NPX267, a first-in-class monoclonal antibody targeting KIR3DL3, blocks HHLA2-mediated immunosuppression and potentiates T and NK cell-mediated antitumor immunity

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Background Killer cell immunoglobulin like receptor, three Ig domains and long cytoplasmic tail 3 (KIR3DL3) is a member of the killer cell Ig-like (KIR) receptor family and is expressed by both NK and T cells. KIR3DL3 has recently been shown to be a co-inhibitory receptor for the B7 ligand, human endogenous retrovirus H long terminal repeat–associating protein 2 (HHLA2).1,2 KIR3DL3, expressed on T and NK cells in the tumor microenvironment, suppresses immune responses following engagement with HHLA2. Upon HHLA2-induced KIR3DL3 activation, SHP-1 and SHP-2 are recruited to KIR3DL3’s cytoplasmic immunoreceptor tyrosine-based inhibitory motif (ITIM) and downstream activation signals are blunted. As a result, T and NK cell activity is suppressed. HHLA2 has limited expression in normal tissues, but is highly expressed in many cancers and is often associated with poor patient outcomes. In renal cell carcinoma (RCC), HHLA2 expression is often not co-expressed with PD-L1. However, co-expression of HHLA2 and PD-L1 in tumors from patients with RCC is associated with worse progression free survival that those with tumors exclusively expressing PD-L1. Thus, the KIR3DL3-HHLA2 axis represents a novel immune checkpoint pathway and blockade of KIR3DL3 signaling may be a promising strategy to promote antitumor immunity.3

Methods To explore the therapeutic potential of HHLA2-KIR3DL3 blockade, we generated NPX267, a first-in-class, monoclonal antibody that binds with high affinity to human KIR3DL3.

Results NPX267 blocks HHLA2 engagement with KIR3DL3 on primary human NK and T cells in a dose dependent fashion. The ability of NPX267 to block KIR3DL3-mediated suppression of T cell activation was assessed with a T cell reporter system and primary CD8+ T cell functional assays. KIR3DL3 blockade with NPX267 inhibited HHLA2-mediated suppression of T cell activation in a dose dependent manner. The anti-tumor activity of KIR3DL3 blockade with NPX267 was also demonstrated in NK-cell mediated cytotoxicity assays. NPX267 treatment augmented the ability of human NK cell lines and primary NK cells to kill HHLA2+ tumor cells in vitro. Finally, NPX267 blockade of HHLA2 mediated KIR3DL3 signaling enhanced anti-tumor immunity in humanized mouse models bearing HHLA2+ human tumors.

Conclusions Collectively, these data demonstrate that the KIR3DL3-HHLA2 pathway is a novel immune checkpoint axis that facilitates tumor escape by attenuating both innate and adaptive antitumor immune responses. NPX267, a first-in-class KIR3DL3 blocking antibody, potentiates anti-tumor immunity against HHLA2+ tumors and may represent a promising approach to treat certain cancers.

REFERENCES