438 A PHASE 1 TRIAL OF CUE-101, A NOVEL HPV16 E7-PHLA-IL2-FC FUSION PROTEIN, ALONE AND IN COMBINATION WITH PEMBROLIZUMAB IN PATIENTS WITH RECURRENT/METASTATIC HPV16+ HEAD AND NECK CANCER

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Background Immuno-STATs™ are novel, modular fusion proteins designed to selectively activate tumor-antigen-specific CD8+ T cells. CUE-101 is comprised of a human leukocyte antigen (HLA) complex, HLA-A*0201, a peptide epitope derived from the HPV16 E7 protein, and 4 molecules of a reduced affinity human interleukin-2 (IL-2) and is designed to bind and activate HPV16-specific T cells for treatment of HPV16-driven cancers. In preclinical studies CUE-101 demonstrated selective binding, activation, and expansion of HPV16 E7-specific CD8+ T cells, and a murine surrogate activated anti-tumor immunity.[1]

Methods CUE-101-01 is a first-in-human study in HLA-A*0201 positive patients with HPV16+ recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC). Safety of escalating monotherapy and combination doses was evaluated to establish the recommended phase 2 dose (RP2D) for expanded enrollment. Patients with R/M HNSCC refractory to 1 or more prior platinum or pembrolizumab based systemic treatments received CUE-101 monotherapy, and patients with R/M HNSCC and PD-L1 tumor expression received combination CUE-101 and 200 mg pembrolizumab as first line treatment. Study treatment was administered intravenously every 3 weeks until progression or toxicity. Objectives included evaluation of safety, pharmacokinetics (PK), pharmacodynamics (PD), and antitumor activity.

Results As of June 30, 2021, 39 patients have received CUE-101 monotherapy ranging from 0.06 to 8 mg/kg. The maximum tolerated dose (MTD) was not identified. Based on PK, PD and clinical data, a monotherapy RP2D of 4 mg/kg was selected. The combination cohort of 1 mg/kg CUE-101 and pembrolizumab has been tested and dose escalation is ongoing. Adverse events have included CTCAE grade 2 or less fatigue (41%), anemia (31%), lymphopenia (24%), chills (21%), decreased appetite (19%) and dyspnea (17%). CUE-101 PK data demonstrate dose-dependent increases in drug exposure that are sustained upon repeat dosing. PD data demonstrate dose-dependent expansion of HPV-16 E711-20-specific CD8+ T cells, sustained increase in natural killer cells and transient increase in Treg cells. An increase in CD3+ GZMB+ tumor infiltrating T cells was observed in tissue following treatment with CUE-101 in one patient with available pre- and post-treatment biopsies. One patient at the CUE-101 monotherapy RP2D has an ongoing partial response and 8 of 33 patients have experienced stable disease $\geq$ 12 weeks based on RECIST 1.1 criteria.

Conclusions CUE-101 is a novel immunotherapeutic demonstrating acceptable safety and tolerability with encouraging PD signals, supporting selective activation of tumor-specific T cells, and promising antitumor activity. Enrollment continues in both monotherapy and combination cohorts.

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Trial Registration ClinicalTrials.gov NCT03978689

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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), IRB 191714 (Vanderbilt University Medical Center Vanderbilt-Ingram Cancer Center), HRPO# 201905108 (Washington University School of Medicine), 2019–087 Karmanos Cancer Institute, DF/HCC IRB# 19-374 (Massachusetts General Hospital), WIRB 2000026098 (Yale Cancer Center), WIRB 1908869642 (University of Arizona Cancer Center), WIRB STUDY00008948 (University of Washington, Seattle), IRB (IRBMED) HUM00165746 (University of Michigan Comprehensive Cancer Center), WIRB IRB00112341(Winship Cancer Institute/Emory University), 2019–0578 (The University of Texas MD Anderson Cancer Center), IRB 20-073 (Memorial Sloan Kettering Cancer Center), IRB00255391 (Johns Hopkins University School of Medicine).

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