

A NOVEL 'OFF THE SHELF' TCR-NK CELL THERAPY PLATFORM FOR THE TREATMENT OF SOLID TUMOURS: DEVELOPMENT OF OPTIMISED MAGE-A4 TARGETING TCR-NK CELLS FOR ADVANCEMENT INTO THE CLINIC

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Background T cell receptor (TCR)-T based therapies, such as MAGE-A4 TCR-T cells, have shown compelling data demonstrating effective infiltration into and targeting of solid tumours with clinical responses across various solid cancers.¹ However, heterogeneity and down-regulation of target expression limit the durability and curative potential of these types of treatments. On the other hand, owing to their clinical potency, favourable safety profile and applicability as 'off the shelf' therapy, natural killer (NK) cells have emerged as promising modalities in recent years. Unguided NK cells have shown limited potential against solid cancers, due to lacking infiltration into tumours. With our proprietary TCR-NK platform, we combine the solid tumour targeting capabilities of TCRs with the pan-cancer cytotoxic potential of highly potent killer cells, redirecting and arming NK cells with a fully functional TCR-CD3 complex.

Here we present our lead, an optimised TCR-NK cell product, ZI-MA4-1, expressing an affinity enhanced TCR directed to the HLA class I-restricted clinically validated cancer-testis antigen MAGE-A4, broadly expressed across solid tumours.

Methods The ZI-MA4-1 TCR was successfully engineered from a naturally occurring wild-type TCR increasing the affinity to MAGE-A4-peptide-HLA complex and resulting in enhanced recognition of tumour cells expressing the target antigen. ZI-MA4-1 is produced by transducing healthy peripheral blood derived NK cells (PB-NK) with the full CD3 complex and a CD8 coreceptor. The process has been optimised to enrich CD3/TCR expression on NK, increasing process robustness, diminishing the impact of donor variability, and producing higher performing TCR-NK cells.

Results We show for the first time, that affinity enhancing a TCR increases the anti-tumour activity of TCR-NK cells compared to the wild-type TCR. Specificity analysis of the affinity enhanced TCR shows an absence of off-target cross-reactivity against normal tissue human cells and iCells. Furthermore, we show the dual functionality of TCR-NK cells: TCR driven cytotoxicity as well as innate NK recognition of antigen knockout or HLA negative cancers. Finally, we demonstrate higher activity of TCR-NKs compared to benchmark TCR-Ts against antigen positive targets, and activity against antigen negative tumour cells escaping TCR-T cell recognition.

Conclusions Taken together, these data demonstrate the feasibility and potential of generating optimised TCR-NK cells from PB-NK resulting in a highly potent cell product combining TCR-mediated and innate NK killing functions. Based on the potency and safety profile, ZI-MA4-1 has advanced into manufacturing with a preclinical package underway to enable a clinical trial for treatment of patients with advanced solid tumours.

REFERENCE

1. David S Hong, Brian A Van Tine, Swethajit Biswas, Cheryl McAlpine, Melissa L Johnson, Anthony J Olszanski, Jeffrey M Clarke, Dejka Araujo, George R Blumenschein, Partow Kebriaei, Quan Lin, Alex J Tipping, Joseph P Sanderson, Ruoxi Wang, Trupti Trivedi, Thejo Annareddy, Jane Bai, Stavros Rafail, Amy Sun, Lilliam Fernandes, Jean-Marc Navenot, Frederic D Bushman, John K Everett, Derin Karadeniz, Robyn Broad, Martin Isabelle, Revashnee Naidoo, Natalie Bath, Gareth

Betts, Zohar Wolchinsky, Dzmityr G Batrakou, Erin Van Winkle, Erica Elefant, Armin Ghobadi, Amanda Cashen, Anne Grand'Maison, Philip McCarthy, Paula M Fracasso, Elliot Norry, Dennis Williams, Mihaela Druta, David A Liebner, Kunle Odunsi, Marcus O Butler, Autologous T cell therapy for MAGE-A4+ solid cancers in HLA-A*02+ patients: a phase 1 trial. *Nature Medicine*. 2023;**29**:104–114.

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