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A Phase 2, Open-Label, Multicenter Study of INCAGN01876 (Anti-GITR mAb) in Combination With Anti–PD-1 Immunotherapy in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma

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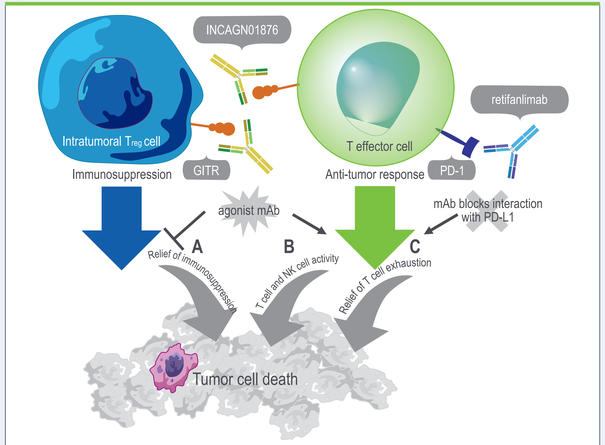
Introduction

- Reactivation of T-cell co-stimulatory pathways may overcome lack of tumor response or development of resistance to anti–programmed cell death protein (PD)-ligand (L)1 therapies[1]
  - The overall response rate of recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) to first-line anti–PD-1 monotherapy remains low (19%), and therapeutic options are particularly limited for patients with recurring or metastatic HNSCC whose disease has progressed on anti–PD-(L)1 therapies[2,3]
  - Glucocorticoid-induced tumor necrosis factor receptor family-related protein (GITR) is a co-stimulatory receptor
    - GITR promotes the proliferation and activation of T effector cells while inhibiting the suppressive effects of regulatory T cells in animal models[4-6] (**Figure 1**)
  - In preclinical tumor models, combination of anti–PD-1 with anti-GITR antibodies led to long-term survival[7]
- INCAGN01876 is a humanized anti-GITR immunoglobulin G1 monoclonal antibody (mAb) agonist of GITR
  - Preliminary clinical responses have been observed in patients with solid tumors on combination treatment with anti-GITR and anti–PD-(L)1 therapy, including PD-(L)1–naive HNSCC patients treated with INCAGN01876 plus nivolumab[8-10]

Figure 1: Mechanism of Action



INCAGN01876 (anti-GITR) and anti–PD-1 monoclonal antibodies may promote tumor cell death through multiple pathways to help overcome resistance to anti-PD-1 monotherapy. INCAGN01876 is a mAb that binds GITR and works as an agonist. Retifanlimab is a mAb that binds PD-1 and blocks its interaction with PD-L1. **A.** Intratumoral T_{reg} cells express high levels of GITR, and an agonist of GITR may induce depletion of these immunosuppressive cells.[1,11] **B.** An agonist of GITR may increase T-cell receptor (TCR)-mediated cell proliferation, survival, and cytokine production to help kill tumor cells.[1,11] **C.** PD-1/PD-L1 blockade via mAbs can lead to relief of T cell exhaustion and tumor cell death.[12]

Objective

- This trial in progress will assess the safety, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of INCAGN01876, an anti-GITR mAb, in combination with retifanlimab, an anti–PD-1 inhibitor, in patients with GITR-positive recurrent or metastatic HNSCC whose disease has progressed on or after prior systemic treatment, including PD-(L)1 therapy

Methods

Patients

- Part 1 (safety lead-in): Adults with recurrent/metastatic HNSCC who had prior anti–PD-(L)1 therapy (with or without systemic therapy) and whose tumors express GITR (tumor proportion score [TPS] ≥10%)
- Part 2 (expansion): Adults with recurrent/metastatic HNSCC who had prior systemic therapy (chemotherapy and/or PD-[L]1 inhibitor) and whose tumors express GITR (TPS ≥10%)
  - Treatment group A: Patients in 2nd line treatment setting who had prior anti–PD-(L)1 therapy
  - Treatment group B: Patients in 1st/2nd line treatment setting who are anti–PD-(L)1-naive, received up to 1 prior line of chemotherapy for recurrent/metastatic HNSCC, and who have PD-L1–positive tumors (combined positive score ≥1%)

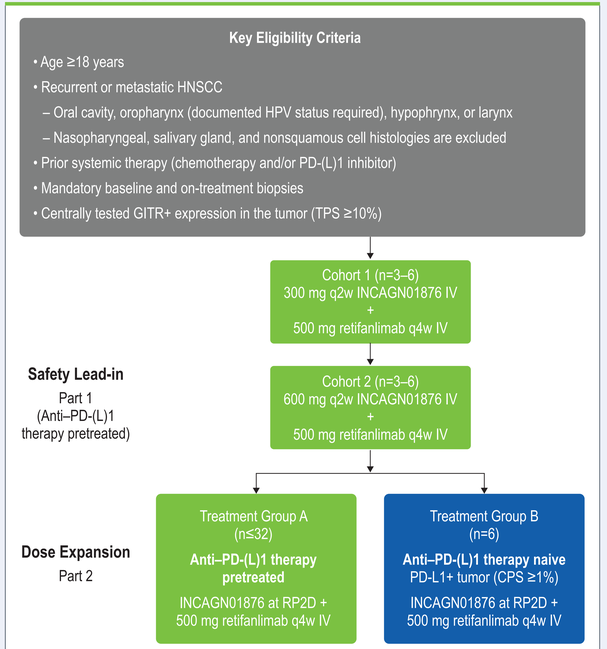
Study Design

- Multicenter, open-label, single-arm phase 2 clinical study (NCT05359692; **Figure 2**)
- Key eligibility criteria are shown in **Figure 2**
- Part 1 (safety lead-in) will be a dose-escalation phase and will determine safety and tolerability of INCAGN01876 in combination with retifanlimab
  - 2 doses will be tested, and the dose that is pharmacologically active and tolerable in combination with retifanlimab will be selected as the recommended phase 2 dose (RP2D)
- Part 2 (expansion) will determine the efficacy of INCAGN01876 in combination with retifanlimab at the RP2D, selected from part 1
- Treatment will be administered in 4-week cycles for up to 2 years

Endpoints and Assessments

- The primary endpoints are the safety, tolerability, and efficacy of INCAGN01876 in combination with retifanlimab (**Table 1**)
- Assessments of treatment-emergent adverse events (TEAEs) will be performed on a weekly schedule during cycle 1, a biweekly schedule during cycles ≥2, at end of treatment, and at 30 (±7) and 90 (±7) days after end of treatment for safety follow-up
  - TEAE severity (grades 1–5) will use National Cancer Institute Common Terminology Criteria for Adverse Events v5.0
- Radiologic tumor assessments will occur every 8 (±1) weeks for the first year, then every 12 (±1) weeks until disease progression or start of new therapy

Figure 2. Study Design



CNS, central nervous system; CPS, combined positive score; GITR, glucocorticoid-induced tumor necrosis factor receptor family-related protein; HNSCC, head and neck squamous cell carcinoma; HPV, human papilloma virus; IV, intravenous; RP2D, recommended phase 2 dose; q2w, every 2 weeks; q4w, every 4 weeks; TPS, tumor proportion score.

Statistical Analyses

- In part 1, up to 12 patients who have been previously treated with anti–PD-(L)1 therapy will be enrolled using a Bayesian optimal interval design in safety lead-in cohorts of 3–6 patients each
- In part 2 Group A, the sample size will be guided by an interim futility analysis using the Bayesian predictive probability method to allow early termination if response is insufficient[13]
  - Sample size for the efficacy population (ie, PD-[L]1 pretreated patients) was calculated using a historical control response rate for immune checkpoint inhibitor rechallenge (≈10%),[14–17] a power of 80%, and a 1-sided type I error (α) of 9%

Table 1: Study Endpoints

Endpoints
Primary: safety and tolerability of INCAGN01876 in combination with retifanlimab
In part 1 cohorts • Frequency and severity of adverse events
Primary: preliminary efficacy of INCAGN01876 in combination with retifanlimab
In all patients with prior PD-(L)1 treatment (part 1 plus part 2 treatment group A) • Objective response rate (CR or PR)*
Secondary: preliminary efficacy of INCAGN01876 in combination with retifanlimab
In all patients with prior PD-(L)1 treatment (part 1 plus part 2 treatment group A) • DOR (earliest date of CR or PR until disease progression or death)* • DCR (percentage of patients with CR, PR, or SD)* • PFS (treatment start date until disease progression or death)*
Secondary: safety and tolerability of INCAGN01876 in combination with retifanlimab
Includes all patients in study (parts 1 and 2) • Frequency and severity of adverse events
Exploratory
Includes all patients in study (parts 1 and 2) • PK and immunogenicity of INCAGN01876 in combination with retifanlimab • Assess biomarkers and their associations with clinical activity • OS (time from treatment start date until death from any cause)

CR, complete response; DCR, disease control rate; DOR, duration of response; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; SD, stable disease.
* Objective responses and disease progression are determined by investigator assessment per Response Evaluation Criteria in Solid Tumors (RECIST v1.1).

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NB, SI, FZ, and ZD are employees and shareholders of Incyte Corporation (Wilmington, DE, USA).

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