606 SAR444245 (THOR-707), AN ENGINEERED NON-ALPHA IL-2, ENHANCES NK MEDIATED ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY

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Background SAR444245 is a non-alpha IL-2 Synthorin ™ molecule designed with a site-specific non-natural amino acid serving as a bioconjugation site for a single PEG. The non-natural amino acid is positioned to enable the PEG bioconjugation to obscure block binding to the IL-2 alpha receptor, while retaining near-native affinity with the intermediate affinity βγ IL-2 receptor. The non-alpha features of SAR444245 minimize activation of immune suppressive regulatory CD4+ T cells, while retaining activity on CD8+ T cells and NK cells expressing the IL-2 βγ receptors. NK cells exert anti-tumor activity through antibody dependent cellular cytotoxicity (ADCC) of IgG antibodies as well as antibody independent mechanisms.

Methods Here, we utilized a panel of human primary PBMC based immunoassays and transcriptomic analysis to evaluate whether SAR444245 may improve ADCC function of IgG1 anti-tumor target antibodies.

Results We characterized the ability of SAR444245 to enhance the cytolytic function of NK cells towards the prototypic NK target cell K562 as well as to modulate NK cell ADCC in combination with EGFR or CD20-targeting antibodies. In vitro assays demonstrated that SAR444245 can activate NK cells, promote NK cell proliferation and improve cytotoxicity of NK cells against K562 cells and across a panel of human EGFR and CD20 positive cell lines. In PBMC based ADCC assays with 1ug/ml of antibody, SAR444245 improved ADCC function maximally by 9-fold for an anti-EGFR antibody and at 5-fold for an anti-CD20 antibody. SAR444245 exhibited dose-dependent enhancement of NK cell ADCC function. Notably, this activity was observed in cell lines expressing varying levels of EGFR and CD20. SAR444245 treatment was associated with dose dependent increases in NK cell degranulation and IFN-γ production. Transcriptomic profiling revealed that SAR444245 had broad effects on NK cell biology leading to changes in inhibitory and activating receptors.

Conclusions In summary, these results indicate that SAR444245 can enhance the cytolytic activity of NK cells and enhance the ADCC effect of tumor-directed antibodies by activating NK cells.

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