1395  CLN 619 A CLINICAL STAGE MICA B SPECIFIC IGG1 ANTIBODY WHICH RESTORES THE MICA B-NKG2D AXIS REQUIRES FC FUNCTION FOR POTENT ANTI-TUMOR ACTIVITY


**Background** MICA and MICB are stress-inducible, highly polymorphic, surface glycoproteins that are expressed on a wide variety of human tumors but restricted in normal tissues. Engagement of MICA/B by NKG2D on natural killer (NK) cells and certain T cell subsets stimulates immune cell activation and subsequent target cell lysis. In cancer patients, tumor cells can escape NKG2D-mediated lysis by shedding MICA/B from the cell surface via proteases in the tumor microenvironment. High concentrations of shed MICA have been observed in serum from patients across multiple tumor types, correlating with poor survival. CLN-619 is a humanized anti-MICA/MICB monoclonal IgG1 antibody being developed for the treatment of multiple cancer indications. It has broad reactivity across MICA/B alleles, prevents shedding of MICA/B from the tumor cell surface, enhances the interaction of MICA with NKG2D, and engages Fcγ receptors on effector cells to collectively drive potent anti-tumor activity. We herein describe the significance of Fc functionality for the therapeutic activity of CLN-619.

**Methods** MICA/B levels were measured in supernatants by ELISA and on the cell surface by flow cytometry. The Promega ADCC Bioassay Complete Kit was used to evaluate ADCC. MICA binding to NKG2D was measured by flow cytometry. In vitro killing was assessed in a co-culture assay of donor PBMC and MICA-expressing tumor cells. In vivo studies were conducted in human xenograft tumor models.

**Results** CLN-619 inhibited the shedding of MICA/B shedding and enhanced the interaction of MICA with NKG2D. The latter was mediated by CLN-619 Fc effector function as well as by intrinsic enhancement of MICA-NKG2D binding by CLN-619. A functional Fc domain was also found necessary for CLN-619 induced immune-mediated cell killing of MICA/B expressing cells in vitro and for efficacy in mice bearing subcutaneous HCC1534 human xenograft tumors (figure 1). An Fc-silenced version of CLN-619 had no anti-tumor activity in HCC1534 at 3 mg/kg whereas CLN-619 showed significant tumor control even at 0.03 mg/kg.

**Conclusions** CLN-619 treatment resulted in robust anti-tumor activity in mice bearing MICA/B-expressing xenograft models. Activity of CLN-619 was dependent on a functional Fc domain. Simultaneous stimulation of the NKG2D-MICA/B axis and ADCC by CLN-619 may uniquely synergize in activating the lytic potential of NK cells. CLN-619 is currently in a Phase 1 clinical trial for the treatment of patients with advanced malignancies (ClinicalTrials.gov Identifier: NCT05117476).