98 NX-0255, A SMALL MOLECULE CBL-B INHIBITOR, EXPANDS AND ENHANCES TUMOR INFILTRATING LYMPHOCYTES (TIL) FOR USE IN ADOPTIVE CANCER IMMUNOTHERAPY

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Background Adoptive cell transfer (ACT) of TIL effects durable responses in patients with melanoma and some epithelial tumors. It is thought that poor in vitro cell expansion and inefficient T-cell migration to the tumor limits the broader application of this approach. The E3 ubiquitin ligase, Casitas B-lineage lymphoma b (CBL-B) is expressed in T-cells where it functions as a regulator of immune cell activation, in part by requiring CD28 co-stimulation in addition to T-cell receptor activation. We have developed NX-0255, a highly potent small molecule inhibitor of CBL-B, demonstrating its ability to increase T-cell derived cytokine secretion and proliferation in the presence or absence of co-stimulation. Here, we investigated the effects of NX-0255 on the ex vivo growth and characteristics of human TIL to create drug-enhanced TIL (DeTIL-0255) as an ACT product for treating patients with cancer.

Methods TIL from ovary, colon, lung, head and neck, breast, and vulva carcinomas were cultured with IL-2 and compared in two experimental groups: NX-0255 without IL-2, or NX-0255 in combination with IL-2. Following 22 days of culture, cell number, and phenotype were assessed by flow cytometry and single-cell transcriptomics.

Results Culturing of TIL in the presence of NX-0255 alone resulted in the expansion of cells, with numbers comparable to that of conventionally cultured TIL with IL-2. The addition of NX-0255 in combination with IL-2 significantly increased the number of cells expanded compared to TIL (n=16, p=0.004). Flow cytometric analysis demonstrated that DeTIL-0255 were significantly less exhausted compared to TIL, as shown by the significant reduction of CD8+ T-cells expressing PD-1 (p=0.02), and co-expressing PD-1+TIM-3+ (p=0.03) and PD-1+LAG-3+ (p=0.03).Furthermore, upon stimulation, the functional capacity of DeTIL-0255 was differentially enhanced, with significant increases in the absolute numbers of CD8+ T-cells expressing intracellular perforin (p=0.001), granzyme-B (p=0.005) and CD107a (p=0.01) when comparing DeTIL-0255 to TIL. An increase of CD8+ T-cells expressing CD137/4-1BB, a biomarker of CD8+ T-cell tumor reactivity was also observed (p=0.03). TCR repertoire and single-cell sequencing analysis demonstrated that DeTIL-0255 had increased TCR diversity and enhanced expression of genes associated with stemness (CD127+,CCR7+,CD62L+) and cytotoxicity (GNLY+,GZMB+,NKG7+).

Conclusions Collectively, these data suggest that DeTIL-0255 increases the proportion and absolute numbers of less exhausted CD8+ memory T-cells, enhancing cytolytic T-cell function. Adoptive transfer of DeTIL-0255 may increase persistence and exhibit broader functional activity than conventional TIL, potentially conferring improved anti-tumor activity. Taken together, these data support the clinical development of DeTIL-0255 for the treatment of patients with cancer.

http://dx.doi.org/10.1136/jitc-2021-SITC2021.098