ABSTRACT #2532

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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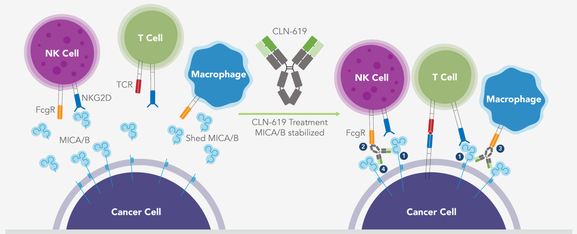
Background: CLN-619 Multiple Modes of Action

CLN-619 is a human IgG1 antibody that binds to and prevents proteolytic cleavage of NKG2D ligands MICA and MICB from tumor cells, thereby increasing tumor cell lysis by innate and adaptive immune cells.

IMMUNE EVASION | RESTORATION OF IMMUNOSURVEILLANCE



1. Prevention of MICA/MICB shedding
2. Antibody-dependent cellular cytotoxicity (ADCC)
3. Antibody-dependent cellular phagocytosis (ADCP)
4. Enhanced binding of MICA to NKG2D

CLN-619-001 Phase 1 Study Design

- 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
- Patients have been enrolled at 19 sites in 4 countries: United States, Spain, Poland, and Australia
- Preliminary results of the monotherapy (Module A) dose escalation and dose-level extension phase of the study are presented

Objectives and Endpoints

Objective

- To characterize the safety, tolerability, dose-limiting toxicities, and preliminary antitumor activity of intravenously administered CLN-619 monotherapy in patients with advanced solid tumors

Endpoints

- Adverse events (CTCAE v5.0), Dose Limiting Toxicity (DLT), Response (RECIST v1.1), and PK Parameters (C_{max}, AUC $_{0\text{-}504h}$, $t_{1/2}$, etc.)

Key Inclusion & Exclusion Criteria

INCLUSION CRITERIA	EXCLUSION CRITERIA
• Patients aged ≥ 18 years	• Investigational therapy within 25 days (or 5 half-lives) of C1D1
• Metastatic or locally advanced solid tumors that progressed after prior therapy and for whom no further standard treatments are available	• Serious and/or uncontrolled medical disorder, including active autoimmune disease requiring immunosuppressive medication
• ECOG 0 or 1	• Treatment for acute infection ≤ 7 days of C1D1
• Estimated life expectancy ≥ 12 weeks	• Grade ≥ 3 immunological AE with prior checkpoint inhibitor therapy
• Adequate liver and kidney function and hematological parameters	• Active CNS metastases
• Measurable disease based on RECIST v1.1	

Treatment Plan

Cycle = 3 weeks | ▼ CLN-619 | ▲ RECIST v1.1 response

- CLN-619 monotherapy was administered intravenously over 1 hour every three weeks
- Standard pre-medications (acetaminophen or ibuprofen) were given 30-60 minutes prior to each dose and per institutional practice thereafter
- Corticosteroid pre-medication for infusion related reaction (IRR) prophylaxis was mandated prior to the first dose only starting at the 3 mg/kg dose level.
- Patients may continue therapy until progressive disease, intolerable toxicity, or a maximum of 34 cycles
- Patients with progressive disease may continue treatment if the investigator judges clinical benefit and acceptable tolerability

Patient Enrollment and Disposition

- Standard 3+3 escalation began at the first dose level tested 0.1 mg/kg*
- Dose levels cleared for DLT were expanded up to total n = 10
- Patients enrolled into extension cohorts underwent pre- and on-treatment (C2 D8) biopsies for biomarker assessments

DOSE ESCALATION*	DOSE-LEVEL COHORT EXTENSIONS	TOTAL BY DOSE LEVEL
10 mg/kg n = 6	10 mg/kg** n =1	10 mg/kg n = 7
6 mg/kg n = 3	6 mg/kg n = 7	6 mg/kg n = 10
3 mg/kg n = 3	3 mg/kg n = 7	3 mg/kg n = 10
1 mg/kg n = 4		1 mg/kg n = 4
0.3 mg/kg n = 3		0.3 mg/kg n = 3
0.1 mg/kg* n = 3		0.1 mg/kg n = 3

- 37 patients treated across all dose-levels
- Median number (range) of cycles initiated was 2 (0–13)
- 24 patients (65%) discontinued treatment.
- Reasons for discontinuation were progressive disease (20, 55%) and adverse events (4, 11%)

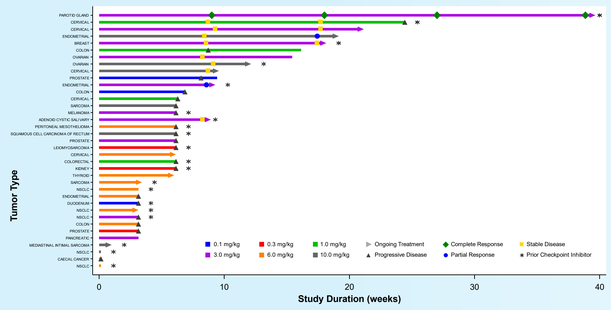
*Protocol permitted accelerated titration until Gr ≥2 TRAE, which occurred at the 0.1 mg/kg dose level
**Enrollment ongoing

Baseline Patient Characteristics

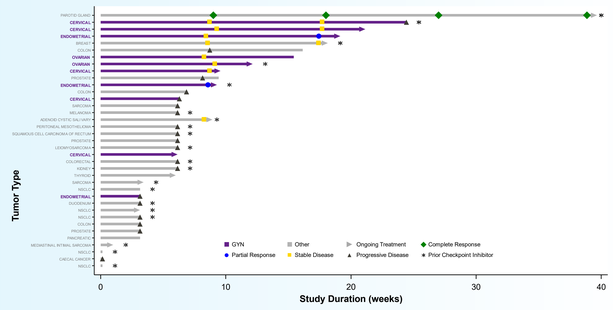
Characteristics	All Patients (n = 37)
Median Age, y (range)	63 years (26 – 83)
Sex Female, n (%)	23 (62%)
ECOG PS 1, n (%)	22 (60%)
Tumor Type	Colon and Rectal Cancers (6), Cervical (5), NSCLC (5), Sarcoma (4), Endometrial (3), Prostate (3) Ovarian (2), Breast (1), Duodenum (1), Adenoid Cystic Carcinoma Salivary Gland (1), Renal Cell (1), Melanoma (1), Pancreas (1), Parotid gland (1), Peritoneal Mesothelioma (1), Thyroid (1)
Time from Diagnosis, median (range)	36.8 months (9 – 207)
# Prior Systemic Therapies, median (range)	3 (1 – 7)
Prior Immune Checkpoint Inhibitor , n (%)	20 (54%)

MONOTHERAPY EFFICACY

Time on Treatment and Clinical Activity



All Patients (n = 37) by Dose Level



All Patients (n = 37) by Diagnosis

Objective Response Summary

Dose Level	Tumor Type	Prior Therapy	Response Detail
3 mg/kg	**Parotid** (mucoepidermoid)	2 prior therapies Prior anti-PD1 (PR x 30 months)	Confirmed CR at C4D1 **ongoing**
	Endometrial (serous)	5 prior therapies Prior anti-PD1 + lenvantinib (SD x 9 months)	uPR at C4D1 **ongoing**
10 mg/kg	**Endometrial** (endometrioid)	3 prior therapies No prior anti-PD1	uPR at C7D1 **ongoing**

- **Stable Disease for >3 cycles has been observed in 7 other patients**
  - ✓ 1 mg/kg: 1 cervical (PD after 9 cycles)
  - ✓ 3 mg/kg: 1 ovarian (clinical PD after 6 cycles), 1 breast (ongoing after 6 cycles), 1 cervical (ongoing after 6 cycles), 1 adenoid cystic carcinoma salivary gland (ongoing after 3 cycles)
  - ✓ 10 mg/kg: 1 ovarian (ongoing after 3 cycles), 1 cervical (ongoing after 6 cycles)

Best Monotherapy Response

	All Patients (n=37)	Response Evaluable[1] at ≥1 mg/kg (n=22)	Response Evaluable[1] GYN Malignancy[2] (n=10)
Complete Response (CR)	1	1	0
Partial Response (PR)	2	2	2
Stable Disease (SD)	7	7	5
CR + PR + SD	10	10	7
Progressive Disease (PD)	18	12	3
Not Evaluable (NE)	9	NA	NA

[1]Patients who underwent at least one RECIST response assessment or who had clinically assessed PD prior to first planned response assessment
[2]Endometrial, cervical, and ovarian

Monotherapy Durable Complete Response

83 male patient with mucoepidermoid parotid cancer. Systemic therapy for relapse included anti-PD1 antibody therapy with 30 month sustained PR before PD (last dose 4 months before study entry)

SAFETY

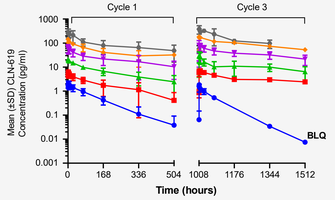
Treatment Emergent Adverse Events (TEAE) in ≥ 10% of Patients

Adverse Event	Any n (%)	Grade 1/2 N (%)	Grade 3+ n (%)
Infusion Related Reaction	8 (21.6)	8 (21.6)	0 (0)
Pyrexia	8 (21.6)	8 (21.6)	0 (0)
Abdominal Pain	8 (21.6)	6(16.2)	2 (5.4)
Decreased Appetite	6 (16.2)	6 (16.2)	0(0)
Diarrhea	5 (13.5)	5 (13.5)	0 (0)
Fatigue	5 (13.5)	5 (13.5)	0 (0)
Nausea	5 (13.5)	5 (13.5)	0 (0)
Vomiting	4 (10.8)	4 (10.8)	0 (0)
Back Pain	4 (10.8)	4 (10.8)	0 (0)

- Patients experiencing at least one TEAE = 34 (91.9%)
- Patients experiencing at least one Grade 3 TEAE 11 (29.7%); no Grade ≥ 4 TEAE
- TEAE leading to discontinuation [2, 5.4%: Grade 3 Laryngeal Edema (related), Grade 3 Dehydration(unrelated)]

- CLN-619 was well-tolerated and most TEAEs were Grade 1/2
- Grade 3 TEAEs included: abdominal pain (2 pts), anemia (2), acute kidney injury (1), AST increased (1), blood bilirubin increased (1), bone pain (1), dehydration (1), dyspnea (1), hypercalcemia (1), laryngeal edema (1), neutropenia (1), pulmonary embolism (1), rash maculopapular (1), and sepsis (1)
- No AEs met protocol-defined DLT criteria, and no Grade ≥4 TEAE
- The most common TRAEs in ≥5% of pts were IRR (21.6%), pyrexia (8.1%), and fatigue (8.1%)
  - ✓ Only 1 Gr3 TRAE of laryngeal edema occurred at the 10 mg/kg DL in the absence of mandated steroid premedication
  - ✓ IRRs (n=8 patients) occurred only in Cycle 1 and were all Grade 1/2 in patients who received protocol-mandated steroid pre-medication

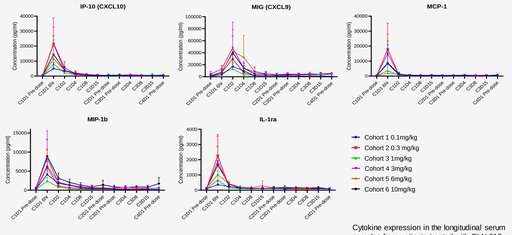
PK Analysis for CLN-619 Monotherapy Dose Escalation



Dose (mg/kg)	Cycle	Statistic	C_{max} (µg/mL)	$T_{1/2}$ (hr)	$AUC_{0\text{-}504h}$ (hr*µg/mL)
0.1	1 (n=3)	Mean	2.04	87.6	219
		SD	0.608	43.9	70.9
	3 (n=2)	Mean	1.68	61.3	123
		SD	0.219	10.9	4.12
0.3	1 (n=2)	Mean	5.99	141	875
		SD	1.61	65.8	489
	3 (n=2)	Mean	7.13	443	1620
		SD	0.332	313	309
1	1 (n=4)	Mean	20.7	220	3220
		SD	2.32	125	1090
	3 (n=4)	Mean	29.5	237	5630
		SD	14.2	109	3630
3	1 (n=9)	Mean	64.2	324	10800
		SD	21.7	156	5330
	3 (n=4)	Mean	85.5	438	19000
		SD	42.8	151	5110
6	1 (n=3)	Mean	144	307	21800
		SD	27.2	170	9770
	3 (n=1)	Mean	181	344	44000
10	1 (n=5)	Mean	298	338	44200
		SD	97.3	149	15200
	3 (n=4)	Mean	428	202	62300
		SD	90.7	129	19300

- CLN-619 half-life ranged from 61.3 to 443 hours (2.5 to 18.45 days) for dose levels ranging from 0.1 to 10 mg/kg.
- Nearly dose-proportional increase in exposure as measured by C_{max} was observed between 0.1 and 10 mg/kg.
- More than dose proportional increase in CLN-619 exposure as measured by $AUC_{0\text{-}504h}$ was observed between 0.1 and 1 mg/kg and nearly dose-proportional increase in CLN-619 exposure was observed between 1 and 10 mg/kg dose levels.

Peripheral Cytokines in Response to CLN-619



- Transient increases in cytokine levels were observed at 2-6hrs after the first dose of CLN-619 and decreased to baseline by day 4-8.
- No dose-dependent increase in cytokine secretion was observed at the periphery.

Cytokine expression in the longitudinal serum samples from patients treated with CLN-619 monotherapy tested using Myriad RBM Inflammation and custom MAPs on the Luminex platform. Graphs depict average absolute cytokine levels (pg/ml) per dose level over time. Error bars represent SD.

CONCLUSIONS

- CLN-619 was tolerated at doses up to 10 mg/kg, and dose-limiting toxicities have not been observed at any dose tested
  - ✓ No Grade ≥3 TRAE in patients who received protocol-mandated pre-medications
- Single agent activity, including objective responses, has been observed across multiple tumor types in both checkpoint-experienced and checkpoint-naïve patients
- Notable single-agent clinical activity observed in multiple gynecological malignancies
  - ✓ Expansion cohorts in endometrial and cervical cancers are planned
- Additional monotherapy expansion cohorts may be opened based upon clinical activity observed in the current trial
- A parallel dose-escalation arm in combination with pembrolizumab is ongoing