1193 SYNERGISTIC TARGETING OF MULTIPLE ACTIVATING PATHWAYS WITH NATURAL KILLER CELL ENGAGERS

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Background Tumor microenvironment induced antigens present a unique opportunity to effectively target diseased tissue over normal and to modulate the immune suppression they might elicit. MICA and MICB (MICA/B) are stress-induced antigens expressed in a range of cancers. MICA/B antigens are recognized by NKG2D, an activating receptor on NK and CD8+ T cells. While the membrane-bound form of MICA/B is immuno-stimulatory, the cleaved soluble form found in the tumor microenvironment prevents NKG2D mediated tumor cell recognition. To stop tumor escape and, concurrently, stimulate the innate and adaptive immune responses, we developed antibodies targeting MICA/B. Anti-MICA/B antibodies block proteolytic cleavage, increase MICA/B membrane surface densities, and activate NK and CD8+ T cells by bringing membrane bound MICA/B to NKG2D. To enhance the anti-tumor activities of MICA/B antibodies, we designed multi-specific NK cell engaging antibodies that simultaneously target MICA/B antigens and an orthogonal activating receptor NKp46.

Methods Expanding on Xencor's XmAb therapeutic protein platform, we developed multi-specific NK cell Engager (NKE) molecules that simultaneously activate several stimulatory pathways including NKG2D, NKp46, and FcγRIIIa via the Fc domain. The multi-specific NKEs were assessed for their ability to induce tumor cell cytotoxicity, secrete proinflammatory cytokines, and activate effector cells.

Results To address the polymorphic nature of MICA and MICB antigens, anti-MICA/B antibodies were developed that recognize multiple MICA/B allelic variants. Subsequent screens selected for antibodies that block the proteolytic cleavage of membrane bound MICA/B. These antibodies induce tumor cell lysis and stimulate IFNγ production by effector cells. The functional activity of these MICA/B antibodies is dependent on agonism of the NKG2D pathway. To enhance the activity of our MICA/B antibodies the Fc was engineered to have increased affinity for the FcγR receptors. Antibodies with enhanced Fc effector function showed superior activity over their IgG1 counterparts. To capitalize on the ability of NK cells to integrate activating and inhibitory signals, we designed NK cell engagers targeting MICA/B, agonism via the NKG2D pathway, and NKp46 to stimulate an orthogonal NK cell activation pathway. These multi-specific NKEs stimulate both activating receptors and show enhanced functional activity compared to antibodies only targeting MICA/B. These findings indicate that multi-specific NKE antibodies are superior for activating NK cells for the targeted killing of tumor cells.

Conclusions Multi-specific XmAb NKEs engineered to stimulate multiple activating pathways show potent tumor cell lysis and induce production of proinflammatory cytokines. Next steps include assessment of in vivo activity and safety profile evaluation.

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