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

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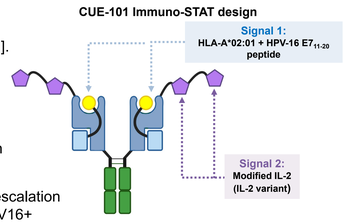
Background and Study Design

- Immuno-STATs™ (ISTs) are TCR-selective engager 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.
- The CUE-100 series ISTs are designed to deliver attenuated interleukin-2 (IL-2) selectively to tumor-specific CD8+T cells [1].
- 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 when given intravenously (IV) every 3 weeks (Q3W).
- CUE-101-01 (NCT03978689) is a Phase 1, open label, dose escalation and expansion study in HLA-A*0201 positive patients with HPV16+ recurrent/metastatic HPV16+ head and neck cancer (R/M HNSCC). Patients with R/M HNSCC that progressed following platinum or checkpoint inhibiter-based therapies are eligible for CUE-101 monotherapy. Newly diagnosed R/M HNSCC patients are eligible for treatment with CUE-101 plus pembrolizumab. Trial eligibility includes HLA-A*0201 genotype and HPV16+ HNSCC, determined by p16 IHC and HPV16 mRNA in-situ hybridization. Pembrolizumab combination patients are also required to have a CPS ≥ 1.
- Previously, we have shown the results of CUE-101 dose escalation in monotherapy (in dose ranges from 0.06 – 8 mg/kg), and in combination with pembrolizumab 200 mg IV Q3W (in dose ranges from 1 – 4 mg/kg) [2]. Here we report the preliminary results of the CUE-101 recommended phase 2 dose (RP2D) of 4 mg/kg in both monotherapy and in combination with pembrolizumab, 200 mg Q3W; monotherapy immunogenicity data and updated demographic and adverse events on all study patients.



Patient Demographics & Prior Therapies

Treatment Arm		Monotherapy	Combination with Pembro
Patients		N = 49	N = 22
Age (years)	Mean (range)	63.7 (48-82)	64.0 (43-77)
Sex	Male	47 (95.9%)	22 (100.0%)
	Female	2 (4.1%)	0 (0.0%)
Race	White	45 (91.8%)	21 (95.5%)
	Black/ African American	1 (2.0%)	0 (0.0%)
	Other	3 (6.1%)	1 (4.5%)
ECOG	0	23 (46.9%)	13 (59.1%)
	1	26 (53.1%)	9 (40.9%)
CPS SCORE	≥ 1 to < 20	---	13 (59.1%)
	≥ 20	---	9 (40.9%)
Prior Lines of Therapy*	No prior lines of therapy	0 (0.0%)	5 (22.7%)
	Median (range)	3 (1-10)	1 (0-2)
	• Platinum Based	45 (91.8%)	16 (72.7%)
	• Checkpoint Inhibitor	49 (100.0%)	1 (4.5%)
	○ PD-1	46 (93.9%)	0 (0.0%)
	○ PD-L1	6 (12.2%)	1 (4.5%)
	○ CTLA-4	1 (2.0%)	0 (0.0%)
	• EGFR Inhibitor	35 (71.4%)	2 (9.1%)
	• Other	43 (87.8%)	3 (16.6%)

Data extracted from EDC 28-Apr-2023. All patients are HLA-A*0201 positive, HPV16+; combination patients 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. Combination patients with initial presentation of metastatic disease will have no prior treatments.

Adverse Events All Patients (Monotherapy and Combination)

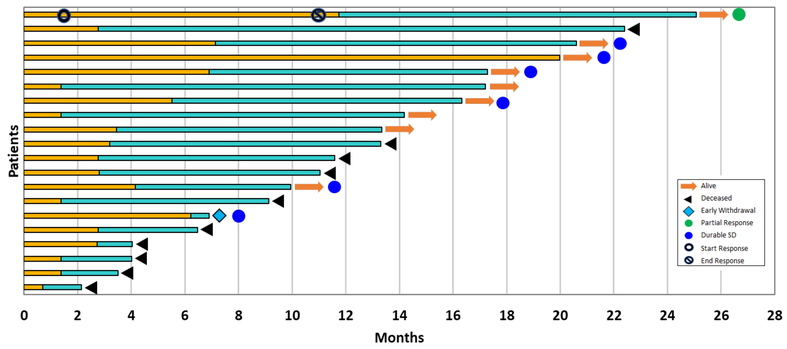
	Treatment Related Adverse Events (N=71)		All Adverse Events (N=71)	
Preferred Term	≥ Grade 3	All Grades	≥ Grade 3	All Grades
Overall Frequency	**18 (25.4%)**	**58 (81.7%)**	**34 (47.9%)**	**68 (95.8%)**
Fatigue	2 (2.8%)	25 (35.2%)	2 (2.8%)	36 (50.7%)
Anemia	2 (2.8%)	5 (7.0%)	5 (7.0%)	25 (35.2%)
Chills	0	19 (26.8%)	0	22 (31.0%)
Nausea	1 (1.4%)	16 (22.5%)	1 (1.4%)	18 (25.4%)
Decreased appetite	0	6 (8.5%)	4 (5.6%)	16 (22.5%)
Hyponatremia	1 (1.4%)	4 (5.6%)	2 (2.8%)	16 (22.5%)
Infusion related reaction	3 (4.2%)	16 (22.5%)	3 (4.2%)	16 (22.5%)
Constipation	0	4 (5.6%)	0	15 (21.1%)
Cough	0	7 (9.9%)	0	14 (19.7%)
Dysphagia	0	0	2 (2.8%)	14 (19.7%)
Lymphocyte count decreased	3 (4.2%)	3 (4.2%)	8 (11.3%)	14 (19.7%)
Weight decreased	0	2 (2.8%)	0	14 (19.7%)
Pyrexia	0	11 (15.5%)	0	13 (18.3%)
Rash maculo-papular	2 (2.8%)	9 (12.7%)	2 (2.8%)	12 (16.9%)
Arthralgia	0	6 (8.5%)	0	11 (15.5%)
Dyspnea	0	3 (4.2%)	1 (1.4%)	11 (15.5%)
Hypertension	0	2 (2.8%)	0	11 (15.5%)
Rash	0	7 (9.9%)	0	11 (15.5%)
Blood lactate dehydrogenase increased	0	1 (1.4%)	0	10 (14.1%)
Hypophosphatemia	0	5 (7.0%)	1 (1.4%)	10 (14.1%)
Pruritus	0	6 (8.5%)	0	10 (14.1%)
Vomiting	2 (2.8%)	8 (11.3%)	2 (2.8%)	10 (14.1%)
Diarrhea	2 (2.8%)	5 (7.0%)	2 (2.8%)	9 (12.7%)
Dry skin	0	6 (8.5%)	0	9 (12.7%)
Headache	0	3 (4.2%)	0	9 (12.7%)
Hyperglycemia	0	1 (1.4%)	0	9 (12.7%)
Hyperkalemia	0	0	0	9 (12.7%)
Hypoalbuminemia	0	2 (2.8%)	0	9 (12.7%)
Lipase increased	0	4 (5.6%)	0	9 (12.7%)

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 12-Apr-2023. At each level of summation patients reporting >1 occurrence of the same AE are counted once at highest toxicity. Of the 71 patients, one patient discontinued treatment due to a Grade ≥3 treatment-related adverse event.

Preliminary Pharmacokinetic and Immunogenicity Assessment

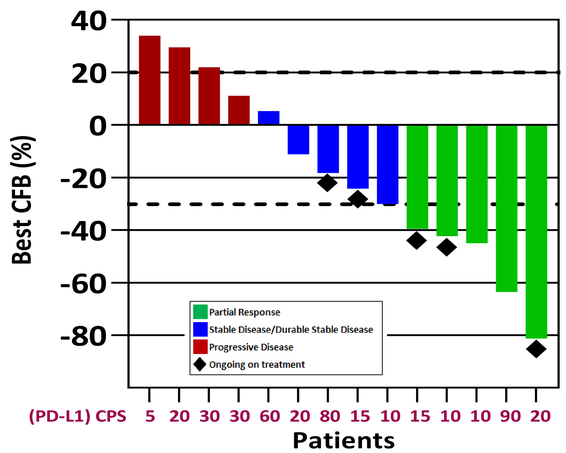
- Following monotherapy treatment, preliminary pharmacokinetic analysis indicates CUE-101 exhibits approximately dose proportional exposure and low inter-subject variability
- Anti-drug antibodies (ADA) following CUE-101 monotherapy occur transiently, decreasing over time in all patients with confirmed ADAs, and generally do not persist throughout a subject's treatment course
- Presence of ADA is associated with little to no effect on CUE-101 exposure
- Clinically significant adverse events possibly related to ADAs have not been observed

Survival in Monotherapy Patients at the RP2D



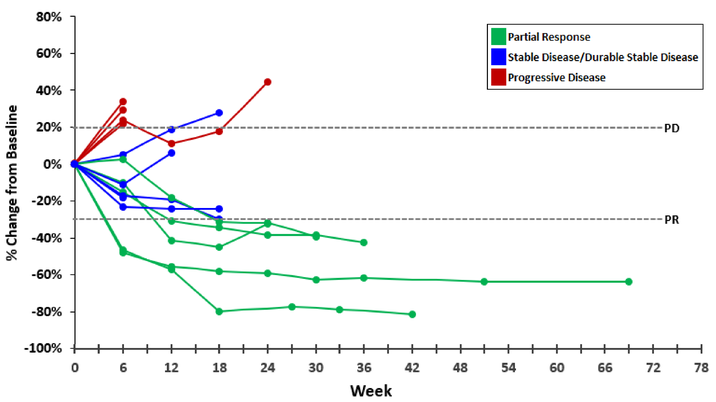
Overall survival (months) in patients treated with 4 mg/kg CUE-101 (N=20), from time of first dose of drug as of 12-Apr-2023. Durable stable disease (DSD) requires stable disease (SD) on ≥ 2 consecutive scans. Onset and duration of response are indicated on the plot. Kaplan-Meier estimate of median OS 22.4 months [95% CI; 11.0, NA].

Best Overall Response in Combination Patients at the RP2D



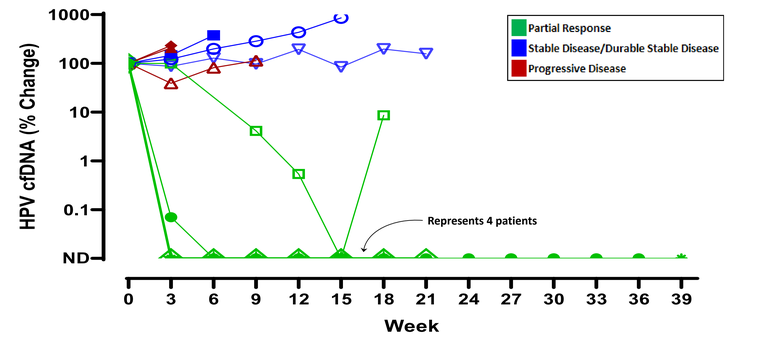
Waterfall plot illustrates best change from baseline (CFB) in the sum of diameters of target lesions with best overall response as measured by RECIST 1.1. 14 patients treated with 4 mg/kg CUE-101 and pembrolizumab with ≥ 1 post-dose scan as of 28-Apr-2023 are included. Overall Response Rate (ORR) 36%, Disease Control Rate (DCR) 57%.

Temporal Changes in Tumor Burden in Combination Patients at the RP2D



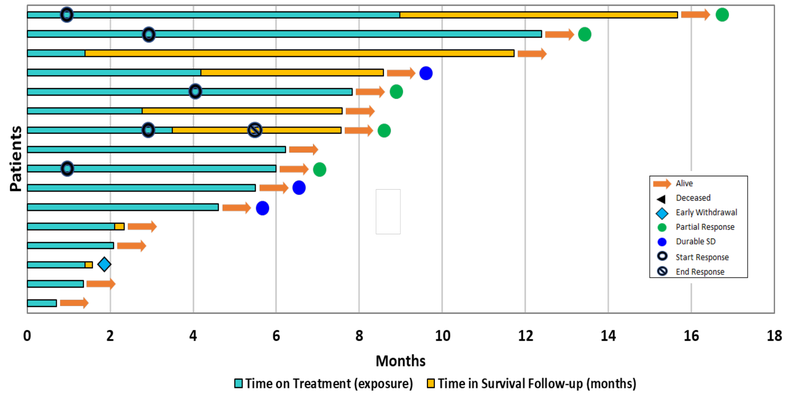
Spider plot shows change from baseline in the sum of diameters of target lesions over time as measured by RECIST 1.1 as of 28-Apr-2023. Patients treated with 4 mg/kg CUE-101 and pembrolizumab with ≥ 1 post-dose scan are included. Scans are obtained at baseline and Q6 weeks thereafter. Median Duration of Response (DOR) 35.1 weeks.

Change in HPV16 cfDNA in Combination Patients at the RP2D



Circulating cell-free HPV DNA (HPV cfDNA) in patients treated with 4 mg/kg CUE-101 plus pembrolizumab was measured using a ddPCR assay to screen for the presence of HPV16 E7 DNA from plasma samples taken at baseline and prior to each cycle of treatment. HPV cfDNA was not detectable in 4 of 5 patients with confirmed partial responses within 6 weeks of starting treatment. Plot includes 11 of 16 patients treated to date at this dose level. One patient with cfDNA values < LLOQ (scrn → C6), is not included, and four patients did not have post-treatment samples available at time of analysis

Survival in Combination Patients at the RP2D



Overall survival (months) in patients treated with 4 mg/kg CUE-101-01 and pembrolizumab (N=16), from time of first dose of drug as of 12-Apr-2023. Durable stable disease (DSD) requires stable disease (SD) on ≥ 2 consecutive scans. Onset and duration of the response is indicated on the plot. Kaplan-Meier estimate of median PFS 4.9 months [95% CI; 2.5, NA]

Summary

- Forty-nine (49) patients were treated with CUE-101 monotherapy at doses ranging from 0.06 to 8 mg/kg and a maximum tolerated dose (MTD) was not established. The 4 mg/kg cohort was expanded to 20 patients.
- Twenty-two (22) 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.
- Adverse events are 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.
- ADAs following CUE-101 monotherapy occur transiently, decreasing over time in all patients with confirmed ADAs and generally do not persist throughout a patient's treatment course.
- Overall survival data in patients treated at the monotherapy RP2D continues to mature, Kaplan-Meier estimate of median OS 22.4 months [95% CI; 11.0, NA] with 9 of 20 patients alive at the time of data cut-off.
- Clinical activity of CUE-101 in patients treated with combination therapy is encouraging, ORR of 36% (4 out of 5 PRs occurring in tumors with CPS of 20 or less), DCR of 57% and median DOR of 35.1 weeks. Kaplan-Meier estimate of median PFS 4.9 months [95% CI; 2.5, NA].

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[2]Chung CH, Colevas AD, Adkins A, et al. JCO. 2022; 40:16_suppl, 6045-6045

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