681 A phase 1 study of CUE-101, a novel HPV16 E7-pHLA-IL2-Fc fusion protein, as monotherapy and in combination with pembrolizumab in patients with recurrent/metastatic HPV16+ head and neck cancer

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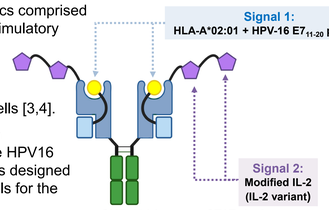
Background

- Head and neck squamous cell carcinomas (HNSCCs) 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% of these cases [2]. Despite current standard of care treatments, ~30% of patients with advanced HPV16+ HNSCC will experience recurrence, representing a significant unmet need.
- Immuno-STATs™ (ISTs) 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 IST in clinical trials, is composed of an 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.



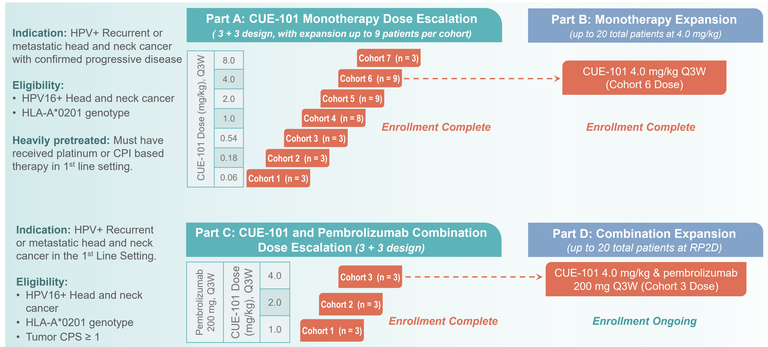
CUE-101 Immuno-STAT design

[1]Sung H, Ferlay J, Siegel RL, et al. CA Cancer J Clin. 2021 May;71(3):209-249.
[2]Ndiaye C., Mena M., Alemany L., et al. Lancet. Oncol. 2014;15:1319–1331.
[3]Quayle SN, Girgis N, Thapa DR, et al. Clin Cancer Res. 2020; 26:1953-64.
[4]Seidel, RD, Merazga, Z, Thapa, DR, et al. Sci Rep 2021;11(1):19220.

Methods

- CUE-101-01 is a 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.
- Trial eligibility includes HLA-A*0201 genotype and diagnosis of HPV16+ HNSCC, determined by p16 IHC and HPV16 mRNA in-situ hybridization (ISH).
- Objectives include determination of safety, PK, PD, immunogenicity, maximum tolerated dose (MTD), recommended phase 2 dose (RP2D), preliminary anti-tumor activity and overall survival.
- CUE-101 is given intravenously once every 3 weeks either alone (Parts A and B) or following infusion of pembrolizumab 200 mg/kg once every 3 weeks (Parts C and D).

Schema of Dose Escalation and Dose Expansion of CUE-101 as Monotherapy and in Combination with Pembrolizumab



Part A monotherapy dose escalation through seven cohorts completed. An MTD was not established. Evidence of immune response was seen at doses ≥1 mg/kg and Cohorts 4, 5 and 6 were expanded up to 9 patients each for further evaluation. The monotherapy dose of 4 mg/kg (Cohort 6) was selected for the RP2D expansion in Part B, which completed enrollment in March 2022. In Part C, combination therapy with CUE-101 in escalating doses combined with pembrolizumab at 200 mg/kg Q3W completed in April 2022 with no DLTs observed. Cohort 3 (CUE-101 4 mg/kg + pembrolizumab 200 mg) was selected for expansion in Part D, which is currently enrolling. **Abbreviations:** CPI, checkpoint inhibitor; CPS, combined positive score; PK/PD, pharmacokinetics/pharmacodynamics; Q3W, once every 3 weeks.

Monotherapy Patient Demographics & 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 23-SEP-2022. All patients are HLA-A*0201 positive and HPV16+.
*Patients reporting > 1 prior line of therapy are counted once per category and may be included in > 1 category.

ClinicalTrials.gov ID: *NCT03978689*

Combination Therapy Patient Demographics & Prior Treatments

Patients		N = 17
Age (years)	Mean (range)	62.4 (43-72)
Sex	Male	17 (100.0%)
	Female	0 (0.0%)
Race	White	16 (94.1%)
	Other	1 (5.9%)
ECOG	0	10 (58.8%)
	1	7 (41.2%)
CPS SCORE	≥ 1 to < 20	9 (52.9%)
	≥ 20	8 (47.1%)
Prior Lines of Therapy for Initial Treatment*	Patients with no prior treatment	4 (23.5%)
	Median (range)	1 (0-2)
	• Platinum Based	12 (70.6%)
	• Checkpoint Inhibitor	1 (5.9%)
	○ PD-L1	1 (5.9%)
	• EGFR Inhibitor	2 (11.8%)

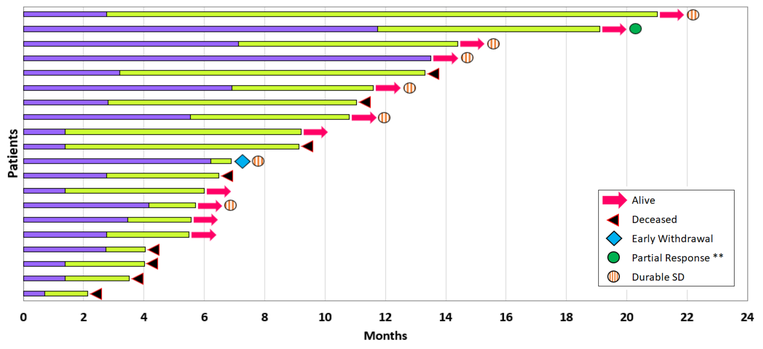
Data extracted from EDC 23-SEP-2022. All patients are HLA-A*0201 positive, HPV16+, with tumor expression of PD-L1 (CPS ≥ 1).
*Patients reporting > 1 prior line of therapy are counted once per category and may be included in > 1 category. Patients with initial presentation of metastatic disease will have no prior treatments.

Adverse Events All Patients (Monotherapy and Combination)

	Treatment Related Adverse Events (N=66)		All Adverse Events (N=66)	
Preferred Term	**≥ Grade 3**	**All Grades**	**≥ Grade 3**	**All Grades**
Overall Frequency	**14 (24.1%)**	**54 (81.8%)**	**27 (40.9%)**	**63 (95.5%)**
Fatigue	2 (3.0%)	20 (30.3%)	2 (3.0%)	30 (45.5%)
Anemia	2 (3.0%)	4 (6.1%)	5 (7.6%)	22 (33.3%)
Chills	0 (0.0%)	15 (22.7%)	0 (0.0%)	17 (25.8%)
Infusion related reaction	3 (4.5%)	17 (25.8%)	3 (4.5%)	17 (25.8%)
Hyponatremia	1 (1.5%)	4 (6.1%)	2 (3.0%)	15 (22.7%)
Lymphocyte count decreased	3 (4.5%)	3 (4.5%)	8 (12.1%)	15 (22.7%)
Constipation	0 (0.0%)	4 (6.1%)	0 (0.0%)	14 (21.2%)
Nausea	1 (1.5%)	12 (18.2%)	1 (1.5%)	14 (21.2%)
Weight decreased	0 (0.0%)	4 (6.1%)	0 (0.0%)	14 (21.2%)
Cough	0 (0.0%)	7 (10.6%)	0 (0.0%)	13 (19.7%)
Decreased appetite	0 (0.0%)	4 (6.1%)	3 (4.5%)	12 (18.2%)
Dysphagia	0 (0.0%)	0 (0.0%)	2 (3.0%)	12 (18.2%)
Dyspnea	0 (0.0%)	3 (4.5%)	1 (1.5%)	11 (16.7%)
Hypertension	0 (0.0%)	2 (3.0%)	0 (0.0%)	11 (16.7%)
Rash maculo-papular	1 (1.5%)	9 (13.6%)	1 (1.5%)	11 (16.7%)
Arthralgia	0 (0.0%)	5 (7.6%)	0 (0.0%)	10 (15.2%)
Hypophosphatemia	0 (0.0%)	5 (7.6%)	1 (1.5%)	10 (15.2%)
Pyrexia	0 (0.0%)	9 (13.6%)	0 (0.0%)	10 (15.2%)
Diarrhea	2 (3.0%)	5 (7.6%)	2 (3.0%)	9 (13.6%)
Dry skin	0 (0.0%)	6 (9.1%)	0 (0.0%)	9 (13.6%)
Rash	0 (0.0%)	7 (10.6%)	0 (0.0%)	9 (13.6%)
Alanine aminotransferase increased	0 (0.0%)	7 (10.6%)	0 (0.0%)	8 (12.1%)
Blood lactate dehydrogenase increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (12.1%)
Hyperkalemia	0 (0.0%)	1 (1.5%)	0 (0.0%)	8 (12.1%)
Hypoalbuminemia	0 (0.0%)	2 (3.0%)	0 (0.0%)	8 (12.1%)
Myalgia	0 (0.0%)	7 (10.6%)	0 (0.0%)	8 (12.1%)
Pruritus	0 (0.0%)	5 (7.6%)	0 (0.0%)	8 (12.1%)
Vomiting	2 (3.0%)	7 (10.6%)	2 (3.0%)	8 (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 23-SEP-22. At each level of summation patients reporting > 1 occurrence of the same AE are counted once at highest toxicity.

Overall Survival in Monotherapy Patients at RP2D



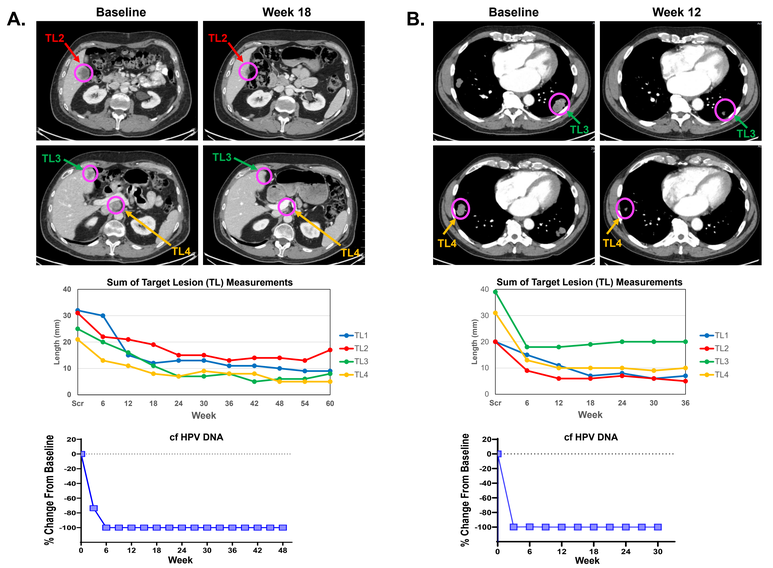
Overall survival in months for all monotherapy patients treated in CUE-101-01, at 4 mg/kg, from time of 1st dose of drug (Cycle 1 Day 1). PR (partial response) is indicated by a green circle; Durable SD (stable disease) is indicated by a hatched orange circle (requires SD at ≥ 2 consecutive scans at 6-week and 12-week visits). ** *Onset and duration of the response is not indicated on the plot.* Kaplan-Meier Analysis mOS 13.3 month; [95% Confidence Interval (9.1, NA)]. Data extracted from EDC 23-SEP-2022.

Responses with CUE-101 in Combination with Pembrolizumab

Dose Level / Responses	CUE-101 1 mg/kg + Pembrolizumab N = 3	%	CUE-101 2 mg/kg + Pembrolizumab N = 3	%	CUE-101 4 mg/kg + Pembrolizumab N = 10	%
Objective Response (CR, PR or uPR)	0	0%	1	33.3%	4	40%
Durable Stable Disease (SD sustained for ≥ 12 weeks*)	1	33.3%	1	33.3%	1	10%
Clinical Benefit (CR/PR + durable SD)	1	33.3%	2	66.6%	5	50%

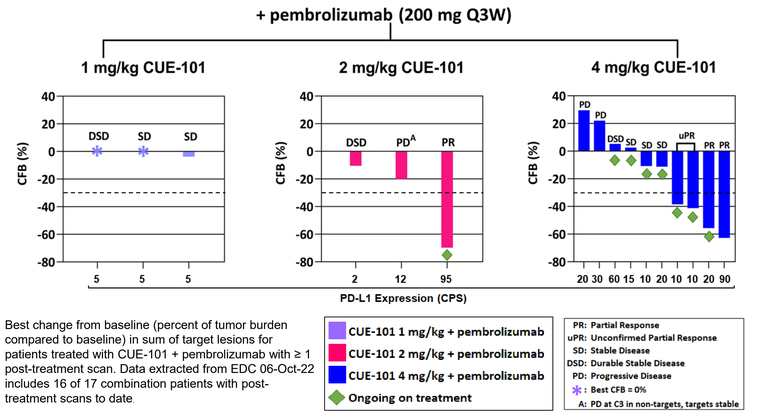
Data extracted from EDC 06-OCT-2022. N = Response Evaluable Population which requires minimum of 1 post-treatment scan.

Tumor Responses for CUE-101 in Combination with Pembrolizumab



Following treatment with CUE-101 at 2 mg/kg **(panel A)** and 4 mg/kg **(panel B)** in combination with pembrolizumab, reductions in all target lesions were observed. Concurrently, a >90% reduction of circulating cell-free HPV DNA (cf HPV DNA) was observed in both patients. Data extracted from EDC 06-Oct-22.

Best Change from Baseline (CFB) in Patients treated with CUE-101 in Combination with Pembrolizumab



Best change from baseline (percent of tumor burden compared to baseline) in sum of target lesions for patients treated with CUE-101 + pembrolizumab with ≥ 1 post-treatment scan. Data extracted from EDC 06-Oct-22 includes 16 of 17 combination patients with post-treatment scans to date.

Summary

- Forty-nine (49) patients were treated with CUE-101 as monotherapy at doses ranging from 0.06 to 8 mg/kg and a maximum tolerated dose (MTD) was not established. Based on the totality of safety, PK, PD and preliminary anti-tumor activity data, the 4 mg/kg cohort was expanded to 20 patients.
- Seventeen (17) patients were treated with CUE-101 at doses ranging from 1 to 4 mg/kg in combination with 200 mg pembrolizumab and no dose-limiting toxicity (DLT) was observed. The 4 mg/kg + pembrolizumab dose was chosen for expansion and enrollment to a total of 20 patients is ongoing.
- Continued accrual of safety data demonstrates adverse events consistent with the CUE-101 mechanism of action and underlying disease. No unanticipated, significant safety concerns have emerged, and AEs have been readily managed with appropriate care in the clinical setting.
- Overall survival data in patients treated at the monotherapy RP2D continues to mature, with 11 of 20 patients alive at the time of data cut-off.
- Clinical activity of CUE-101 in patients treated with combination therapy is encouraging, with early differentiation of the 4 mg/kg expansion cohort. Five (5) patients treated with combination therapy have experienced partial response, with 1 confirmed PR at the 2mg/kg dose level and 4 PRs (2 confirmed, 2 pending follow-up scans) at the expanded 4 mg/kg dose level.

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