#750 A phase 1 trial of CUE-102, a novel WT1-pHLA-IL2-Fc fusion protein in HLA-A*0201 positive patients with WT1-positive recurrent/metastatic cancers

J. Eva Selfridge[1], Nataliya V. Uboha[2], Yvonne Saenger[3], Jorge Chaves[4], Lei Zheng[5], John Powderly[6], Dae Won Kim[7], Olatunji Alese[8], Siqing Fu[9], Jun Gong[10], Nashat Gabrail[11], Zhaohui Jin[12], Tanios Bekaii-Saab[13], Angela Alistar[14], Laura Agensky[15], Apollina Goel[15], Steven P. Margossian[15], Steven N. Quayle[15], Matteo Levisetti[15].

[1]University Hospitals Cleveland Medical Center, Cleveland, OH, USA; [2]Carbone Cancer Center, University of Wisconsin School of Medicine, Madison, WI, USA; [3]Albert Einstein Cancer Center, Bronx, NY, USA; [4]Northwest Medical Specialties, Tacoma, WA, USA; [5]Johns Hopkins University School of Medicine, Baltimore, MD, USA; [6]Carolina BioOncology, Huntersville, NC, USA; [7]H. Lee Moffitt Cancer Center, Tampa, FL, USA; [8]Emory University, Atlanta, GA, USA; [9]The University of Texas MD Anderson, Houston, TX, USA; [10]Samuel Oschin Cancer Center, Cedars-Sinai Medical Center, Los Angeles, CA, USA; [11]Gabrail Cancer Center, Canton, OH, USA; [12]Mayo Clinic, Rochester, MN, USA; [13]Mayo Clinic, Phoenix, AZ, USA; [14]Angela Alistar, Carol G. Simon Cancer Center, Morristown, NJ, USA; [15]Cue Biopharma, Inc., Boston, MA, USA;

Background

WT1 is highly expressed in several solid tumor and hematologic malignancies and was previously ranked as the highest priority antigen for therapeutic targeting in an effort by the National Cancer Institute [1]. Development of novel modalities targeting WT1 provides a significant opportunity to address high unmet medical need in WT1-positive malignancies.

CUE-102, the second Immuno-STAT in clinical trials, is comprised of a human leukocyte antigen (HLA) complex, HLA-A*0201, a peptide epitope derived from the Wilms' Tumor 1 (WT1) protein, and 4 molecules of a reduced affinity human interleukin-2 (IL-2). CUE-102 is designed to selectively bind and activate $WT1_{37-45}$-specific T cells for the treatment of HLA-A*0201 patients with WT1-expressing cancers.

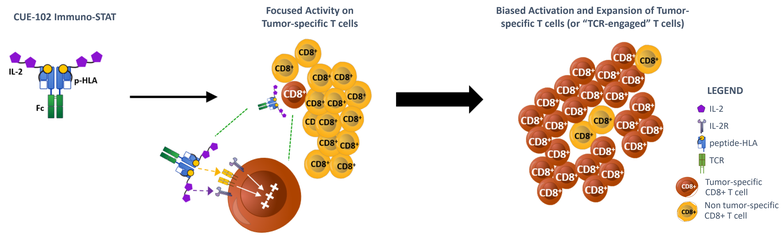
This novel mechanism of selective engagement and expansion of tumor antigen-specific T cells has the potential for enhanced anticancer efficacy with reduced toxicity relative to non-targeted forms of immunotherapy that induce systemic activation of the immune system. In pre-clinical studies, CUE-102 elicits selective expansion of WT1-specific cytotoxic CD8+ T cells in vitro and in vivo, supporting its potential for clinical efficacy [2].

CUE-102-01 is a phase 1, open-label, 2-part, multi-center study evaluating the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), immunogenicity, and preliminary antitumor activity of CUE-102 monotherapy administered every three weeks in HLA-A*0201 positive patients with WT1 positive recurrent/metastatic Colorectal, Gastric/Gastroesophageal Junction (GEJ), Pancreatic and Ovarian cancer who have failed conventional therapies.

[1]Cheever MA, Allison JP, Ferris AS, et al. The prioritization of cancer antigens: a national cancer institute pilot project for the acceleration of translational research. Clin Cancer Res. 2009 Sep 1;15(17):5323-37.

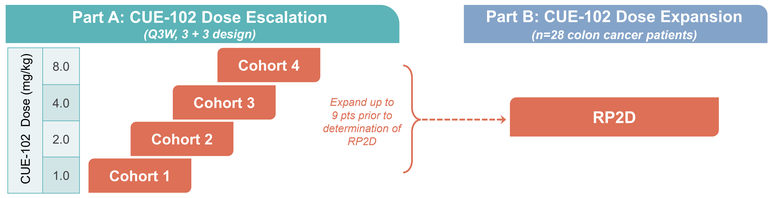
[2]Girgis N, Zhang C, Merazga Z, et al. CUE-102 Selectively Activates and Expands WT1-Specific T Cells for the Treatment of Patients with WT1+ Malignancies. Abstract #1323 SITC 2022.

CUE-102 Immuno-STAT Approach



The CUE-100 series framework is designed to selectively deliver modified IL-2 to tumor-specific T cells to drive their expansion. CUE-102 selectively interacts with T cells targeting the $WT1_{37-45}$-A*0201 peptide-HLA complex. This targeted immune activation provides the potential for anticancer efficacy with reduced toxicity relative to non-targeted forms of immunotherapy that induce systemic activation of the immune system.

Dose Escalation and Expansion Schema

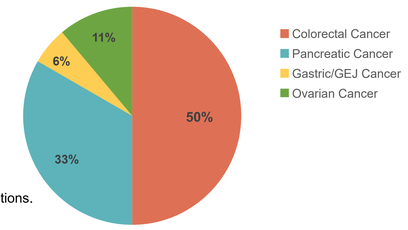


Key Eligibility Criteria:
- HLA-A*0201 Expressing genotype
- WT1+ Cancers
  - Part A: Colorectal, Gastric/GEJ, Pancreatic and Ovarian
  - Part B: Colorectal only
- Measurable disease by RECIST 1.1
- Life expectancy ≥ 12 weeks

Objectives:
- *Primary:* Safety and tolerability
- *Secondary:* PK/PD, Anti-tumor activity (RECIST 1.1), OS

Biomarkers:
- WT1-specific CD8+ T cell frequency and functionality
- Immunophenotyping, cytokine release, and TCR sequencing

Enrollment by Cancer Type



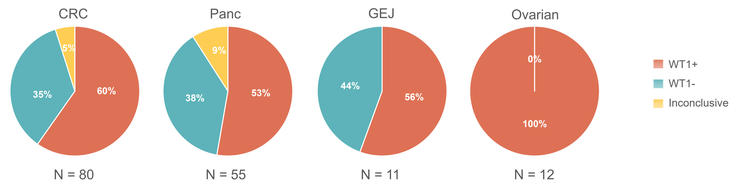
Breakdown of the patients enrolled in the study as of 03-Oct-2023 by each of the four eligible cancer indications.

Patient Demographics

		Patients N = 18
Age (years)	Mean (range)	58.8 (36 – 77)
Sex	Male	7 (38.9%)
	Female	11 (61.1%)
Race	White	13 (72.2%)
	Black / African American	0 (0.0%)
	Asian	3 (16.7%)
	Other / Not Reported	2 (11.1%)
Cancer Type	Colorectal	9 (50.0%)
	Pancreatic	6 (33.3%)
	Gastric / Gastroesophageal junction (GEJ)	1 (5.6%)
	Ovarian	2 (11.1%)
ECOG	0	5 (27.8%)
	1	13 (72.2%)
Prior Lines of Therapy	Median (range)	3.5 (1 – 9)

Eighteen of 20 patients enrolled had data in EDC at data extract on 01-Oct-2023.

WT1 Prevalence by Cancer Type in Prescreened Patients



- 158 patient tumor samples have been tested for expression of WT1 by IHC as of 30-Sep-21.
- Any sample with WT1-staining tumor cells with nuclear and/or cytoplasmic staining at any intensity is scored as positive for enrollment eligibility. H-scores are collected for retrospective analyses.

Safety and Tolerability

	All Patients (N = 18)			
	Treatment-Related Adverse Events		All Adverse Events	
Preferred Term	**≥ Grade 3**	**Any Grade**	**≥ Grade 3**	**Any Grade**
Anemia	0	2 (11.1%)	1 (5.6%)	6 (33.3%)
Fatigue	0	4 (22.2%)	0	5 (27.8%)
Pyrexia	0	4 (22.2%)	0	5 (27.8%)
Abdominal pain	0	1 (5.6%)	1 (5.6%)	4 (22.2%)
Nausea	0	3 (16.7%)	1 (5.6%)	4 (22.2%)
Urinary tract infection	0	0	0	4 (22.2%)
Abdominal pain upper	0	1 (5.6%)	0	3 (16.7%)
Chills	0	2 (11.1%)	0	3 (16.7%)
Constipation	0	0	0	3 (16.7%)
Decreased appetite	0	1 (5.6%)	0	3 (16.7%)
Dyspnea	0	0	0	3 (16.7%)
Pruritus	0	3 (16.7%)	0	3 (16.7%)
Ascites	0	0	1 (5.6%)	2 (11.1%)
Aspartate aminotransferase inc.	0	0	1 (5.6%)	2 (11.1%)
Back pain	0	1 (5.6%)	0	2 (11.1%)
Diarrhea	0	0	0	2 (11.1%)
Hypokalemia	0	0	0	2 (11.1%)
Hyponatremia	0	1 (5.6%)	1 (5.6%)	2 (11.1%)
Infusion related reaction	0	2 (11.1%)	0	2 (11.1%)
Lymphocyte count decreased	2 (11.1)	2 (11.1)	2 (11.1%)	2 (11.1%)
Peripheral Edema	0	0	0	2 (11.1%)
Platelet count decreased	0	0	1 (5.6%)	2 (11.1%)
Pleural effusion	0	0	0	2 (11.1%)
Vomiting	0	2 (11.1%)	0	2 (11.1%)

Adverse Events occurring at ≥ 10% frequency in all patients treated with ≥1 dose of CUE-102. AEs coded using MedDRA V21.0 and NCI-CTCAE v5.0 as of 02-Oct-2023. At each level of summation patients reporting >1 occurrence of the same AE are counted once at highest toxicity.

Patient Status to Date by Cohort

Cohort	Treated	Evaluable	SD	DCR	Status
C1 (1 mg/kg)	3	3	1	33%	0/3 on treatment
C2 (2 mg/kg)	6	5	4	80%	3/6 on treatment
C3 (4 mg/kg)	5	4	3	75%	4/5 on treatment
C4 (8 mg/kg)	4	2	1	50%	2/4 on treatment

Fourteen of the 18 patients with data in EDC had at least 1 post dose scan as of 01-Oct-2023 and were evaluable for disease response. SD = stable disease by RECIST 1.1 criteria on a scan 6 weeks after 1st dose, duration of SD ranges from 6-24 weeks. DCR = Disease control rate (OR+PR+SD). Nine subjects remain on treatment.

Reductions in Target Lesions in Two Early Patients

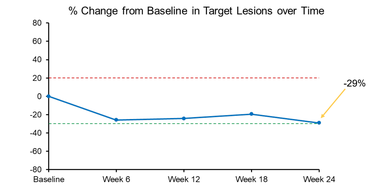
64 year old male
Gastric Cancer T4N2Mx
Diagnosed July 2021

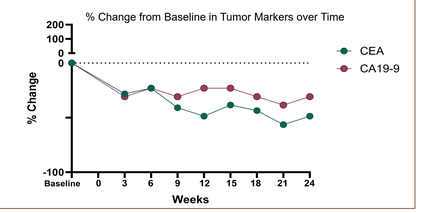
Prior Therapy:
1. Neo-adjuvant FLOT x 4 cycles
   Total Gastrectomy with LN dissection
2. Adjuvant FLOT x 4 cycles
   PET/CT Nodal recurrence 8 months off-therapy
3. FOLFOX + Nivolumab x 2 cycles.
   Progressive disease on CT scan

Enrolled in Cohort 2 (2 mg/kg)

WT1 staining

Intensity	Nuclear	Cytoplasmic
1+	0%	40%
2+	0%	5%
3+	0%	0%
H-Score	0	50





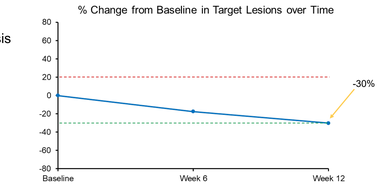
52 year old female
Ovarian Cancer FIGO stage IVA (T3N0M1)
Right Ovary & Fallopian Tube with peritoneal carcinomatosis
Diagnosed August 2021

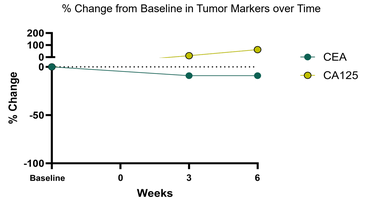
Prior Therapy:
1. Neoadjuvant Carboplatin + Paclitaxel
   Debulking surgery :
   Laparoscopic hysterectomy, bilateral salpingo-oophorectomy and omentectomy
2. Adjuvant Carboplatin + Paclitaxel
   New lesion Left Hemipelvis 8 months off-therapy
3. Carboplatin + Doxorubicin x 6 cycles
   Progressive disease on CT scan
4. Cytoxan + Avastin palliation x 3 months
   Progressive disease on CT scan

Enrolled in Cohort 2 (2 mg/kg)

WT1 staining

Intensity	Nuclear	Cytoplasmic
1+	0%	2%
2+	5%	0%
3+	95%	0%
H-Score	295	2





Details on two patients in dose escalation cohort 2 (2 mg/kg) with stable disease. Both remain on treatment at time of data cut-off, 02-Oct-2023. Both patients have advanced disease and were heavily pre-treated prior to enrollment. WT1 staining in patient with gastric carcinoma predominantly cytoplasmic while patient with ovarian adenocarcinoma exhibits predominately nuclear staining of WT1.

Summary

- CUE-102-01 is a phase 1, open label, two-part dose escalation and expansion study for patients with late-stage Colorectal, Gastric/GEJ, Pancreatic and Ovarian cancers that express WT1.
- Tumor WT1 expression is detected in in 50-60% of patients with GI cancers and 100% of patients with ovarian cancer to date, which is consistent with expected prevalence of WT1 expression in these tumor types described in the literature.
- Enrollment has been rapid. Patients have been treated with 1–8 mg/kg of CUE-102 IV every 3 weeks, with no dose-limiting toxicities (DLT) reported to date. A maximum tolerated dose (MTD) has not been reached. Cohorts 2, 3 and 4 are being expanded to obtain additional safety and pharmacodynamic information to support the selection of RP2D for Part B (dose expansion).
- Two patients, one with gastric cancer and one with ovarian cancer have demonstrated reduction in tumor burden.

ACKNOWLEDGEMENTS:
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