

**NTX-1088, A POTENT ANTI-PVR MAB INDUCES DNAM1-MEDIATED ANTITUMOR IMMUNITY**

<sup>1</sup>Anas Atieh, <sup>1</sup>Akram Obiedat, <sup>1</sup>Guy Cinamon, <sup>2</sup>Tihana Lenac Rovis, <sup>2</sup>Paola Kucan Brlic, <sup>2</sup>Lea Hirs, <sup>3</sup>Ofer Mandelboim, <sup>2</sup>Stipan Jonjic, <sup>1</sup>Keren Paz, <sup>1</sup>Pini Tsukerman\*. <sup>1</sup>*Nectin Therapeutics, Jerusalem, Israel*; <sup>2</sup>*University of Rijeka, Rijeka, Croatia*; <sup>3</sup>*Hebrew University, Jerusalem, Israel*

**Background** Poliovirus receptor (PVR, CD155) represents a resistance mechanism to approved immune checkpoint inhibitors (ICIs). It is a key regulator of immune activation, that modifies function through multiple mechanisms. Increased PVR expression levels on tumor cells have been associated with resistance to anti-PD-(L)1 therapy, while loss of PVR led to reduced tumor growth. Targeting PVR using mAbs offers an attractive therapeutic approach for patients with advanced cancer, who are not responding to other ICIs. NTX-1088 is a first-in-class, anti-PVR mAb developed for the treatment of solid tumors and will enter clinical trials early 2022. The antibody binds PVR with high affinity, blocks its interactions with TIGIT and CD96, preventing their inhibitory signaling. Moreover, NTX-1088 forte is manifested through its ability to block the critical interaction between PVR and DNAM1 (CD226). This blockade prevents internalization of DNAM1, restores its expression on the surface of immune cells and results in a robust antitumor activity.

**Methods** NTX-1088 was rigorously tested in vitro and in-vivo. Various cancer cell lines were incubated with immune effector cells from healthy human donors, in the presence of NTX-1088, alone and in combination with anti-PD-1 mAb (pembrolizumab).

**Results** NTX-1088 significantly increased immune cell activation, as measured by IFN $\gamma$  release from activated polyclonal CD8+ T cells, induction of CD137 and killing of tumor cells. When tested in combination with pembrolizumab, NTX-1088 further increased all measured activation parameters, suggesting a potential synergistic effect. A synergistic effect was obtained when NTX-1088 was combined with the anti-CD112R mAb, NTX-2R13, superior to TIGIT-CD112R combinations. When compared to anti-TIGIT mAb (tiragolumab), NTX-1088 demonstrated clear superiority in activating T and NK cells as stand-alone agent. Furthermore NTX-1088 in combination with pembrolizumab, was superior to the combination of pembrolizumab with anti-TIGIT. Importantly, NTX-1088 was the only intervention that significantly restored DNAM1 levels, whereas DNAM1 blockade reduced the activity of NTX-1088 to levels comparable to that of anti-TIGIT mAb. Humanized murine models confirmed the above observations; NTX-1088 exhibited a robust tumor growth inhibition, accompanied by significantly higher prevalence of CD137+, DNAM1+, CD8+ T cells, compared to mice treated by other ICIs.

**Conclusions** This is the first report of drug-induced DNAM1 restoration and immune activation. NTX-1088 shows, for the first time, exclusive triple mechanism of action, whereby simultaneous and effective blockade of TIGIT and CD96 is complemented by the efficient restoration of DNAM1. This is a step change in antitumor immune activation, which will be validated in the clinic starting early 2022.

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