

FIRST-IN-CLASS ANTI-PVR MAB NTX1088 RESTORES EXPRESSION OF DNAM1 AND AUGMENTS ANTITUMOR IMMUNITY

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Background Poliovirus receptor (PVR, CD155) is a novel oncology target, differentially overexpressed in a wide range of solid tumors, which recently emerged as a main resistance mechanism to approved immune checkpoint inhibitors (ICIs). It is a key regulator of immune activation, that modifies function through multiple mechanisms, through interaction with the immune receptors DNAM1 (CD226), TIGIT and CD96. Increased PVR expression levels on tumor cells have been associated with resistance to anti-PD1 and PDL1 therapy in patients, while loss of PVR led to reduced tumor growth. Targeting PVR offers an attractive therapeutic approach for patients with advanced cancers, who are not responding to other ICIs.

NTX1088 is a first-in-class, humanized, anti-PVR mAb, currently investigated in a Phase I. By binding PVR with high affinity, NTX1088 has a multi-faceted immune-stimulating role. It blocks the interaction between PVR and its receptors, leading to the restoration of DNAM1 expression and its immune activation function, while simultaneously neutralizing TIGIT and CD96 inhibitory signals in immune cells. DNAM1 downmodulation by PVR was recently identified as a key effector of immune surveillance, and its distinctive restoration by NTX1088 was never seen before by other therapies.

Methods In vitro mechanistic studies demonstrated that NTX1088, as a monotherapy, significantly increased immune cell activation, and was superior to TIGIT, CD112R, and PD1 antibody blockade, leading to superior immune-mediated tumor cell killing, IFN γ release, and CD137 induction. Importantly, only NTX1088 was able to restore DNAM1 to the surface of immune cells in all settings. Synergy was observed when NTX1088 was combined with PD1 blockers or with the anti-CD112R mAb, NTX2R13, in line with the restoration of DNAM1 expression.

Results Numerous humanized murine xenograft models were investigated. NTX1088 as a monotherapy exhibited robust tumor growth inhibition of the PDAC cell line, HPAFII, co-engrafted with human PBMC in NOD/SCID mice. The effect was significantly improved when NTX1088 was combined with a PD1 inhibitor. Furthermore, tumor growth inhibition by NTX1088 was observed in humanized A549 xenograft in which TIGIT and PD1 blockers failed to impact tumor growth. Tumor-infiltrating lymphocytes, harvested from NTX1088-treated mice, demonstrated a significantly higher prevalence of CD137+, DNAM1+, CD8+ T cells compared to all other interventions.

Conclusions These promising preclinical findings, together with a clean safety profile in cynomolgus monkeys, paved the way to a Ph1 clinical study in which NTX1088 is tested as a monotherapy and in combination with pembrolizumab, in patients with locally advanced and metastatic solid tumors (NCT05378425).

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