POSTER #771

A Phase 1 Study to Assess Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of Intratumoral CLN-617 (IL2/IL12 Fusion Protein) Combined with Pembrolizumab in Patients with Advanced Solid Tumors

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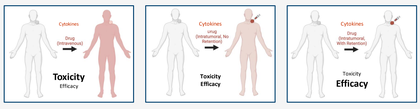
Background: Enhancing Cytokine Therapy in Oncology

- Cytokine therapy can mediate a pro-inflammatory microenvironment that promotes the effector function and proliferation of immune cells.
- Currently approved cytokine therapies are systemically administered, and can be toxic at efficacious dose levels resulting in a narrow therapeutic index
- To address this challenge, intratumoral cytokine injection has been explored but has failed to sufficiently address the safety limitations of cytokines in the absence of effective retention in the tumor microenvironment (TME).
- One path forward is to leverage creative cytokine engineering to ensure retention within the TME during intratumoral cytokine injection.

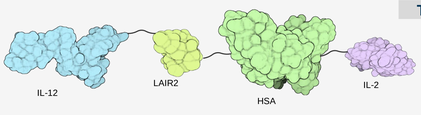


Unleashing the Power of Cytokines

- Combined intratumoral administration of IL-2 and IL-12:
  - Synergically drive anti-tumoral immunity by activating both NK and T-cells.
  - Stimulate an adaptive immune response within the tumor which can trigger systemic immunosurveillance, i.e., an abscopal effect
- For the co-delivery of IL-2 and IL-12 to the TME to be successful, tumor retention is key to improving the safety and therapeutic index.
- Combining certain cytokines with checkpoint inhibitors (CPI) will modulate immune cell responses and further enhance efficacy in difficult-to-treat tumor types.

CLN-617: IL-2 x IL-12 Fusion Protein

- CLN-617 is a single-chain fusion protein combining IL-2 and IL-12, with leukocyte associated Ig-Like receptor-2 (LAIR2) and human serum albumin (HSA), specifically engineered for intratumoral delivery and retention within the TME via LAIR2-mediated collagen binding.
- All components are fully human.

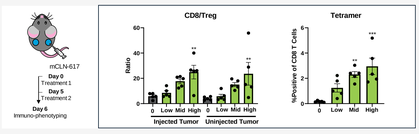


Two Mechanisms of Tumor Retention

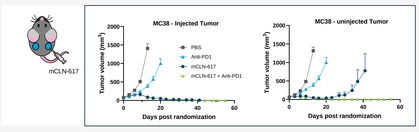
- LAIR2 imparts collagen binding
- HSA imparts bulky overall size

See CLN-617 Poster #1093 for Details

Scientific Rationale: murine CLN-617 Induces Increased Immune Cells in the TME and Demonstrates Anti-Tumor Activity in Distal Untreated Tumor (Abscopal Effect) *in vivo*



- In both injected and uninjected tumors, the CD8/Treg ratio is increased with mCLN-617 dose
- In peripheral blood, tumor-specific T cells are preferentially expanded with mCLN-617 treatment



- Robust abscopal effect of mCLN-617 and synergy with anti-PD1 Therapy
- No body weight loss seen at efficacious dose levels

CLN-617-001 Study Design

This is an open label, first-in-human, multicenter, dose escalation (Part 1), dose optimization (Part 2) and dose expansion (Part 3) study of CLN-617 administered alone and in combination with pembrolizumab in patients with advanced solid tumors.

Part 1: Dose Escalation

CLN-617 Monotherapy Followed By Combination with Pembro

n=3~6 Per cohort Continual Reassessment Model

CLN-617 2000 ug q1w x3	CLN-617-2000 ug + Pembro 200 mg q3W	1.5 X
CLN-617 1300 ug q1w x3	CLN-617-1300 ug + Pembro 200 mg q3W	1.6 X
CLN-617 800 ug q1w x3	CLN-617-800 ug + Pembro 200 mg q3W	2.0 X
CLN-617 400 ug q1w x3	CLN-617-400 ug + Pembro 200 mg q3W	2.0 X
CLN-617 200 ug q1w x3	CLN-617-200 ug + Pembro 200 mg q3W	2.9 X
CLN-617 70 ug q1w x3	CLN-617-70 ug + Pembro 200 mg q3W	1.0

Part 2: Dose Optimization

CLN-617 + Pembro Combination

Test two dose levels, e.g., Top 2 tolerable doses

CLN-617 q1w x3 + Pembro (q3w) for Cycle 1, CLN-617 + Pembro combo given q3w for Cycle 2 and beyond

Target selected tumor types n=10 each

Part 3: Dose Expansion

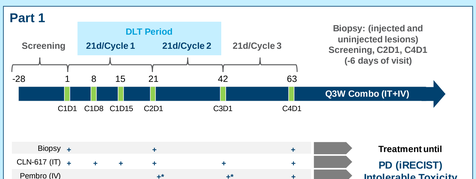
To be initiated at SRC/Sponsor's discretion at the optimized dose level for CLN-617 in combination with Pembro

CLN-617 + Pembro Combination

Cohort 1, n=15 Advanced or metastatic Melanoma

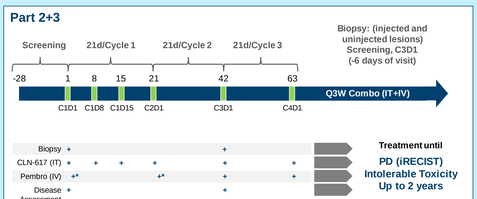
Cohort 2, n=15 Advanced or metastatic HNSCC

Part 1



*Pembro administered approximately 24h after CLN-617 IT (the first 2 doses)

Part 2+3



*Pembro administered approximately 24h after CLN-617 IT (the first 2 doses)

Treatment in Parts 1-3 continues until disease progression, intolerable toxicity, or up to 2 years. In Part 3 cohort, if 4/15 patients observed objective response, it may be expanded to an additional 15 patients.

Study Objectives and Endpoints

	Primary	End Points
Part 1: Dose Escalation	Safety, tolerability, DLT	AE, SAE, DLT incidence
Part 2: Dose Optimization	Safety, tolerability, preliminary efficacy	AE, SAE, ORR, DOR, DCR, PFS, OS per iRECIST
Part 3: Dose Expansion	Preliminary efficacy	ORR, DOR, DCR, PFS, OS per iRECIST
	Secondary	**End Points**
Part 1-3	PK profile	PK parameters
	Immunogenicity	ADA
	Exploratory	**End Points**
Part 1-3	Biomarkers	Tumor PD, cytokines
	Relationship between biomarker and clinical efficacy	Correlative analysis

Study Information and Site List

Protocol Identifiers:

- CLN-617-001
- NCT06035744

Status: Site activation, Recruiting to Part 1

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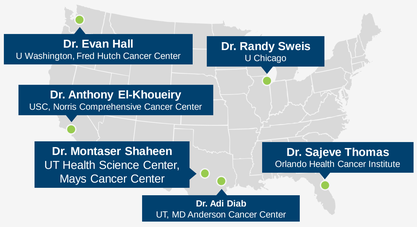
Acknowledgements:

- Cullinan Team (Irina Shapiro, Megan Sardinha, Kavya Rakhra, Liz Kiely, Karen Blatchford)
- ICON Study Team



Eligibility Criteria

Inclusion

- Aged ≥ 18 years.
- Part 1 Dose Escalation Cohorts: Histologically or cytologically confirmed advanced incurable or metastatic non-neurological solid tumor with accessible injectable lesions.
- Part 2 Dose Optimization: Histologically or cytologically confirmed select advanced incurable or metastatic cancer types with accessible injectable lesions.
- Part 3 Dose Expansions:
  - Cohort 1: Histologically or cytologically confirmed metastatic or locally advanced, unresectable melanoma with accessible injectable lesions.
  - Cohort 2: Histologically or cytologically confirmed metastatic or locally advanced, unresectable HNSCC with accessible injectable lesions.
- Patients must have 2 or more measurable lesions for Part 1, or one or more measurable lesions for Part 2 and Part 3 that meet RECIST v1.1. Also, patients must have tumors that are accessible without encasing with blood vessels, and amenable to direct injection.
- Patients deemed appropriate for pembrolizumab treatment based on the tumor type and prior available therapy, per the judgment of the investigator.
- Eastern Cooperative Oncology Group (ECOG) performance scale 0 or 1.
- Estimated life expectancy of at least 12 weeks or longer.
- Have adequate liver and kidney function and hematological parameters within a normal range
- Patients must agree to provide a fresh biopsy at baseline, and on-treatment biopsies.

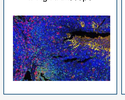
Exclusion

- 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
- Patient on anticoagulant agents at the time of IT injection or biopsy or with significant bleeding diathesis due to risk of hematoma at the injection site.
- Risk of vascular catastrophe.
- Diagnosed with HIV1/2 primary immunodeficiency disease with the following conditions:
  - CD4+ T-cell counts ≤ 350 cells/uL.
  - History of AIDS-defining opportunistic infections within the past 12 months.
  - Received active antiretroviral therapy within 4 weeks
  - HIV viral load > 400 copies/mL.
- Diagnosed with active and detectable Hepatitis B or hepatitis C (HCV) infection.
- Prior organ allograft or allogeneic hematopoietic cell transplantation
- Active CNS metastases and/or carcinomatous meningitis
- History of drug-related anaphylactic reactions to any components of CLN-617 or pembrolizumab. History of Grade 4 anaphylactic reaction to any monoclonal antibody therapy

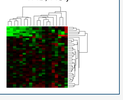
Exploratory Biomarkers in the Tumor and in the Periphery

Intra-tumoral PD/MoA

Multiplex IF
T/NK infiltration
IFNg RNAscope



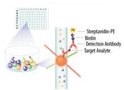
WES/RNASeq/TCRSeq
(Gene expression/TCR clonality, TMB, MSI)



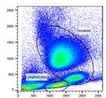
Sequential tumor biopsies obtained at baseline and on-treatment (injected and uninjected)

Peripheral PD/MoA

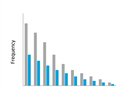
Cytokines/Chemokines
(Luminex)



Immuno-phenotyping
T/NK/DC panel
(Flowcytometry)



Peripheral TCRSeq
Peripheral TCR Clonality



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