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

Kerry A. Whalen1, Naveen K. Mehta3, Kristan Meetze1, Neil W. Gibson2, Jennifer S. Michaelson1, Patrick A. Baeuerle3
1Cullinan Oncology, One Main Street, Cambridge, MA, USA. 2COI Pharmaceuticals, Inc., San Diego, CA, USA

**Background**

- MICA/MICB are stress-inducible, surface glycoproteins that are up-regulated on a wide variety of human tumors and act as activating ligands for the Natural Killer Group 2 member D (NKG2D) receptor expressed on NK cells, NKT cells, CD8 and γ/δ T cells.1-2
- While MICA/MICB expression marks cells for lysis by NKG2D-expressing immune cells, tumors can shed these proteins via cleavage by proteases present in the TME, thereby preventing immune cells from recognizing and destroying the tumor.3
- MICA/MICB are highly polymorphic, with >150 MICA and 47 MICB alleles.4
- High concentrations of shed MICA have been observed in sera from patients across multiple tumor types and correlate with poor survival.4
- MICA/MICB is highly polymorphic, with >150 MICA and 47 MICB alleles in humans. Expression level, binding affinity to NK and NKT cells, and degree of MICA/MICB shedding is thought to be allele-dependent.5,6

**Features of CLN-619**

- CLN-619 is a humanized IgG1 monoclonal antibody that specifically binds to human MICA and MICB and is cross-reactive to the non-human primate orthologs.
- CLN-619 prevents the proteolytic release of MICA/MICB from the tumor cell surface thereby exposing tumor cells for immune destruction through NKG2D-mediated and Fc-dependent mechanisms (ADCC & ADCP).
- CLN-619 is currently being investigated in a Phase 1 clinical trial as a humanized IgG1 monoclonal antibody which restores the MICA/B-NKG2D axis requires Fc function for potent anti-tumor activity.

**Results**

**Figure 1: CLN-619 Multiple Modes of Action**

- Prevention of MICA/MICB shedding, restoring recognition of tumor cells by immune cells
- Antibody-dependent cellular cytotoxicity (ADCC)
- Antibody-dependent cellular phagocytosis (ADCP)
- Enhanced binding of MICA to NKG2D

**Figure 2: MICA and MICB Are Broadly Expressed in Human Cancers**

**Figure 3: CLN-619 Inhibits MICA/MICB Shedding**

A-B) Cells were incubated with antibodies for 24 hours, N=2. A) Shed MICA/MICB was measured in the cell supernatant by ELISA. B) MICA/MICB cell surface expression was measured by flow cytometry.

**Figure 4: CLN-619 Activates CD16/FcγRIII Signaling Leading to ADCC**

**Figure 5: CLN-619 Mediates ADCP**

**Figure 6: CLN-619 Enhances Binding of MICA to NKG2D**

**Figure 7: CLN-619 Induction of Immune-Mediated Tumor Cell Killing In Vitro Depends Upon a Functional Fc-Domain**

**Figure 8: Efficacy of CLN-619 Depends Upon a Functional Fc-Domain**

- Jurkat cells expressing human FcRγIIA and an NFAT-luciferase reporter (Promega) were co-cultured with MICA/MICB-expressing tumor cells and incubated with FcγII or CLN-619. Luciferase activity was measured at 4 hours. CLN-619 activates CD16/FcγRIII signaling leading to ADCC.

**Conclusions**

- CLN-619 prevents proteolytic release of membrane bound MICA/MICB from tumor cells resulting in increased cell surface expression of MICA/MICB.
- CLN-619 elicits both ADCC and ADCP in the presence of MICA/MICB-expressing cells in a dose dependent fashion.
- CLN-619 enhances the binding of recombinant MICA to NKG2D on NK cells. This activity was attributed to both Fcγ receptor engagement on NK cells as well as an intrinsic enhancement of binding of MICA to NKG2D.
- CLN-619 treatment of MICA/MICB-expressing tumor cells resulted in immune-mediated cell killing in vitro and was dependent upon a functional Fc-domain.