395 ENHANCEMENT OF BISPECIFIC T CELL ENGAGERS (BISPECIFIC TCE) KILLING POTENCY IN AML WITH THE NEXIMMUNE ARTIFICIAL IMMUNE MODULATION (AIM™) ADOPTIVE CELL THERAPY (ACT) T CELLS

Ruipeng Wang, Mathias Oelke, Shweta Jain, Sojung Kim, Jack Ragheb, Adam Parks, Rui Wang, Charles Reed, Brian Alvarez, Jerome Zeldis, Daniel Bednarik*. *Nelmmune, Gaithersburg, MD, USA*

Background Bispecific TCEs are a new class of immunotherapeutic molecules for the treatment of cancer. Bispecific TCE molecules enhance the patient's immune response to tumors by retargeting T cells to tumor cells. However, Bispecific TCEs show rapid clearance with a serum half-life of a few hours, therefore the administration of bispecific TCE often requires high doses and continuous intravenous infusion, which can result in T cell exhaustion at higher doses.

Methods Here we evaluated if combining bispecific TCE treatment with NexImmunes AIM ACT T cells (AIM ACT) can further improve the effect of the bispecific TCE. For this study we have generated 5 AML specific bispecific TCEs targeting FLT3 (two different molecules), CD123, CD33 and Siglec-6 and tested them *in vitro* for AML-specific tumor cell killing in combination with either AML-specific AIM ACT or non-specific bulk CD4 and CD8 T cells.

Results We present data that the combination of bispecific TCE and AIM ACT is superior to bispecific TCE monotreatment that relies on engaging with the host endogenous tumor non-specific T cell repertoire. All bispecific TCE mediated killing of AML cell lines, when combined with CD8 T cells, although the Siglec-6 specific TCE had the lowest effect due to low surface expression of Siglec6 in these tested cell lines. Specifically, we interrogated the potency of different types of T cells as bispecific effectors including CD4 and CD8 control T cells from healthy volunteers in comparison to our AIM ACT. Analysis of TCR-mediated killing (without bispecific TCE) showed that, both non-specific bulk CD4 and CD8 T cells had little potency while AML-specific AIM ACT can mediate effector to target cell ratio dependent target cell killing. Overall target cell killing was most efficient when using AIM ACT as effector cells. Notably, bispecific TCE concentrations in the picomolar range achieved greater than 80% target cell killing with AIM ACT.

Conclusions Together these *in vitro* studies demonstrate the synergistic effect of bispecific TCEs and our multi-antigen-specific AIM ACT with the potential to enhance the therapeutic effect while at the same time lowering the requirement for high dose and continuous infusion of the bispecific TCE. In addition, to validate our findings *in vivo* we will present data from our ongoing *in vivo* study evaluating the combination of a CD123 specific bispecific TCE in combination with either our multi-AML antigen-peptide specific AIM ACT or freshly isolated bulk $CD8^+$ T cells in a THP-1/NSG humanized mouse model.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0395