Background Immuno-STATs™ are modular fusion proteins designed for the selective delivery of IL-2 to tumor-antigen specific CD8+ T cells. CUE-101, the first Immuno-STAT in clinical trials, is composed of a human leukocyte antigen (HLA) complex, HLA-A*0201, a peptide epitope derived from the HPV16 E7 protein, and 4 molecules of reduced affinity human interleukin-2 (IL-2) designed to bind, expand, and activate HPV16-specific CD8+ T cells for the treatment of HPV16+ cancers.

Methods CUE-101-01 is a first-in-human study in patients with HLA-A*0201 genotype and HPV16+ recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC). R/M HNSCC patients refractory to ≥1 platinum- or checkpoint-inhibitor-based systemic therapies received CUE-101 monotherapy. Patients with previously untreated PD-L1+ (CPS ≥ 1) R/M HNSCC received CUE-101 and pembrolizumab 200 mg. Therapy was administered every 3 weeks until disease progression or unacceptable toxicity. Escalating doses of CUE-101 monotherapy or in combination with pembrolizumab were evaluated, followed by expanded enrollment at the recommended phase 2 dose (RP2D). Objectives included evaluation of safety, pharmacokinetics (PK), pharmacodynamics (PD), and antitumor activity.

Results As of July 25, 2022, 62 patients have received CUE-101 ranging from 0.06 to 8 mg/kg/dose. The most common adverse events included fatigue (46%), anemia (24%), chills (24%), and hyponatremia (22%). In the monotherapy dose escalation portion, a MTD was not identified, and 4 mg/kg was chosen as the RP2D based on PK, PD, and preliminary clinical activity. CUE-101 dose escalation from 1 to 4 mg/kg in combination with pembrolizumab 200 mg has been completed with no DLTs observed and expansion of CUE-101 at 4 mg/kg with pembrolizumab is ongoing. PK data demonstrate dose-dependent increases in drug exposure that are sustained upon repeat dosing. PD data demonstrate selected expansion of HPV-16 E711-20-specific CD8+ T cells in the peripheral blood. Of the 19 evaluable patients treated with CUE-101 monotherapy at the RP2D of 4 mg/kg, 1 patient experienced partial response (PR) and 7 stable disease (SD) for ≥12 weeks. Of the 10 evaluable patients treated with CUE-101 plus pembrolizumab, 3 patients experienced PR (2 confirmed) and 2 patients SD for ≥12 weeks.

Conclusions CUE-101 has a manageable safety profile and demonstrates activity alone and in combination with pembrolizumab.

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Trial Registration ClinicalTrials. gov NCT03978689

Ethics Approval This study was approved by Ethics and Institutional Review Boards (IRBs) at all study sites. IRB reference numbers: Advarra Pro00037736 (Moffitt Cancer Center), IRB 52744 (Stanford University School of Medicine), HIRPO# 201905108 (Washington University School of Medicine), DF/HCC IRB# 19-374 (Massachusetts General Hospital), WIRB STUDY00008948 (University of Washington, Seattle), IRB 191714 (Vanderbilt University Medical Center Vanderbilt-Ingram Cancer Center).

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