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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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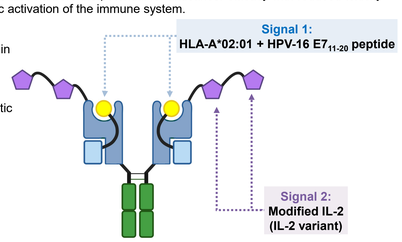
Background

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 HPV16 E7$_{11-20}$-specific T cells for the treatment of HLA-A*0201 patients with HPV16-driven cancers. while eliminating the bias toward Treg activation that compromises antitumor immunity. This novel mechanism of selective engagement and expansion of tumor antigen-specific T cells also harbors the potential for anticancer efficacy with reduced toxicity relative to non-targeted forms of immunotherapy that induce systemic activation of the immune system.

Preclinical studies demonstrated targeted expansion of an HPV16 E7$_{11-20}$-specific population of cytotoxic CD8+ T cells, and in vitro and in vivo evidence supporting potential clinical efficacy [1].

The first indication under investigation with CUE-101, is a study in HLA-A*0201 positive patients with HPV16+ recurrent and/or metastatic head and neck squamous cell carcinoma (R/M HNSCC). Head and neck carcinomas are the 6th 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 with HPV16 detectable in 80%-90% of these cases [4,5]. Despite current standard of care treatments, >50% of patients with advanced disease will experience recurrence.



CUE-101 ImmunoSTAT design

[1]Quayle SN, Girgis N, Thapa DR, et al. Clin Cancer Res. 2020;26:1953-64.
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Methods

- CUE-101-01 is Phase 1 open label 4-part study to characterize the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), immunogenicity and Maximum Tolerated Dose (MTD) of CUE-101 either alone (Parts A and B) or in combination with pembrolizumab (Parts C and D) in patients with HPV16+ R/M HNSCC.
- 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).
- Objectives include determination of safety, PD, PK, recommended phase 2 dose (RP2D), and preliminary anti-tumor activity.
- 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.

Parts A and B: Monotherapy Dose Escalation and ongoing Dose Expansion

No maximal tolerated dose (MTD) observed in patients dosed up to 8 mg/kg

Eligibility:
- HPV16+ R/M HNSCC
- ≥ 2nd Line; must have received platinum 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 1-week safety follow up of 1st patient required at each dose level prior to dosing patients 2 and 3
- Part A: PD and activity expansion up to 9 patients
- Part B: Expansion to total of 20 patients at RP2D (parts A and B)

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

Molar IL-2 content equivalent to approved rhIL-2 (aldesleukin) dose

PART A ENROLLMENT COMPLETED

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

RP2D Chosen
4.0 mg/kg (Cohort 6 dose)

PART B CURRENTLY ENROLLING

Objectives:
- *Primary:* Safety and tolerability
- *Secondary:* PK/PD, Anti-tumor activity

Biomarkers:
- HPV16 E7-specific CD8+ T cell frequency and functionality pre/post CUE-101 dose
- Immunophenotyping, cytokine release, 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; RECIST, Response Evaluation Criteria for Solid Tumors; RP2D, Recommended Phase 2 Dose

In Part A, dose escalation through all seven cohorts has completed. An MTD was not established. There was one DLT (anemia) in Cohort 4. 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 is currently enrolling.

Parts A and B: Patient Demographics and Prior Treatments

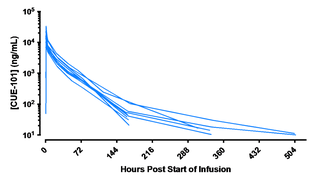
Patients		N = 43
Age (years)	Mean (range)	64.1 (48-82)
Sex	Male	41 (95.3%)
	Female	2 (4.7%)
ECOG	0	18 (41.9%)
	1	25 (58.1%)
Prior Lines of Therapy*	Median (range)	3 (1-6)
	• Platinum Based	40 (93.0%)
	• Checkpoint Inhibitor	39 (90.7%)
	○ PD-1	36 (83.7%)
	▪ Nivolumab	17 (39.5%)
	▪ Pembrolizumab	24 (55.8%)
	○ PD-L1	6 (14.0%)
	○ CTLA-4	1 (2.3%)
	• TK Inhibitor	3 (7.0%)
	• EGFR Inhibitor	30 (69.8%)

Data extracted from EDC 31-Oct-2021. Forty-three of 43 patients have demographics and prior therapy data entered in EDC at time of data extract.
**To be eligible for parts A and B, patients must have progressed following at least one prior therapy for relapsed or metastatic disease and must have previously received either a platinum-based regimen and/or pembrolizumab. Patients reporting > 1 prior line of therapy are counted once per category and may be included in > 1 category.*

ClinicalTrials.gov ID: *NCT03978689*

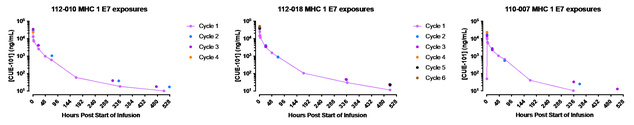
Low Inter-Patient Variability and Sustained Exposure with Repeat Dosing at the RP2D (4 mg/kg)

A.



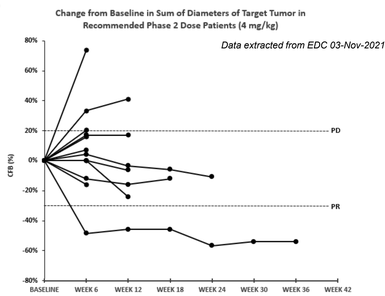
Serum CUE-101 concentrations over time are determined using a validated hybrid capture liquid chromatography tandem mass spectrometry (LC-MS/MS)-based assay that simultaneously measures the concentrations of 2 unique peptide analytes derived from the IL2 and HLA domains of CUE-101. Low inter-patient variability is observed, and exposures are comparable following repeated administration. **A.** Cumulative data set for Cycle 1 in all patients treated in Part A cohort 6 (4 mg/kg). **B.** Representative data sets from 3 of the 9 patients in cohort 6 illustrates comparable CUE-101 exposure with repeat administration.

B.



Preliminary Tumor Responses for CUE-101 Monotherapy at the RP2D (4 mg/kg)

A.



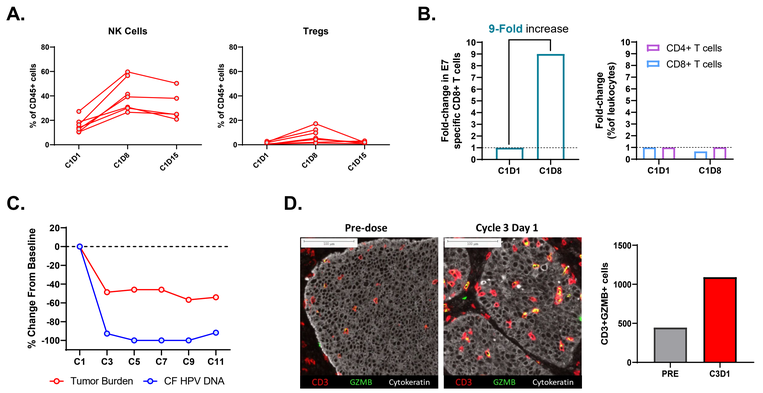
B.

Responses	N	%
Objective Response (CR or PR confirmed ≥ 4 weeks)	1	7.7%
Durable Stable Disease (SD sustained for ≥ 12 weeks*)	5	38.5%
Clinical Benefit (CR/PR + durable SD)	6	46.2%

Data extracted from EDC 03-Nov-2021
**Durable Stable Disease is defined as SD at ≥ 2 consecutive post-treatment scans through week 12.*

A. Change from baseline in the sum of target tumor lesions measured by RECIST 1.1 criteria in all patients in parts A and B treated at the RP2D of 4 mg/kg. Per protocol scans are obtained at baseline and after every other cycle. Of the 15 patients treated at 4 mg/kg, 8 patients remain on treatment, 3 are in follow-up and 4 are deceased. 13/15 patients with ≥ 1 post-dose scan are included (3 patients have 0.0% CFB at Week 6); 2/15 patients are ongoing with no post-dose scans at time of data extraction. **B.** Summary of responses per RECIST 1.1 criteria seen in all patients from Parts A and B treated at the RP2D of 4 mg/kg. There were 13 evaluable patients at time of data extraction. One patient has a PR and 5 additional patients have Durable SD, defined as stable disease on at least 2 consecutive post-treatment scans through week12, for an overall clinical benefit rate of 46.2%.

Proliferation and Distribution of CD8 T cells, Tregs and NK cells following CUE-101 administration



A. Flow Cytometry demonstrates a notable and dose-dependent increase in NK cells. In contrast, a transient increase in Tregs is observed on Day 8 post dose which subsequently returns to pretreatment levels. **B.** Increase in T cells are target-specific in the patient with observed PR. Flow cytometry demonstrates a ~9-fold increase in E7 specific T cells between Cycle 1 Day 1 (pre-administration) and a sample taken 1-week post-dose. At the same time there is essentially no change in overall circulating total T cells. **C.** Assessment of circulating cell-free HPV DNA (cf HPV DNA) in this same patient with PR by RECIST 1.1 revealed a notable decrease in cf HPV DNA levels that correlated with the observed change from baseline of tumor target lesions by RECIST 1.1 criteria. The range of decrease in cf DNA ranged from non-detectable levels to sustained > 90% reduction. **D.** Paired Biopsy from a patient prior to treatment with CUE-101 and after Cycle 3 demonstrates an increase in tumor infiltrating T cells within a target tumor lesion following CUE-101 monotherapy. Left panel IHC of tumor biopsy stained for CD3 in red and Granzyme (GZMB) in green as marker for activated T cells. Right panel quantification of CD3+ and GZMB+ cells in paired samples.

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

Part C: CUE-101 and Pembrolizumab Combination Dose Escalation | **Part D: Combination Expansion at RP2D Dose**

Initiated February 2021

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

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

Cohort 3 → *Currently Enrolling, DLT period Ongoing*
Cohort 2 → *Dosing Complete*
Cohort 1 → *Dosing Complete*

Design:
- Dosing Q3W
- Part C: 3 + 3 Dose escalation with 1-week safety follow up of 1st patient required at each dose prior to dosing patients 2 and 3
- Part C: PD and activity expansion up to 9 patients
- Part D: Expansion to total of 10-20 patients 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 and functionality
- Immunophenotyping, cytokine release, and TCR sequencing

Abbreviations: CPI, checkpoint inhibitors; HPV, human papilloma virus; PK/PD, pharmacokinetics/pharmacodynamics; Q3W, once every 3 weeks; RECIST, Response Evaluation Criteria for Solid Tumors; RP2D, Recommended Phase 2 Dose

Schema for combination therapy with CUE-101 in escalating doses combined with pembrolizumab at fixed dosing of 200 mg/kg. In Part C, dose escalation through Cohorts 1 and 2 has completed. No DLTs have been reported. Enrollment in Cohort 3 is ongoing. No decision has been made regarding further expansion of cohorts based upon observed immune activity.

Part C: Patient Demographics and Prior Treatments

Patients		N = 6
Age (years)	Mean (range)	64.5 (57-72)
Sex	Male	6 (100.0%)
	Female	0 (0.0%)
ECOG	0	1 (16.7%)
	1	5 (83.3%)
Prior Lines of Therapy*	Median (range)	1 (1-2)
	• Platinum Based	4 (80.0%)
	• Checkpoint Inhibitor	1 (20.0%)
	○ PD-L1	1 (20.0%)
	• EGFR Inhibitor	1 (20.0%)

Data extracted from EDC 31-Oct-2021. Five of 6 patients have prior therapy data entered in EDC at time of data extract.
**Prior therapies are for initial treatment of disease, patients eligible for the combination arm have had no prior treatment for recurrent and/or metastatic disease. Patients reporting >1 prior line of therapy are counted once per category.*

Adverse Events All Patients (Monotherapy and Combination)

	Treatment Related Adverse Events (N=47)		All Adverse Events (N=47)	
Preferred Term	≥ Grade 3	All Grades	≥ Grade 3	All Grades
Overall Frequency	**11 (23.4%%)**	**32 (68.1%)**	**20 (42.6%)**	**41 (87.2%)**
Fatigue	2 (4.3%)	13 (27.7%)	2 (4.3%)	19 (40.4%)
Anaemia	1 (2.1%)	2 (4.3%)	2 (4.3%)	13 (27.7%)
Lymphocyte count decreased	3 (6.4%)	3 (6.4%)	7 (14.9%)	12 (25.5%)
Chills	0 (0.0%)	7 (14.9%)	0 (0.0%)	9 (19.1%)
Decreased appetite	0 (0.0%)	4 (8.5%)	3 (6.4%)	9 (19.1%)
Hyponatraemia	1 (2.1%)	2 (4.3%)	1 (2.1%)	9 (19.1%)
Weight decreased	0 (0.0%)	2 (4.3%)	0 (0.0%)	8 (17.0%)
Cough	0 (0.0%)	2 (4.3%)	0 (0.0%)	7 (14.9%)
Dyspnoea	0 (0.0%)	1 (2.1%)	1 (2.1%)	7 (14.9%)
Nausea	1 (2.1%)	7 (14.9%)	1 (2.1%)	7 (14.9%)
Infusion reaction	1 (2.1%)	6 (12.8%)	1 (2.1%)	6 (12.8%)
Blood lactate dehydrogenase increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (12.8%)
Dysphagia	0 (0.0%)	0 (0.0%)	1 (2.4%)	6 (12.8%)
Muscular weakness	1 (2.1%)	4 (8.5%)	1 (0.0%)	6 (12.8%)
Hypophosphataemia	0 (0.0%)	3 (6.4%)	1 (2.4%)	6 (12.8%)
Myalgia	0 (0.0%)	6 (12.8%)	0 (0.0%)	6 (12.8%)
Vomiting	1 (2.1%)	4 (8.5%)	1 (0.0%)	6 (12.8%)
Arthralgia	0 (0.0%)	3 (6.4%)	0 (0.0%)	5 (10.6%)
Diarrhoea	1 (2.1%)	3 (6.4%)	1 (2.4%)	5 (10.6%)
Dizziness	0 (0.0%)	1 (2.1%)	0 (0.0%)	5 (10.6%)
Dry Mouth	0 (0.0%)	1 (2.1%)	0 (0.0%)	5 (10.6%)
Hyperkalemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (10.6%)
Hypertension	0 (0.0%)	2 (4.3%)	0 (0.0%)	5 (10.6%)
Hypoalbuminemia	0 (0.0%)	2 (4.3%)	0 (0.0%)	5 (10.6%)
Hypokalaemia	0 (0.0%)	1 (2.1%)	1 (2.1%)	5 (10.6%)
Rash maculo-papular	1 (2.1%)	4 (8.5%)	1 (2.1%)	5 (10.6%)

Adverse Events (AEs) occurring at >10% 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-Oct-21, The most common adverse events of any grade seen to date have included fatigue (40.4%), anemia (27.7%), lymphopenia (25.5%), chills (19.1%), decreased appetite (19.1%), hyponatremia (19.1%) and weight decrease (17%). At each level of summation patients reporting > 1 occurrence of the same AE are counted once at highest toxicity.

Summary

- As of 31-Oct-2021, 44 participants have received CUE-101 monotherapy. Doses ranging from 0.06 to 8 mg/kg were determined to be safe and well-tolerated. Six patients have been administered CUE-101 in combination with pembrolizumab across 2 dose escalation cohorts with no DLTs reported.
- Preliminary PK data demonstrate dose-dependent increases in drug exposure which are sustained upon repeat dosing, with low inter-subject variability. Preliminary data from systemic blood analyses show early signals of expansion of HPV-16 E7$_{11-20}$-specific CD8+ T cells. An MTD was not established. Based upon the totality of safety, PD, PK and preliminary anti-tumor activity, Cohort 6 (4 mg/kg) was chosen for RP2D expansion. PD and PK analyses are ongoing.
- Safety data reported here were received by Cue Biopharma thru 22-OCT-2021. AEs reported were generally mild and resolved despite continued therapy.
- CUE-101 is a novel agent that is demonstrating acceptable tolerability, favorable PK, and preliminary pharmacodynamic signals that support selective activation of tumor-specific CD8+ T cells. One patient has experienced a PR with an ongoing duration of 30 weeks and an additional 5 patients have experienced durable SD, as determined by RECIST 1.1 criteria, at the RP2D.
- Early signs of activity of CUE-101 in combination with pembrolizumab are encouraging, with 3 of 3 patients from cohort 2 (2mg/kg) demonstrating tumor reductions in their target lesions on their first scan after two cycles of therapy. PD and PK analyses are ongoing as dose escalation continues. Cohort 3 is currently enrolling.

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