CUE-102 Selectively Activates and Expands WT1-Specific T Cells for the Treatment of Patients with WT1-Malignancies

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Background

- **Immunoswitching** (IS) are rationally engineered biologics comprised of a lyophilized peptide-MHC complex and covalently linked cytokine molecules built upon an Fc framework to enable stability, solubility, favorable PK, and manufacturability.
- **CUE-100 series** ISTs are designed to selectively deliver attenuated IL-2 to WT1-specific tumor-infiltrating and/or WT1-specific tumor-infiltrating dendritic cells (DCs).
- Development of novel modalities targeting WT1 provides a significant opportunity to address high unmet medical need in WT1-positive malignancies, including AML, ovarian, endometrial, breast, lung, gastric, colorectal and pancreatic cancer.

**CUE-102** is being developed as a novel therapeutic fusing protein to selectively activate tumor-antigen-specific T cells to treat WT1-expressing cancers.

CUE-100 Series Immuno-STAs

**Objectives:**
- Generate the maximum dose of WT1-specific CD8+ T cells from whole human PBMCs in vitro.
- Identify WT1-specific CD8+ T cells that produce IFN-γ and TNF-α in response to peptide restimulation of splicing or donor-infiltrating lymphocytes (FL)

**Biomarkers:**
- WT137-45-Specific CD8+ T Cells in naïve HLA-A2 Transgenic Mice
- WT137-45-Specific CD8+ T Cells from Human PBMCs
- Attenuation of IL-2 Activity in CUE-102

**Methods:**
- Schematic of CUE-102 molecule.
- Human IL-2 molecules on CUE-102 are functionally attenuated and much less potent than recombinant IL-2 (Proleukin®) in a CTLL-2 cell proliferation assay.
- The IL-2 specificity of CUE-102 facilitates selective phosphorylation of STATs (pSTATs) immediately downstream of LIR-2 on target cells.
- CUE-102 induces pSTATs with greater potency in WT1-specific CD8+ T cells compared to CMV-specific CD8+ T cells.

**Results:**
- CUE-102 expanded WT1-specific CD8+ T cells in naïve HLA-A2 Transgenic Mice.
- Figure 5 – Schematic of CUE-102 molecule.

**Conclusions:**
- CUE-102 is a novel fusion protein designed to selectively deliver attenuated IL-2 to tumor-specific CD8+ T cells.
- CUE-102 demonstrates selective binding, activation, and expansion of polyfunctional and cytotoxic WT1-specific primary human CD8+ T cells from healthy and cancer patients.
- The novel mechanism of action of CUE-102, namely selective expansion of tumor-specific CD8+ T cells via delivery of reduced affinity mutant IL-2, supports its potential for anti-cancer efficacy in a Phase I clinical trial in HLA-A2-matched malignant cancers.

**Figure 11 – CUE-102 expands functional CTLs in vivo.** (A) The majority of WT1-specific CD8+ T cells (red) isolated from the spleen of naïve HLA-A2-transgenic mice immunized with 4 doses of CUE-102 produced IFN-γ, TNF-α and Granzyme B in response to ex vivo restimulation. (B) HLA-A2 mice immunized with CUE-102 show an in vivo killing of HLA-A2-target cells, whereas WT1-specific WT1-377-45 peptide, or an irrelevant peptide, as shown by the loss of WT1-WT1-transfected target cells in CUE-102 immunized HLA-A2 transgenic mice (red), but not in naïve mice (black).

**Figure 12 – Repeated treatment with CUE-102 expands WT1-specific CD8+ T cells.** Graphs display frequencies of WT1-specific CD8+ T cells among total CD8+ T cells in PBMCs from mice that received multiple doses of CUE-102 at 3 mg/kg CUE-102, or 0.3 mg/kg CUE-102 at week 0 and week 2. (C) WT1-specific CD8+ T cells were detectable in blood at all the 3 mg/kg and 0.3 mg/kg dose levels but the peak level increased with repeated treatment.

**Figure 13 – CUE-102 is a Phase 1, FIH study to characterize the safety, tolerability, PK, PD, immunogenicity, and preliminary antitumor activity of CUE-102 in subjects who are HLA-A2/1+ positive, naïve-positive, nonrecipients/cancer donors, and have failed conventional therapies.**