A phase 1 dose-escalation and expansion study of CUE-101, a novel HPV16 E7-pHLA-IL2-Fc fusion protein, given alone and in combination with pembrolizumab in patients with recurrent/metastatic HPV16+ head and neck cancer.

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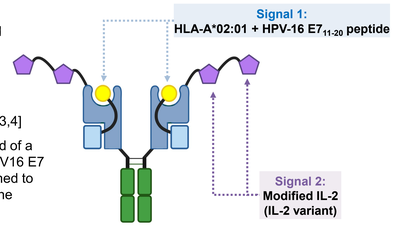
Background

- Head and neck carcinomas (HNSCC) are the 8th most common cancer in the world [1]. A significant subset of the cases of HNSCC includes human papillomavirus (HPV) associated oropharyngeal tumors, with HPV16 detectable in 80%-90% of these cases [2]. Despite current standard of care treatments, >50% of patients with advanced HNSCC will experience recurrence presenting a significant unmet need.
- Immuno-STATs are rationally engineered biologics comprised of a bivalent peptide-MHC complex and multivalent co-stimulatory molecules built on an Fc framework to enable stability, valency, favorable PK and manufacturability.
- CUE-100 series ISTs are designed to deliver attenuated interleukin-2 (IL-2) selectively to tumor-specific CD8+T cells [3,4]
- CUE-101, the first Immuno-STAT in clinical trials, is composed of a HLA-A*0201 complex, a peptide epitope derived from the HPV16 E7 protein, and 4 molecules of reduced affinity IL-2 that is designed to bind, expand, and activate HPV16-specific CD8+ T cells for the treatment of HPV16+ cancers.



CUE-101 Immuno-STAT design

Methods

- CUE-101-01 is Phase 1 open label 4-part study in HLA-A*0201 positive patients with HPV16+ R/M HNSCC.
- Parts A and C are dose escalation phases following 3+3 design rules with a Bayesian Logistic Regression Model (BLRM) overlay. Parts B and D are dose expansion/confirmation phases. In dose escalation cohorts, any dose level at which an immune response is seen may be expanded up to 9 patients as permitted by 3+3 safety rules and BLRM to further characterize activity and toxicity.
- Objectives include determination of safety, PD, PK, immunogenicity, maximum tolerated dose (MTD), recommended phase 2 dose (RP2D), and preliminary anti-tumor activity.
- Trial eligibility includes HLA-A*0201 genotype and diagnosis of HPV16+ HNSCC, determined by p16 IHC and HPV16 mRNA ISH.
- CUE-101 is given intravenously once every 3 weeks either alone (Parts A and B) or immediately following infusion of pembrolizumab 200 mg/kg (Parts C and D).

Parts A and B: Monotherapy Dose Escalation and Dose Expansion

Eligibility:
- HPV16+ R/M HNSCC
- ≥ 2nd Line; must have received platinum and/or CPI based therapy in 1st line setting.
- HLA-A*0201 genotype
- Life expectancy ≥ 12 weeks

Design:
- Dosing Q3W
- Part A: 3 + 3 Dose escalation with BLRM overlay. PD and activity expansion up to 9 patients
- Part B: Expansion to total of 20 patients at RP2D

Objectives:
- *Primary:* Safety and tolerability, pharmacokinetics
- *Secondary:* Immune activity, anti-tumor activity, immunogenicity

Part A: Monotherapy Dose Escalation
(Q3W, 3 + 3 design, with expansion up to 9 patients per cohort)

CUE-101 Dose (mg/kg): 8.0, 4.0, 2.0, 1.0, 0.54, 0.18, 0.06

Dosing Complete
Cohort 7
Cohort 6
Cohort 5
Cohort 4
Cohort 3
Cohort 2
Cohort 1

Expanded up to 9 pts per cohort

PART A ENROLLMENT COMPLETED
No MTD observed in patients dosed up to 8 mg/kg

Part B: Monotherapy Expansion
(up to 20 total patients @ RP2D)

RP2D Chosen
4.0 mg/kg (Cohort 6 dose)

PART B ENROLLMENT COMPLETED

Biomarkers: (Pre/Post CUE-101 dose)
- HPV16 E7-specific CD8+ T cell frequency and functionality
- Immunophenotyping, serum cytokines, and TCR sequencing

Abbreviations: CPI, checkpoint inhibitors; HPV16, human papilloma virus serotype 16; PK/PD, pharmacokinetics/pharmacodynamics; Q3W, once every 3 weeks; rhIL-2, recombinant human interleukin-2;RP2D, Recommended Phase 2 Dose

In Part A, dose escalation through all seven cohorts has completed. An MTD was not established. Evidence of immune responses were seen at doses ≥ 1 mg/kg and cohorts 4, 5 and 6 were expanded up to 9 patients each for further evaluation. Based on the totality of the PK, PD and clinical data, a monotherapy dose of 4 mg/kg (cohort 6) was selected for the RP2D expansion in Part B, which completed enrollment in March 2022.

Parts A and B: Patient Demographics and Prior Treatments

Patients		N = 49
Age (years)	Mean (range)	63.7 (48-82)
Sex	Male	47 (95.9%)
	Female	2 (4.1%)
Race	White	46 (93.9%)
	Black/ African American	1 (2.0%)
	Other	2 (4.1%)
ECOG	0	23 (46.9%)
	1	26 (53.1%)
Prior Lines of Therapy*	Median (range)	3 (1-6)
	• Platinum Based	44 (89.8%)
	• Checkpoint Inhibitor	44 (89.8%)
	○ PD-1	41 (83.7%)
	▪ Nivolumab	19 (38.8%)
	▪ Pembrolizumab	26 (53.1%)
	○ PD-L1	6 (12.2%)
	○ CTLA-4	1 (2.0%)
	• EGFR Inhibitor	33 (67.3%)
	• Other	41 (83.7%)

*Data extracted from EDC 22-APR-2022. All patients are HLA-A*0201-positive and HPV16-positive*
**Patients reporting > 1 prior line of therapy are counted once per category and may be included in > 1 category.*

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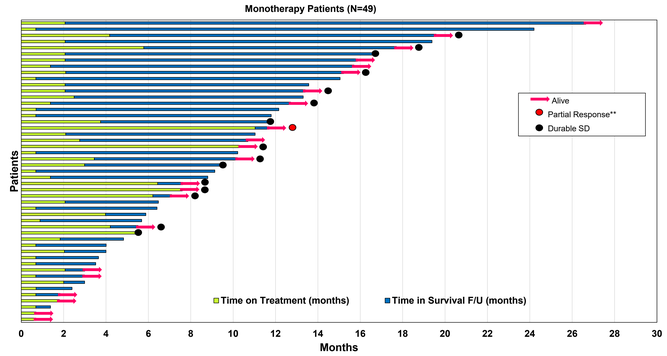
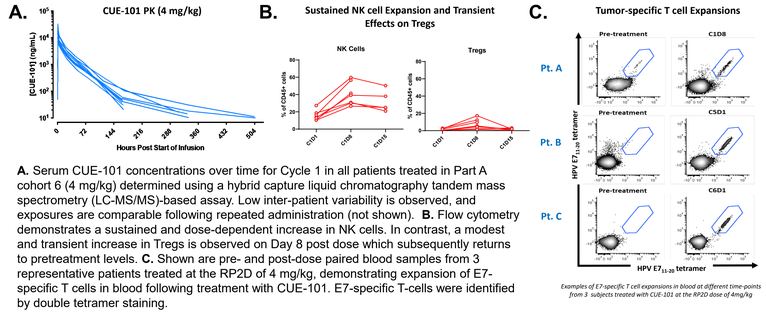
Clinical Outcomes in Monotherapy Patients all Cohorts



Overall survival in months for all patients treated in CUE-101-01 Parts A and B from time of 1st dose of drug (Cycle 1 Day 1). Patient experiencing Partial Response is indicated by the red dot, patients experiencing Durable Stable Disease by black dots (requires SD at ≥ 2 consecutive scans at 6-week and 12-week visits). *** Response symbols indicate patient experienced PR or Durable SD during the study. Onset and duration of the response is not indicated on the plot.* Data extracted from EDC 22-APR-2022

PK, Proliferation and Distribution of CD8 T cells, Tregs and NK Cells Following CUE-101 Administration at RP2D (4 mg/kg)



A. Serum CUE-101 concentrations over time for Cycle 1 in all patients treated in Part A cohort 6 (4 mg/kg) determined using a hybrid capture liquid chromatography tandem mass spectrometry (LC-MS/MS)-based assay. Low inter-patient variability is observed, and exposures are comparable following repeated administration (not shown). **B.** Flow cytometry demonstrates a sustained and dose-dependent increase in NK cells. In contrast, a modest and transient increase in Tregs is observed on Day 8 post dose which subsequently returns to pretreatment levels. **C.** Shown are pre- and post-dose paired blood samples from 3 representative patients treated at the RP2D of 4 mg/kg, demonstrating expansion of E7-specific T cells in blood following treatment with CUE-101. E7-specific T-cells were identified by double tetramer staining.

Examples of E7-specific T cell expansions in blood at different time-points from 3 subjects treated with CUE-101 at the RP2D dose of 4mg/kg

Parts C and D: CUE-101 Dose Escalation in Combination with Pembrolizumab and Planned Dose Expansion

Eligibility:
- HPV16+ R/M HNSCC
- Tumor CPS score ≥ 1
- 1st Line Therapy
- Eligible for pembrolizumab in the 1st line setting
- HLA-A*0201 genotype
- Life expectancy ≥ 12 weeks

Design:
- Dosing Q3W
- Part C: 3 + 3 Dose escalation with BLRM overlay. Part D: Expansion to total of 20 patients at RP2D

Objectives:
- *Primary:* Safety and tolerability, pharmacokinetics
- *Secondary:* Immune activity, anti-tumor activity, immunogenicity

Part C: CUE-101 and Pembrolizumab Combination Dose Escalation

Pembrolizumab 200 mg, Q3W
CUE-101 Dose (mg/kg): 4.0, 2.0, 1.0

Cohort 3 → *no DLTs* → **Part D: Combination Expansion at RP2D Dose (N = 20)**
Cohort 2 → *no DLTs*
Cohort 1 → *no DLTs*

CUE-101 4.0 mg/kg and Pembrolizumab 200 mg, Q3W (Cohort 3)

PART C ENROLLMENT COMPLETED

PART D ENROLLMENT ONGOING

Biomarkers: (Pre/Post CUE-101 dose)
- HPV16 E7-specific CD8+ T cell frequency and functionality
- Immunophenotyping, serum cytokines, and TCR sequencing

Schema for combination therapy with CUE-101 in escalating doses combined with pembrolizumab at fixed dosing of 200 mg/kg Q3W. In Part C, dose escalation through Cohorts 1, 2 and 3 has completed. No DLTs were observed and CUE-101 4 mg/kg plus pembrolizumab was selected as the RP2D for expansion.

Part C: Patient Demographics and Prior Treatments

Patients		N = 9
Age (years)	Mean (range)	61.6 (43-72)
Sex	Male	9 (100.0%)
	Female	0 (0.0%)
Race	White	8 (88.9%)
	Other	1 (11.1%)
ECOG	0	4 (44.4%)
	1	5 (55.6%)
CPS SCORE	≥ 1 to < 20	6 (66.7%)
	≥ 20	3 (33.3%)
Prior Lines of Therapy for Initial Treatment*	Patients with no prior treatment	1 (11.1%)
	Median (range)	1 (0-2)
	• Platinum Based	7 (77.8%)
	• Checkpoint Inhibitor	1 (11.1%)
	○ PD-L1	1 (11.1%)
	• EGFR Inhibitor	2 (22.2%)

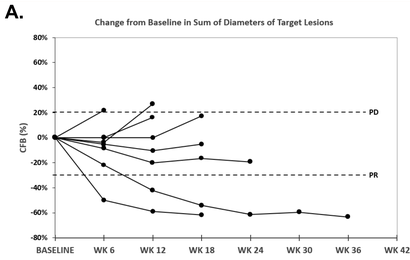
*Data extracted from EDC 22-APR-2022. All patients are HLA-A*0201-positive, HPV16-positive, with tumor expression of PD-L1 (CPS ≥ 1)*
**Patients reporting > 1 prior line of therapy are counted once per category and may be included in > 1 category. Patients with initial presentation of metastatic disease will have no prior treatments.*

Adverse Events All Patients (Monotherapy and Combination)

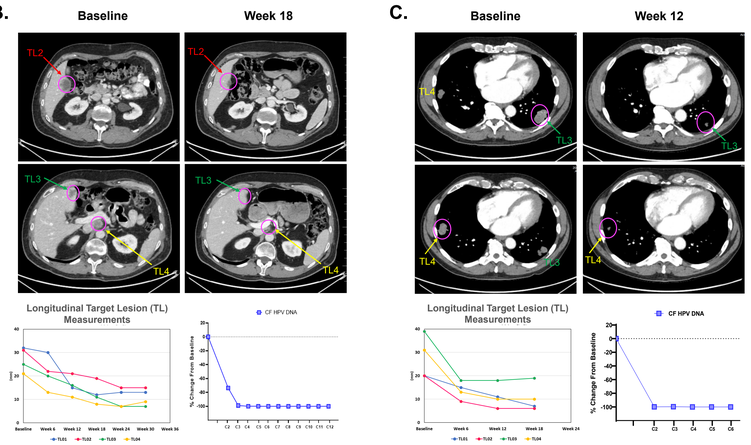
	Treatment Related Adverse Events (N=58)		All Adverse Events (N=58)	
Preferred Term	**≥ Grade 3**	**All Grades**	**≥ Grade 3**	**All Grades**
Overall Frequency	**14 (24.1%)**	**47 (81.0%)**	**25 (43.1%)**	**55 (94.1%)**
Fatigue	2 (3.4%)	19 (32.8%)	2 (3.4%)	27 (46.6%)
Anemia	1 (1.7%)	2 (3.4%)	3 (5.2%)	16 (27.6%)
Lymphocyte count decreased	3 (5.2%)	3 (5.2%)	8 (13.8%)	14 (24.1%)
Chills	0 (0.0%)	12 (20.7%)	0 (0.0%)	14 (24.1%)
Nausea	1 (1.7%)	10 (17.2%)	1 (1.7%)	12 (20.7%)
Hyponatremia	2 (3.4%)	4 (6.9%)	2 (3.4%)	12 (20.7%)
Weight decreased	0 (0.0%)	3 (5.2%)	0 (0.0%)	12 (20.7%)
Infusion reaction	2 (3.4%)	11 (19.0%)	2 (3.4%)	11 (19.0%)
Decreased appetite	0 (0.0%)	4 (6.9%)	3 (5.2%)	10 (17.2%)
Cough	0 (0.0%)	4 (6.9%)	0 (0.0%)	10 (17.2%)
Constipation	0 (0.0%)	3 (5.2%)	0 (0.0%)	10 (17.2%)
Diarrhea	2 (3.4%)	5 (8.6%)	2 (3.4%)	9 (15.5%)
Hypophosphatemia	0 (0.0%)	4 (6.9%)	1 (1.7%)	9 (15.5%)
Dysphagia	0 (0.0%)	0 (0.0%)	2 (3.4%)	9 (15.5%)
Vomiting	2 (3.4%)	7 (12.1%)	2 (3.4%)	8 (13.8%)
Pyrexia	0 (0.0%)	7 (12.1%)	0 (0.0%)	8 (13.8%)
Rash maculo-papular	1 (1.7%)	6 (10.3%)	1 (1.7%)	8 (13.8%)
Pruritus	0 (0.0%)	5 (8.6%)	0 (0.0%)	8 (13.8%)
Dyspnea	0 (0.0%)	2 (3.4%)	1 (1.7%)	8 (13.8%)
Lactate dehydrogenase increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (13.8%)
Arthralgia	0 (0.0%)	5 (8.6%)	0 (0.0%)	7 (12.1%)
Hyperkalemia	0 (0.0%)	1 (1.7%)	0 (0.0%)	7 (12.1%)
Thyroid stimulating hormone increased	0 (0.0%)	5 (8.6%)	0 (0.0%)	7 (12.1%)
Hypertension	0 (0.0%)	2 (3.4%)	0 (0.0%)	7 (12.1%)

Adverse Events (AEs) occurring at >12% frequency in all patients treated with ≥ 1 dose of CUE-101. AEs coded using MedDRA V21.0 and NCI-CTCAE v5.0 as of 22-Apr-21. At each level of summation patients reporting > 1 occurrence of the same AE are counted once at highest toxicity.

Preliminary Tumor Responses for CUE-101 in Combination with Pembrolizumb (Part C: Dose Escalation)



A. Change from baseline in the sum of target tumor lesions measured by RECIST 1.1 criteria. As of 22-Apr-2022 8 of 9 patients treated with combination therapy in Part C had at least one post dose scan. 2 patients have confirmed ongoing PRs and 2 additional patients have durable SD, defined as SD on at least 2 consecutive post-treatment scans through Week 12. **B. and C**. CT scans from baseline and the indicated times following combination treatment with CUE-101 and pembrolizumab. Patients were treated with CUE-101 at 2 mg/kg (**panel B**) and 4 mg/kg (**panel C**). Responses were seen in all target lesions for each patient as indicated in the graphs below each scan. Assessment of circulating cell-free HPV DNA (cf HPV DNA) in these patients reveals a notable decrease in cf HPV DNA levels that coincides with the objective responses.



Summary

- As of 31-Mar-2022, 49 participants have received CUE-101 monotherapy. Doses ranging from 0.06 to 8 mg/kg were generally well-tolerated and an MTD was not established. Based upon the totality of safety, PD, PK and preliminary anti-tumor activity data, Cohort 6 (4 mg/kg) was expanded to a total of 20 patients in Part B.
- Nine patients have been treated with CUE-101 from 1 to 4 mg/kg in combination with pembrolizumab across 3 dose escalation cohorts with no DLTs observed. CUE-101 4 mg/kg + pembrolizumab 200 mg was chosen for the RP2D expansion in Part D.
- Adverse events were generally mild to moderate and related to underlying disease.
- Preliminary data from peripheral blood analyses show selective expansion of HPV-16 E7$_{11-20}$-specific CD8+ T cells, with dose-dependent, sustained increases in NK cells and minimal, transient increases in Tregs.
- At the CUE-101 monotherapy RP2D, 1 patient experienced a PR with a duration of 42 weeks and an additional 6 patients experienced durable SD with a median duration of 23.9 weeks (range 11 – 36 weeks) as determined by RECIST 1.1 criteria.
- Overall survival in patients treated with CUE-101 monotherapy continues to mature with 22 of 49 patients alive in follow-up at the time of data cut-off.
- Early signs of activity of CUE-101 in combination with pembrolizumab in the dose escalation cohorts are encouraging, with 1 patient each in cohorts 2 and 3 experiencing a confirmed PR and an additional 2 patients experiencing durable stable disease.

ClinicalTrials.gov ID: *NCT03978689*

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