Background  Although anti-programmed cell death (PD)-ligand (L)1 therapies have improved clinical outcomes in patients with PD-L1+ recurrent or metastatic head and neck squamous cell carcinoma (r/m HNSCC), many patients do not respond or develop resistance. Reactivation of antitumor immune responses through a combination of co-inhibitory and co-stimulatory pathways may offer improved patient outcomes. Engagement of the glucocorticoid-induced tumor necrosis factor receptor family-related protein (GITR) promotes effector T-cell proliferation and activation while inhibiting regulatory T cells. In preclinical cancer models, the combination of PD-1 blockade and anti-GITR agonist monoclonal antibodies has led to long-term survival. Preliminary clinical data suggest that combined blockade using anti–PD-(L)1 and anti-GITR antibodies has an acceptable safety profile and antitumor activity in solid tumors including HNSCC. Therefore, this study aims to assess the safety and tolerability of INCAGN01876 in combination with retifanlimab (anti–PD-1) in patients with r/m HNSCC with GITR+ tumors whose disease has progressed on or after prior systemic treatment.

Methods  This open-label, multicenter, single-arm, phase 2 clinical study (NCT05359692) will enroll approximately 50 patients into part 1 (safety lead-in; n≤12) and part 2 (expansion; n≤38). In part 1, patients will receive intravenous (IV) INCAGN01876 at 2 dose levels (300 or 600 mg) every 2 weeks (q2w) plus IV retifanlimab 500 mg every 4 weeks (q4w). Dose escalation will follow the BOIN design algorithm until identification of a pharmacologically active dose or the maximum tolerated dose, or the maximum dose of 600 mg q2w is reached. Part 2 will enroll up to 32 anti–PD-(L)1 treatment-experienced and 6 anti–PD-(L)1 naïve patients. Patients will receive IV INCAGN01876 at the recommended phase 2 dose in combination with IV retifanlimab 500 mg q4w for up to 2 years. The primary endpoints are the safety and tolerability of INCAGN01876 in combination with retifanlimab (part 1) and the objective response rate determined by investigator assessment per Response Evaluation Criteria in Solid Tumors (RECIST v1.1) in all patients previously treated with anti–PD-(L)1 therapy (parts 1 and 2). Secondary endpoints include duration of response, disease control rate, progression-free survival according to RECIST v1.1, and safety and tolerability of INCAGN01876 in combination with retifanlimab in anti–PD-(L)1 naïve and previously treated patients. Exploratory endpoints include pharmacokinetics, pharmacodynamics, and overall survival assessments of INCAGN01876 in combination with retifanlimab.

Trial Registration  Clinicaltrials.gov identifier NCT05359692

Ethics Approval  The study protocol was approved by institutional review boards or independent ethics committees at participating centers.