Background Pembrolizumab alone and in combination with platinum-based chemotherapy have become standard first-line treatment options for recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC), and there is a growing unmet need for safe and efficacious treatment options for R/ M HNSCC that has progressed on or after platinum-based chemotherapy and immunotherapy. Data from Study 111/KEY-NOTE-146 showed promising antitumor activity and acceptable safety for the PD-1 inhibitor pembrolizumab given in combination with the multikinase inhibitor lenvatinib in patients with metastatic HNSCC.1 LEAP-009 (NCT04428151), a global, randomized, open-label, phase 2 trial, will assess the efficacy and safety of pembrolizumab in combination with lenvatinib versus SOC chemotherapy, as well as the efficacy and safety of lenvatinib monotherapy, in patients with R/M HNSCC that has progressed after platinum-based chemotherapy and a PD-(L)1 inhibitor.

Methods Eligible patients are adults with histologically confirmed, locally incurable R/M HNSCC of the oral cavity, oropharynx, hypopharynx, or larynx, disease progression at any time during or after platinum-containing chemotherapy (with or without cetuximab), disease progression within 12 weeks from the last dose of treatment with ≥2 doses of a PD-(L)1 inhibitor, measurable disease based on RECIST v1.1 as confirmed by BICR, ECOG performance status of 0 or 1, and no major blood vessel invasion/infiltration. Patients will be randomized 3:3:2 to pembrolizumab (200 mg IV Q3W for up to 35 cycles) plus lenvatinib (20 mg orally once daily), investigator’s choice of SOC chemotherapy (docetaxel, paclitaxel, cetuximab, or capecitabine), or lenvatinib monotherapy (24 mg orally once daily). Randomization will be stratified by PD-L1 tumor proportion score (<50% versus ≥50%) and ECOG performance status (0 versus 1). Treatment will continue until centrally verified disease progression, unacceptable toxicity, or decision to withdraw. Patients in the chemotheraphy and lenvatinib monotherapy arms may be eligible to receive pembrolizumab plus lenvatinib upon disease progression. The primary endpoint is ORR according to modified RECIST v1.1 as assessed by BICR. Secondary endpoints include PFS, OS, DOR, and safety. Intrimum futility analysis will be conducted for the lenvatinib monotherapy arm. Tumor imaging by CT or MRI will be performed 6 weeks after randomization, every 6 weeks through year 1, and every 9 weeks thereafter. Safety will be monitored throughout the study and for 30 days after treatment end (90 days for serious AEs if no new antican cer treatment is initiated, and at any time if the AE is considered treatment-related). Recruitment is ongoing; Planned enrollment is ~400 patients.

Results N/A

Conclusions N/A

Trial Registration ClinicalTrials.gov Identifier, NCT04428151

Ethics Approval The study and protocol were approved by the Institutional Review Board or ethics committee at each site.

Consent All patients provided written informed consent to participate in the clinical trial.

REFERENCE

Methods IPI-549-01 (NCT02637531) evaluates eganelisib in advanced solid tumors, as monotherapy and in combination with nivolumab. The combination expansion dose was eganelisib 40 mg QD PO + nivolumab 240 mg Q2W IV. Combination expansion cohorts include SCCHN patients resistant to immediate prior anti-PD(L)1 therapy. Safety, preliminary clinical activity, PK, and correlative study of blood and tumor biopsy samples were mandated.

**Results** As of June 1, 2020, 180 patients were treated with eganelisib + nivolumab including 21 with SCCHN. The most common (>20% of patients) treatment-emergent adverse events in patients treated with eganelisib + nivolumab (N = 180) were fatigue (34.4%), increased AST (30.0%), increased ALT (26.7%), nausea (25.0%), pyrexia (25.0%), anemia (22.8%), decreased appetite (20.6%), and cough (20.6%). 85 (47.2%) patients experienced at least 1 treatment-emergent serious adverse event (SAE) and 19 (10.6%) had a treatment-related SAE. There were no treatment-related grade 5 adverse events as assessed by investigators. Preliminary data from the SCCHN cohort show that in the efficacy-evaluable population which includes all patients (n=20) who had at least 1 post-baseline response assessment or discontinued treatment due to disease progression, the overall response rate (ORR, ie. CR [complete response] or PR [partial response] per RECIST v1.1) is 10.0%, the disease control rate (DCR, ie. CR, PR, or SD [stable disease]) is 45.0%, and the clinical benefit rate (CBR, ie. CR, PR, or SD of at least 24 weeks from first treatment) is 25.0%, per RECIST v1.1. For patients that received ≤2 lines of prior systemic therapy (n=11), the ORR is 20.0%, the DCR is 40.0%, and the CBR is 30.0%. In total, there are 2 patients with PR (duration of response 1.6–9.3 months) and 3 with SD for greater than 6 months’ treatment duration. Translational data including T cell proliferation in peripheral blood as well as markers of inflammation in baseline biopsy of PR patient will be presented.

**Conclusions** Eganelisib + nivolumab demonstrates an acceptable safety profile and preliminary clinical activity in patients with SCCHN who were resistant to immediate prior anti-PD(L)1 therapy. Updated clinical and translational data will be presented.

**Ethics Approval** The study was approved by WIRB, Study Number 1188591 and IRB Tracking Number: 20180297.

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0352

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**Abstract 353 Figure 1** Iovance LN-145 (autologous TIL cell therapy product) Manufacturing

**Abstract 353 Figure 2** IOV-COM-202 Study Schema

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**Background** Single-agent checkpoint inhibitors (CPI) are an approved first or second-line therapy in head and neck squamous cell carcinoma (HNSCC), but their efficacy is limited. Adoptive cell therapy with tumor infiltrating lymphocytes (TIL, LN-145) has demonstrated efficacy in multiple malignancies alone or in combination with CPI. To improve HNSCC therapy, a combination of pembrolizumab and LN-145 was explored.

**Methods** IOV-COM-202 is an ongoing Phase 2 multicenter, multi-cohort, open-label study evaluating LN-145 in multiple settings and indications, and here we report cohort 2A which enrolled CPI naïve HNSCC patients who received the combination of LN-145 and pembrolizumab. Key eligibility criteria include up to 3 lines of prior therapy, ECOG <1, at least one resectable metastasis for LN-145 production, and at least another measurable lesion after tumor resection. Primary endpoints are ORR per RECIST v1.1 by investigator and safety as measured by the incidence of grade ≥3 treatment-emergent adverse events (TEAEs). LN-145 production method uses central GMP manufacturing in a 22-day process yielding a cryopreserved TIL product (figure 1). Preconditioning chemotherapy consists of cyclophosphamide/fludarabine, followed by LN-145, and then <6 doses of IL-2 over <3 days. Pembrolizumab is initiated post-tumor harvest but prior to LN-145 and continues after LN-145 infusion Q3W until toxicity or progression (figure 2).

**Results** Nine (N=9) HNSCC patients have received LN-145 plus pembrolizumab, with a median duration of follow up of 6.9 months. Nine and 8 patients were evaluable for safety and efficacy, respectively. Mean number of prior therapies was 1.1 with 89% of the patients having received prior chemotherapy. Four were HPV+, 2 HPV−, 3 unknown. The Treatment Emergent Adverse Event (TEAE) profile was consistent with the underlying advanced disease and the known AE profiles of pembrolizumab, the lymphodepletion and IL-2 regimens. The most common TEAE were chills, hypotension, anemia, thrombocytopenia, pyrexia, fatigue and tachycardia. Four patients had a confirmed, objective response with an ORR of 44% (1 CR, 3 PR, 4 SD, 1 NE) per RECIST 1.1. The disease control rate at data cutoff was 89% in 9 patients, and 7 of the 8 evaluable patients (87.5%) had a reduction in target lesions. Median DOR was not reached.