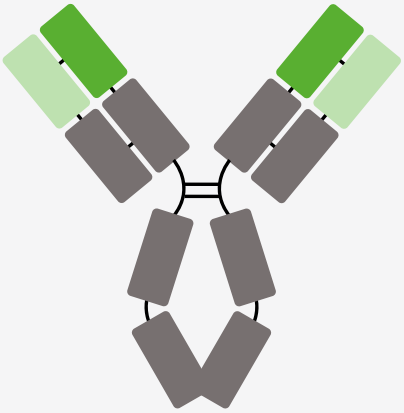
About CLN-619

One of the hallmarks of cancer is the ability to avoid destruction by immune cells. Cancer cells develop escape mechanisms that can render them invisible to the human immune system. This immune evasion enables unrestricted tumor growth and potential metastasis. Restoring immune surveillance can potentially improve cancer treatment across many tumor types and is a significant unmet need.

CLN-619



ABOUT THE MOLECULE

CLN-619 is a potential first in class MICA/MICB directed IgG1 antibody that restores the MICA/MICB-NKG2D axis to promote NK-mediated tumor cell lysis.

WHERE IT'S BEING STUDIED

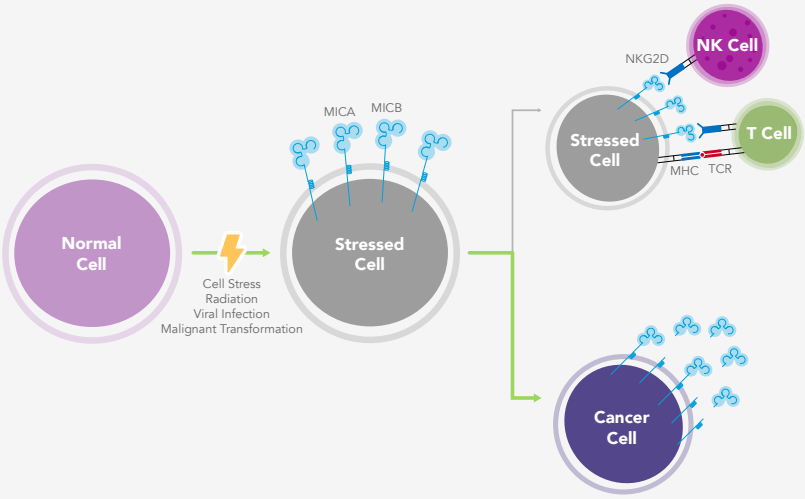
CLN-619 is currently being studied in a global Phase 1 dose-escalation clinical trial as a monotherapy and in combination with pembrolizumab in patients with advanced solid tumors.

WHAT ARE MICA/MICB PROTEINS?

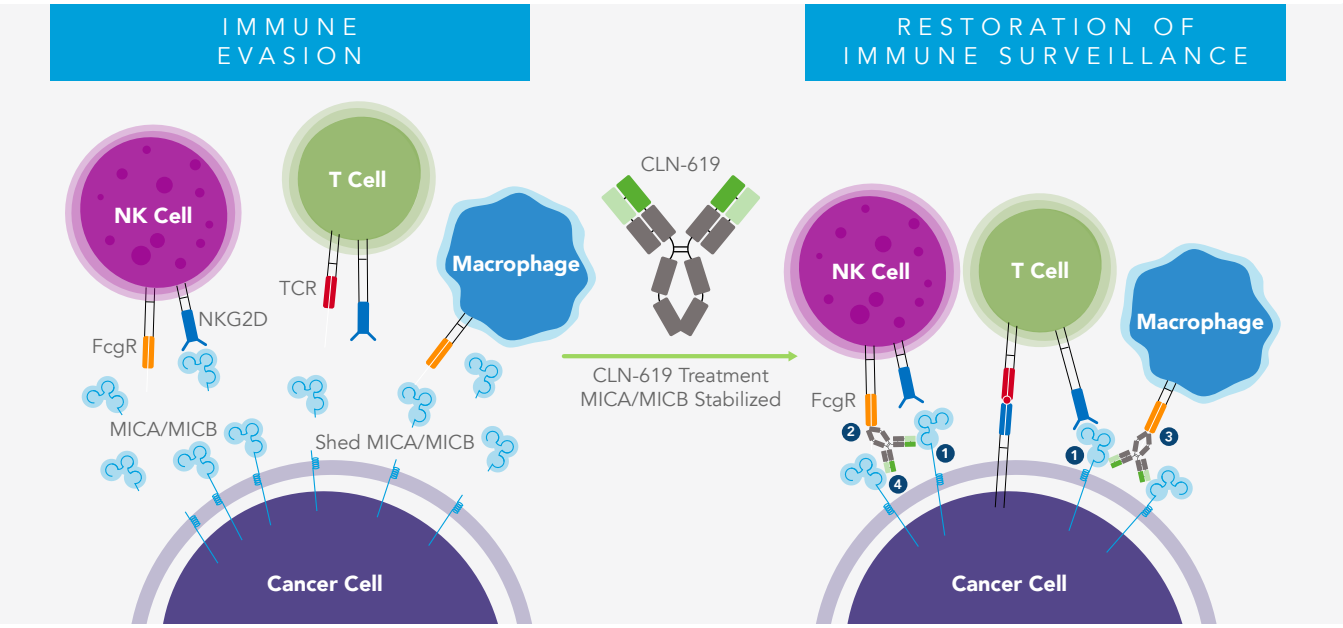
MICA and MICB proteins are found on the surface of stressed cells and serve as warning flags to the immune system that the cell is damaged, targeting the flagged cells for elimination by immune cells. MICA/MICB are minimally expressed on normal cells and are upregulated in most solid tumor types and hematologic malignancies, providing the potential opportunity to treat many patients.

MICA/MICB bind to the NK group 2 member D (NKG2D) receptor on natural killer (NK) cells and certain T cells. Receptor binding stimulates cytokine release and targets cell destruction by NKG2D-expressing immune cells.

Tumor cells can escape NKG2D-mediated lysis by shedding MICA/MICB from the cell surface via proteases present in the tumor microenvironment.



CLN-619 TARGETS AND MECHANISM OF ACTION



Pre-clinical data shows CLN-619 works to restore immune surveillance and activation by 4 mechanisms:

1. Prevention of MICA/MICB shedding, restoring NKG2D engagement of tumor cells
2. Antibody-dependent cytotoxicity
3. Antibody-dependent cellular phagocytosis
4. Enhancement of binding of MICA and NKG2D

Engagement of NK cells for immunotherapy offers novel attributes in relation to other immune effector cell types, including:

- NK cells are the first line of defense and do not require prior exposure to antigens to be activated efficiently and rapidly.
- Potentially reduced toxicity from cytokine release compared to T cell-directed therapies.
- NK cells have the potential to "see" cancer cells that are invisible to other immune cells, even in the absence of MHC class I presented antigens

PRECLINICAL EVIDENCE AND CLN-619'S POTENTIAL

- CLN-619 has demonstrated potent efficacy at low doses in pre-clinical mouse xenograft models.
- Due to MICA/MICB serving as an immune signal from stressed cells, CLN-619 could potentially be studied in combination with:
  - Standard-of-care therapies like radiation and chemotherapy, which can enhance MICA/MICB expression.
  - Enhancers of NK activation and function such as cytokines (IL-15).
  - Immunotherapies targeting distinct immune activation pathways, such as checkpoint inhibitors, that reinvigorate the adaptive immune response.