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CUE-102 SELECTIVELY ACTIVATES AND EXPANDS WT1-SPECIFIC T CELLS FOR THE TREATMENT OF PATIENTS WITH WT1+ MALIGNANCIES

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Background Wilms' Tumor 1 (WT1) was ranked as the highest priority antigen for therapeutic targeting in an effort by the National Cancer Institute. Development of novel modalities targeting WT1 provide a significant opportunity to address high unmet medical need in WT1-positive malignancies, including AML, ovarian, endometrial, breast, lung, colorectal and pancreatic cancer. Leveraging the Immuno-STAT™ platform of targeted IL-2 therapies, and the ongoing development of CUE-101, CUE-102 is being developed as a novel therapeutic fusion protein to selectively activate tumor antigen-specific T cells to treat WT1-expressing cancers. CUE-102 consists of two human leukocyte antigen (HLA) molecules presenting a WT1 peptide, four affinity-attenuated human interleukin-2 (IL-2) molecules, and an effector attenuated human immunoglobulin G (IgG1) Fc domain.

Methods Cellular activity and specificity of CUE-102 were demonstrated in human PBMCs, while the in vivo activity of CUE-102 was assessed in HLA-A2 transgenic mice. HLA-A2/WT1-specific TCRs were validated and expressed in primary human CD8+ T cells. Antigen-specific cells were identified by flow cytometry using tetramer staining, activation markers and cytokine production.

Results Multiple in vitro assessments demonstrated that CUE-102 selectively binds, activates, and expands naturally occurring WT1₃₇₋₄₅-specific CD8+ T cells from PBMCs of healthy and cancer patient donors, consistent with its design. These CD8+ T cells exhibit polyfunctional and cytotoxic responses upon challenge with WT1-presenting target cells. In addition, significant functional attenuation of the IL-2 components of CUE-102 was shown, similar to preclinical results obtained with CUE-101. In vivo studies in HLA-A2 transgenic mice confirmed that CUE-102 elicits and expands polyfunctional WT1-specific CD8+ T cells from naïve and previously immunized mice without significantly altering the frequencies of other immune lineages. The WT1-specific CD8+ T cells expanded in vivo exhibit polyfunctional cytokine responses upon restimulation and selectively kill target cells presenting WT1 peptide in vivo. WT1-specific CD8+ T cells elicited in vivo by CUE-102 were detectable for >180 days following the last CUE-102 treatment, demonstrating the establishment of a long-term memory response to this tumor antigen.

Conclusions CUE-102 elicits selective expansion of WT1-specific cytotoxic CD8+ T cells both in vitro and in vivo. These results, together with its similarity to CUE-101, support its anticipated tolerability profile and potential for clinical efficacy in an ongoing Phase 1 clinical trial (NCT05360680).

Ethics Approval Studies using animals were conducted in accordance with guidelines established by the Smart Labs Institutional Animal Care and Use Committee under protocol 21SL09-0007.

<http://dx.doi.org/10.1136/jitc-2022-SITC2022.1323>