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A Phase 1 Trial of CUE-101, a Novel HPV16 E7-pHLA-IL2-Fc Fusion Protein, in Patients with Recurrent/Metastatic HPV16+ Head and Neck Cancer

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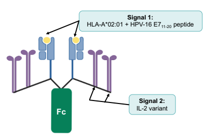
Background

Human papillomavirus (HPV) associated cancers present a significant unmet medical need. Immuno-STATs™ (*Selective Targeting and Alteration of T cells*) 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 HPV type 16 E7 protein, and 4 molecules of a reduced affinity human interleukin-2 (IL2), designed to bind and activate HPV-specific T cells for eradication of HPV16-driven cancers (**Figure 1**). Preclinical studies demonstrated targeted expansion of an HPV16 $E7_{11\text{-}20}$-specific population of cytotoxic CD8+ T cells, reduced potential for off target toxicity, and in vitro and in vivo evidence supporting potential clinical efficacy of CUE-101[1].

Figure 1. CUE-101 Immuno-STAT Design



This novel mechanism of selective engagement and expansion of tumor antigen-specific T cells has the potential for anticancer efficacy with reduced toxicity relative to non-targeted forms of immunotherapy that induce systemic activation of the immune system. CUE-101 is designed to target HPV16 $E7_{11\text{-}20}$-specific T cells for the treatment of HLA-A*0201 patients with HPV16-positive malignancies: predominantly oropharyngeal, cervical, anal, vaginal, vulvar and penile.

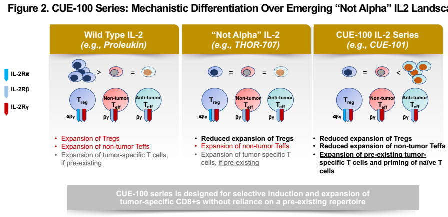
The first indication under study, in the ongoing Part A and planned Part B of this trial, is HPV16+ head and neck squamous cell carcinoma (HNSCC), in patients who have been refractory to or relapsed after initial therapy (NCT03978689). Head and neck carcinomas are the sixth most common cancer in the world, accounting for approximately 630,000 new cases and more than 350,000 deaths each year [2,3]. A significant subset of the cases of HNSCC includes approximately 85,000 HPV-associated (oropharyngeal) tumors, which means that the head and neck region is the second most common HPV+ tumor site. In fact, at the current pace, oropharyngeal cancer incidence is expected to surpass cervical cancer incidence by 2020 in the US [3,4,5].

Protocol amendment CUE-101-01 Version 3 includes Parts C and D. Part C is a CUE-101 dose escalation phase and Part D is a dose expansion phase in combination with an anti-programmed cell death 1 (PD-1) antibody, KEYTRUDA® (pembrolizumab) in patients with recurrent/metastatic HPV16+ HNSCC, as an initial therapy. In mice, the activity of a CUE-101 surrogate molecule provided direct evidence for induction of a specific antitumor immune response in vivo resulting in tumor rejection and immunologic memory, which was further enhanced in combination with anti-PD-1 treatment.

Mechanistic Differentiation from "Not-Alpha"-Directed IL2 Molecules

Through structure-based protein engineering, CUE-100 series molecules are designed for selective delivery of IL2 to tumor-specific T cells. The pHLA component directs IL2 to T cells bearing the antigen-specific TCRs. To increase selectivity for target T cells and to minimize the potential for toxicity mediated through global IL2-driven activation of IL2 receptor (IL-2R) expressing cells, two point mutations (H16A and F42A) were introduced into the IL-2 sequences of CUE-101. These mutations were previously demonstrated to reduce IL2 interaction with the IL2Rα chain and IL2Rβ, respectively [6,7]. Taken together, this molecular framework biases the selective activation of tumor-specific T cells while avoiding the global stimulation of IL2R expressing cells, elimination of the bias toward Treg activation that compromises antitumor immunity, and minimization of toxicities associated with wildtype IL2 administration.

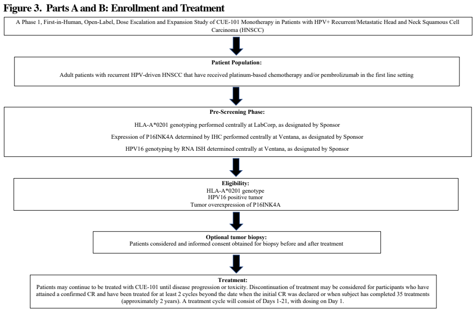
Figure 2. CUE-100 Series: Mechanistic Differentiation Over Emerging "Not Alpha" IL2 Landscape



Methods

Parts A and B of this Phase 1, open-label, 2-part study aim to characterize the safety, tolerability, PK, PD, immunogenicity, and preliminary antitumor activity of CUE-101 administered by IV infusion once Q3W as monotherapy in HLA-A*0201-positive patients with HPV16+ recurrent/metastatic HNSCC tumors.

Figure 3. Parts A and B: Enrollment and Treatment



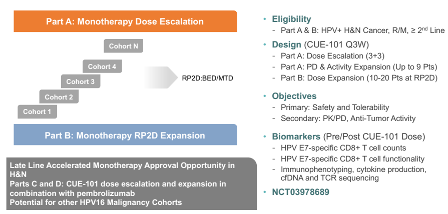
Phase 1 Study Design

The goal of Part A is to characterize the safety, tolerability, and biological effects of CUE-101: to describe the DLTs and immune responses for each dose level studied, and to define the MTD based on the incidence of DLTs in each cohort during the period up to Study Day 21 of Cycle 1. Seven dose levels are planned for evaluation as shown in **Table 1**.

Table 1: Planned Dose Levels for Part A

Cohort	CUE-101 Dose
Cohort 1	0.06 mg/kg (starting dose)
Cohort 2	0.18 mg/kg
Cohort 3	0.54 mg/kg
Cohort 4	1 mg/kg
Cohort 5	2 mg/kg
Cohort 6	4 mg/kg
Cohort 7	8 mg/kg

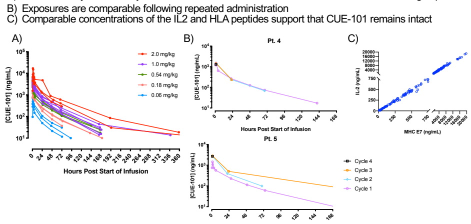
A total of 69 doses of CUE-101 has been administered to 24 patients at 10 US sites. Based on the 3 + 3 design, dose escalation continues. Dosing proceeded from a starting dose of 0.06 mg/kg in Cohort 1 to a dose of 4 mg/kg in Cohort 6. Escalation proceeded from 0.06 mg/kg to 0.18 mg/kg to 0.54 mg/kg in Cohort 3, without observation of DLT. A single DLT was observed in Cohort 4 (1 mg/kg), but additional DLTs were not observed upon cohort expansion to 6 patients, allowing dose escalation to 2 mg/kg in Cohort 5, where no DLTs were reported, resulting in approval of escalation to 4 mg/kg in Cohort 6.



- **Eligibility**
  - Part A & B: HPV+ H&N Cancer, R/M, ≥ 2nd Line
- **Design** (CUE-101 Q3W)
  - Part A: Dose Escalation (3+3)
  - Part A: PD & Activity Expansion (Up to 9 Pts)
  - Part B: Dose Expansion (10-20 Pts at RP2D)
- **Objectives**
  - Primary: Safety and Tolerability
  - Secondary: PK/PD, Anti-Tumor Activity
- **Biomarkers** (Pre/Post CUE-101 Dose)
  - HPV E7-specific CD8+ T cell counts
  - HPV E7-specific CD8+ T cell functionality
  - Immunophenotyping, cytokine production, cfDNA and TCR sequencing
- **NCT03978689**

Pharmacokinetics

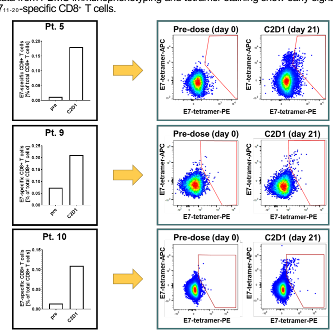
Serum CUE-101 concentrations over time are determined using a validated hybrid capture liquid chromatography tandem mass spectrometry (LC-MS/MS)-based assay that simultaneously measures the concentrations of 2 unique peptide analytes derived from the IL2 and HLA domains of CUE-101.
A) Low inter-subject variability is observed, and increased dose correlates with increased drug exposure
B) Exposures are comparable following repeated administration
C) Comparable concentrations of the IL2 and HLA peptides support that CUE-101 remains intact



Pharmacodynamics

Assessment of the potential to generate an antitumor immune response with CUE-101 treatment is an important secondary objective of the trial. Blood samples are collected prior to dosing and at several different time points following CUE-101 administration.

Preliminary data from PBMC immunophenotyping and tetramer staining show early signals of expansion of HPV-16 $E7_{11\text{-}20}$-specific $CD8^+$ T cells.



Safety

In Cohorts 1-5, all patients remained on study for the 21-day DLT evaluation period. The DLT period has not yet been completed by the 3 patients in Cohort 6. The number of cumulative doses received ranged from 1 to 6. Following a review of data from the first 21 patients, the following were identified as serious adverse reactions (SAE Grade 3) related to CUE-101 treatment: anemia (n=1), diarrhea (n=1), dyspnea (n=1), fatigue (n=2), muscular weakness (n=1), nausea (n=1) and vomiting (n=1), bullous pemphigoid (BP; n=1), and infusion-related reactions (n=1). Data for the first 21 patients in Cohorts 1-5 are shown in in **Table 2**.

Table 2: Serious Treatment-Related Adverse Events

CUE-101 Dose (mg/kg)	AE[1]	Relationship to Study Drug[2]	Toxicity Grade[3]	N[4]
0.06[5]	Worsening of Bullous Pemphigoid	P	3	1
1.0	Anemia	P	3	1
1.0	Diarrhea	P	3	1
1.0	Dyspnea	P	3	1
1.0	Infusion-related reaction	D	3	1
1.0	Muscle weakness[6]	P	3	1
1.0	Nausea	P	3	1
1.0	Vomiting	P	3	1
1.0	Worsening fatigue	P	3	1

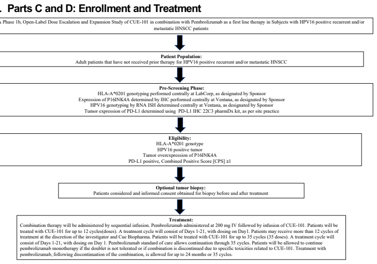
1 AE: Adverse Event
2 Relatedness to CUE-101 treatment: D=Definite; P=Possible; Pr=Probable
3 Event severity graded according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE, version 5]
4 The number of subjects reporting this AE with this toxicity grade. The AE reported in a single patient, who experienced an AE with different toxicity grades at different points in time, is reported for the highest grade observed. In this table, only the BP was observed after the C1D1 dose 1 and the C2D1 dose (see footnote 5).
5 Patient experienced a Grade 2 worsening of BP following a C1D1 dose and a Grade 3 worsening of BP following a C2D1 dose. The C1D1 dose was as per protocol, 0.06 mg/kg. Due to a dosing error, the C2D1 dose administered was 0.30 mg/kg.
6 Lower limb

Other treatment-related AEs categorized as moderate (Grade 2) were anorexia (n=1), dysphagia (n=1), muscle weakness (n=1), fecal incontinence (n=1), lymphocyte count decrease (n=1), neutropenia (n=1), and thrombocytopenia (n=1). Treatment-related AEs reported as mild in nature (Grade 1) were arthralgia (n=1), bloating (n=1), burping (n=1), anorexia (n=1), body aches (n=1), fatigue (n=5), fever (n=1), hypokalemia (n=1), muscular weakness (n=1), rash (n=1), rigors (n=1), parasthesia (n=1), upper chest discomfort (n=1), vomiting (n=1), and weight loss (n=1).

Parts C and D: CUE-101 in Combination with Pembrolizumab

Recent data suggest a role of the PD-1 pathway in creating a favorable tumor immune microenvironment for HPV infection and for subsequent tumor progression in HPV-related oropharyngeal cancer [9]. A 2-part combination study with CUE-101 and pembrolizumab in tumors with CPS ≥1 will include Part C, CUE-101 dose escalation in combination with pembrolizumab and Part D, CUE-101 dose confirmation in combination with pembrolizumab. The goal of Part C is to characterize the safety, tolerability, and biological effects of CUE-101 in combination with pembrolizumab. The starting dose of CUE-101 for the pembrolizumab combination study in first-line recurrent and/or metastatic (R/M) HNSCC patients is 1 mg/kg, a dose that was demonstrated to be safe in Part A. CUE-101 escalation will be as in **Table 1**, in combination with pembrolizumab dosed at 200 mg Q3W, shown to be the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. The goal of Part D is to confirm safety and immune activity at the preliminary CUE-101 combination RP2D identified in Part C, and to evaluate preliminary antitumor activity of CUE-101 in combination with pembrolizumab as a first-line therapy in HPV16-positive R/M HNSCC.

Figure 4. Parts C and D: Enrollment and Treatment



Summary

CUE-101-01 is a first-in-human (FIH) phase 1 study in patients diagnosed with HPV16+ (R/M HNSCC) refractory to one or more lines of therapy. Trial eligibility includes HLA class I expression, HLA-A*0201, and a diagnosis of an HPV16+ HNSCC, as assessed by p16 IHC and confirmed by HPV16 mRNA ISH. CUE-101 is administered intravenously over 60 minutes every 21 days. Objectives include determination of safety, pharmacodynamics (PD), pharmacokinetics (PK), recommended phase 2 dose (RP2D), and preliminary anti-tumor activity.

24 participants have received CUE-101 monotherapy as of 21 Oct 2020. Doses ranging from 0.06 to 2 mg/kg were determined to be safe and well-tolerated, enabling dose escalation to 4 mg/kg. Preliminary PK data demonstrate dose-dependent increases in drug exposure which are sustained upon repeat dosing, and low inter-subject variability. Preliminary data from systemic blood analyses show early signals of expansion of HPV-16 $E7_{11\text{-}20}$-specific CD8+ T cells.

CUE-101 is a novel agent that is demonstrating acceptable tolerability, favorable PK, and preliminary pharmacodynamic signals that support selective activation of tumor-specific T cells. Stable disease (SD), as determined by RECIST 1.1, was observed in several participants, with one subject maintaining SD up to 19 weeks. Safety data reported here were from 15 May 2019 to 21 Oct 2020. AEs reported were generally mild and resolved despite continued therapy. The maximum tolerated dose (MTD) has not yet been reached nor has the monotherapy RP2D been established. PD and PK analyses are ongoing as dose escalation continues.

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