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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-L1–Positive Recurrent/Metastatic Squamous Cell Carcinoma of the Head and Neck

Christophe Le Tourneau,[1–3,*] Lisa F. Licitra,[4] Nawel Bourayou,[5] Richard Schaub,[6] Matthias Bartenstein,[5] Wendy Wei,[6] Ezra E. Cohen[7]

[1]Institut Curie, Paris, France; [2]INSERM U900 Research Unit, Saint-Cloud, France; [3]Paris-Saclay University, Paris, France; [4]Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy; [5]Incyte Biosciences International Sàrl, Morges, Switzerland; [6]Incyte Corporation, Wilmington, DE, USA; [7]Moores Cancer Center, University of California San Diego, La Jolla, CA, USA

*Presenting author.

Introduction

- Squamous cell carcinoma of the head and neck (SCCHN) treatment has been improved with anti–PD-(L)1 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 develop resistance[1]
- 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[2,3]
- 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[4-6]
- 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[7-9]
- Triple combination of PD-1, LAG-3, and TIM-3 inhibitors reinvigorated tumor-infiltrating lymphocytes taken from ovarian cancer patients more effectively than PD-1 blockade alone[6]
- This study investigates 3 immune checkpoint inhibitors as first-line treatment for PD-L1–positive recurrent or metastatic SCCHN:
  - Retifanlimab: humanized, hinge-stabilized immunoglobulin G4κ (IgG4κ) monoclonal antibody that blocks PD-1 ligand interactions
  - INCAGN02385: Fc-modified IgG1κ monoclonal antibody that blocks LAG-3 ligand interactions
  - INCAGN02390: fully human, aglycosylated IgG1κ monoclonal antibody that blocks TIM-3 ligand interactions

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-L1–positive recurrent or metastatic SCCHN vs retifanlimab alone

Methods

Patients

- Adult patients with treatment-naive recurrent or metastatic PD-L1+ SCCHN are eligible for inclusion (**Table 1**)

Study Design

- Randomized, double-blind, placebo-controlled, multicenter phase 2 study (NCT05287113)
- Patients will be randomized 1:1:1 to receive 1 of 3 treatments intravenously for up to 2 years (**Figure 1**):
  - Treatment group 1: retifanlimab monotherapy 500 mg every 4 weeks (q4w) plus 2 placebo controls
  - Treatment group 2: retifanlimab 500 mg q4w plus INCAGN02385 350 mg every 2 weeks (q2w) plus one placebo control
  - Treatment group 3: retifanlimab 500 mg q4w plus INCAGN02385 350 mg q2w plus INCAGN02390 400 mg q2w
  - Randomization is stratified by LAG-3 expression status (positive [≥5%] or negative [<5%] tumor proportion score), PD-L1 expression status (combined positive scores 1%–19% vs ≥20%), and human papillomavirus p16 status (positive vs negative; oropharyngeal tumors only)

Table 1: Patient Eligibility

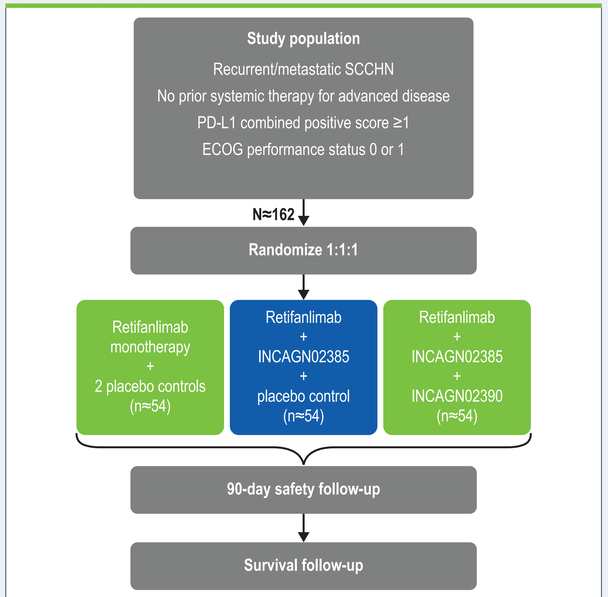
Inclusion Criteria	Exclusion Criteria
≥18 years of age	Prior systemic therapy for metastatic or recurrent SCCHN*
ECOG performance status of 0 or 1	Progressive or recurrent disease ≤6 months from end of last systemic treatment for locally advanced SCCHN
Recurrent or metastatic SCCHN • Histologically or cytologically confirmed • Primary tumors in oropharynx,† oral cavity, hypopharynx, larynx • Not amenable to potentially curative surgery or radiation therapy	SCCHN primary tumors of the nasopharynx, sinonasal cavity, or salivary gland
PD-L1–positive tumor status • ≥1% combined positive score determined at a central laboratory	Prior PD-(L)1, LAG-3, TIM-3, or other ICI therapies in any treatment setting
≥1 measurable tumor lesion per RECIST v1.1	Tumor invasion of major blood vessels with active bleeding
	Laboratory values indicative of cytopenia, renal/hepatic impairment, or hypercoagulable state

CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor; LAG-3, lymphocyte-activation gene 3; PD-L1, programmed cell death ligand 1; PD-1, programmed cell death protein 1; RECIST, Response Evaluation Criteria in Solid Tumors; SCCHN, squamous cell carcinoma of the head and neck; TIM-3, T-cell immunoglobulin and mucin domain 3.
* Prior adjuvant or neoadjuvant chemotherapy for locally advanced disease is acceptable if completed ≥6 months before study enrollment and all other criteria met.
† Oropharyngeal tumors must also have documentation of human papillomavirus p16 status (positive or negative based on local institutional standard).

Endpoints and Assessments

- The primary endpoint is progression-free survival (PFS) per 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
- Radiologic tumor assessments will be performed every 8 weeks for the first 12 months, then every 12 weeks

Figure 1. Study Design



ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed cell death ligand 1; p16, human papillomavirus p16 (measured only for oropharyngeal tumors); RECIST, Response Evaluation Criteria in Solid Tumors; SCCHN, squamous cell carcinoma of the head and neck.

Table 2: Study Endpoints

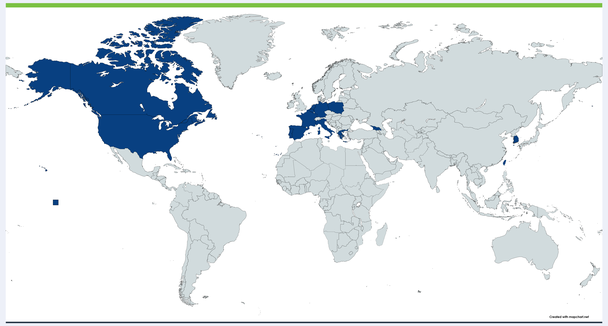
Primary efficacy
• PFS (randomization date to earliest date of disease progression* or death)
Secondary efficacy
• Objective response (PR + CR)* • Duration of response (earliest date of PR or CR until earliest date of disease progression or death)* • Disease control (CR + PR + SD†) • OS (randomization date until death from any cause)
Safety
• AE (physical examinations, changes in vital signs, blood chemistry) • AE leading to study interruption, reduction, or discontinuation

AE, adverse event; CR, complete response; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease.
* Disease progression and tumor response per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
† Stable disease defined as ≥6 months.

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 calculation is based on a median PFS of 3 months, based on historical data for α–PD-1 monotherapy in the first-line treatment setting for PD-(L)1–positive advanced/metastatic SCCHN[10]
  - PFS and DOR data will be analyzed with 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 use 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 ≥1 treatment dose
  - Adverse events will be defined using the Medical Dictionary for Regulatory Activities; severity of adverse events (grades 1–5) will use National Cancer Institute Common Terminology Criteria for Adverse Events v5.0

Figure 2. Countries Selected for Study



Disclosures

CLT participated in advisory boards from BMS, MSD, Merck Serono, Roche, Celgene, AstraZeneca, Nanobiotix, Seattle Genetics, MaxiVax, and ALX Oncology; LFL and EEC declare no conflicts of interest. NB, RS, MB, and WW are employees and shareholders of Incyte Corporation (Wilmington, DE, USA).

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