#636 A phase 1, open-label, dose escalation and expansion study of CUE-102 monotherapy in HLA-A*0201 positive patients with WT1-positive recurrent/metastatic cancers

John Powderly[1], Nashat Gabrail[2], Yvonne Saenger[3], J. Eva Selfridge[4], Nataliya Uboha[5], Jun Gong[6], Brian A. Van Tine[7], Olatunji Alese[8], Dae Won Kim[9], Wen Wee Ma[10], Tanios Bekaii-Saab[11], Jeremy Jones[12], Angela Alistar[13], Laura Agensky[14], Apollina Goel[14], Reena Lynam[14], Christie Zhang[14], Raymond J. Moniz[14], Steven N. Quayle[14], Kenneth Pienta[15], Matteo Levisetti[14], Steven P. Margossian[14]

[1]Carolina BioOncology, Huntersville, NC, USA; [2]Gabrail Cancer Center, Canton, OH, USA; [3]Albert Einstein Cancer Center, Bronx, NY, USA; [4]UH Cleveland, Cleveland, OH, USA; [5]Carbone Cancer Center, Madison, WI,USA; [6]Cedar Sinai, Los Angeles, CA, USA; [7]Washington University School of Medicine, St. Louis, MO, USA; [8]Emory University, Atlanta, GA, USA; [9]H. Lee Moffitt Cancer Center, Tampa, FL, USA; [10]Mayo Clinic, Rochester, MN, USA; [11]Mayo Clinic, Phoenix, AZ, USA; [12]Mayo Clinic, Jacksonville, FL, USA; [13]Carol G. Simon Cancer Center, Morristown, NJ, USA; [14]Cue Biopharma, Cambridge, MA, USA; [15]Johns Hopkins University School of Medicine, Baltimore, MD, USA.

Background

Immuno-STATs™ are novel, modular fusion proteins designed to selectively activate tumor-antigen-specific CD8+ T cells. 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). WT1 was previously ranked as the highest priority antigen for therapeutic targeting in an effort by the National Cancer Institute. WT1 is highly expressed in several solid tumor and hematologic malignancies [1]. Development of novel modalities targeting WT1 provides a significant opportunity to address high unmet medical need in WT1-positive malignancies.

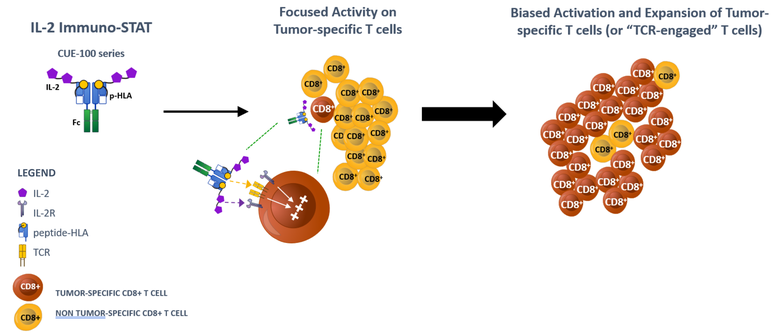
CUE-102 is designed to bind and activate $WT1_{37-45}$-specific T cells for the treatment of HLA-A*0201 patients with WT1-expressing cancers while eliminating the bias toward Treg activation that compromises antitumor immunity. This novel mechanism of selective engagement and expansion of tumor antigen-specific T cells 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.

Clinical trial, CUE-102-01, will establish a safety and PK profile across multiple doses, with evaluation of clinical and PD effects. Dose optimization from this enabling trial will support expansion into multiple indications.

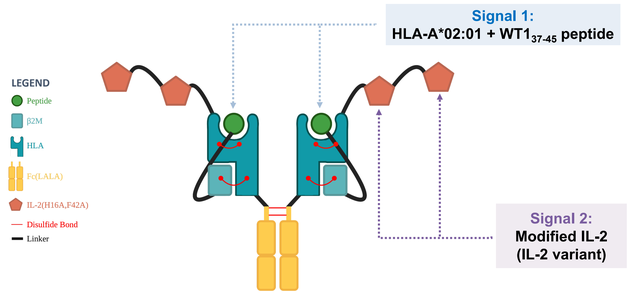
[1]Cheever MA, Allison JP, Ferris AS, et al. The prioritization of cancer antigens: a national cancer institute pilot project for the acceleration of translational research. Clin Cancer Res. 2009 Sep 1;15(17):5323-37.
[2]Girgis N, Zhang C, Merazga Z, et al. CUE-102 Selectively Activates and Expands WT1-Specific T Cells for the Treatment of Patients with WT1+ Malignancies. Abstract #1323 SITC 2022.

CUE-100 Series Immuno-STATs



The Immuno-STAT Approach. The rationally engineered and modular biologics of the Immuno-STAT platform incorporate natural biological signals ("cues") for selective engagement and modulation of disease-relevant T cells. The CUE-100 series framework is designed to selectively deliver modified IL-2 to tumor-specific T cells to drive their expansion. 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.

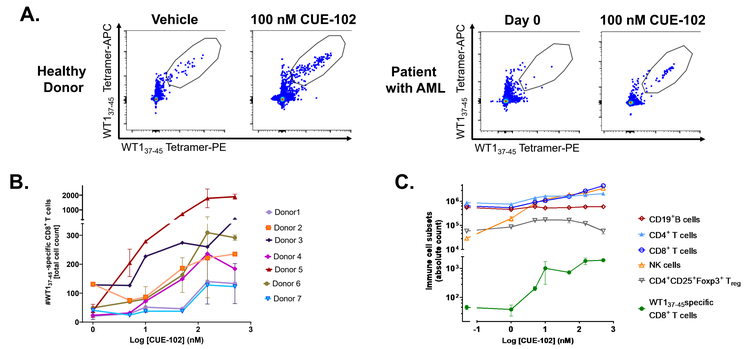
CUE-102 Immuno-STAT Design



Schematic of CUE-102 molecule. CUE-102 is comprised of a human leukocyte antigen (HLA) complex, HLA-A*0201, a peptide epitope derived from the N-terminus of the WT1 protein, and 4 molecules of a reduced affinity human IL-2. CUE-102 is designed to bind and activate WT1-specific T cells for the eradication of WT1-expressing cancers.

For Further Details on CUE-102 Preclinical Activity, see CUE-102 Companion Poster #1323

CUE-102 Selectively Expands $WT1_{37-45}$-Specific CD8+ T Cells from Human PBMCs in vitro

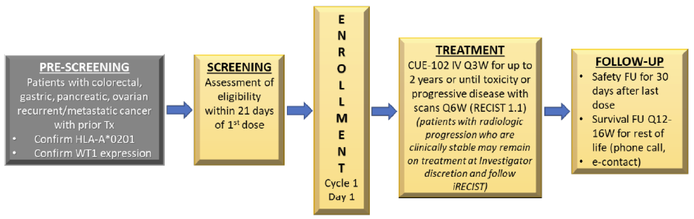


(A) Primary human PBMCs of healthy donors or acute myeloid leukemia (AML) patients were exposed to 100 nM CUE-102 for 10 days. CUE-102 expanded a population of $WT1_{37-45}$-specific $CD8^+$ T cells as measured by double tetramer staining, while vehicle treatment did not. **(B)** CUE-102 induces expansion of $WT1_{37-45}$ specific $CD8^+$ T cells in PBMCs of multiple donors in a dose-dependent manner. **(C)** Expansion of total NK cells was also observed in response to CUE-102 treatment. Other immune cells in donor PBMCs were not expanded, including $CD4^+$ T_{regs}. **For Further details on preclinical studies with CUE-102 please see our companion poster #1323**

Methods

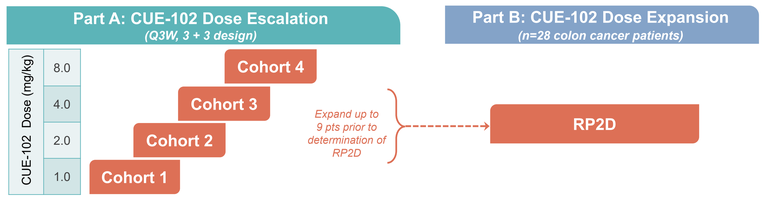
- CUE-102-01 is Phase 1 open label 2-part study to characterize the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), immunogenicity and Maximum Tolerated Dose (MTD) of CUE-102 monotherapy in patients with WT1 positive recurrent/metastatic Colorectal, Gastric/Gastroesophageal Junction (GEJ), Pancreatic or Ovarian cancer who have failed conventional therapies.
- Trial eligibility includes HLA-A*0201 genotype and diagnosis of WT1 expressing cancer, determined by WT1 IHC.
- CUE-102 is administered intravenously once every 3 weeks.
- Objectives include determination of safety, PD, PK, recommended phase 2 dose (RP2D), and preliminary anti-tumor activity.
- Part A is a dose escalation phase following 3+3 design rules with a Bayesian Logistic Regression Model (BLRM) overlay. 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.
- Part B is a dose expansion/confirmation phase in patients with Colorectal Cancer only.

Overall Study Design



Schema of study design. Patients can be pre-screened for HLA-A genotype and WT1 expression prior to meeting other protocol eligibility criteria.

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)

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

Eligible WT1 Expressing Cancers

- Colorectal cancer that has progressed following at least 2 prior systemic therapies (CUE-102 will be 3rd line therapy or greater).
  - Approved therapies must have included all the following: a fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, and cetuximab or panitumumab if clinically indicated).
  - Recurrence ≤ 1 year from completion of adjuvant chemotherapy with fluoropyrimidine and oxaliplatin will qualify as progression on one prior therapy.
  - Prior use of and failure after regorafenib or trifluridine/tipiracil is allowed but not mandated.
- Gastric/GEJ cancer that has progressed following at least 1 prior systemic therapy (CUE-102 will be 2nd line therapy or greater).
  - Patients whose cancers are HER2+ should be offered Fam-trastuzumab deruxtecan-nxki prior to being treated with CUE-102.
- Pancreatic cancer that has progressed following at least 1 prior systemic therapy (CUE-102 will be 2nd line therapy or greater).
  - Prior systemic treatment must include either a fluoropyrimidine-based or gemcitabine-based regimen in either adjuvant or relapsed setting.
- Ovarian cancer that has progressed following at least 1 prior systemic therapy (CUE-102 will be 2nd line therapy or greater).
  - Prior systemic treatment must include a platinum-based regimen.
  - For patients determined to have platinum-sensitive disease (CR and relapse ≥6 months after completing chemotherapy), treatment with a second platinum-based combination regimen +/-bevacizumab should be considered prior to treatment with CUE-102 (CUE-102 will be 3rd line therapy or greater).
  - Patients with known germline BRCA1/2 mutations may benefit from PARPi therapy in relapse or maintenance setting, but prior treatment with a PARPi is not required.
- For all cancer types:
  - Metastatic or locally advanced/unresectable disease
  - Patients whose cancers harbor NTRK gene fusions should be offered an Entrectinib class TKI first.
  - Patients with MSI-H or high tumor mutational burden should be offered a CPI first.

Participating Sites

The CUE-102-01 protocol is currently in the process of opening at 17 sites as shown. If your site is interested in participating, please contact Reena Lynam (rlynam@cuebio.com) or Steven Margossian (smargossian@cuebio.com)

Summary

- CUE-102 is the 2nd Immuno-STAT in the CUE-100 series in clinical trials, building upon the experience of CUE-101 in HPV16+ Head and Neck Squamous Cell Carcinoma.
- CUE-102 is designed to selectively activate T cells against WT1 expressing cancers through the targeted delivery of attenuated IL-2.
- CUE-102-01 is a phase 1, open label, two-part dose escalation and expansion study. Eligible cancers include Colorectal, Gastric/GEJ, Pancreatic and Ovarian cancers that express WT1 via central testing.
- The CUE-102-01 study will generate the preliminary benefit-risk profile of CUE-102 to support streamlined expansion into other WT1 target cancers, including both solid tumor and hematologic malignancies.
- CUE-102-01 is open and enrolling as of June 14, 2022.

ACKNOWLEDGEMENTS:
The authors would like to thank all the patients participating in this trial as well as their families and caregivers. Many thanks also to the investigators and study personnel for their hard work in support of this study. This study is sponsored by Cue Biopharma Inc. and conducted in collaboration with LG Chem, a subsidiary of LG Corp., Seoul, South Korea.

ClinicalTrials.gov ID: *NCT05360680*