#363 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 Powderly1, Nashat Gabr2, Yvonne Sanger1, J. Eva Selfridge1, Nataliya Uboha3, Jun Gong3, Brian A. Van Tine1, Olatunji Alese4, Dave Won Kim5, Wen Wei Ma6, Tanios Bakel Saab7, Jeremy Jones7, Angela Altis1, Laura Agensky1, Apollina Goell1, Reena Lyman1, Christie Zhang8, Raymond J. Moniz1, Steven N. Quayle1, Kenneth Pienta1, Matteo Levisetti1, Steven P. Margossian1

1Cue Biopharma Center, Diamond Bar, CA, USA; 2Cue Biopharma, Cambridge, MA, USA; 3Cedar Sinai, Los Angeles, CA, USA; 4Washington University School of Medicine, St. Louis, MO, USA; 5Tommy University, Athens, GA, USA; 6Yale, Lee Moffitt Cancer Center, Tampa, FL, USA; 7Mayo Clinic, Rochester, MN, USA; 8Mayo Clinic, Phoenix, AZ, USA; 9Mayo Clinic, Jacksonville, FL, USA; 10Carol G. Simon Cancer Center, Montclair, NJ, USA; 11UC Riverside, Cambridge, MA, USA; 12Sotera Development, Baltimore, MD, USA.

Day 0 100 nM CUE-102

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

13Carol G. Simon Cancer Center, Morristown, NJ, USA; 14Cue Biopharma, Cambridge, MA, USA; 15Johns Hopkins University School of Medicine, Baltimore, MD, USA.

Background

Immuno-STAT™ 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 a designed to bind and activate WT1+ 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 antitumor efficacy with reduced toxicity relative to non-targeted forms of immunotherapy that induce systemic activation of the immune system. In preclinical 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).

Methods

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 Colon, Gastro/Esophageal 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.

CUE-102 Selectively Expands WT137-45-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+ specific CD8+ T cells as measured by double tetramer staining, while vehicle treatment did not. (B) CUE-102 induces expansion of WT1+ 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 cells. For further details on preclinical studies with CUE-102 please see our companion poster #1323.

Overall Study Design

CUE-102 is designed to be administered intravenously once every 3 weeks. Methods include determination of safety, PK, PD, 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) to further characterize activity and toxicity.

Part B is a dose expansion/confirmation phase in patients with Colorectal Cancer only.

For patients determined to have platinum-sensitive disease (CUE-102 will be 2nd line therapy or greater).

Patients with prior use of and failure after regorafenib or trifluridine/tipiracil is allowed but not mandated.

Eligible WT1 Expressing Cancers

- Colorectal cancer that has progressed following at least 2 prior systemic therapiest (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 nivolumab or tremelimumab is allowed but not mandated.
- Gastro/GEJ 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 (CUE-102 will be 2nd line therapy or greater).
- Patients with recurrent germ cell/BTC/malignancies 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/irresistable disease
  - Patients whose cancers harbor BRCA2 mutations should be offered a platinum-based regimen.
  - Patients with MSI-H or high tumor mutational burden should be offered a CPI first.

CUE-102 is the 2nd Immuno-STAT in the CUE-100 series in clinical trials, building upon the experience of CUE-101 in HPV+ 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 is a phase 1, open label, two-part dose escalation and expansion study. Eligible cancers include Colon, Gastro/GEJ, Pancreatic and Ovarian cancers that express WT1 via central testing.

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 clinicaltrials@cuebiopharma.com.

CUE-102 Series Immuno-STATs

The Immuno-STAT Approach: The rationally engineered and modular biologics of the Immuno-STAT platform incorporate natural biological signals (“sires”) for selective engagement and modulation of disease-related T cells. The CUE-102 series expands on this approach by rationally designing and building a novel modular biologic that elicits selectively expanded CD8+ T cells. CUE-102 incorporates the WT1-specific WT137-45 epitope for tumor antigen recognition, an IL-2 analog that provides highly specific activation, and a transgene for the production of IL-2 in the absence of tumor antigens. 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 clinicaltrials@cuebiopharma.com.

CUE-102 Immuno-STAT Design

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Summary

- CUE-102 is the 2nd Immuno-STAT in the CUE-100 series in clinical trials, building upon the experience of CUE-101 in HPV+ 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 Colon, Gastro/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:
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ClinicalTrials.gov ID: NCT05360680

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

Participating Sites

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-terminal of the WT1 protein, and 4 molecules of a reduced affinity human interleukin-2 (IL-2). CUE-102 is designed to bind and activate specific T cells for the evaluation of WT1-expressing cancers.

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

Dose Escalation and Expansion Schema

Part A: CUE-102 Dose Escalation

Part B: CUE-102 Dose Expansion

Key Eligibility Criteria:

- CUE-102-01: 100-nM CUE-102 Expected expression
- WT1+ Cancers
- Part A: Colon, Gastro/GEJ, Pancreatic and Ovarian
- Part B: Colon, Gastro/GEJ
- Measurable disease by RECIST 1.1
- Life expectancy ≥ 12 weeks

Objectives:

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

Biometrics:

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

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

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