The Structural Basis for Inhibition of MICA Shedding and Anti-tumor Activity of the Monoclonal Anti-MICA/B Antibody, CLN-619

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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 (NK) cell receptor NKG2D.
- While MICA/MICB expression marks cells for lysis by NK/G2D-expressing immune cells, tumors can shed these proteins via cleavage by proteases present in the TME, thereby preventing immune cells from recognizing and destroying tumor cells.
- High concentrations of shed MICA have been observed in sera from patients across multiple tumor types, where they correlate with poor survival.
- MICA/MICB is highly polymorphic with >150 MICA and 47 MICB alleles in humans.
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- CLN-619 is a humanized IgG1 monoclonal antibody that specifically binds to both human MICA and MICB, and to non-human primate orthologs.
- CLN-619 is currently being investigated in a Phase 1 clinical trial as a monotherapy and in combination with pembrolizumab for the treatment of patients with advanced solid tumors (NCT05117476).

Features of CLN-619

- CLN-619 is a humanized IgG1 monoclonal antibody that specifically binds to both human MICA and MICB.
- CLN-619 prevents the proteolytic release of MICA/MICB, thereby exposing tumor cells for immune cell destruction through both NK/G2D-mediated and Fc-dependent effector mechanisms, including antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent phagocytosis (ADCP).
- CLN-619 is currently being investigated in a Phase 1 clinical trial as a monotherapy and in combination with pembrolizumab for the treatment of patients with advanced solid tumors (NCT05117476).

Results

- CLN-619 binds to a discontinuous epitope comprising 19 amino acids in the alpha 3 domain of MICA.
- X-ray crystal structures of the human Fab antibody fragment CLN-619 in complex with the antigen MICA at 1.9 Å resolution. The binding epitope of CLN-619 is comprised of two separate and mobile regions of the alpha 3 domain of MICA.
- Sequence analysis of the CLN-619 discontinuous epitope for MICA/B alleles with ≥1% frequency in the population reveals high sequence conservation across all MICA/B alleles.

Conclusions

- CLN-619 prevents proteolytic release of MICA/MICB from cells resulting in increased cell surface expression of MICA/MICB.
- CLN-619 exhibits potent in vivo anti-tumor activity in mice bearing MICA/MICB-expressing human tumor xenografts.
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- CLN-619 is highly conserved, resulting in broad MICA/B allelic coverage.
- A Phase 1 clinical trial with CLN-619 as monotherapy and in combination with pembrolizumab is in progress.