DM919: A POTENT ANTI-MICA/B ANTIBODY REINFORCES NKG2D MICA/B AXIS AND PROMOTES ANTI-TUMOR ACTIVITIES IN PRECLINICAL MODELS

Guangan Hu, Quanju Zhao, Lai Shi, Xiaochun Chen, Xiaodong Jiang, Sheng Yin, Nan Bing, Dong Zhang*. D2M Biotherapeutics Inc, Natick, MA, USA

Background Genome-wide association studies have identified MICA/B proteins as a causal factor for multiple cancers. Membrane MHC-I related MICA/MICB are stress-responding proteins and trigger the cytotoxic effector activity of NK cells and co-stimulatory activation of CD8+ T cells through NKG2D receptor. Many human tumors develop immune escape mechanism via proteolytic cleavage of MICA/B from the cell surface. Shedding of MICA/B leads to lack of recognition by NKG2D. Soluble shed MICA/B not only are natural decor of NKG2D, but also downmodulate NKG2D receptor and inhibit NK cell function. DM919, a potent anti-MICA/B antibody, prevents MICA/B shedding and stabilizes surface MICA/B, and presents shed MICA/B to activate NKG2D on NK or T cells and mediates ADCC.

Methods Mice were immunized with recombinant proteins of a3-domain from multiple alleles of MICA/B proteins to maximize allotype coverage in human population (~99.1%). Resulted IgG H&L chain variable regions were PCR amplified from plasma cells and built into yeast displayed scFv libraries. The libraries was screened for specifically binding to multiple alleles of MICA/B and evaluated for ability to prevent the shedding of MICA/B and activate NK and T cells via NKG2D. The selected anti-MICA/B hits were humanized, and affinity maturation was carried out using yeast display technology. Optimized hits were further screened and characterized in series of assays to evaluate functional activities and physicochemical properties. The lead candidate DM919 was identified based on its desirable characteristics and further evaluated in multiple syngeneic and xenograft mouse tumor models.

Results DM919 binds specifically to multiple alleles of MICA/B proteins with sub nanomolar affinities. DM919 inhibits the MICA/B shedding and stabilizes their surface expression. DM919 captures soluble MICA/B and activate NK cells and co-stimulate T cells through NKG2D. DM919 enhances the activation and degranulation of primary human NK cells and increases the cytotoxicity of human NK cells to lyse tumor cells. DM919 demonstrated excellent stability in vitro and in vivo. DM919 significantly inhibited xenograft tumor growth in vivo in SCID mice. DM919 inhibited in vivo growth of syngeneic mouse tumor cells transgenically expressing human MICA/B in a dose dependent manner. DM919 treatment reduced serum soluble MICA/B, which is a pharmacodynamic biomarker.

Conclusions DM919, a high affinity and potent the anti-MICA/B antibody has been developed. DM919 has demonstrated desirable functional and physicochemical characteristics in vitro. DM919 has shown significant antitumor activities in multiple syngeneic and xenograft tumor models. The data support further development of DM919 as an immunotherapeutic for solid tumor malignancies.

Ethics Approval All animal studies and procedures were approved by the Institutional Animal Care and Use Committee (IACUC) of Worcester polytechnic Institute. The protocol ID is #21-134.

Consent Written informed consent was obtained from the patient for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.