#636 A phase 1 trial of CUE-102, a novel WT1-pHLA-IL2-Fc T cell engager in HLA-A*0201 positive patients with WT1-positive recurrent/metastatic cancers

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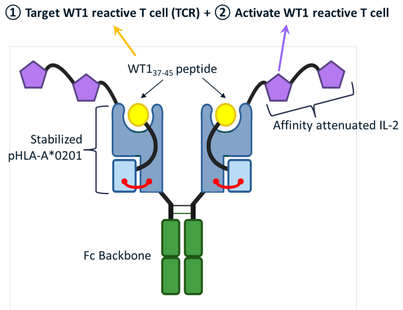
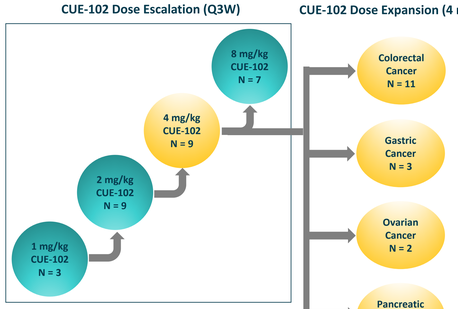
CUE-102 Immuno-STAT

- Wilms' Tumor 1 (WT1) is highly expressed in multiple solid tumors and hematologic malignancies, making it an attractive target for enhancing anti-tumor immunity.
- CUE-102 is comprised of a human leukocyte antigen (HLA) complex, HLA-A*02:01, a peptide epitope derived from the WT1 protein, and 4 molecules of a reduced affinity human interleukin-2 (IL-2).
- CUE-102 selectively expands and activates WT1-specific CD8 T cells to target WT1-expressing tumor cells.
- The selective targeting of IL-2 to tumor-specific T cells reduces the potential of non-specific T cell activation and toxicity.
- CUE-102 shares 99% identity with CUE-101, which is being developed in HPV+ cancer.



Study Design



- 3+3 dose escalation with Bayesian Logistic Regression overlay.
- Observation for dose-limiting toxicity.
- Additional enrollment permitted at any dose level based on safety/tolerability.

Includes all patients treated with CUE-102 at 4 mg/kg from Parts A and B.

Key Eligibility Criteria

- HLA-A*02:01 genotype
- WT1+ colorectal, gastric/GEJ, ovarian or pancreatic cancer
- Measurable disease by RECIST 1.1
- Disease progression after prior systemic treatment for advanced or metastatic disease

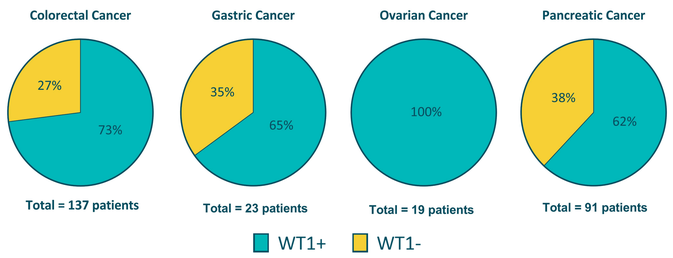
Objectives

- Primary: Safety and tolerability
- Secondary: PK/PD, objective response, disease control, survival

Biomarkers

- Immunophenotyping and monitoring of immune cell subsets, including WT1-specific CD8 T cells
- Serum biomarkers, cytokines, cfDNA, and TCR sequencing

WT1 Prevalence in Prescreened Patients



Patient Enrollment

INDICATION	1 mg/kg	2 mg/kg	4 mg/kg	8 mg/kg	TOTAL
Colorectal	3	4	11	4	**22**
Gastric	0	1	3	0	**4**
Ovarian	0	1	2	1	**4**
Pancreatic	0	3	7	2	**12**
TOTAL	**3**	**9**	**23**	**7**	**42**

Patient Demographics

		All (N = 42) N (%)	Colorectal (N=22) N (%)	Gastric (N=4) N (%)	Ovarian (N=4) N (%)	Pancreatic (N=12) N (%)
Age (years)	Mean (range)	60 (36–77)	56 (36-75)	65 (56-76)	59 (47-77)	65 (50-77)
Sex	Male	19 (45.0)	11 (50.0)	3 (75.0)	-	5 (42.0)
	Female	23 (55.0)	11 (50.0)	1 (25.0)	4 (100)	7 (58.0)
Race	White	33 (78.6)	18 (81.8)	3 (75.0)	3 (75.0)	9 (75.0)
	Asian	3 (7.1)	1 (4.6)	-	-	2 (17.0)
	Black / African American	4 (9.5)	3 (13.6)	1 (25.0)	-	-
	Other / Not Reported	2 (4.8)	-	-	1 (25.0)	1 (8.0)
ECOG	0	16 (38.0)	7 (32.0)	3 (75.0)	2 (50.0)	4 (33.0)
	1	26 (62.0)	15 (68.0)	1 (25.0)	2 (50.0)	8 (67.0)
Prior Lines of Therapy	Median (range)	4 (1-9)	4 (1-9)	4 (3-4)	4 (4-9)	4 (1-4)
CRC with Liver Metastasis		-	19 (86.0)	-	-	-

Data extract 11-Sep-2024.

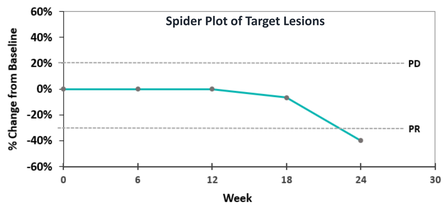
Safety and Tolerability

Event	All Treatment Emergent AEs	Grade 1 or 2 N (%) Treatment Emergent AE	Grade 1 or 2 N (%) Treatment Related AE	Grade ≥ 3 N (%) Treatment Emergent AE	Grade ≥ 3 N (%) Treatment Related AE
Vomiting	14 (33.3)	13 (31.0)	10 (23.8)	1 (2.4)	-
Nausea	13 (31.0)	11 (26.2)	10 (23.8)	2 (4.8)	-
Fatigue	11 (26.2)	11 (26.2)	7 (16.7)	-	-
Infusion related reaction	11 (26.2)	11 (26.2)	11 (26.2)	-	-
Pyrexia	10 (23.8)	10 (23.8)	7 (16.7)	-	-
Abdominal pain	9 (21.4)	8 (19.0)	2 (4.8)	1 (2.4)	-
Anemia	9 (21.4)	7 (19.0)	2 (4.8)	2 (4.8)	-
Decreased appetite	7 (16.7)	7 (16.7)	1 (2.4)	-	-
AST increased	6 (14.3)	5 (11.9)	1 (2.4)	1 (2.4)	-
Chills	6 (14.3)	6 (14.3)	5 (11.9)	-	-
ALP increased	5 (11.9)	4 (9.5)	3 (7.1)	1 (2.4)	-
Constipation	5 (11.9)	5 (11.9)	-	-	-
Diarrhea	5 (11.9)	5 (11.9)	1 (2.4)	-	-
Hypokalemia	5 (11.9)	5 (11.9)	1 (2.4)	-	-

Adverse Events occurring in ≥ 10% patients treated with CUE-102. AEs are coded using MedDRA V21.0 and CTCAE v5.0. At each level of summation patients reporting >1 occurrence of the same AE are counted once at the highest toxicity. Data extract 11-Sep-2024.

Tumor Response and Disease Control at 4 mg/kg

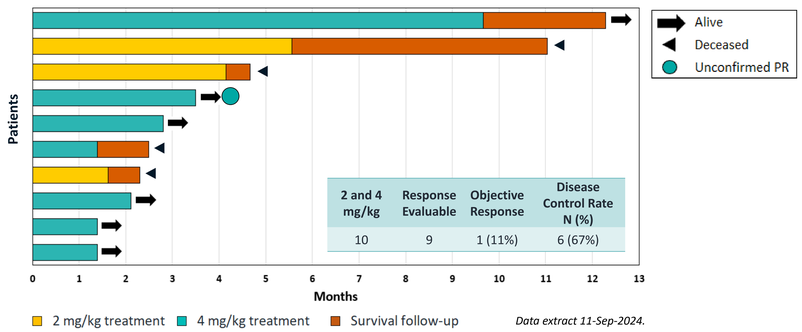
INDICATION	Response Evaluable§ (N)	Objective Response Rate N (%)	Disease Control Rate§§ N (%)
Colorectal	11	-	3 (27%)
Gastric	3	-	1 (33%)
Ovarian	1	-	1 (100%)
Pancreatic	7	1 (14%)*	4 (57%)
TOTAL	**22**	**1 (5%)**	**9 (41%)**



§ Response Evaluable Population includes patients with a post-dose scan. §§ Disease Control Rate = Patients with Objective Response + Stable Disease where SD requires, at a minimum, stable disease per RECIST 1.1 at the 1st post-dose scan (through Week 6). Data extract 11-Sep-2024.

**A patient with pancreatic cancer exhibits an unconfirmed Partial Response (PR), with a 40% decrease from baseline in sum of diameters of target lesions, per RECIST 1.1. at the scan obtained on 29-Oct-2024. The confirmatory scan is pending.*

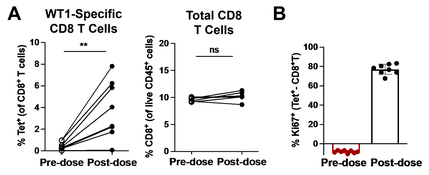
Swimmer Plot in Pancreatic Cancer Patients



2 and 4 mg/kg	Response Evaluable	Objective Response	Disease Control Rate N (%)
10	9	1 (11%)	6 (67%)

Data extract 11-Sep-2024.

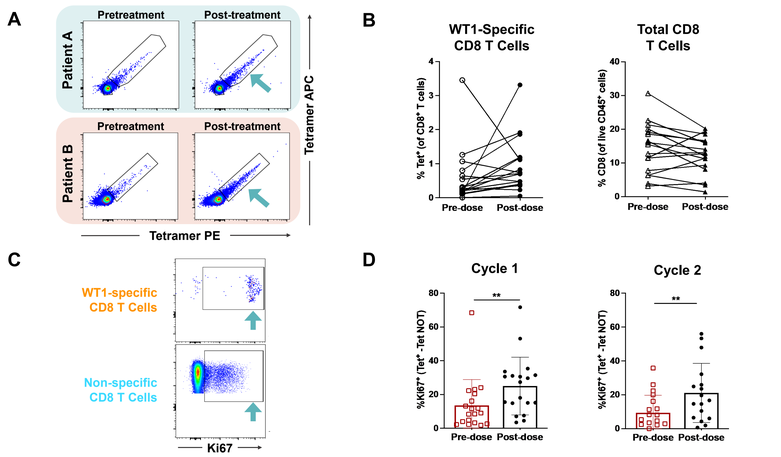
Preclinical CUE-102 Studies Demonstrate Selective Activation of WT1-Specific CD8 T Cells



(A) Preclinical experiments in HLA-A2 transgenic mice demonstrated that CUE-102 treatment selectively expands WT1-specific CD8 T cells within 5 days post-dose, while total CD8 T cell frequencies remain unchanged.

(B) CUE-102 treatment of HLA-A2 mice also increased the frequency of WT1-specific CD8 T cells expressing the proliferation marker Ki67 over that observed in total CD8 T cells. Differences in % Ki67+ between Tet+ CD8 T cells and total CD8 T cells are shown pre- and post-dosing of CUE-102.

Selective Expansion and Proliferation of WT1-Specific CD8 T Cells in Patients Following CUE-102 Treatment



(A) Increased frequency of WT1-specific CD8 T cells is observed in patients following CUE-102 treatment. Representative plots are shown following direct flow staining of PBMCs from 2 patients. **(B)** Consistent with the preclinical findings, amongst all patients tested to date (n=22), a trend of increased frequency of WT1-specific CD8 T cells is apparent at C1D3, while the frequency of total CD8 T cells is unchanged at this timepoint. **(C)** Increased proliferation, as indicated by Ki67 expression, is noted in WT1-specific CD8 T cells of treated patients whereas the non-specific CD8 T cells exhibit significantly lower expression of Ki67. Representative plots are shown following direct flow staining of patient PBMCs. **(D)** Amongst patients tested to date, by 7 days following each treatment at Cycle 1 and Cycle 2 a significantly greater frequency of WT1-specific T cells express Ki67 relative to the non-specific CD8 T cells.

Summary and Conclusions

- CUE-102-01 is a phase 1 study evaluating CUE-102 treatment in patients with late-stage WT1+ colorectal, gastric/GEJ, ovarian, and pancreatic cancers.
- Patient prescreening indicates substantial WT1 expression using a validated IHC method across these target indications (CRC 73%, gastric/GEJ 65%, ovarian 100% and pancreatic 62%).
- Twenty-eight patients were enrolled in Part A (dose-escalation) and 14 patients were enrolled in Part B at the selected expansion dose of CUE-102 at 4 mg/kg Q3W.
- At the data cut-off, CUE-102 appears safe and exhibits a manageable tolerability profile; the majority of AEs were CTCAE Grade 1-2 and no DLTs were observed.
- Preliminary PK and PD analyses demonstrate approximately dose proportional exposure of CUE-102 and evidence of selective stimulation and expansion of WT1-specific CD8 T cells relative to the total repertoire of CD8 T cells, consistent with preclinical models.
- Reductions in tumor burden and disease control, based on RECIST 1.1, have been observed across indications. Data is encouraging in late-stage pancreatic cancer patients with an unconfirmed partial response (confirmatory scan pending) and 67% of patients exhibiting disease control.
- The safety and tolerability profile of CUE-102 together with preliminary evidence of selective immune stimulation and clinical activity as measured by response and disease control supports additional testing of CUE-102 in combination regimens in the future.

Acknowledgements

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