CLN-619, a clinical-stage MICA/MICB-specific IgG1 antibody, restores the MICA/MICB-NKG2D axis to promote NK-mediated tumor cell lysis

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Abstract # 3506

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 NKp46 (NKG2D) 
- MICA/MICB is highly polymorphic, with >150 MICA and 47 MICB alleles in humans. 
- 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.1
- High concentrations of shed MICA have been observed in sera from patients across multiple tumor types and correlate with poor survival.2
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- 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
- High concentrations of shed MICA have been observed in sera from patients across multiple tumor types and correlate with poor survival.4

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 NHP orthologs.5
- CLN-619 prevents the proteolytic release of MICA/MICB thereby exposing tumor cells for immune destruction through both NKG2D-mediated and antibody-dependent cell-mediated cytotoxicity (ADCC).
- 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 (NCT01517475).

Results

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

A. Shed MICA/B B. Cell surface MICA/B C. Kinetics of MICA/B Stabilization

- CLN-619 binding to human tumor xenografts and reduced levels of shed MICA/sMICB in sera from CLN-619 treated animals.

Figure 3: CLN-619 Binds with High Affinity to MICA and MICB Allelic Variants

- CLN-619 enhances the binding between recombinant MICA and NKG2D on NK cells expressing human tumor xenografts and reduced levels of shed MICA/sMICB in sera from CLN-619 treated animals.

Figure 4: CLN-619 Binds with High Affinity to MICA and MICB Allelic Variants

- CLN-619 exhibits high affinity binding to all common allelic variants of MICA and the canonical allelic variant of MICB.

Figure 5: CLN-619 Enhances Binding of MICA to NKG2D

- CLN-619 enhances the binding between recombinant MICA and NKG2D on NK cells. This activity was attributed to both FcγR engagement on NK cells as well as an intrinsic enhancement of binding of MICA to NKG2D.

Figure 6: CLN-619 Induces Immune-Mediated Tumor Cell Killing In Vitro

- CLN-619 enhances MICA/MICB specific antibody, 6D4, was previously demonstrated to have relatively broad reactivity in the Luminex assay and was used as a positive control.6

Figure 7: In Vivo Efficacy of CLN-619 In Human Xenograft Models

- CLN-619 treatment of MICA-expressing tumor cells resulted in immune-mediated cell killing in vivo and was dependent upon a functional Fc-domain.

Figure 8: PK and Safety of CLN-619 in NHPs

- CLN-619 exhibited high affinity binding to all common allelic variants of MICA and the canonical allelic variant of MICB.

- CLN-619 treated mice expressing human xenograft tumors resulted in increased cell surface expression of MICA/MICB, peaking at 24 hours in vitro.

- CLN-619 enhances the binding between recombinant MICA and NKG2D on NK cells.

Conclusions

- CLN-619 exhibited high affinity binding to all common allelic variants of MICA and the canonical allelic variant of MICB.
- CLN-619 prevents proteolytic release of MICA/MICB from cells resulting in increased cell surface expression of MICA/MICB, peaking at 24 hours in vitro.
- CLN-619 enhances the binding between recombinant MICA and NKG2D on NK cells.
- CLN-619 treatment of MICA-expressing tumor cells resulted in immune-mediated cell killing in vivo and was dependent upon a functional Fc-domain.
- In the pivotal GLP toxicology study in monkeys, no CLN-619-related findings were noted, and the NOAEL was defined as the highest dose administered, i.e., 101.4 mg/kg/week.
- CLN-619 exhibited potent in vivo anti-tumor activity in mice bearing MICA/MICB expressing human tumor xenografts and reduced levels of shed MICA/MICB in sera from CLN-619 treated animals.
- A Phase 1 clinical trial with CLN-619 as monotherapy and in combination with pembrolizumab is in progress.