UNIVERSAL EXPANSION OF CBL-B-INHIBITED TUMOR INFILTRATING LYMPHOCYTES, DETIL-0255, FROM WOMEN WITH OVARIAN CANCER: PROCESS VALIDATION

1Pranav Murthy, 1Neil Namitha Narasappa, 1Xiaoyan Liang, 1Xianzu Wu, 1Irene Lu, 1Jeevitha Jeevan, 1Sagar Sharma, 1Alison Ross, 1Caleb Lampefeld, 1Sam Zahn, 1Thomas Musial, 1Jennifer Bone, 1John Nakayama, 1David Bartlett, 1Ioulieh Chapman, 1Greta Ganido, Nicholas Shinners, 1Arthur Sands, 1Michael Blackton, 1Ewa Wang, 1Michael Lotze, 1Nunix Therapeutics, San Francisco, CA, USA; 2Allegheny Health Network, Pittsburgh, PA, USA; 3UCSF Medical Center, San Francisco, CA, USA

Background Despite objective responses to immune checkpoint blockade in patients with ovarian cancer (OC), therapies providing durable clinical benefit are lacking. An increased density of OC tumor infiltrating lymphocytes (TIL), specifically memory T cells with enhanced CD28 signaling, are associated with improved survival and immunotherapy response. Adoptive cell therapy (ACT) utilizing ex vivo expanded TIL has demonstrated durable complete responses in several epithelial malignancies, but has shown limited clinical benefit in OC. This is due in part to extended manufacturing times and use of TIL products with a differentiated and exhausted phenotype. Casitas B lineage lymphoma-B (CBL-B) is an E3 ubiquitin ligase that limits T cell activation in the absence of CD28 co-stimulation following T cell receptor engagement. Ex vivo inhibition of CBL-B with the small molecule inhibitor NX-0255 increases the expansion of stem-like TIL with enhanced in vivo tumor cytotoxicity and persistence compared to conventional TIL expanded in IL-2 alone. Here we present our pre-clinical and early manufacturing experience of drug enhanced TIL therapy (DeTIL-0255) in OC.

Methods Tumor tissue from N=21 consenting patients undergoing resection for OC across multiple US clinical sites was fragmented and cultured with IL-2 and NX-0255 under going resection for OC across multiple US clinical sites were characterized by multiparameter spectral flow cytometry. OC DeTIL-0255 were primarily effector memory CD4 T cells (research scale) and 2.5x10^10 cells (clinical scale). OC DeTIL-0255 was reproducibly expanded from primary products, OC DeTIL-0255 were primarily effector memory (CD4: 59.7±30.6%; CD8: 55.6±29.8%) and central memory cells (CD4: 21.0±23.7%; CD8: 12.4±16.9%) displaying limited T cell exhaustion (CD4: PD-1 26.2±22.8%, LAG-3 15.1±13.5%, CD57 4.4±4.3%; CD8: PD-1 17.7±19.6%, LAG-3 45.4±28.4%, CD57 2.9±2.5%).

Conclusions OC DeTIL-0255 demonstrate a favorable phenotype amenable for ACT. A Phase 1 clinical study of DeTIL-0255 in women with recurrent/platinum resistant OC is ongoing (NCT05107739).

REFERENCES

Ethics Approval All studies were performed in full accordance with the guidelines for good clinical practice and the Declaration of Helsinki and approved by the cited institutional protocol review committee and IRB.

Consent Written informed consent was obtained from the patient for use of patient specimens for research and subsequent publication.