Phase 2 Trial of Enoblituzumab Plus Retifanlimab or Tebotelimab in First-Line Treatment of Patients with Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma

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Background

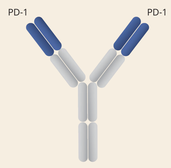
Monoclonal Antibodies

- Enoblituzumab (MGA271) is an investigational, humanized immunoglobulin G (IgG) 1κ monoclonal antibody (mAb) that binds the B7-homolog 3 (B7-H3) immunoligand with enhanced binding to the activating Fc gamma receptors CD16A, particularly the low-affinity allele CD16A-158F (**Figure 1**)[1]
- Retifanlimab (MGA012, INCMGA00012) is an investigational humanized, hinge-stabilized, IgG4κ anti-programmed death (PD)-protein 1 (PD-1) mAb blocking binding of PD-ligand 1 (PD-L1) or PD-ligand 2 (PD-L2) to PD-1 (**Figure 1**)[2]

Bispecific DART® Molecule

- Tebotelimab (MGD013) is an investigational humanized, Fc-bearing, bispecific, tetravalent DART molecule that concomitantly binds to PD-1 and lymphocyte-activation gene 3 (LAG-3), inhibiting their interaction with PD-L1 or PD-L2 and major histocompatibility complex class II (**Figure 2**)[3]

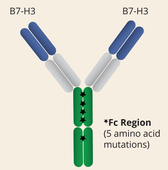
Figure 1. Mechanism of Action of Monoclonal Antibodies in this Study



RETIFANLIMAB[a]

Fab
- Binds PD-1 with high affinity (>4× greater than nivolumab and >6× greater than pembrolizumab)
- Blocks binding of PD-L1 or PD-L2 to PD-1

Fc
- Humanized, hinge-stabilized IgG4κ



ENOBLITUZUMAB

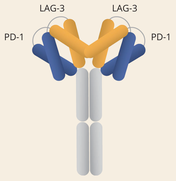
Fab
- Binds B7-H3 with high affinity

Fc
- Humanized, engineered to enhance Fc-mediated tumor cell killing
  - ↑ Affinity for activating FcγRIIIA (CD16A)
  - ↓ Affinity for inhibitory FcγRIIB (CD32B)
- Potential enhancement of adaptive immune responses

[a]Retifanlimab is licensed to Incyte

B7-H3, B7-homolog 3; Fab, antigen-binding fragment; Fc, fragment crystallizable; FcγR, Fc gamma receptors; IgG, immunoglobulin G; PD-1, programmed death-protein 1; PD-L1, programmed death-ligand 1; PD-L2, programmed death-ligand 2.

Figure 2. Mechanism of Action of Tebotelimab



TEBOTELIMAB

Fab
- Bispecific, tetravalent DART molecule PD-1 × LAG-3 co-engages both molecules (PD-1 and LAG-3) for blockade
- Blocks binding of PD-L1 or PD-L2 to PD-1
- Blocks binding of MHC-II to LAG-3

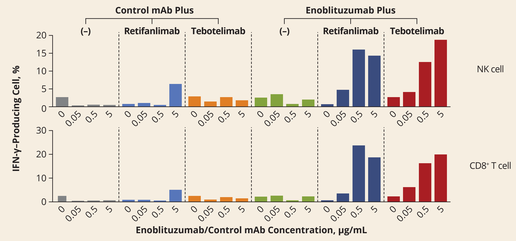
Fc
- Humanized, hinge-stabilized IgG4κ

Fab, antigen-binding fragment; Fc, fragment crystallizable; IgG, immunoglobulin G; LAG-3, lymphocyte-activation gene 3; MHC-II, major histocompatibility complex class II; PD-1, programmed death-protein 1; PD-L1, programmed death-ligand 1; PD-L2, programmed death-ligand 2.

Rationale for Study

- The simultaneous targeting of either PD-1 and B7-H3, or PD-1, LAG-3, and B7-H3 is supported by the complementary biology of these 3 molecules in modulating the immune response against tumor cells[4]
- In vitro data suggest that both retifanlimab and tebotelimab have potential to sustain enoblituzumab-mediated immune activation and antitumor activity
- Combination of enoblituzumab with retifanlimab or tebotelimab sustained the ability of natural killer cells and CD8⁺ T cells from peripheral blood mononuclear cells co-cultured with tumor cells to produce interferon gamma upon restimulation (**Figure 3**)

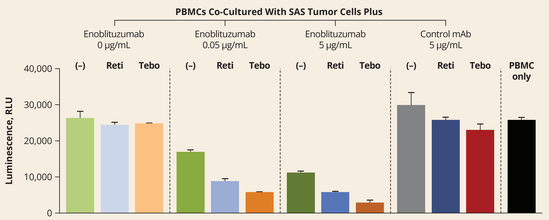
Figure 3. Effect of Enoblituzumab With Retifanlimab or Tebotelimab on the Ability of Natural Killer Cells and CD8⁺ T Cells to Produce Interferon-γ Upon Restimulation[a]



[a]Peripheral blood mononuclear cells were co-cultured with SAS tumor cells in the presence of enoblituzumab alone, or in combination with retifanlimab or tebotelimab for 6 days. Cells were collected and restimulated with PMA/ionomycin in the presence of GolgiStop. Levels of NK cell– and CD8⁺ cell–specific intracellular IFN-γ were measured by fluorescence-activated cell sorting.
IFN-γ, interferon gamma; mAb, monoclonal antibody; NK, natural killer; PMA, phorbol 12-myristate 13-acetate; SAS, B7-homolog 3–expressing head and neck cancer cell line.

- Both retifanlimab and tebotelimab enhanced enoblituzumab-dependent cytotoxicity targeting B7-H3–expressing tumor cells (**Figure 4**)

Figure 4. Effect of Retifanlimab and Tebotelimab on Enoblituzumab-Dependent Cytotoxicity[a]



[a]PBMCs were co-cultured with SAS tumor cells in the presence of enoblituzumab alone, or in combination with retifanlimab or tebotelimab for 6 days. The values in fluorescence-activated cell sorting plots represent the percent of positive cells within the natural killer cell (CD3⁻CD56⁺) gate. Cells were collected and used as effector cells to measure the cytotoxicity targeting B7-homolog 3–expressing tumor cell line (NCI H1975-Luc) at an enoblituzumab:tebotelimab ratio of 15:1. The loss of luminescence signal was used to measure the target cell lysis.
mAb, monoclonal antibody; PBMC, peripheral blood mononuclear cell; reti, retifanlimab; RLU, relative light units; SAS, B7-homolog 3–expressing head and neck cancer cell line; tebo, tebotelimab.

- Enoblituzumab mediated antibody-dependent cellular cytotoxicity (ADCC) activity in preclinical studies across multiple cancer cell lines expressing B7-H3, including melanoma, lung cancer, prostate cancer, breast cancer, bladder cancer, and renal cancer[1]
- In a multicenter Phase 1/2 study (NCT02475213), combination of enoblituzumab and pembrolizumab demonstrated safety and antitumor activity in patients with checkpoint inhibitor-naïve squamous cell carcinoma of head and neck (SCCHN) and non–small cell lung cancer, with objective response rates (ORR) of 33.3% and 35.7%, respectively (**Table 1**)[5]
- The observed ORR for patients treated with the combination of enoblituzumab and pembrolizumab represent a potential strategy to improve tumor responses in patients treated with checkpoint inhibitors monotherapy (**Table 1**)

Table 1. Summary of Efficacy Data With Anti-B7-H3 Blockade Plus Anti-PD-1 Blockade in the Context of Anti-PD-1 Blockade Monotherapy in Patients With SCCHN or NSCLC

SCCHN				
Blockade	**Anti-PD-1 + anti-B7-H3**	**Anti-PD-1 only**		
Agent(s)	**Pembrolizumab + enoblituzumab**	**Nivolumab**	**Pembrolizumab**	**Pembrolizumab**
Study	CP-MGA271-03 (NCT02475213)[5]	CheckMate-141 (NCT02105636)[6]	KEYNOTE-012 (NCT01848834)[7]	KEYNOTE-040 (NCT02252042)[8]
N	18	240	174	247
ORR	33%	13%	16%	15%

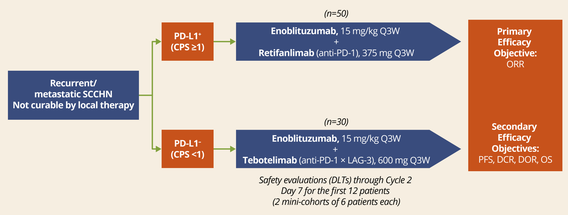
NSCLC				
Blockade	**Anti-PD-1 + anti-B7-H3**	**Anti-PD-1 only**		
Agent(s)	**Pembrolizumab + enoblituzumab**	**Nivolumab**	**Nivolumab**	**Pembrolizumab**
Study	CP-MGA271-03 (NCT02475213)[5]	CheckMate-057 (NCT01673867)[9]	CheckMate-017 (NCT01642004)[10]	KEYNOTE-001 (NCT01295827)[11]
Histology	Squamous and non-squamous	Non-squamous	Squamous	Squamous and non-squamous
N	14	108	54	87
ORR	36%	9%	19%	8%

B7-H3, B7-homolog 3; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD-1, programmed death-protein 1; SCCHN, squamous cell carcinoma of head and neck.

Study Design

- This study (NCT04634825) is a Phase 2, open-label, non-randomized trial 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
- The study is planned to be conducted at approximately 35 centers in approximately 5 countries
- Approximately 80 patients will be enrolled based on the combined positive score (CPS) in 1 of the following cohorts (**Figure 5**):
  - Retifanlimab Cohort (PD-L1–positive CPS ≥1; N=50)
  - Tebotelimab Cohort (PD-L1–negative CPS <1; N=30)
- Patients in the Retifanlimab Cohort will receive enoblituzumab 15 mg/kg and retifanlimab 375 mg once every 3 weeks, in cycles of 3 weeks' duration, for a maximum of 35 cycles
- Patients in the Tebotelimab Cohort will receive enoblituzumab 15 mg/kg and tebotelimab 600 mg once every 3 weeks, in cycles of 3 weeks' duration, for a maximum of 35 cycles
- Key study end points are summarized in **Table 2**
- In the Tebotelimab Cohort, safety (dose-limiting toxicities) will be monitored through Cycle 2 Day 7 after dosing the first 6 patients and the second 6 patients
- The initial tumor assessment will occur at the end of Cycle 2 (after approximately 6 weeks), and at the end of every 3 cycles thereafter (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
- The study started in March 2021, and patients continue to be recruited

Figure 5. NCT04634825 Study Schema: An Open-Label, Non-Randomized Phase 2 Study



CPS, combined positive score; DCR, disease control state; DOR, duration of response; LAG-3, lymphocyte-activation gene 3; ORR, objective response rate; OS, overall survival; PD-1, programmed death-protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Q3W, every 3 weeks; SCCHN, squamous cell carcinoma of head and neck.

Table 2. Key Study Objectives

Cohort	Primary objective	Secondary objectives	Exploratory objectives
Enoblituzumab + retifanlimab	▪ Investigator-assessed ORR by RECIST v1.1	▪ Investigator-assessed PFS, DCR, DOR, and OS ▪ Safety and tolerability ▪ PK and immunogenicity of enoblituzumab + retifanlimab	▪ Relationships between PK, pharmacodynamics, safety, and antitumor activity ▪ Population PK and exposure–response analyses ▪ Relationships between PD-1, PD-L1, B7-H3, and LAG-3 expression on tumor cells and response ▪ The immune-regulatory activity in vivo
Enoblituzumab + tebotelimab	▪ Safety and tolerability ▪ Investigator-assessed ORR by RECIST v1.1	▪ Investigator-assessed PFS, DCR, DOR, and OS ▪ PK and immunogenicity of enoblituzumab + tebotelimab	▪ Circulating immune cells and effect of treatment ▪ Peripheral biomarkers and correlation with potential clinical response ▪ Gene expression profiles and FcγR polymorphism in PBMCs and/or pretreatment tumor biopsies and correlation with clinical response

B7-H3, B7-homolog 3; DCR, disease control rate; DOR, duration of response; FcγR, Fc gamma receptors; LAG-3, lymphocyte-activation gene 3; ORR, objective response rate; OS, overall survival; PBMC, peripheral blood mononuclear cell; PD-1, programmed death-protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PK, pharmacokinetics; RECIST, Response Evaluation Criteria in Solid Tumors.

Key Inclusion Criteria

- Patients ≥18 years of age with histologically proven recurrent or metastatic SCCHN not curable by local therapy
- No prior systemic therapy for SCCHN in the recurrent or metastatic setting
  - Patients who completed systemic therapy >6 months before the study, if given as part of multimodal treatment for locally advanced disease, are eligible
- Primary tumor locations of oropharynx, oral cavity, hypopharynx, or larynx
- Eastern Cooperative Oncology Group performance status of 0 or 1, verified within 3 days before Day 1
- Life expectancy ≥6 months
- At least 1 radiographically measurable lesion (target lesion), as defined in Response Evaluation Criteria in Solid Tumors version 1.1
- An identified formalin-fixed, paraffin-embedded tumor specimen for immunohistochemical evaluation of pharmacodynamic markers of interest
- PD-L1 expression level that is either:
  - Positive (CPS ≥1) for the Retifanlimab Cohort, or
  - Negative (CPS <1) for the Tebotelimab Cohort

Key Exclusion Criteria

- Primary tumor site of upper esophagus, salivary gland, or nasopharynx (any histology)
- Disease suitable for local therapy administered with curative intent
- Progressive disease within 6 months of completion of curatively intended systemic treatment for locoregionally advanced SCCHN
- Radiation therapy (or other nonsystemic therapy) within 2 weeks before the first dose of study drug
- Prior therapy with an anti-B7-H3, anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-LAG-3 agent
- 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
- 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 before the first dose of study drug

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Disclosures

G. Obara has no conflict of interest to declare.

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