A Phase 1 Dose-Escalation Study to Investigate the Safety, Efficacy, Pharmacokinetics, and Pharmacodynamic Activity of CLN-619 (Anti-MICA/MICB Antibody) Alone and in Combination with Pembrolizumab in Patients with Advanced Solid Tumors

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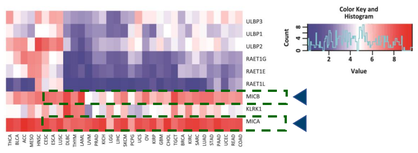
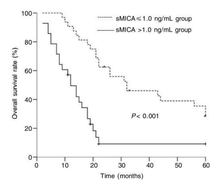
Background: MICA/MICB are Pan-Cancer Targets

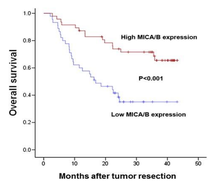
MICA/B ligands are highly expressed across 32 different tumor types (by TCGA)



Shed MICA[1]



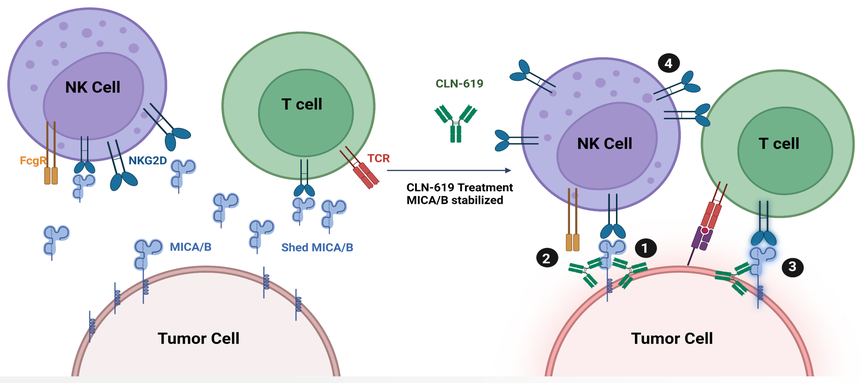
Cell Surface MICA[2]



- MICA/B expression is highly restricted on normal tissues, and is only expressed on the cell surface in response to cellular stress, such as infection, radiation, or malignant transformation
- Levels of shed MICA and MICB in serum show strong negative correlation with survival, whereas high expression on cancer cells shows a beneficial impact on survival

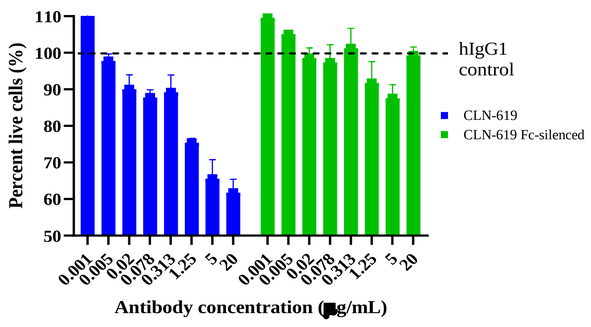
Background: CLN-619 Proposed Modes of Action

Immune Evasion | **Restoration of Immunosurveillance**



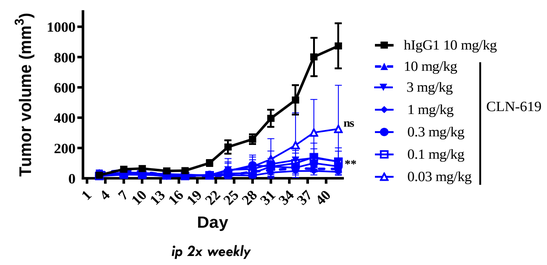
1. Prevention of MICA/MICB shedding from tumor cells, thereby restoring interaction with NKG2D and activation of immune cells
2. Fc-mediated antibody-dependent cytotoxicity (ADCC) of tumor cells
3. Enhancement of binding of MICA to NKG2D
4. Reduction in shed MICA/MICB decoy, thereby preventing NKG2D decoy/ decreased functionality

CLN-619 induces immune-mediated tumor cell killing *in vitro*[3]



HCC1534 tumor cells were pre-incubated with CLN-619 or CLN-619 Fc-silenced for 24 hours, and then co-incubated with human PBMC. Cytotoxicity was measured at 12 hours.

CLN-619 is efficacious *in vivo* at low doses[3]



BALB/c SCID mice were inoculated with HCC1534 lung cancer xenograft cells (N=10/group). Treatment with CLN-619 or control hIgG1 was administered IP 2X weekly for 6 weeks IP. ns-not significant, ** p<0.005 by one-way ANOVA.

Study Information

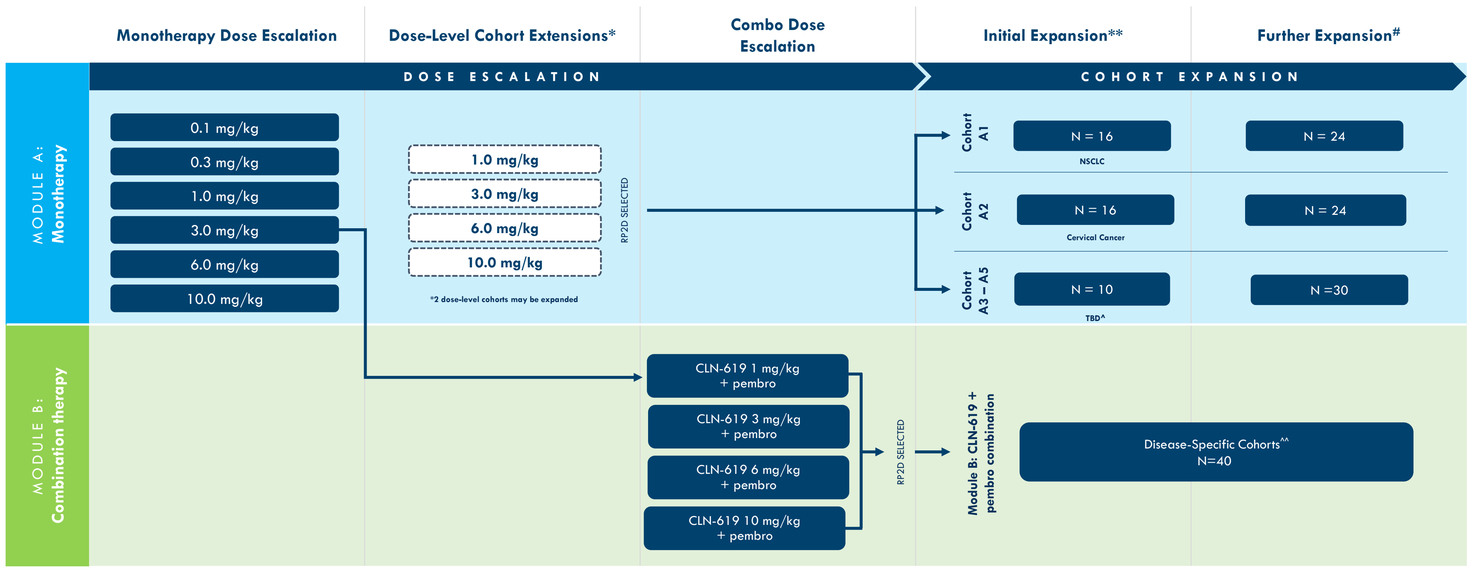
- Protocol Number: CLN-619-001
- Status: Recruiting; monotherapy dose escalation ongoing
- ClinicalTrials.gov Identifier: NCT05117476
- Contact: Timna Serino clinops@cullinanoncology.com

References

1. Li JJ, Pan K, Gu MF, Chen MS, Zhao JJ, Wang H, Liang XT, Sun JC, Xia JC. Prognostic value of soluble MICA levels in the serum of patients with advanced hepatocellular carcinoma. Chin J Cancer. 2013 Mar;32(3):141-8.
2. Fang L, Gong J, Wang Y, Liu R, Li Z, Wang Z, Zhang Y, Zhang C, Song C, Yang A, Ting JP, Jin B, Chen L. MICA/B expression is inhibited by unfolded protein response and associated with poor prognosis in human hepatocellular carcinoma. J Exp Clin Cancer Res. 2014 Sep 18;33(1):76.
3. Whalen KA, Mehta NK, Yalcin S, Meetze K, Gibson NW, Michaelson JS, Baeuerle PA. CLN-619, a clinical-stage MICA/MICB-specific IgG1 antibody, restores the MICA/MICB-NKG2D axis to promote NK-mediated tumor cell lysis. AACR 2022 Abstract #3506.

CLN-619-001 Study Schema

This is an open label, first-in-human, multicenter, dose escalation and dose expansion study of CLN-619 administered alone (Module A) or in combination with pembrolizumab (Module B) in patients with advanced solid tumors.



#Enrollment may be extended in up to two dose-level cohorts (total N = 16) that have been cleared for safety; **Initial disease-specific expansion cohorts N = up to 16 per dose level; #Further expansion dependent on efficacy signal or other emerging data; ^Disease-specific cohorts TBD based on emerging data from Module A dose escalation; ^^Disease-specific cohorts TBD

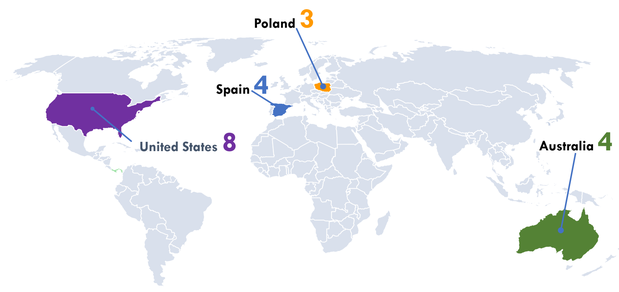
Study Objectives

Primary Objectives:
To characterize the safety, tolerability, and preliminary anti-tumor activity of CLN-619 administered alone (Module A) or in combination with pembrolizumab (Module B) in patients with advanced solid tumors

Secondary Objectives:
To assess the PK profile and immunogenicity of CLN-619 administered alone or in combination with pembrolizumab in patients with advanced solid tumors

Exploratory Objectives:
To explore various PK, pharmacodynamic, and predictive biomarkers and their relationship to measures of clinical anti-tumor activity including overall response rate (ORR), duration of response (DOR), progression-free (PFS) and overall survival (OS) in patients treated with CLN-619 alone or in combination with pembrolizumab

Global Site Footprint



Key Eligibility Criteria

Inclusion Criteria

- Age >= 18 years
- ECOG 0 or 1
- Estimated life expectancy >=12 weeks
- Adequate liver and kidney function and hematological parameters
- Dose Escalation Cohorts: Histologically or cytologically-confirmed metastatic or locally advanced, unresectable solid tumors
- Module A Expansion Cohorts
  - ✓All: • Patients should have received any other available standard therapy
    • Measurable disease based on RECIST v1.1
  - ✓A1: • Histologically or locally advanced, unresectable NSLCL
    • Progressed on/after prior treatment with checkpoint inhibitor-containing regimen and/or an approved therapy for epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations if present.
  - ✓A2: • Histologically or cytologically-confirmed metastatic or locally advanced, unresectable cervical cancer
- Module B Expansion Cohorts
  - ✓ All patients should have received any other available standard therapy
  - ✓ Measurable disease based on RECIST v1.1

Exclusion Criteria

- Investigational drug within 28 days (or 5 half-lives) of dosing on C1D1
- Active autoimmune disease or history of known/suspected autoimmune disease, or history of a syndrome that requires systemic corticosteroids or immunosuppressive medications
- Serious, uncontrolled medical disorder that would impair the ability of the patient to receive protocol therapy or whose control may be jeopardized by the complications of this therapy
- Treatment with systemic antimicrobial agent for acute infection within <= 7 days of dosing on C1D1
- Prior organ allograft or allogeneic hematopoeitic transplantation
- Active CNS metastases and/or carcinomatous meningitis
- History of grade >= 3 immunological adverse event or liver dysfunction satisfying Hy's Law in conjunction with prior checkpoint inhibitor immunotherapy

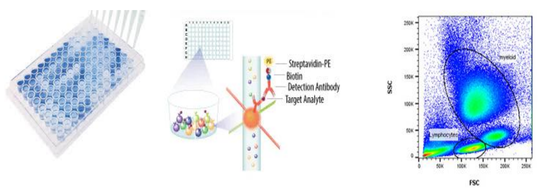
Exploratory Biomarker Plan

Pharmacodynamic and Predictive Biomarker Analysis in the tumor and at the periphery

Pharmacodynamic (PD) Biomarkers/ Mechanism of Action (MoA)

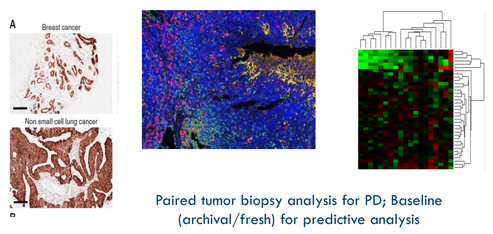
Peripheral PD/ MoA

- **ELISA** (sMICA)
- **Luminex** (46 cyto-/chemokine panel)
- **Immuno-phenotyping** (flow cytometry)



Intra-tumoral PD/MoA

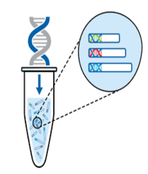
- **IHC** (MICA/B/ &NKG2D)
- **Multiplex IF** (NK- and T-cell infiltration)
- **WES/RNASeq** (immune gene expression)



Paired tumor biopsy analysis for PD; Baseline (archival/fresh) for predictive analysis

Predictive/Genotyping

- **NGS typing** (MICA/B alleles)
- **Real-time PCR** NKG2D haplotype FCgRIIIA SNP (ADCC)



Whole blood at baseline

* **retrospective analysis**