2 SYNOPSIS

Name of Sponsor/Company: MacroGenics, Inc.	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**
Name of Finished Product: Enoblituzumab (also known as MGA271) Retifanlimab (also known as MGA012 or INCMGA00012) Tebotelimab (also known as MGD013)		
Name of Active Ingredient(s): Enoblituzumab: Humanized anti-B7-H3 monoclonal antibody Retifanlimab: Humanized anti-PD-1 monoclonal antibody Tebotelimab: Humanized PD-1 x LAG-3 DART® protein		

Study Number: CP-MGA271-06

Title of Study:

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

Coordinating Principal Investigator:

The coordinating principal investigator was Dan Zandberg, MD, UPMC Hillman Cancer Center, Pittsburgh, PA, USA.

Study Center(s):

This study was conducted at 41 sites in 7 countries: Australia (7 sites), Bulgaria (6 sites), Hungary (5 sites), Poland (5 sites), Spain (6 sites), Ukraine (6 sites), and United States (6 sites).

Publication (Reference):

Not required for an abbreviated report.

Study Period: 17-Mar-2021 (first patient dosed) 25-Aug-2022 (last patient end of study)	**Phase of development:** Phase 2

Objectives:

Primary Objective

Retifanlimab Cohort

- 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).

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).

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Secondary Objectives

Retifanlimab Cohort

- 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.

Exploratory Objectives

Retifanlimab and Tebotelimab Cohorts

- To explore the relationships between PK, pharmacodynamics, patient safety, and antitumor activity.
- To explore population pharmacokinetics (PPK) and exposure-response analyses.
- To explore the relationships between programmed cell death protein 1 (PD-1), programmed death ligand 1 (PD-L1), B7 homolog 3 (B7-H3), and lymphocyte-activation gene 3 (LAG-3) expression on tumor cells and response.
- To investigate the immune-regulatory activity in vivo, including various measures of T-cell and natural killer (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 peripheral blood mononuclear cells (PBMCs) and/or pre-treatment tumor biopsies and correlate with clinical response (when applicable).

Methodology:

This was 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).

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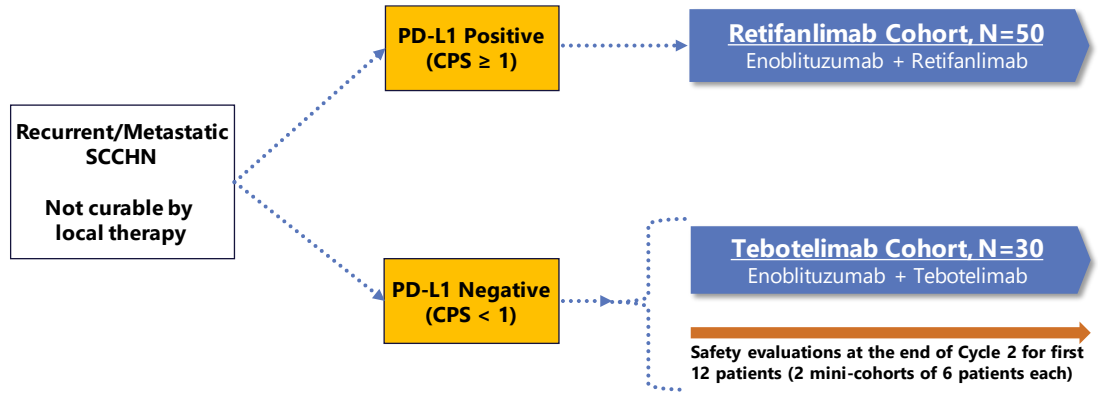
The study planned to enroll approximately 80 patients in 2 cohorts, to receive enoblituzumab in combination with either retifanlimab (Retifanlimab Cohort, PD-L1 positive [combined positive score {CPS} ≥ 1] patients, N=50) or tebotelimab (Tebotelimab Cohort, PD-L1 negative [CPS < 1] patients, N=30; see **Figure 1**). As the study sponsor terminated the study early, actual enrollment was n=48 in the Retifanlimab Cohort and n=14 in the Tebotelimab Cohort. Enrollment into each cohort occurred independently, based on CPS score, in a non-randomized fashion. Patients did not crossover between cohorts. PD-L1 expression was prospectively collected and prospectively analyzed. B7-H3 and LAG-3 expression were prospectively collected for retrospective analysis; due to early termination of the study these LAG-3 analysis was not completed.

An independent data safety monitor, the sponsor, and investigators maintained regular oversight of patient safety throughout the trial. Additionally, the Tebotelimab Cohort incorporated an interim analysis of safety after the first 12 patients (2 mini-cohorts of 6 patients each) completed Cycle 2 Day 7.

Figure 1 **Study Schema**



Abbreviations: CPS: combined positive score; DCR: disease control rate; DoR: duration of response; ORR: objective response rate; OS: overall survival; PFS: progression free survival; Q3W: every 3 weeks; SCCHN: squamous cell carcinoma of the head and neck.

The data for each of the Retifanlimab and Tebotelimab Cohorts were analyzed upon termination of enrollment in each cohort for presentation in this CSR.

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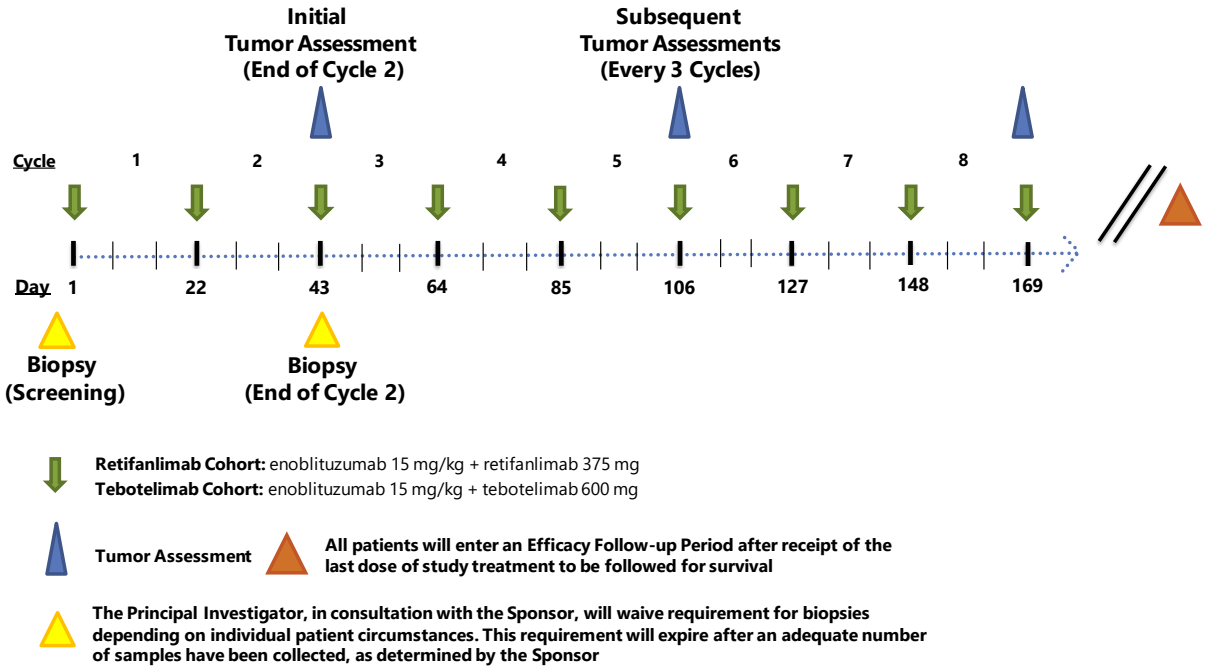
Patients received the assigned study drugs (enoblituzumab 15 mg/kg and either retifanlimab 375 mg or tebotelimab 600 mg) intravenously on a every 3 weeks (Q3W) basis, in cycles of 3 weeks duration (see **Figure 2**). Tumor assessments were scheduled to occur at the end of Cycle 2 (i.e., after approximately 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 were to enter an Efficacy Follow-up Period and be followed for survival; however, upon early termination of the study, all remaining patients were discontinued from study treatment and then from the study after completing a 30-day safety follow-up.

Figure 2 **Treatment Cycles**



Study treatment continued 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 was 35 cycles for each study drug.

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

Patients who had radiographic progression were allowed to remain on study treatment until the next scheduled radiographic evaluation if the following conditions are met: absence of clinical symptoms or signs indicating

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clinically significant disease progression; no decline in Eastern Cooperative Oncology Group (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.

On 07-Jul-2022, the sponsor notified investigators of the decision to close the CP-MGA271-06 study, effective immediately, after identifying an unusually high incidence of fatal hemorrhage of the tumor or respiratory tract in participants on both arms of the study. Investigators were advised to stop enrollment, discontinue study treatment in all patients, and have all patients complete an End of Treatment Visit within 30 days of stopping study treatment as per the study protocol. Further information about the fatal hemorrhages can be found in the body of this CSR.

Number of Patients (planned and analyzed):

Planned: approximately 80 patients
Enrolled: 62
Safety Population: 62
Response Evaluable Population: 62

Diagnosis and Criteria for Inclusion:

The patient population to be enrolled in this study consisted 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 had 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.

Test Product, Dose, Mode of Administration, and Batch Number:

Drug: Enoblituzumab
Dose: 15 mg/kg Q3W.
Mode of Administration: IV infusion over 120 minutes.
Batch Number(s): 1-FIN-3365, 1-FIN-3570, and 1-FIN-3945.

Drug: Retifanlimab
Dose: 375 mg Q3W.
Mode of Administration: IV infusion over 60 minutes.
Batch Number(s): 009F19A and 036H21A.

Drug: Tebotelimab
Dose: 600 mg Q3W.
Mode of Administration: IV infusion over 60 minutes.
Batch Number(s): 1-FIN-3357.

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Name of Finished Product: Enoblituzumab (also known as MGA271) Retifanlimab (also known as MGA012 or INCMGA00012) Tebotelimab (also known as MGD013)		
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On days when the patient received both enoblituzumab and retifanlimab or tebotelimab, retifanlimab or tebotelimab was administered first, followed by enoblituzumab.

Reference Product, Dose, Mode of Administration, and Batch Number:

Not applicable.

Duration of Treatment:

The maximum total duration of treatment was up to 105 weeks (see under Methodology, Overview, for more details).

Patients who tolerated treatment continued to receive treatment with the study drug(s) as specified in the protocol until any one of the following conditions were met:

- Adverse Event (AE) Requiring Treatment Discontinuation
  - Patients who discontinued study treatment due to AEs were to be followed by radiographic evaluation until disease progression by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, if the patients' condition allowed. If not, patients were to be followed for OS without radiographic evaluation upon the discussion with the sponsor's medical monitor.
- Completed Treatment per Protocol
- Death
- Physician Decision (only after discussion with the sponsor's medical monitor)
- Lost to Follow-up
- Pregnancy
- Progressive Disease - Clinical Progression
- Progressive Disease - Objective Progression
  - Patients who had radiographic progression according to RECIST v1.1 may have remained on study treatment until the next scheduled radiographic evaluation if the following conditions were 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.

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- 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

Criteria for Evaluation:

Efficacy Assessments

Disease Response Assessments

Tumor assessments were obtained using computed tomography (CT) and/or magnetic resonance imaging (MRI) scans, and tumor response was evaluated according to RECIST v1.1. Target and non-target lesions were 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 were to enter an Efficacy Follow-up Period, during which tumor assessments were obtained.

The overall responses were categorized as 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 was to be determined. In the context of the statistical analysis for this trial, objective response determination and the assessment of best overall response (BOR) were defined using RECIST v1.1.

Survival Assessments

Patients who discontinued from study treatment were assessed for survival status. Prior to the final OS analysis, all current survival data were to be requested regardless of interval from the prior assessment to collect the most up-to-date survival data for the final OS analysis. As a result of the sponsor's decision to terminate the study early, this analysis was not performed.

Pharmacokinetic and Immunogenicity Assessments

Serum concentrations of enoblituzumab, retifanlimab, and tebotelimab were monitored using a validated electrochemiluminescence (ECL) method, enzyme-linked immunosorbent assay (ELISA), and Affinity Capture Elution (ACE) method, respectively. Single and multiple dose PK parameters were derived from serum concentration versus time data. PPK analyses for enoblituzumab were conducted using data from this study combined with data from Study CP-MGA271-03.

Anti-drug antibodies (ADA) were measured using a validated ECL method for enoblituzumab, a validated ELISA for retifanlimab, and a validated ACE method for tebotelimab.

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Pharmacodynamic, Genotyping, and Other Biomarker Assessments

The following pharmacodynamic and biomarker assessment assay was performed: determination of PD-L1 expression via IHC (archival tumor biopsy specimens).

The following assay was conducted in a limited number of samples for exploratory endpoints relating to pharmacodynamics, genotyping, and other biomarkers: B7-H3 expression. No data are presented in this report for this assay. Per FDA "Guidance for Industry Submission of Abbreviated Reports and Synopses in Support of Marketing Applications" these data are not required for an abbreviated report. The remaining assays for exploratory endpoints were not performed, since the sponsor decided to terminate the study early.

Safety Assessments

The safety assessment were based on the evaluation of AEs that occurred 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 determined based on signs, symptoms, physical examination findings, and/or laboratory test results from enrolled patients as appropriate. Severity of AEs was 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) was to be documented as an antitumor activity outcome, not reported as an AE or SAE; they were collected as efficacy endpoints. Conversely, AEs and SAEs were reported if it was unclear if the event was due to PD.

Statistical Methods:

Analysis Populations

The study analyses were performed on the following populations:

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

Analysis Methods

As a result of the sponsor's decision to terminate the study early, a number of analyses were not performed.

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

Study drug exposures and concomitant medications were summarized by descriptive statistics. The summary of study drug exposure included 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 was calculated as percentage of total dose actually administrated divided by total dose intended during whole treatment period.

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

The proportion of patients who were negative for ADA at baseline and become positive in this assay, the proportion of patients who were 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 were summarized. Analysis was conducted separately for enoblituzumab, retifanlimab, and tebotelimab.

The primary efficacy endpoint was 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 was categorized as CR, PR, SD, PD, or NE. To qualify as an objective response, CR and PR required confirmation at least 4 weeks after initial observation of such response, and SD required an observation at least once after 6 weeks. BOR was evaluated from the start of study treatment. Number and percent of patients with their BOR were summarized. The ORR and its 2-sided 95% exact binomial confidence interval (CI) was calculated for each cohort.

DCR was 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 was to be calculated.

PFS was defined as the time from the first dose date to the date of first documented progression or death from any cause, whichever occurred first. The documented progression was to be determined by objective assessment of disease per RECIST v1.1.

DoR was 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 occurred first. The DoR was to be calculated only for the responders. The DoR analyses was to be performed only if there were enough responders to render the analyses meaningful.

AEs were summarized in tables and in listings. AEs were summarized by System Organ Class and Preferred Term, by relationship to study drugs, and by highest severity. Summaries of laboratory values display descriptive statistics for numerically quantified labs.

Summary of Results:

Patient Disposition

Retifanlimab+Enoblituzumab

A total of 48 patients were enrolled and received retifanlimab+enoblituzumab. All 48 patients discontinued treatment. The most common reason for treatment discontinuation was study terminated by sponsor (22 patients, 45.8%). The most common end of study status (reason for study discontinuation) was study terminated by sponsor (34 patients, 70.8%).

Tebotelimab+Enoblituzumab

A total of 14 patients were enrolled and received tebotelimab+enoblituzumab. All 14 patients discontinued treatment. The most common reason for treatment discontinuation was study terminated by sponsor (5 patients,

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35.7%). The most common end of study status (reason for study discontinuation) was study terminated by sponsor (11 patients, 78.6%).

Demography

Retifanlimab+Enoblituzumab

The mean age was 61.2 years. The majority of patients were male (38 patients, 79.2%), white (42, 87.5%), not Hispanic or Latino (47, 97.9%), and had an ECOG status of 1 (31, 64.6%).

Tebotelimab+Enoblituzumab

The mean age was 65.1 years. The majority of patients were male (11 patients, 78.6%), white (14, 100%), not Hispanic or Latino (12, 85.7%), and had an ECOG status of 1 (10, 71.4%).

Efficacy Results

The ORR of 6.3% (95% CI: 1.3-17.2) observed in the Retifanlimab Cohort was numerically lower than the target ORR of 28% in that cohort, while the ORR of 14.3% (95% CI: 1.8-42.8) observed on the Tebotelimab Cohort was numerically higher than the target ORR of 10% in that cohort. However, as enrollment and study treatment on both cohorts were terminated early due to a higher than expected rate of fatal hemorrhage on the study, these results should be interpreted with caution.

Pharmacokinetic Results

PPK parameters for enoblituzumab are presented in **CP-MGA271-06-Pop-PK-Rpt-2023**. Retifanlimab and tebotelimab concentrations are listed in **Section 16.2**.

Five out of 822 enoblituzumab and 2 out of 856 retifanlimab PK samples were not assayed due to early termination of the study. Exclusion of these data did not impact characterization of the PK of enoblituzumab or retifanlimab.

Immunogenicity Results

Two out of 231 retifanlimab ADA samples were not assayed due to early termination of the study. Exclusion of these data did not impact characterization of the immunogenicity of retifanlimab.

Enoblituzumab Anti-Drug Antibodies

ADA induction by enoblituzumab occurred in 10.4% of patients in both arms.

Retifanlimab Anti-Drug Antibodies

There was no ADA induction by retifanlimab.

Tebotelimab Anti-Drug Antibodies

ADA induction by tebotelimab occurred in 25.0% of patients.

Safety Results

On 07-Jul-2022, study treatment was stopped in all patients due to a high incidence of fatal hemorrhagic events including tumor hemorrhage, including 7 patients (14.6%) in the Retifanlimab Cohort and 2 patients (14.3%) in

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the Tebotelimab Cohort. Although there is an absence of a clear theoretical basis for the risk of hemorrhage based on the mechanism of action of enoblituzumab, retifanlimab, or tebotelimab, the biological function of B7-H3 is not well known. The reported safety data suggested an overall increase in the incidence of serious fatal treatment-emergent bleeding/hemorrhage events reported in participants with SCCHN exposed to enoblituzumab in combination with either retifanlimab or tebotelimab in the CP-MGA271-06 study as compared to participants with SCCHN or other malignancies exposed to enoblituzumab monotherapy or enoblituzumab in combination with other agents, and is higher than the published incidence of fatal hemorrhage in patients with SCCHN. As risk mitigation measures are very limited and evidence of clinical activity in SCCHN was modest, the safety data generated on this study does not support further investigation of enoblituzumab in combination with either retifanlimab or tebotelimab in patients with SCCHN.

Conclusion:

Retifanlimab+Enoblituzumab

- Enoblituzumab 15 mg/kg in combination with retifanlimab 375 mg demonstrated modest antitumor activity in patients with recurrent or metastatic SCCHN. Overall results are inconclusive because of the sponsor's decision to terminate the study early.
    - ORR was 6.3% (95% CI: 1.3-17.2).
- Enoblituzumab in combination with retifanlimab did not demonstrate an acceptable safety profile in patients with recurrent or metastatic SCCHN due to the increased incidence of fatal hemorrhagic events observed on the study.
- Enoblituzumab and retifanlimab PK was well characterized.
- ADA induction by enoblituzumab occurred in 10.4% of patients in both arms.
- There was no ADA induction by retifanlimab.

Tebotelimab+Enoblituzumab

- Enoblituzumab 15 mg/kg in combination with tebotelimab 600 mg demonstrated modest activity in patients with recurrent or metastatic SCCHN. Overall results are inconclusive because of the sponsor's decision to terminate the study early.
    - ORR was 14.3% (95% CI: 1.8-42.8).
- Enoblituzumab in combination with tebotelimab did not demonstrate an acceptable safety profile in patients with recurrent or metastatic SCCHN due to the increased incidence of fatal hemorrhagic events observed on the study.
- Enoblituzumab and tebotelimab PK was well characterized.
- ADA induction by enoblituzumab occurred in 10.4% of patients in both arms.
- ADA induction by tebotelimab occurred in 25.0% of patients.

Date of the Report: 27 March 2023