV
- Dexamethasone 10-20 mg IV, IV steroid

No pre-infusion prophylactic steroids administration is required for subsequent infusions. Non-steroidal pre-medications may be administered prior to the subsequent infusion, if warranted.

For patients who had infusion reactions following the first dose of enoblituzumab, retifanlimab, or tebotelimab that were not adequately or only moderately controlled with

acetaminophen, diphenhydramine, or famotidine, IV corticosteroids may be added to the pre-medication for subsequent administration of the applicable study drug. Dexamethasone (10 to 20 mg IV), may be used as premedication in addition to acetaminophen, diphenhydramine, and famotidine if patient experiences a ≥ Grade 2 infusion reaction with the first infusion. Premedication with steroids should be reduced by 50% with subsequent dose and stopped thereafter, if there are no reactions.

If a dose delay is greater than 11 days (i.e., > 35 days since the last dose) then the premedication and prophylaxis procedures should be the same as those done on Cycle 1, Day 1.

7.1.3 Management of Observed Infusion Reactions

≥ Grade 3 infusion reactions should be reported as AESIs and/or SAEs, as applicable.

The following are suggested treatment guidelines for the Investigator regarding the management of infusion reactions. Equivalent medications may be substituted based on the local practice of medicine and availability.

Grade 1:

- Slow the infusion rate by 50%.
- Monitor the patient for worsening of condition.
- Continue rate at 50% reduction and increase dose rate to the original rate by doubling the infusion rate after 30 minutes, as tolerated to the initial rate. Consideration can be given to beginning subsequent infusions at 50% rate and increasing as tolerated.
- The following prophylactic pre-infusion medications are recommended prior to future infusions of study treatment for patients who experience Grade 1 infusion reactions:
    - Diphenhydramine 25 to 50 mg PO/IV.
    - Acetaminophen 650 mg PO and/or ibuprofen 400 mg PO at least 30 minutes before additional study drug administrations.
    - Famotidine 40 mg PO or 20 mg IV before additional study drug administrations.

Grade 2:

- Stop the infusion.
    - Administer diphenhydramine hydrochloride 25 to 50 mg IV.
    - Acetaminophen 650 mg PO or ibuprofen 400 mg PO for fever.
    - Oxygen and bronchodilators for mild bronchospasm.

- Resume the infusion at 50% of the prior rate once the infusion reaction has resolved or decreased to Grade 1. The rate may then be escalated to the original rate after 30 minutes, as tolerated. Consideration can be given to beginning all subsequent infusions at 50% rate and increasing as tolerated.
- Monitor for worsening condition. If symptoms recur, discontinue the infusion; no further study drug will be administered at that visit.
- Prophylactic pre-infusion medications should be given prior to subsequent study treatment infusions. Patients who experience Grade 2 infusion reaction, for subsequent doses of study treatment, pre-medicate with diphenhydramine hydrochloride 25 to 50 mg IV/PO and acetaminophen 650 mg PO and/or ibuprofen 400 mg PO at least 30 minutes before additional study drug administrations. For patients with Grade 2 infusion reactions, despite premedication with diphenhydramine and acetaminophen and/or ibuprofen, corticosteroids (10 to 20 mg dexamethasone IV) may be added to the premedication regimen for the next dosing of study treatment. Reduce corticosteroid dosing by 50% for the subsequent dose and hold thereafter, if there are no reactions.

Grade 3:

- STOP THE INFUSION AND DISCONNECT THE INFUSION TUBING FROM THE PATIENT.
- TO AVOID EXACERBATION OF INFUSION REACTION OR CRS: DO NOT FLUSH THE TUBING – ASPIRATE RESIDUAL DRUG FROM THE PORT LUMEN.
- Administer diphenhydramine hydrochloride 25 to 50 mg IV, dexamethasone 20 mg IV, and other medications/treatment as medically indicated. Higher doses of corticosteroids (e.g., methylprednisolone 2 to 4 mg/kg IV) may also be considered for acute management.
- Consider administering tocilizumab (an IL6 receptor antagonist) 4-8 mg/kg IV.
- IV fluids, supplemental oxygen, H2 blockers such as famotidine, and bronchodilators should be considered, as appropriate.
- If the Grade 3 infusion reaction occurs with any study treatment, it will be discontinued for that day. If symptoms have resolved to baseline within 12 hours, study treatment may be infused at the next scheduled dose, with a 50% reduction of infusion rate. In addition, patients should be pre-medicated for this re-challenge and for any subsequent doses of study treatment with the following: diphenhydramine hydrochloride 25 to 50 mg IV, acetaminophen 650 mg PO and/or ibuprofen 400 mg PO; corticosteroids may be considered as well (dexamethasone 10 to 20 mg IV). Reduce corticosteroid dosing by 50% for the subsequent dose and hold thereafter, if there are no reactions.
- Patients who have a Grade 3 infusion reaction that does not resolve within 12 hours despite medical management should not receive further study treatment.

- Patients who experience a second Grade 3 infusion reaction at the time of re-challenge of study treatment (the same study treatment for which the first Grade 3 infusion reaction was seen) will permanently discontinue study treatment.

Grade 4:

- STOP THE INFUSION AND DISCONNECT THE INFUSION TUBING FROM THE PATIENT.
- TO AVOID EXACERBATION OF INFUSION REACTION OR CRS: DO NOT FLUSH THE TUBING.
- Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 20 mg IV (or higher doses of steroids, e.g., methylprednisolone 2 to 4 mg/kg IV or the equivalent, as considered appropriate).
- Consider administering tocilizumab (an IL6 receptor antagonist) 4-8 mg/kg IV.
- Give epinephrine or bronchodilators as indicated.
- Support ventilation and blood pressure as indicated.
- Patients who have a Grade 4 infusion reaction should not receive further study treatment.

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

7.2 Immune-Related Adverse Events

Blockade of immune checkpoints is associated with immune mediated adverse events (irAEs) due to disruption of normal immune tolerance **(43, 66, 79)**. These irAEs include but are not limited to autoimmune diarrhea, colitis, hepatitis, pneumonitis, encephalitis, nephritis, myositis, autoimmune endocrinopathies, myocarditis, and Stevens Johnson Syndrome/Toxic Epidermal Necrolysis. Occurrence of such events may call for interruption and/or discontinuation of study drug pending further evaluation and reporting to the Sponsor as AESIs. Most low-grade irAEs can be managed symptomatically. Persistent low grade or moderate toxicities may require treatment with corticosteroids or in refractory cases other immune suppressing agents such as mycophenolate or infliximab. High-grade immune-related toxicities in most cases require treatment with high-dose corticosteroids.

Temporary interruptions of study drugs may be required in the event of treatment-related, immune-related toxicity. General guidelines for specific toxicity regarding dosing and treatment are provided below. Unless otherwise specified Grade 1 immune-related toxicities may be monitored without administering specific interventions. Guideline principles may be adapted to local standard of care at the Investigator's discretion.

7.2.1 Diarrhea or Colitis

Diarrhea that develops in patients while receiving study drugs may reflect immune reactivity against normal colonic epithelium and careful monitoring for potential immune-related colitis should be instituted. Patients who develop signs or symptoms including abdominal pain, bloating, nausea, vomiting, diarrhea, or blood in the stools should be evaluated carefully for potential colitis.

- Grade 1 diarrhea - Closely monitor the diarrhea until resolution.
- Grade 2 diarrhea - Increase frequency of monitoring until resolution. For management of symptoms:
    - Loperamide/diphenoxylate.
    - Low-dose steroids if clinically indicated.
    - Consider management of prolonged Grade 2 event lasting more than 5 to 7 days or relapsed diarrhea as Grade 3 diarrhea (see below).
- Grade 3 diarrhea - Hold study treatment. Hospitalize patient promptly for further evaluation and management, including the following:
    - Bowel rest.
    - Supplemental IV fluids with close monitoring of fluid and electrolyte status.
    - Monitor frequency of bowel movements.
    - Consider imaging to rule out bowel obstruction or perforation.
    - Consideration of colonoscopy as appropriate.
    - Implementation of initial empiric immune suppression consisting of IV corticosteroids using methylprednisolone at a dosage of 2 mg/kg/day (or equivalent) divided twice daily. As tolerated, patients may be converted to oral corticosteroids (i.e., prednisone 2 mg/kg/day divided twice daily) and tapered as appropriate guided by the patients' clinical status.
    - Taper corticosteroids as clinically indicated.
    - For patients with severe colitis, or those who do not respond to corticosteroids, additional immune suppression with anti–TNF-α antibodies (i.e., infliximab) should be considered early in the course.
    - Consider restarting study treatment if:
        - It is determined there is no colitis and an alternative cause of diarrhea is found, and
        - Diarrhea resolves to ≤ Grade 1 within 14 days.
- Grade 4 diarrhea - discontinue study treatment and treat as for Grade 3.

7.2.2 Hepatic Toxicity

7.2.2.1 Elevations in Transaminases

- Grade 1 elevations - No specific therapy required.
- Grade 2 elevations - For elevations in transaminases 3 to 5 × ULN, rule out viral and other etiologies. Consider imaging studies such as ultrasound or CT scan and liver biopsy to ascertain etiology of liver dysfunction. Consider starting oral prednisone 60 mg/day divided twice daily, and hold study treatment.
    - If improvement to ≤ Grade 1 does not occur within 48 hours consider IV steroids such as methylprednisolone at 2 mg/kg/day divided twice daily or oral steroids such as prednisone 60 to 120 mg per day, divided twice daily.
    - Monitor liver function tests at least twice weekly (or more frequently as clinically appropriate in the judgment of the Investigator) until transaminases have returned to Grade 1 or baseline.
    - Taper oral steroids as clinically indicated with improvement in liver function.
    - Resume study treatment at the next scheduled dose if no more than two doses were missed.
    - If improvement to ≤ Grade 1 does not occur within 14 days, discontinue study treatment.
- Grade 3 elevations - Hold study treatment.
    - For elevations in transaminases > 8 × ULN, permanently discontinue study treatment.
        - Begin immediate IV steroids; suggest methylprednisolone at a dosage of 2 mg/kg/day divided twice daily.
        - Consider additional immune suppression with mycophenolate for patients who do not respond to corticosteroid therapy within 3 to 5 days.
        - Monitor liver function tests at least twice weekly (or more frequently as clinically appropriate in the judgment of the Investigator) until transaminases have returned to Grade 1 or baseline.
    - For elevations in transaminases > 5 but ≤ 8 × ULN:
        - Begin immediate IV steroids; suggest methylprednisolone at a dosage of 2 mg/kg/day divided twice daily.
        - Consider additional immune suppression as above for patients who do not respond to corticosteroid therapy within 3 to 5 days.

- Monitor liver function tests at least twice weekly (or more frequently as clinically appropriate in the judgment of the Investigator) until transaminases have returned to Grade 1 or baseline.
- If the elevation does not improve to Grade 2 within 7 days and to Grade 1 within 14 days, discontinue study treatment.

- Resume study treatment administration if following conditions are met:
  - Laboratory elevations improved to ≤ Grade 2 within 7 days and improve to ≤ Grade 1 or baseline within 14 days.
  - Steroids have been tapered to ≤ 10 mg per day of prednisone or equivalent.
  - On resuming study treatment, AST, ALT, and total and direct bilirubin laboratory test values will be evaluated at least once per week for 3 consecutive weeks.
- Permanently discontinue study treatment in the case of a second increase of AST or ALT to ≥ Grade 3.

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

7.2.2.2 Elevations in Total Bilirubin

- Grade 1 elevations - No specific therapy required.
- Grade 2 elevations - Hold study treatment until improvement to ≤ Grade 1.
  - Rule out viral and other etiologies. Consider imaging studies such as ultrasound or CT scan and liver biopsy to ascertain etiology of liver dysfunction. Consider oral steroids.
  - If improvement to ≤ Grade 1 does not occur within 14 days, discontinue study treatment and begin oral steroids.
- Grade 3 elevations - Hold study treatment.
  - For elevations in total bilirubin > 5 × ULN, permanently discontinue study treatment and initiate IV steroids, suggest methylprednisolone at a dosage of 2 mg/kg/day divided twice daily, and,
    - If no response to corticosteroid therapy within 3 to 5 days is observed, consider adding immune suppression therapy with mycophenolate.
    - Monitor liver function testing at least twice weekly (or more frequently as clinically appropriate in the judgment of the Investigator) until total bilirubin has returned to Grade 1 or baseline.
  - For elevations in total bilirubin > 3.0 but ≤ 5 × ULN:

- Begin immediate IV steroids, suggest methylprednisolone at a dosage of 2 mg/kg/day divided twice daily. Consider additional immune suppression as above for patients who do not respond to corticosteroid therapy within 3 to 5 days.
- Monitor liver function including total bilirubin testing at least twice weekly (or more frequently as clinically appropriate in the judgment of the Investigator) until total bilirubin has returned to Grade 1 or baseline.
- If the elevation does not improve to Grade 2 within 7 days and to Grade 1 within 14 days, discontinue study treatment.

  - Resume study treatment administration if:
    - Laboratory elevations downgrade to ≤ Grade 2 within 7 days and improve to ≤ Grade 1 or baseline within 14 days.
    - Steroids have been tapered to ≤ 10 mg per day of prednisone or equivalent
    - On resuming study treatment, AST, ALT, and total bilirubin laboratory test values will be evaluated at least once per week for 3 consecutive weeks.
  - Permanently discontinue study treatment in the case of a second increase of total bilirubin to ≥ Grade 3.

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

7.2.3 Pneumonitis

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

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

7.2.4 Dermatologic Toxicity

- Grade 1 or 2 skin reactions
  - Symptomatic treatment with low-dose topical corticosteroids (betamethasone 0.1% or hydrocortisone 1%) or antihistamines (diphenhydramine).
  - Persistent Grade 1 or 2 rash should be managed with higher dose topical corticosteroids and/or oral prednisone (1 to 2 mg/kg/day) if there is not improvement with topical therapies or the rash is associated with other dermal toxicities such as pruritus.
- Grade 3 skin reactions – Hold study treatment.
  - Initiate oral corticosteroids (oral prednisone 1 to 2 mg/kg/day).
  - Study treatment administration may be restarted at the next scheduled dosing if symptoms resolve to ≤ Grade 2 within 14 days.
  - Grade 3 skin toxicity that does not resolve to ≤ Grade 2 within 14 days of initiation of oral corticosteroids requires permanent discontinuation of study treatment.
- Grade 4 skin reactions - Discontinue study treatment.
  - Initiate oral corticosteroids (oral prednisone 1 to 2 mg/kg/day).
  - Consideration should be given to start IV corticosteroids (methylprednisolone 1-2 mg/kg/day) for Grade 4 dermatologic toxicities with tapering on resolution to < Grade 2 over 30 days.

7.2.5 Nephritis

- Grade 1 nephritis - No specific therapy required; close monitoring of renal function.
- Grade 2 nephritis - Hold study treatment.
  - Consider nephrology consultation and renal biopsy to confirm interstitial nephritis.
  - Begin corticosteroids: 1 to 2 mg/kg of oral prednisone or equivalent per day divided twice daily. Taper over 4 weeks as clinically indicated.
  - Resume study treatment administration at next scheduled dose if:

  - Nephritis resolves to ≤ Grade 1 within 14 days with or without treatment

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

7.2.6 Immune-Mediated Hypophysitis

- Grade 1 hypophysitis - No specific therapy required.
- Grade ≥ 2 hypophysitis - Hold study treatment.
  - Consult endocrinologist.
  - Consider hospitalization.
  - Consider short course of high dose IV corticosteroids: e.g., methylprednisolone 2-4 mg/kg IV (or equivalent) divided twice daily.
  - Initiate hormonal replacement as indicated.
  - Study treatment may be resumed as allowed by protocol when:
    - Endocrinopathy is controlled with appropriate replacement therapy.
    - Corticosteroid dose reduced to ≤ 10 mg prednisone or equivalent per day.
  - Brain MRI recommended.

7.2.7 Thyroid Toxicity

Thyroid disorders may occur at any time during treatment with study drugs. Monitor patients 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 interruption and without corticosteroids, and a suggested treatment guideline for hyperthyroidism is described below:

- Grade 1 hyperthyroidism - No specific therapy required.
- Grade 2 hyperthyroidism - Hold study treatment.
  - Consider starting oral corticosteroid therapy.
  - Short course of corticosteroid such as methylprednisolone 1 to 2 mg/kg IV (or equivalent) divided twice daily.

  - Resume study treatment if corticosteroid dose is reduced to ≤ 10 mg prednisone or equivalent per day and stable on hormone replacement therapy (if necessary).

- Grade 3 or 4 hyperthyroidism - Hold study treatment.
  - Consider hospitalization and consulting endocrinologist.
  - Begin IV corticosteroids such as methylprednisolone 2 to 4 mg/kg IV (or equivalent) divided twice daily.
  - Initiate hormonal replacement as necessary.
  - Consider restarting study treatment with complete resolution, or if stable on hormone replacement therapy within 14 days, and if corticosteroid dose is reduced to ≤ 10 mg prednisone or equivalent per day.

8 CONCOMITANT THERAPY AND RESTRICTIONS

8.1 Concomitant Therapy

All concomitant medications, including prophylactic pre-infusion medications, and blood products administered during the patient's participation in the study until 30 days following the last dose of study drug or until the start of a subsequent systemic anticancer therapy, if earlier, must be recorded in the source document and on the electronic Case Report Form (eCRF). All changes in infusions, including interruptions and their duration as well as reductions in rate and duration, must be recorded.

8.1.1 Prohibited Therapy

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

- Any other anti-neoplastic therapies, other than the assigned study treatment, including but not limited to chemotherapy, small molecules, biologics, or radiotherapy are not allowed.
- Patients may not receive other investigational drugs during the period of study participation.
- The use of immuno-suppressive agents is prohibited, unless they are being used to treat an AE.
- Probiotics are not allowed.
- Live vaccines within 4 weeks prior to the first dose of study treatment and while participating in the study are prohibited. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.
    - If an immunization strategy for SARS-CoV-2 becomes available during the study, permissibility of administration of SARS-CoV-2 prophylaxis during the study will be discussed with the Sponsor.
- The use of corticosteroids should be limited to the extent possible. Chronic doses of corticosteroids more than 10 mg/day prednisone or equivalent are prohibited other than for the management of drug-related adverse experiences. Steroids may be employed in the treatment of suspected study treatment-associated irAEs in consultation with the Sponsor's Medical Monitor. Steroids for topical, ophthalmic, inhaled, or nasal administration are allowed.

8.1.2 Permitted Therapies

Patients may receive the following concurrent therapy:

- Antiemetics, antidiarrheal, anticholinergics, antispasmodics, antipyretics, antihistamines, analgesics, antibiotics and other antimicrobials, histamine receptor antagonists or proton pump inhibitors, and other medications intended to treat symptoms or signs of disease.
- Transfusions such as red blood cells and platelets are permitted to treat symptoms or signs of anemia or thrombocytopenia.
- Bisphosphonates or receptor activator of nuclear factor Kappa-B ligand (RANK-L) inhibitors provided treatment with the agent is begun before the start of study treatment.
- Use of granulocyte colony stimulating factor, granulocyte-macrophage colony stimulating factor, or other growth factors is permitted.

8.1.3 Contraception

Male and female patients are required to use highly effective contraceptive measures as specified below. Male patients are required to use a condom regardless of his WOCBP partner's method of contraception.

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner is a highly effective birth control method provided that the vasectomized partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.

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

8.2 Restrictions

8.2.1 Fluid and Food Intake

There are no requirements for fasting and no restrictions for fluid and food intake by the patients during the study, although it is recommended that, to the extent possible, patients have a fluid intake of ≥ 2 liters on days associated with PK sampling, and that electrocardiograms will be obtained pre-meal.

8.2.2 Patient Activity Restrictions

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

9 STUDY PROCEDURES

This section provides a general description of the procedures and assessments associated with this study. The timing of the study procedures is presented in **Appendix 1**. All data should be recorded in source documents and entered into the eCRF.

9.1 Informed Consent

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

9.2 Screening Period

At the screening visit, patients will enter the study upon signing the informed consent document. No screening activities outside of usual standard of care should be performed prior to obtaining informed consent from the patient. However, medical testing that is performed according to local standard of care may be used to qualify patients for participation in the study. Screening procedures, with the exception of obtaining the tumor biopsy specimen, should be performed within 28 days prior to Cycle 1 Day 1.

Patients who sign the informed consent form but fail to meet the inclusion and/or exclusion criteria are defined as screen failures. An eCRF with a minimum of the following information must be completed for patients who fail screening: demographics, reason for screen failure, and serious adverse events related to study procedures.

9.3 Enrollment

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

Instructions for enrollment will be provided via IRT.

9.4 Medical History

A complete medical history should be obtained during the screening visit, including history of use of tobacco and other nicotine-containing products, and history of alcohol use. All concurrent medical conditions in the last 60 days and any significant past medical conditions (e.g., hospitalizations, surgeries, chronic conditions, prior cancer history, etc.) should be collected. Any untoward event that occurs prior to the first dose of study drug should be recorded as medical history and not as an AE, unless it is due to a protocol-related procedure.

9.5 Prior and Concomitant Medications and Procedures

All concomitant medications, blood products, and procedures administered for 30 days prior to study drug administration through the End of Treatment Visit must be recorded in the source document and on the eCRF.

All prior regimens of systemic anti-cancer therapy will be documented in the medical records and on the eCRF.

9.6 Physical Examination

The Investigator will perform physical examination of all patients. Full physical examination will be performed at screening and at the End of treatment visit, and it will include height (screening only), weight, and examination of skin, HEENT (head, eyes, ears, nose, and throat), lymph nodes, heart, chest, lungs, abdomen, extremities, and neurologic system. All other physical examinations will be directed physical examinations based on patient signs, symptoms, tumor location, and as clinically indicated. Directed physical examinations will include weight.

9.6.1 Vital Signs

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

9.7 ECOG Performance Status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work or office work)
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry-on any self-care. Totally confined to bed or chair.
5	Dead

9.8 Clinical Laboratory Tests

Blood and urine samples will be collected. Both local and central laboratory testing will be used.

Local laboratories should be used for all clinical decision-making, including but not limited to decisions regarding dose adjustments, if needed. Necessary laboratory testing should be

performed as required by the clinical situation. Local laboratory testing will be used for confirmation of pregnancy status prior to dosing as indicated.

Central laboratory testing should be used to determine patient eligibility and assess overall safety in the study, unless the Medical Monitor approves the use of a local laboratory in place of an unanalyzable central laboratory sample. Central laboratory test results need not be reviewed prior to dosing on study if local testing is available.

Protocol-specific clinical laboratory requirements are presented in **Appendix 2**. Safety laboratory tests should be performed and reviewed before study drug administration.

9.9 Pharmacokinetic, Immunogenicity, and Pharmacodynamic Biomarker Samples

Unless otherwise stated, PK, immunogenicity, pharmacodynamic, and biomarker assays will be carried out in a central laboratory designated by the Sponsor. Additional details on collection, processing, storage, and shipping of central laboratory samples will be provided in the Laboratory Manual. PK, anti-drug antibodies (ADA), pharmacodynamic, and biomarker specimens will be collected according to the schedules in **Appendix 3**. PK, pharmacodynamic, and biomarker assessments are described in **Section 10**.

9.9.1 Blood Samples

Blood samples will be collected from the arm contralateral to the site of IV infusion. If an indwelling catheter is used, the fluid in the catheter will be removed and discarded prior to the collection of blood sample for PK, ADA, or biomarker assessment. PBMCs, serum, and plasma will be collected according to the schedules in **Appendix 3** for assessment of immunomodulatory activity.

9.9.2 Samples for HPV Status

Local laboratory results are acceptable for evaluation of HPV p16 status. If local laboratory results are not available, evaluation of HPV p16 status will be conducted at a central laboratory designated by the Sponsor.

For evaluation of HPV p16 status, if local laboratory results are not available, patients are required to have an identified tumor specimen (FFPE) or 5 unstained slides.

9.9.3 Biopsy Specimens

Per **Inclusion Criterion 6**, all patients enrolled in this study must have an identified FFPE tumor specimen for immunohistochemical evaluation of pharmacodynamic markers of interest. If no archival specimen is available, tissue from a contemporaneous core or excisional biopsy is acceptable (fine needle aspirate is not sufficient).

Patients must also be willing to provide consent for a baseline and on-treatment (end of Cycle 2) tumor biopsy, if tumor lesions are accessible for biopsy with acceptable risk in the

judgment of the Investigator and after discussion with the Sponsor. This requirement will expire after an adequate number of samples have been collected, as determined by the Sponsor. Submission of an archival sample is highly encouraged but not mandatory for patients that provide a fresh biopsy sample.

Tumor lesions used for biopsy should be lesions that are felt to be accessible with acceptable clinical risk in the judgment of the Investigator, and should not be lesions used as RECIST target lesions unless there are no other lesions suitable for biopsy. If a RECIST target lesion is used for biopsy, the lesion must be ≥ 2 cm in longest diameter. Previously irradiated lesions should not be biopsied unless the lesion has grown in size after at least 14 days from the last dose of radiation. Multiple lesions may be used to obtain the biopsy sample. Lesions to be biopsied should be of sufficient size to enable acquisition of at least 2 tumor biopsy cores using a 16-gauge biopsy needle. Exceptions to the gauge of the needle may be considered after consultation with the Sponsor. Up to 3 additional biopsy cores may be obtained if this can be performed with acceptable clinical risk in the judgment of the Investigator. Excisional biopsies are allowed if these can be performed with acceptable clinical risk in the judgment of the Investigator. Immediate confirmation of the adequacy of the biopsy specimen and the presence of malignant cells in the tumor biopsy are strongly encouraged. Cores may be obtained if this can be performed with acceptable clinical risk in the judgment of the Investigator. Additional instructions for the processing and storage of tumor biopsy specimens will be provided in the Laboratory Manual.

If any new tissue acquisition is performed during the study course, submission of this new sample to the laboratories designated by the Sponsor is highly encouraged (but not mandatory).

9.10 Tumor Assessments

Baseline tumor imaging consists of a CT/MRI scan for all patients. The subsequent tumor assessments on treatment should use the same imaging modality as that for the baseline assessment. Target and non-target lesions will be designated at screening and re-evaluated according to **Appendix 1**.

A CT or MRI scan of the brain will be performed in cases in which it is clinically indicated (e.g., suspicion of brain metastases).

If bone metastases are suspected or present, a bone scintigraphy may be performed at baseline and as clinically indicated on study. Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques for the measurement of bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions. Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable.

9.11 Electrocardiography

Twelve-lead electrocardiograms will be obtained to evaluate the potential cardiac effect, including QTc interval prolongation. Screening and Cycle 1 Day 1 ECGs are performed in triplicate. Subsequent ECGs are obtained as clinically indicated.

Actual times of the ECG assessments will be recorded on the eCRFs.

9.12 End of Treatment Visit

The end of treatment visit (EOTV) should be performed within 30 days after the patient has met study treatment discontinuation criteria, and before initiation of any subsequent anticancer therapies.

It is recognized that patients may go to other facilities for continuing care, or may elect not to return to the study site. Therefore, failure to return for an EOTV will not be considered a protocol deviation. Whenever possible all required procedures and tests should be performed, with the following exception: the EOTV tumor assessment does not need to be conducted if prior tumor assessment was performed within 28 days of the EOTV and results are available for RECIST assessments.

9.13 Post-Treatment Follow-up Visit

The post-treatment follow-up period includes the following:

- Survival follow-up: Patients will be followed via telephone or other electronic contact at approximately 12-week (± 1 week) intervals after the EOTV (or, if no EOTV is conducted, after the decision to end treatment) until LTFU, withdrawal of consent, or death, or until 36 weeks after the last patient's EOTV. Prior to the database lock for final OS analysis, all current survival data will be requested regardless of interval from the prior assessment to collect the most up-to-date survival information for the final OS analysis.
- Tumor assessments: Will be collected every 12 weeks (± 1 week) after the EOTV (or, if no EOTV is conducted, after the decision to end treatment) until evidence of progressive disease (PD), initiation of another anticancer therapy, withdrawal of consent, LTFU, death, or 36 weeks after the last patient's EOTV. Patients who discontinue study treatment due to AEs are followed by radiographic evaluation until PD by RECIST v1.1, if the patients' condition allows. If not, patients will be followed for OS without radiographic evaluation upon the discussion with the Sponsor's Medical Monitor.
- PK and ADA: For patients with evidence of ADA from any prior visit, samples will be collected for PK and ADA at 12 and 24 weeks after the EOTV (or, if no EOTV is conducted, after the decision to end treatment).

10 ASSESSMENT OF PHARMACOKINETICS AND PHARMACODYNAMICS

10.1 Pharmacokinetics Assessments

Serum concentrations of enoblituzumab, retifanlimab, and tebotelimab will be analyzed using validated assay methods that will be carried out in the Sponsor's designated central laboratory. Analysis of PK data will be carried out using industry standard software.

Single and multiple dose PK parameters, including but not limited to C_{max} and C_{trough}, will be derived from serum concentration versus time data. PPK and exposure-response analyses will be conducted, using data from this study alone or combined with data from other studies. PPK and exposure-response modeling will be performed, and appropriate models and model parameters will be described. The influence of intrinsic and extrinsic covariates on model parameters will be investigated. The PPK and exposure-response analyses will be the subject of separate reports.

10.2 Pharmacodynamic/Biomarker Assessments

Assessment of PD-L1 must be performed prospectively prior to enrollment. Other biomarker assessments will be prospectively collected and retrospectively analyzed. Pharmacodynamic/biomarker assessments will each be carried out in a central laboratory designated by the Sponsor. Assessments will use an archival tumor specimen block (FFPE) or up to 20 unstained slides from an archival tumor specimen as noted below.

10.2.1 PD-L1 Immunohistochemistry Testing

Prospective PD-L1 testing will be performed for all patients, and should be performed on archival tissue if this is available. PD-L1 testing may also be carried out using fresh baseline and on-treatment tumor biopsy specimens, depending on sample availability. Anti–PD-1 agents have demonstrated improved efficacy in SCCHN patients with tumors that express PD-L1 as determined by immunohistochemistry (IHC) **(65)**. PD-L1 protein expression is determined by using CPS, which is the number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100. The specimen should be considered to have PD-L1 expression if CPS $\geq$ 1. PD-L1 expression will be assessed based on IHC staining using the FDA-approved 22C3 pharmDx assay.

10.2.2 B7-H3 Immunohistochemistry Testing

As enoblituzumab is an Fc-optimized antibody targeting B7-H3, IHC to assess B7-H3 expression will be performed in all patients. Testing may be carried out on both archival and fresh baseline and on-treatment tumor biopsy specimens, depending on sample availability.

10.2.3 PD-1/LAG-3 Immunohistochemistry Testing

PD-1/LAG-3 testing will be performed by PD-1 and LAG-3 dual IHC staining. Testing may be carried out on both archival and fresh baseline and on-treatment tumor biopsy specimens, depending on sample availability. Tebotelimab is a dual-affinity targeting agent that binds both PD-1 and LAG-3. While LAG-3 expression is documented in SCCHN, its correlation with response to immunotherapy agents is not completely understood. The selected study antibodies for the IHC staining will include rabbit anti LAG-3 Ab clone EPR4392(2) (Abcam) and mouse anti PD-1 Ab clone NAT105 (Ventana). The dual IHC assay will be carried out on Ventana Discovery Ultra platform according to sponsor established Standard Operating Procedures (SOPs) and controls to ensure validity of the results generated.

10.2.4 Additional Immunohistochemistry Testing

Additional IHC testing may be carried out on fresh baseline and on-treatment tumor biopsy tissue, depending on sample availability. These markers include but are not limited to: MHC class II, Granzyme, Ki67, T-cell infiltrate (e.g., CD3, CD8), immune cell activation markers, and natural killer (NK) cell markers.

10.3 Gene Expression Profiling

Gene expression profiling using Nanostring and tumor mutational burden may be determined retrospectively based on response, and prioritized according to the availability of archival and fresh tumor biopsy specimens.

10.4 Immune-regulatory Activity Testing

Immune-regulatory activity may be assessed at a Sponsor’s designated laboratory by such assays as: peripheral multi-parameter flow cytometry, Fc receptor genotyping, TCR spectratyping, ELISpot analyses, ex-vivo ADCC and CTL activity, IHC analyses, tumor mutation burden, and/or transcript profiling of any post-treatment biopsy samples obtained, and soluble biomarker analyses by ELISA or equivalent detection method.

11 ASSESSMENT OF EFFICACY

11.1 Efficacy Assessments

11.1.1 Disease Response Assessments

Tumor assessments will be obtained using CT and/or MRI scans and tumor response evaluated according to RECIST v1.1. Target and non-target lesions will be designated at screening and assessed at the end of Cycle 2 (i.e., after approximately 6 weeks, with a window of -3 days in relation to the beginning of the next cycle), and at the end of every 3 cycles thereafter (i.e., approximately every 9 weeks, with a window of -7 days in relation to the beginning of the next applicable cycle) until discontinuation of treatment. After receipt of the last dose of study treatment, all patients will enter an Efficacy Follow-up Period, during which tumor assessments will be obtained as described in **Section 9.13**.

The overall responses will be categorized as Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD), or Not Evaluable (NE). At each on-treatment tumor assessment time point, the objective response status will be determined. In the context of the statistical analysis for this trial, objective response determination and the assessment of best overall response (BOR) will be defined using RECIST v1.1 (**Appendix 4**).

11.1.2 Survival Assessments

Patients who are discontinued from study treatment will be assessed for survival status as described in **Section 9.13**. Prior to the final OS analysis, all current survival data will be requested regardless of interval from the prior assessment to collect the most up-to-date survival data for the final OS analysis.

11.2 Immunogenicity Assessments

The generation of ADA for enoblituzumab, retifanlimab, and tebotelimab will be monitored using validated analytical methods carried out in the Sponsor's designated central laboratory.

12 ADVERSE EVENT REPORTING AND ASSESSMENT OF SAFETY

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

12.1 Definitions

12.1.1 Adverse Event

Adverse event (AE) means any untoward medical occurrence in a patient or clinical trial patient associated with the use of a drug in humans, whether or not considered drug related. An AE can be:

- any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

12.1.2 Adverse Drug Reaction

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

12.1.3 Adverse Event of Special Interest

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

12.1.4 Serious Adverse Event

A serious AE (SAE) is any AE that results in any of the following outcomes:

- Death
- Life-threatening (immediate risk of death)

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

12.1.5 Attribution/Assessment of Causality

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

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

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

- *None:* The event is related to an etiology other than the study drug (the alternative etiology should be documented in the patient's medical record).
- *Unlikely:* The event is unlikely to be related to the study drug and likely to be related to factors other than study drug. An alternative explanation is more likely (e.g., concomitant drugs, concomitant disease), or the relationship in time suggests that a causal relationship is unlikely.

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

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

- *Possible:* There is an association between the event and the administration of the study drug and there is a plausible mechanism for the event to be related to study drug; but there may also be alternative etiology, such as characteristics of the patient's clinical status or underlying disease.
- *Probable:* There is an association between the event and the administration of study drug; there is a plausible mechanism for the event to be related to the study drug and the event could not be reasonably explained by known characteristics of the patient's clinical status or an alternative etiology is not apparent.

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

12.1.6 Severity Criteria

Assessment of severity grade will be made using the NCI-CTCAE Version 5.0.

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

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

12.2 Adverse Event Collection and Documentation

12.2.1 All Adverse Events

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

All adverse events whether serious or non-serious, will be reported from the time a signed and dated informed consent form (ICF) is obtained until 30 days following the last dose of study drug or until the start of a subsequent systemic anticancer therapy, if earlier.

Both protocol-related AEs and SAEs will be collected from the time the patient has consented to study participation. AEs and SAEs reported between the time the patient signs the ICF and the administration of the first dose of study drug will be captured as concurrent medical history unless the events are attributed to protocol-specified procedures.

Disease progression or events deemed related to disease progression will be documented as an antitumor activity outcome, **not reported** as an AE; they will be collected as efficacy endpoints. **Conversely,** AEs should be reported if it is unclear if the event is due to PD.

Events attributed to protocol-specified procedures will be collected on the Adverse Event eCRFs and SAE Report Form, as appropriate.

AEs, regardless of seriousness, severity, or relationship to study drug, are documented in the source and the eCRF, including:

- duration, severity, and seriousness of each adverse event,
- the action taken with respect to the study drug(s),
- the Investigator's attribution/causality assessment,
- the outcome of the event.

Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g. cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). All treatment measures for AE management will be recorded. All non-serious AEs should be entered into the eCRFs within 10 days of study site awareness.

Clinical Laboratory Changes: Safety laboratory assessments will be evaluated by the Investigator to ensure patient safety. The Investigator is responsible for reviewing the results of all laboratory tests as they become available:

- Laboratory values that fall outside of a clinically accepted reference range or values that differ significantly from previous values must be evaluated by the Investigator for clinical significance. The Investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests.

A laboratory abnormality is reported as an AE if any criterion for an SAE is fulfilled, or the event is associated with an intervention including, but not limited to, discontinuation or interruption of treatment, dose reduction/delay, or required initiation of concomitant therapy. Also, any laboratory abnormality may be reported as an AE at the Investigator's discretion, based on clinical significance. Examples include abnormalities for which there are no interventions yet abnormal value(s) suggest(s) disease or organ toxicity. If clinical sequelae are associated with a laboratory abnormality, diagnosis or medical condition should be reported (e.g., renal failure, hematuria) not the laboratory abnormality (e.g., elevated creatinine, urine red blood cells [RBC] increased).

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the Investigator all suspected unexpected serious adverse reactions. The Investigator must report suspected unexpected serious adverse reactions to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol, unless otherwise required and documented by the IEC/IRB.

12.2.2 Serious Adverse Events

All SAEs occurring during the study must be reported to the Sponsor. SAEs considered related to study drug may be reported at any time, even after the patient's final visit.

- **Within 24 hours** of becoming aware of an SAE, the Investigator should send the Sponsor a completed SAE Report form by email, SAEReports@macrogenics.com, or fax, (301) 354-3800. The SAE Report Form and Completion Guidelines, and Contact Information for Reporting SAEs, are found in the Study Procedures Manual. Upon receipt of SAE follow-up information, a follow-up SAE Report form should be submitted within 24 hours of becoming aware of the follow-up information. SAEs should be entered into the eCRFs within 5 calendar days of the site's awareness.
- SAEs related to study drug may be reported at any time, through 30 days after the last dose of study drug or until start of a subsequent anticancer therapy, if earlier.
    - In those cases in which the SAE is considered related to study drug, the study drug may be discontinued, and the patient will continue participation in the study for observational safety and analysis (except for cases where the patient is withdrawn from the study by the Investigator or withdrew the consent).
- After 30 days following the last dose of study drug administration, if an Investigator becomes aware of a SAE that s/he suspects is related to study drug, the Investigator should report the event to the Sponsor. Grade 3 or Grade 4 SAEs considered related to study drug are followed until recovery to ≤ Grade 1.
- The Investigator must follow all SAEs until resolution and record the date of resolution. Resolution of an event is defined as the return to pre-treatment status or stabilization of the condition with the expectation that it will remain chronic. Unresolved SAEs must be followed until:
    - The event resolves.
    - The event stabilizes.
    - The event returns to baseline, if a baseline value/status is available.
    - The event can be attributed to etiology other than the study drug or to factors unrelated to study conduct.
    - It becomes unlikely that any additional information can be obtained (patient or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).
- Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the study must be reported as a SAE, except hospitalizations for the following:

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

- Any SAE of suspected transmission of an infectious agent via a medicinal product will be reported.

Disease progression or events deemed related to disease progression resulting in hospitalization or death without other SAE criteria will be documented as an antitumor activity outcome, **not reported** as a SAE; they will be collected as efficacy endpoints. **Conversely,** SAEs should be reported if it is unclear if the event is due to PD.

12.2.3 Pregnancy

All initial reports of pregnancy in female patient s or partners of male patient s must be reported to the sponsor on the Pregnancy Exposure Form (from the Study Procedures manual) within 24 hours of study site awareness. The reporting period is from consent through 120 days after the last dose of study drug, or initiation of another anticancer therapy. Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs, to be reported on the SAE Report Form by email, SAEReports@macrogenics.com, or by fax, (301) 354-3800. SAEs should be entered into the eCRFs within 5 calendar days of the site's awareness. Patients becoming pregnant during the study must discontinue study drug.

The Investigator must attempt to follow the pregnancy to term or termination in order to report the outcome and health status of the mother and child. The Investigator should discuss with and encourage the pregnant partner to allow collection of follow up information. The Pregnant Partner Consent Form must be signed prior to collecting follow-up information. Follow-up information will be collected for all live newborns at birth and 6 months after birth. Information will be collected to assess study drug effects on the newborn. If appropriate, follow-up will be extended.

12.2.4 Special Reporting Situations

12.2.4.1 Sponsor Notification of Specific AEs

Specific AEs or groups of AEs will be followed as part of standard safety monitoring activities by the Sponsor. The Sponsor must be notified of these events regardless of seriousness (i.e., serious and nonserious AEs). Some AESIs must be reported immediately to

MacroGenics within 24 hours of the study site's awareness of the event. A list of protocol-specific AESIs, with reporting requirements (i.e., timeframe within which events are entered on the eCRF), are displayed in **Table 5**.

Table 5 Adverse Events of Special Interest

AESI	Reporting Requirement
Potential Hy's Law: AST or ALT > 3 × ULN **and** total bilirubin > 2 × ULN and without any alternate etiology	Within 24 hours of the study site's awareness of the event
All IRR or CRS events	**For ≤ Grade 2 IRRs or CRS events:** Within 10 days of the study site's awareness of the event. **For ≥ Grade 3 IRRs or CRS events:** Within 24 hours of the study site's awareness of the event
All immune-related AEs including colitis, pneumonitis, myocarditis, hepatitis, dermatologic toxicity, nephritis, hypophysitis, and hypo/hyperthyroidism, which are considered immune-mediated events (see **Section 7.2**)	**For ≥ Grade 2 events:** Within 24 hours of the study site's awareness of the event

12.2.4.2 Overdose

Overdose is any accidental administration of study drug ≥ 20% more than the assigned dose. In the event of an overdose, the patient should be closely monitored for potential AEs.

If an event of clinical consequence occurs due to the overdose an AE and needs to be reported to MacroGenics **within 24** hours of awareness. All AEs associated with an overdose should be recorded in the eCRF.

12.2.4.3 Product Quality Issues

Any suspected transmission of an infectious agent via a medicinal product, or other product quality issue that results in an event of clinical consequence are considered AEs. The AE resulting from a product quality issue should be reported within 24 hours of awareness of the event.

12.2.4.4 Discontinuation of Study Therapy Due to an Adverse Event

Any AE not related to disease progression that results in the discontinuation of the patient from study therapy must be reported to MacroGenics within 24 hours of the discontinuation. Follow up of the AE will continue until resolution or stabilization of the AE unless the patient withdraws consent for further follow up.

13 PRODUCT QUALITY COMPLAINT HANDLING

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

13.1 Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to **Section 12.2.2**, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2 Contacting Sponsor Regarding Product Quality

The name(s) (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed on the Contact Information page(s), which will be provided as a separate document.

14 STATISTICAL ANALYSIS

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

14.1 Determination of Sample Size

The total sample size is planned to be approximately 80 patients, with approximately 50 and approximately 30 patients in the Retifanlimab and Tebotelimab Cohorts, respectively.

Enrollment into the Retifanlimab and Tebotelimab Cohorts will occur independently in a non-randomized fashion.

The sample size for each cohort is primarily based on providing preliminary estimation of ORR. **Table 6** provides 2-sided 95% confidence intervals (CI) for a number of potential responses.

Table 6 Response Rates and 95% Confidence Intervals

Sample Size	Number of Responses	Response Rate (%)	95% Confidence Interval (%)
30	2	6.7	0.8 – 22.1
30	3	10.0	2.1 – 26.5
30	4	13.3	3.8 – 30.7
50	10	20.0	10.0 – 33.7
50	14	28.0	16.2 – 42.5
50	16	32.0	19.5 – 46.7

ORRs of 19% and 5% were observed in first-line SCCHN patients with CPS ≥ 1 and CPS < 1, respectively, in pembrolizumab monotherapy (**Section 2.2**). In the Retifanlimab Cohort, based on an exact binomial test, 50 patients will distinguish a favorable true ORR of 36% from an unfavorable rate of 19% with 91% power and a 1-sided type 1 error rate of 0.079. Thus, at least 14 responses out of 50 patients are to be achieved. In the Tebotelimab Cohort, 3 responses out of 30 patients will have 80% confidence that the true ORR is > 5% (the lower limit of 1-sided 80% CI for the response rate is > 5%).

14.2 Analysis Populations

The study analyses will be performed on the following populations:

- **Safety Population:** All patients who received at least one dose of any study drug. This population will be used for analyses of safety, PK, pharmacodynamics, and immunogenicity. It will also be used for summary of baseline data and analyses of PFS and OS.
- **Response Evaluable Population:** All patients who received at least one dose of any study drug and had baseline radiographic tumor assessment. This population will be used for summary of tumor assessment data and analyses of responses.

14.3 Demographics and Baseline Characteristics

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

14.4 Study Drug Exposures and Concomitant Medications

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

14.5 Pharmacokinetic/Pharmacodynamic Analysis

14.5.1 Pharmacokinetic Analysis

Summary statistics will be tabulated for PK parameters by study drug. Population PK analyses may be conducted using data from this study alone or combined with data from other studies. Analysis will be conducted separately for enoblituzumab, retifanlimab, and tebotelimab.

14.5.2 Immunogenicity Analysis

The proportion of patients who are negative for ADA at baseline and become positive in this assay, the proportion of patients who are negative at baseline and remain negative, and those who have positive ADA at baseline that increase or decrease in titer over the course of treatment will be summarized. Analysis will be conducted separately for enoblituzumab, retifanlimab, and tebotelimab.

14.5.3 Pharmacodynamic Analysis

Summary statistics for pharmacodynamic parameters, such as, but not limited to, those listed under in **Section 10.2** and corresponding changes from baseline, will be summarized and/or may also be presented graphically. Possible associations between changes in pharmacodynamic measures of interest and enoblituzumab, retifanlimab, and tebotelimab dose and exposure may be explored.

14.6 Efficacy and Endpoint Analyses

14.6.1 Response Endpoints and Analyses

The primary efficacy endpoint is the Investigator-assessed ORR per RECIST v1.1, defined as the proportion of patients in the response evaluable population who achieve the BOR of CR or PR (called responders) per RECIST v1.1. The BOR will be categorized as CR, PR, SD, PD, or NE. To be qualified as an objective response, CR and PR require confirmation at least 4 weeks after initial observation of such response, and SD requires an observation at least once after 6 weeks. BOR will be evaluated from the start of study treatment. Number and percent of patients with their BOR will be summarized. The ORR and its 2-sided 95% exact binomial CI will be calculated for each cohort.

DCR is defined as the percentage of response evaluable patients who experienced response of CR, PR, or SD for at least 3 months. The 2-sided 95% exact binomial CI of DCR will be calculated.

14.6.2 Analysis of Tumor Size Change Over Time

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

14.6.3 Time-to-Event Endpoints and Analyses

The time-to-event efficacy endpoints include the Investigator-assessed PFS, DoR, and OS as defined below.

Progression-free survival (PFS) will be defined as the time from the first dose date to the date of first documented progression or death from any cause, whichever occurs first. The documented progression is determined by objective assessment of disease per RECIST v1.1. For patients who are not known to be dead or progressed at the time of data cut-off for PFS analysis, the PFS will be censored at the date of the last tumor assessment. Specifically, the following censoring rules will be applied (**Table 7**).

Table 7 Censoring Rules for PFS

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

Duration of Response (DoR) is defined as the time from the date of initial response (CR or PR) to the date of first documented progression or death from any cause, whichever occurs first. The DoR is calculated only for the responders. For responders who are not known to be dead or progressed at the time of data cut-off for DoR analysis, the DoR will be censored at the date of the last tumor assessment. Specifically, the last 3 situations described in **Table 7** will be applied. The DoR analyses will be performed only if there are enough responders to render the analyses meaningful.

Overall survival (OS) is defined as the time from the first dose date to the date of death from any cause. For patients who are not known to be dead at the time of data cut-off for OS analysis, the OS will be censored at the time they are last known to be alive.

The Kaplan-Meier method will be applied to estimate PFS, DoR and OS curves, their median times, PFS rates at 6 and 12 months, and OS rates 12 and 24 months, respectively. The method of Brookmeyer and Crowley **(15)** will be used to construct 95% CI for median time of each time-to-event endpoint. The 95% CIs for PFS and OS rates at each time point of interest will be calculated by normal approximation after log(-log) transformation.

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

14.7 Safety Endpoints and Analyses

14.7.1 Adverse Events

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

- All AEs
- AEs with CTCAE severity ≥ Grade 3
- Study drug related AEs
- Study drug related AEs with CTCAE severity ≥ Grade 3
- SAEs
- Study drug related SAEs
- AEs that resulted in discontinuation of study treatment
- AEs that led to interruption of individual study drug
- Fatal AEs
- AEs of special interest

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

14.7.2 Laboratory Values

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

14.7.3 Other Safety Endpoints

ECGs will be collected and analyzed for evidence of cardiac toxicity, especially prolongation of QT interval. Vital signs will be summarized with descriptive statistics at each visit and time point where they are collected. Shift tables may be performed.

14.8 Other Assessments or Analyses

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

15 QUALITY CONTROL AND ASSURANCE

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

- Provide instructional material to the study sites, as appropriate.
- Sponsor a start-up training session (Investigator Meeting or Study Initiation Visit) to instruct the Investigators and study coordinators. This session will give instruction on the protocol, the completion of the eCRFs, and study procedures.
- Make periodic visits to the study site to monitor protocol compliance and general Good Clinical Practice (GCP) compliance.
- Be available for consultation and stay in contact with the study site personnel by mail, e-mail, telephone, and/or fax.
- Review and evaluate eCRF data and use standard computer checks to detect and query errors in data collection.
- Conduct a quality review of the database.

15.1 Monitoring, Auditing and Inspections

To ensure the safety of patients in the study, compliance with applicable regulations, and ensure accurate, complete, and reliable data, the Investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as source documents for the study.

MacroGenics or its designee will monitor the study on a regular basis throughout the study period according to the study Monitoring Plan. The Investigator will allocate adequate time for such monitoring activities. The study monitor periodically will conduct a cross-check of the patient data recorded on eCRFs against source documents at the study site. The Investigator will also ensure that the monitor is given access to all the above noted study-related documents, source documents (regardless of media) and study-related facilities (e.g., investigational pharmacy, etc.), and has adequate space to conduct the monitoring visit. Queries may be raised if any datum is unclear or contradictory. The Investigator and study site personnel must address all queries in a timely manner.

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

15.2 Data Collection and Management

Site personnel record all data for each patient through electronic case report forms (eCRFs) using the Medidata RAVE™, an Electronic Data Capture (EDC) system provided and approved by the Sponsor. Refer to the Study Procedures Manual for additional information regarding eCRFs, if any that will be used as source documentation. Study sites must complete eCRFs for each patient in a timely manner shortly after each patient visit. The Investigator must sign the Investigator's Statement in each patients eCRF.

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

16 ADMINISTRATIVE CONSIDERATIONS

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

The study protocol, any related documents, and patient-facing materials will be submitted to the IRB/IEC for review and approval. Written approval of the study protocol and the informed consent forms (ICFs) will be in the possession of the Investigator and the Sponsor before the study drug is shipped to the Investigator's site. This approval must include the date of review, the protocol title and/or study number and version number, and ICF version number or date. A stamped version of the IRB-approved consent is acceptable. If the IRB/IEC or institution uses its own unique number for the protocol instead of the Sponsor's number, that unique number should be noted on the approval statement. The Investigator should provide the Sponsor with a statement of compliance from the IRB/IEC indicating compliance with the applicable regulations in the region and ICH.

Protocol modifications or changes may not be initiated without approval from the Sponsor and prior written IRB/IEC approval (when required), except when necessary to eliminate immediate hazards to the patients. Such modifications will be submitted to the IRB/IEC; and written verification that the modification was submitted should be obtained. The Investigator must submit all changes and updates to required documents to the IRB/IEC.

16.2 Ethical Conduct of the Study

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

16.3 Patient Information and Consent

The Investigator will obtain, document and retain IRB/IEC-approved written informed consent from the patient, as specified in **Section 9.1**. Where required, the Investigator will use an appropriately translated and IRB/IEC-approved version. The Sponsor reserves the right to delay initiation of the study at a site where ICFs do not meet the standards of applicable local regulations or ICH E6.

Information should be given to the patient in both oral and written form, and patients must be given ample opportunity to inquire about details of the study. The ICF must be signed and dated by the patient, and by the person who conducted the discussion of the informed consent.

16.4 Patient Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified by a coded number. Clinical information will not be released without written permission of the patient, or the patient's legally authorized representation, except as necessary for monitoring by the relevant regulatory authorities, the Sponsor, or the Sponsor's representative. The

Investigator must comply with all local applicable privacy regulations regarding the protection of patient data.

16.5 Source Documents

Source data in a clinical study are the original records or certified copies where clinical observations are first recorded, which may include, but are not limited to, the patient's medical file, original laboratory reports, histology, and pathology reports (as applicable). The Investigator is responsible for maintaining adequate and accurate medical records from which accurate information will be entered into the eCRFs

16.6 Retention of Data

All essential documents, including eCRFs, source documents (regardless of media), and signed ICFs, should be retained by the Investigator, per the guidance in ICH E6 or other regulatory retention requirement. There may be other circumstances for which MacroGenics is required to maintain study records for longer periods; therefore, MacroGenics should be contacted before study records are removed from the control of the study site for any reason. The Investigator must obtain written permission from MacroGenics prior to destruction of study documents.

16.7 Sample Retention and Further Testing

Samples acquired for protocol-specified assays are retained for

- at least 1 year following the end of the study, and may be retained for
- up to 2 years after last approval of a marketing application in an ICH region or
- until there are no pending or contemplated marketing applications in an ICH region or
- until at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product.

If the patient consents, or the patient's legal representative consents, to the use of their study samples for non-study research purposes, these samples may also be used for exploratory testing (including assay development) and may be retained up to 15 years from the end of study.

16.8 Financial Disclosure

The Investigator and Sub-Investigators will be required to disclose in writing any applicable financial arrangement as defined in US regulation. The Principal Investigator's disclosure will be signed and dated prior to participating in the study.

The information, as defined in 21 CFR 54, will be collected about the Investigators, their spouse and each dependent child. Investigators must update the Sponsor with any changes in reported information up to 1 year following the end of the study.

In accordance with Securities and Exchange Commission regulation (17 CFR 229.404), Investigators and Sub-Investigators must disclose if they are employees of MacroGenics, or if an immediate family member of a MacroGenics employee, officer, or director.

16.9 Publication and Disclosure Policy

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

16.10 Discontinuation of the Study or Study Sites

Site participation may be discontinued by MacroGenics, the Investigator, a regulatory authority, or an IRB/IEC. The study may be discontinued by a regulatory authority or at the discretion of the Sponsor.

16.11 Identification of the Coordinating Principal Investigator

A Coordinating Principal Investigator will be appointed by the Sponsor Medical Monitor prior to the end of the study.

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

17 REFERENCE LIST

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Appendix 1 Time and Events Schedule

EVALUATION/ PROCEDURE	Screening D (-28 to -1)	Cycle 1					Subsequent Cycles		EOTV [b]	Follow-Up
		D1	D2	D3	D8 (± 1d)	D15 (± 1d)	D1 (± 3d) [a]	End of Cycle		
Enoblituzumab + retifanlimab or tebotelimab		X	*In clinic visit for PK/ADA/biomarker assessments only*				X			
Informed Consent (no time constraint)	X									
Inclusion/Exclusion Criteria	X									
Demographics	X									
Medical/Cancer History	X									
Tumor biopsy [c]	X							X		
Archival tumor specimen (no time constraint) [c]	X									
HPV p16 Status (no time constraint) [d]	X									
Enrollment	X									
Physical Examination [e]	X	X					X		X	
Height	X									
Weight	X	X					X		X	
ECOG Performance Status	X	X					X		X	
ECG (12-lead) [f]	X	X								
Vital Signs [g]	X	X					X		X	
Clinical Laboratory Tests [h]	X	X					X		X	
Coagulation [i]	X	X								
Urinalysis [j]	X	X					X			
Pregnancy Test [k]	X	X					X		X	
Tumor Assessment [l]	X							X	X	X
Pharmacokinetics	See **Appendix 3**									
ADA	See **Appendix 3**									
PBMCs, Serum, and Plasma for PD and Exploratory Biomarkers	See **Appendix 3**									
Concomitant Medications	Continuous									
Concomitant Procedures	Continuous									
Adverse Events	Continuous									
Survival										X [m]

EVALUATION/ PROCEDURE	Screening D (-28 to -1)	Cycle 1					Subsequent Cycles		EOTV [b]	Follow-Up
		D1	D2	D3	D8 (± 1d)	D15 (± 1d)	D1 (± 3d) [a]	End of Cycle		

a A cycle is 21 days ± 3 days from the previous dosing day. There should be at least 18 days between administrations.

b The EOTV, if conducted, should be performed within 30 days after the patient has met study treatment discontinuation criteria specified in **Section 4.4**, and before initiation of any subsequent anticancer therapies.

c All patients enrolled in this study must have an identified formalin-fixed, FFPE tumor specimen for assessment of PD-L1 status prior to study entry. If no archival specimen is available, tissue from a contemporaneous core or excisional biopsy is acceptable (fine needle aspirate is not sufficient). Patients must also be willing to provide consent for a baseline and on-treatment tumor biopsy (end of Cycle 2), if tumor lesions are accessible for biopsy with acceptable risk in the judgment of the Investigator and after discussion with the Sponsor. This requirement will expire after an adequate number of samples have been collected, as determined by the Sponsor. Submission of an archival sample is highly encouraged but not mandatory for patients that provide a fresh biopsy sample. Baseline biopsy to be obtained after confirmation of eligibility and before Cycle 1 Day 1. End of Cycle 2 biopsy to be obtained between 20 and 34 days after Cycle 2 dosing, and preferably before Cycle 3 Day 1 dosing. Cycle 3 Day 1 dosing should not be delayed beyond the window of 21 ± 3 days from the previous dosing day, unless there is another reason to delay dosing per **Section 4.3.1**.

d See **Section 9.9.2** for details.

e Full physical examination at screening and EOTV, directed physical examination at other time points.

f Cycle 1 Day 1 ECG is conducted prior to the first infusion of any study treatment and at the end (± 15 minutes) of the last study treatment infusion (retifanlimab, tebotelimab, or enoblituzumab, as applicable). Subsequent ECGs are obtained as clinically indicated. Screening and Cycle 1 Day 1 ECGs are performed in triplicate.

g Vital signs are obtained within 15 minutes before the first infusion and within 10 minutes after the end of infusion of each study treatment (retifanlimab, tebotelimab, or enoblituzumab, as applicable), and as clinically indicated.

h Includes hematology, serum chemistry, endocrine tests, and cardiovascular disease markers (see **Appendix 2**). Laboratory assessment samples may be collected up to 3 days in advance of Day 1 of all cycles. If the screening samples are collected within 3 days before Cycle 1 Day 1 these laboratory assessments do not need to be repeated on Cycle 1 Day 1.

i Coagulation tests (see **Appendix 2**) performed at screening and Cycle 1 Day 1 (with a window of -3 days in relation to Day 1), then as clinically indicated.

j Urinalysis (see **Appendix 2**) performed at screening, Day 1 of each cycle (with a window of -3 days in relation to the beginning of each cycle), and as clinically indicated.

k Serum or urine pregnancy test for women of child-bearing potential (with a window of -3 days in relation to the beginning of each cycle).

l Tumor assessments are performed at the end of Cycle 2 (with a window of -3 days in relation to the beginning of the next cycle), and at the end of every 3 cycles (Cycles 5, 8, 11, etc.) thereafter (with a window of -7 days in relation to the beginning of the next applicable cycle) until treatment discontinuation. Patients who discontinue from study treatment should be assessed every 12 weeks (± 1 week) after the EOTV (or, if no EOTV is conducted, after the decision to end treatment) until evidence of PD, initiation of another anticancer therapy, withdrawal of consent, LTFU, death, or 36 weeks after the last patient's EOTV. EOTV tumor assessment does not need to be conducted if prior tumor assessment was performed within 28 days of the EOTV and results are available for RECIST assessments. Patients who discontinue study treatment due to AEs are followed by radiographic evaluation until PD by RECIST v1.1, if the patients' condition allows. If not, patients will be followed for OS without radiographic evaluation upon the discussion with the Sponsor's Medical Monitor.

m Survival follow-up occurs every 12 weeks (± 1 week) after the EOTV (or, if no EOTV is conducted, after the decision to end treatment) until withdrawal of consent, LTFU, death, or 36 weeks after the last patient's EOTV.

Appendix 2 Clinical Laboratory Tests

Pregnancy test:	**Coagulation:**
Blood or Urine Human chorionic gonadotropin (hCG)	Prothrombin time (PT)
	Activated Partial Thromboplastin Time (aPTT)
Hematology:	INR
Hemoglobin	Fibrinogen
Platelet count	
White blood cell count	**Endocrine tests:**
Absolute neutrophils, lymphocytes, eosinophils	Free thyroxine (T4)
	Thyroid-stimulating hormone
Serum chemistry:	
Albumin	**Urinalysis:**
Alkaline phosphatase	Protein
Alanine aminotransferase	Occult blood
Amylase	
Aspartate aminotransferase	**Cardiovascular disease markers**
Bicarbonate	Creatine phosphokinase
Bilirubin (Total and Direct)	N-terminal pro b-type natriuretic peptide
Blood urea nitrogen	Troponins
Calcium	
Chloride	
Creatinine	
Gamma glutamyl transferase	
Glucose	
Lipase	
Magnesium	
Phosphate	
Potassium	
Sodium	
Uric Acid	

Appendix 3 Pharmacokinetics, Immunogenicity, and Pharmacodynamic Biomarkers Schedule

Cycle	Day	Time Points	Windows	PK [a]	ADA [a]	Cytokines	PD Biomarker [a,b]	Serum Biomarker [a,b]	Fc Gamma Receptor Genotyping
Cycle 1	1	Pre retifanlimab or tebotelimab infusion	n/a	X	X	X	X	X	X
		End of retifanlimab or tebotelimab infusion	+15 min	X					
		Pre enoblituzumab infusion [c]	n/a	X					
		End of enoblituzumab infusion	+15 min	X		X	X	X	
		4 hours after end of enoblituzumab infusion	±10 min	X		X		X	
	2	No specific time	n/a	X		X	X	X	
	3	No specific time	n/a	X		X	X	X	
	8	No specific time	n/a	X		X	X	X	
	15	No specific time	n/a	X		X	X	X	
Cycle 2 Odd Cycles ≥3	1	Pre retifanlimab or tebotelimab infusion	n/a	X	X	X	X	X	
		End of retifanlimab or tebotelimab infusion	+15 min	X					
		Pre enoblituzumab infusion [c]	n/a	X					
		End of enoblituzumab infusion	+15 min	X		X	X	X	
Cycle 4 Cycle 6	1	Pre retifanlimab or tebotelimab infusion	n/a	X	X		X	X	
		End of retifanlimab or tebotelimab infusion	+15 min	X					
		Pre enoblituzumab infusion [c]	n/a	X					
		End of enoblituzumab infusion	+15 min	X					
IRR-CRS [d]	n/a	No specific time	n/a	X		X			
End of Treatment [e]	n/a	No specific time	n/a	X	X		X	X	
Follow-up	n/a	12 weeks after end of treatment [f]	n/a	X	X				
	n/a	24 weeks after end of treatment [f]	n/a	X	X				

a Do not collect PK, ADA, or biomarker samples from the infusion port. Blood samples will be collected from the arm contralateral to the site of IV infusion. If an indwelling catheter is used, the fluid in the catheter will be removed and discarded prior to the collection of blood sample for PK, ADA, or biomarker assessments. Obtain PK samples as follows: Pre-infusion: Before start of first infusion on visit day (dosing day). When collecting multiple samples, collect the PK sample first.

b PD biomarker and serum biomarker samples to be collected only up to and including Cycle 6.

c Only to be collected if enoblituzumab is not administered on the same day as retifanlimab or tebotelimab.

d Additional samples may be obtained selectively at additional time points in patients who experience signs and symptoms of infusion related reaction or cytokine release syndrome.

e Sample to be collected at EOTV or, if no EOTV is conducted, when the decision is made to end treatment.

f For patients with evidence of ADA from any prior visit. End of treatment refers to EOTV or, if no EOTV is conducted, when the decision is made to end treatment.

Cycle	Day	Time Points	Windows	PK [a]	ADA [a]	Cytokines	PD Biomarker [a,b]	Serum Biomarker [a,b]	Fc Gamma Receptor Genotyping

Notes:

- Actual start and end of infusion times, PK, and ADA sample collection times will be recorded on the CRFs.
- Pre-infusion samples should be collected before the start of infusion on visit day (dosing day).
- End of infusion (EOI) is defined in the Pharmacy Manual.
- Samples required at EOI can be drawn up to 15 minutes after the infusion is complete. For each study drug, up to 10 additional minutes of infusion time are permitted to allow for flushing the line:
  - Retifanlimab infusion duration = 60 minutes.
  - Tebotelimab infusion duration = 60 minutes.
  - Enoblituzumab infusion duration = 120 minutes.

Appendix 4 RECIST 1.1 Guidelines

Adapted from Eisenhauer 2009 **(32)**.

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

1 Measurability of Tumor at Baseline

1.1 Definitions

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

1.1.1 Measurable

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

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

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in *short* axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the *short* axis will be measured and followed. See also notes below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

1.1.2 Non-measurable

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

1.1.3 Special considerations regarding lesion measurability

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

Bone lesions:

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

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

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

1.2 Specifications by methods of measurements

1.2.1 Measurement of lesions

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

1.2.2 Method of assessment

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

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

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

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

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

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

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

2 Tumor Response Evaluation

2.1 Assessment of overall tumor burden and measurable disease

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

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

Where more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as *target lesions* and will be recorded and measured at baseline. For example, in instances where patients have only one or two organ sites involved, a maximum of two and four lesions respectively will be recorded). Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesions which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. As noted above, pathological nodes which are defined as measurable and may be identified as target lesions must meet criterion of a short axis of ≥ 15 mm by CT scan. Only the *short* axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

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

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

2.3 Response criteria

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

2.3.1 Evaluation of target lesions

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

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

Progressive Disease (PD): at least a 20% increase in the sum of diameters of target lesions, taking as reference the *smallest sum on study* (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (*Note:* the appearance of one or more new lesions is also considered progression).

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

2.3.2 Special notes on the assessment of target lesions

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

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

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

2.3.3 Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only *qualitatively* at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis).

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

Progressive Disease (PD): *Unequivocal progression* (see comments below) of existing non-target lesions. (*Note:* the appearance of one or more new lesions is also considered progression).

2.3.4 Special notes on assessment of progression of non-target disease

The concept of progression of non-target disease requires additional explanation as follows:

When a patient also has measurable disease. In this setting, to achieve 'unequivocal progression; on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression *solely* on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease. The same general concepts apply here as noted above, *however*, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

2.3.5 New Lesions

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

A lesion identified on a follow-up study in an anatomical location that was *not* scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain

ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

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

2.4 Evaluation of best overall response

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

2.4.1 Time point response

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

2.4.2 Missing assessments and inevaluable designation

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

2.4.3 Best overall response: all time points

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

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

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

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

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

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

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

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

a. If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration". Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is *not* a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in **Table A-1** and **Table A-2**.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at

the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

2.5 Confirmation/Duration of response

2.5.1 Confirmation

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

2.5.2 Duration of overall response

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

2.5.3 Duration of stable disease

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

Appendix 5 Principal Investigator's Agreement

Study Title:	A Phase 2 Open-Label Trial to Evaluate Enoblituzumab in Combination with Retifanlimab or Tebotelimab in the First-Line Treatment of Patients with Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck
Study Number:	CP-MGA271-06

I have read the protocol described above.

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

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

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

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

Signed:_____

Date:_____

Name (printed):_____

Title:_____

Affiliation:_____

Address:_____

Phone number:_____

CP-MGA271-06 Protocol Amendment 1 (16-Dec-2020)
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User Task: eSignatories Approval	Data Management/Statistics Approval (Intended or Designee) 17-Dec-2020 16:35:43 GMT+0000