THE CBL-B INHIBITOR, NX-0255, ENHANCES HUMAN DRUG ENHANCED TUMOR INFILTRATING LYMPHOCYTE (DETIL) EXPANSION AND T CELL FUNCTION IN FULL-SCALE RUNS


Background Ex-vivo expanded autologous tumor-infiltrating lymphocyte (TIL) therapy is one type of adoptive cellular therapy (ACT) which has demonstrated encouraging clinical responses in patients with melanoma or those with epithelial tumors. Effective methods to obtain sufficient TIL of suitable quality and diversity from tumor samples remains a challenge. The E3 ubiquitin ligase, Casitas B lineage lymphoma B (CBL-B) is expressed in T cells where it regulates signaling through the T Cell Receptor (TCR), limiting T cell activation and differentiation. Our previous studies demonstrated that addition of NX-0255, our highly potent CBL-B inhibitor, during ex-vivo TIL expansion resulted in a favorable TIL phenotype and higher cell yields.

Methods Here we evaluated the comparative effects of the addition of the CBL-B inhibitor NX-0255 on expansion and phenotype of drug-enhanced TIL (DeTIL), in multiple full-scale processes. Six full-scale studies were conducted. All six runs were performed in parallel in TIL expanded either solely in the presence of 3,000-6000 IU/ml rHu IL-2 (TIL arm), or in the presence of rHu IL-2 and 1 μM NX-0255 (DeTIL-0255 arm). DeTIL-0255 and TIL harvested on day 22 were assessed for total cell number, viability, phenotype, and function.

Results Compared with the TIL arm, the addition of NX-0255 increased the total viable cell count on Day 22 in five out of six full-scale experiments. Significant increases in the total number of CD8+ T cells as well as those with a central memory phenotype were observed in all six runs. A significant increase in the proportion of CD4+ central memory DeTIL-0255 was also demonstrated. No significant differences in effector memory populations were observed. DeTIL-0255 have a significantly (p<0.05) higher stem-like population of CD39+CD69+‘double negative’ CD8+ cells as compared to TIL upon TCR and CD28 co-stimulation. CD8+ T cells in DeTIL-0255 displayed higher intracellular expression of granzyme B as well as co-expression of granzyme B and the cell surface CD107α when compared to TIL. Furthermore, significant increases in intracellular IFN-γ expression were observed in activated DeTIL-0255 when compared to TIL using flow cytometric assessment.

Conclusions DeTIL-0255 demonstrates a superior phenotype and greater yield when compared with conventional TIL and is suitable for testing in clinical trials. We have initiated a clinical trial with DeTIL-0255 in patients with gynecologic malignancies. NCT05107739