Phase 2 Trial of Retifanlimab (anti–PD-1) in Combination with INCAGN02385 (anti–LAG-3) and INCAGN02390 (anti–TIM-3) as First-Line Treatment in Patients with PD-1–Positive Recurrent/Metastatic Squamous Cell Carcinoma of the Head and Neck

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Introduction
● Squamous cell carcinoma of the head and neck (SCCHN) treatment has been improved with anti–PD-1 (I) therapies and yet the complexity and heterogeneity of immune checkpoint receptors expressed in the tumor micro-environment still pose a challenge; some tumors do not respond or respond poorly to anti–PD-1 (I) therapies.
● Other immune checkpoint receptors include lymphocyte–activation gene 3 (LAG-3) and T-cell immunoglobulin and mucin domain 3 (TIM-3), which are frequently coexpressed with PD-1 in tumor-infiltrating lymphocytes. 8-10
● Blockade of LAG-3 and/or TIM-3 in combination with PD-1 has synergistic effects on tumor growth in mice compared with PD-1 blockade alone. 11
● Preliminary clinical results indicate that a combination of PD-1 with LAG-3 or TIM-3 inhibitors may be a promising strategy for patients naive to checkpoint inhibitor therapy. 12

Methods

Study Design
● Randomized, double-blind, placebo-controlled, multicenter phase 2 study (NCT03078713)
● Patients will be randomized 1:1:1 to receive 1 of 3 treatments intravenously for 12 months, then every 12 weeks

Table 1: Patient Eligibility

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<tr>
<th>Inclusion Criteria</th>
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<tr>
<td>≥18 years of age</td>
<td>Prior systemic therapy for metastatic or recurrent SCCHN</td>
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<tr>
<td>Recurrent or metastatic SCCHN</td>
<td>Histologically or cytologically confirmed Primary tumor in oropharynx, oral cavity, hypopharynx, larynx</td>
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<td>Not amenable to potentially curative surgery or radiation therapy</td>
<td>Presence or history of a significant unstable medical condition that would preclude the patient from receiving study treatment</td>
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<tr>
<td>PD-L1-positive tumor ≥1% confirmed positive score determined at a central laboratory</td>
<td>History of another severe illness that would preclude the patient from receiving study treatment</td>
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Endpoints and Assessments
● Primary endpoint: progression-free survival (PFS) for Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Table 2)
● Secondary endpoints include objective response per RECIST v1.1, duration of response (DOR), disease control, overall survival, and safety

Study Population

- No prior systemic therapy for advanced disease
- PD-L1–positive advanced/metastatic SCCHN
- At least 1 measurable lesion

Clinical Trial Design
- Randomize 1:1:1 INCAGN02385: Fc-modified IgG1 INCAGN02390: fully human, aglycosylated IgG1 for PD-L1–positive recurrent or metastatic SCCHN vs retifanlimab alone

Objective
● This trial in progress aims to evaluate the efficacy and safety of combinations of 2 (retifanlimab and INCAGN02385) or 3 (retifanlimab, INCAGN02385, and INCAGN02390) immune checkpoint–inhibiting antibodies in PD-1–positive recurrent or metastatic SCCHN vs retifanlimab alone.

Statistical Analyses
● The intent-to-treat population will be used for demographics, baseline disease characteristics, disposition, and efficacy summaries and includes all patients randomized for treatment
● Sample size is based on a median PFS of 3 months, based on historical data for PD-1 monoclonal therapy in the first-line setting for PD-L1–positive advanced/metastatic SCCHN
- PPS and DOR data will be analyzed using Kaplan-Meier method (patients with no observed disease or death will be censored); the hazard ratio for PFS will be determined using a stratified Cox model
- Objective response will be analyzed using a stratified Cochran-Mantel-Haenszel test to compare between treatment groups
- All other data will be summarized with descriptive statistics
- The safety population will include all patients who receive at least 1 treatment dose of study drug, with safety defined as all Laboratory Data
- Safety will be monitored for adverse events (grades 1–5) using the National Cancer Institute Common Terminology Criteria for Adverse Events v5.0

Figure 1: Study Design

Figure 2: Countries Selected for Study

Disclosures
○ CL is supported by advisory boards from Eisai, MSD, Merck Serono, Roche, Calithera, Amsterdam, Nansensla, Seattle Genetics, and Alk Oncology; CI and EEC declare no conflicts of interest. NB, RB, and WR own and share employees and shareholders of triple I oncology (Wilkinson, DE, USA).

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References