Background MICA/MICB are stress-responding proteins and trigger the activation of NKG2D receptor expressed on CD8 + T cell, gd T cells and NK cells. Many human tumors develop an immune escape mechanism via proteolytic cleavage of MICA/B from cell surface. Shedding of MICA/B leads to lack of recognition by NKG2D. Soluble shed MICA/B proteins not only are natural decoy of NKG2D, but also downmodulate NKG2D receptor and inhibit NK cell function. Restoring NKG2D-MICA/B axis is a compelling approach to harness the immune system for treating cancer. DM919 is humanized anti-MICA/B monoclonal IgG1 antibody, being developed to reinforce NKG2D-MICA/B axis and promote anti-tumor immunity.

Methods The binding kinetics of DM919 were measured using BLI technology. The binding affinities and the abilities to prevent the shedding of MICA/B were assessed using FACS. The functions to enhance the activation and effector function of NK and T cells were evaluated in a series of cellular assays using ELISA and FACS. Anti-tumor activity was evaluated in syngeneic or xenograft or huPBMC humanized mouse tumor models. Cytokine response in human PBMC were measured using the Luminex assay. The manufacturability of DM919’s was assessed in industrial standard processes. PK and toxicology were performed in cynomolgus monkeys.

Results DM919 binds human MICA/B proteins with sub nanomolar affinities. DM919 binds to the alleles covering >98% human population and cross-reacts to >90% of ever-reported alleles of cynomolgus monkey. DM919 efficiently binds to membrane MICA/B and stabilizes their surface expression in human cell lines from multiple tumor types. DM919 captures soluble MICA/B and activates NK cells and co-stimulate T cells through NKG2D. DM919 enhances the activation and increases the cytotoxicity of human NK and gd T cells to lyse tumor cells. DM919 demonstrated excellent stability in vitro and in vivo. DM919 treatment reduced serum soluble MICA/B, which is a pharmacodynamic biomarker. DM919 significantly inhibited tumor growth in vivo in multiple mouse models. DM919 demonstrated strong anti-tumor activity in a syngeneic mouse model in a dose-dependent manner and had synergistic effect in combination with anti-PD-1. No DM919-related findings were noted in toxicity studies. The manufacturability of DM919 has been validated.

Conclusions DM919, a high affinity and potent anti-MICA/B antibody, has demonstrated desirable functional and physicochemical characteristics in vitro. DM919 has shown significant antitumor activities in multiple mouse tumor models. Good safety profile in NHP and well-demonstrated manufacturability of DM919 have warranted an IND submission and further investigation in clinical trials.

Ethics Approval All uses of human material have been approved by the Institutional Review Board at ABI-Lab. All animal studies and procedures were approved by the Institutional Animal Care and Use Committee (IACUC) at Worcester Polytechnic Institution (WPI).

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