Poster #2588

CLN-619 (anti-MICA/MICB antibody) alone and in combination with pembrolizumab for advanced solid tumors: Updated results of a phase 1 study

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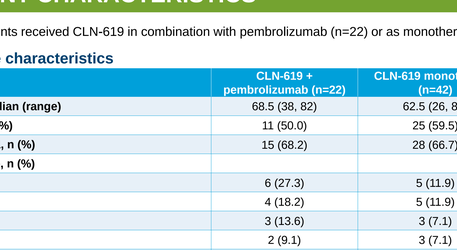
BACKGROUND

- CLN-619 is a humanized IgG1 antibody that prevents shedding of MICA/MICB from cancer cells, increasing tumor-cell lysis by innate and adaptive immune cells[1]



ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; FcgR, Fc gamma receptor; NKG2D, natural killer group 2D receptor; NK, natural killer; TCR, T-cell receptor.

- In a first-in-human, phase 1 study, CLN-619 monotherapy demonstrated favorable safety and promising antitumor activity in multiple solid tumor types[2]
- Here, we present results from CLN-619 dose escalation in combination with pembrolizumab and updated results of monotherapy

METHODS

Phase 1, open-label, first-in-human, multicenter, dose-escalation and dose expansion study (NCT05117476)

Key inclusion criteria

All cohorts
- Adults (≥18 y) with locally advanced or metastatic solid tumors
- Prior treatment with all available therapies, including CPIs, unless contraindicated or not tolerated
- ECOG PS 0 or 1
- Estimated life expectancy ≥12 wks
- Measurable disease (RECIST v1.1)
- No active CNS metastases

3+3 dose escalation

Monotherapy
CLN-619 IV Q3W
(0.1, 0.3, 1, 3, 6, 10 mg/kg)[a]

Combination therapy
CLN-619 IV Q3W (1, 3, 6, 10 mg/kg)[a]
Pembrolizumab 200 mg IV Q3W

Tumor assessment by CT/MRI every 9 wks until Week 27 and every 12 wks thereafter

Continue for up to 34 cycles until PD,[b] intolerable toxicity, or other reasons

Endpoints
- AEs
- DLTs
- Antitumor activity (RECIST v1.1)

Data cutoff date: March 29, 2024

- Corticosteroid, antihistamine, and antipyretic premedications for IRR prophylaxis were required 30–60 minutes before Cycle 1 Day 1
- Patients in extension cohorts were required to provide pre- and on-treatment (Cycle 2 Day 8) biopsy samples for biomarker assessments

Note: 1 cycle=3 wks.
AE, adverse event; CNS, central nervous system; CPI, checkpoint inhibitor; DLT, dose-limiting toxicity; ECOG, Eastern Cooperative Oncology Group; IRR, infusion-related reaction; PD, progressive disease; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors.
[a]CLN-619 was administered intravenously over 1 hour Q3W. [b]Patients who met criteria for treatment discontinuation but were otherwise deriving clinical benefit could continue at the discretion of the investigator.

PATIENT CHARACTERISTICS

- 64 patients received CLN-619 in combination with pembrolizumab (n=22) or as monotherapy (n=42)

Baseline characteristics

	CLN-619 + pembrolizumab (n=22)	CLN-619 monotherapy (n=42)
Age, y, median (range)	68.5 (38, 82)	62.5 (26, 83)
Female, n (%)	11 (50.0)	25 (59.5)
ECOG PS 1, n (%)	15 (68.2)	28 (66.7)
Tumor type, n (%)		
NSCLC	6 (27.3)	5 (11.9)
Cervical	4 (18.2)	5 (11.9)
Ovarian	3 (13.6)	3 (7.1)
Prostate	2 (9.1)	3 (7.1)
Colorectal	1 (4.5)	6 (14.3)
Endometrial	0	3 (7.1)
Other	6 (27.3)[a]	17 (40.5)[b]
Months since diagnosis, median (range)	46.3 (4, 160)	37.4 (9, 207)
No. of prior systemic therapies, median (range)	3 (1, 8)	3 (1, 7)
Prior CPI therapy, n (%)	9 (40.9)	21 (50.0)

NSCLC, non-small cell lung cancer.
[a]Other tumor types in the combination cohorts: gastric (2 patients), esophageal (1), head and neck (1), skin (1), and urothelial cancer (1); [b]Other tumor types in the monotherapy cohorts: breast (2), pancreatic (2), sarcoma (2), adenoid cystic carcinoma (1), caecal cancer (1), duodenum (1), head and neck (1), kidney (1), leiomyosarcoma (1), mediastinal intmal sarcoma (1), melanoma (1), parotid gland (1), peritoneal mesothelioma (1), and thyroid (1).

KEY TAKEAWAYS

- **Objective responses were observed with CLN-619 + pembrolizumab, including in NSCLC patients with oncogenic mutations, tumors that are typically unresponsive to CPIs**
- **CLN-619 + pembrolizumab was well tolerated at doses ranging from 1 to 10 mg/kg**
- **Longer-term follow-up for patients treated with CLN-619 monotherapy confirms durable clinical benefit, with objective responses and prolonged SD in multiple tumor types, including in patients with disease progression after CPI therapy**
- **Based on these findings, monotherapy and combination therapy expansion cohorts have been initiated in NSCLC**

Best confirmed response (RECIST-evaluable patients; dose ≥1 mg/kg)

	CLN-619 + pembrolizumab (n=18)	CLN-619 monotherapy (n=29)
ORR	3 (16.7)	3 (10.3)
CR	0	1 (3.4)
PR	3 (16.7)	2 (6.9)
SD ≥18 wks	0	9 (31.0)
CBR (CR+PR+SD ≥18 wks)	3 (16.7)	12 (41.4)

Values are number of patients (%). CBR, clinical benefit rate; CR, complete response; PR, partial response; ORR, objective response rate; SD, stable disease.

EFFICACY

Combination therapy

- Of 22 patients treated with CLN-619 + pembrolizumab, 18 were RECIST evaluable[a] for response
  - 4 patients did not have post-baseline imaging for response evaluation due to withdrawal of consent (n=2), death due to disease progression (n=1), and transfer to hospice and acute kidney injury (n=1)
- Confirmed responses (all PR) were observed at CLN-619 doses ≥3 mg/kg in combination with pembrolizumab

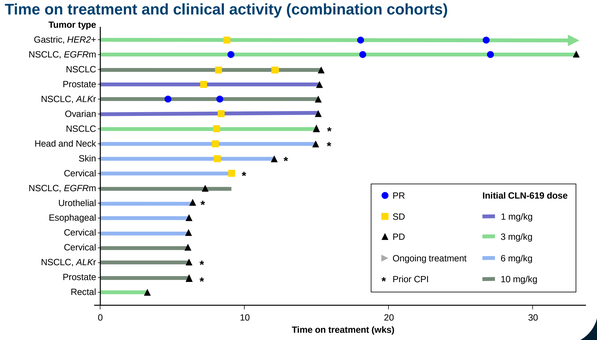
[a]Had ≥1 post-baseline imaging tumor assessment.

Characteristics of responders

Tumor type	No. of prior lines of therapy	Prior CPI	Best response	DoR, wks
NSCLC, *ALK*r	2	No	PR	12.7
Gastric, *HER2*+	3	No	PR	8.9+ (ongoing)
NSCLC, *EGFR*m exon 18/21	6	No	PR[a]	24.0

*ALK*r, anaplastic lymphoma kinase gene rearrangement; DoR, duration of response; *EGFR*m, epidermal growth factor receptor mutation; *HER2*, human epidermal growth factor receptor 2. [a]Confirmed PR followed by clinical progression.

Time on treatment and clinical activity (combination cohorts)



Updated[a] monotherapy

- Among 42 patients treated with CLN-619 monotherapy, 29 received CLN-619 at a dose ≥1 mg/kg and were RECIST evaluable
  - 6 patients did not undergo post-baseline imaging for response evaluation due to clinical progression (n=3), hospice (n=1), or withdrawal of consent (n=2)
  - 7 patients received subtherapeutic doses (<1 mg/kg) or were not RECIST evaluable for response
- The CBR was 41.4% (1 CR, 2 PR, 9 SD ≥18 wks)

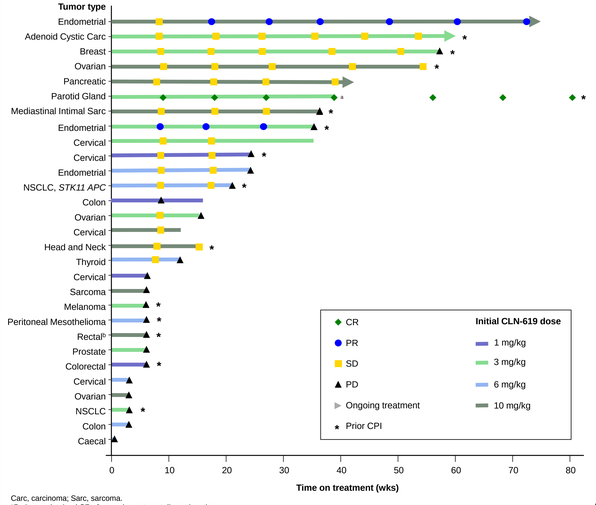
[a]Data cutoff date for previously reported data[2] was March 31, 2023.

Characteristics of patients with response or SD ≥18 wks

Tumor type	No. of prior lines of therapy	Best response	DoR, wks
Responders (n=3)			
Mucoepidermoid parotid	2	CR	71
Endometrial (serous, MMRp)	5	PR	31
Endometrial (endometrioid, MMRp)	3	PR	55+ (ongoing)
SD ≥18 wks (n=9)			
Cervical squamous (n=2); breast (ER/PR+, *HER2*−; n=1); ovarian (n=1); endometrial carcinosarcoma (n=1); mediastinal intimal sarcoma (n=1); adenoid cystic carcinoma (n=1); pancreatic adenocarcinoma (*KRAS* G12V; n=1); NSCLC (*STK11*; n=1)	Mean: 3.6 Range: 1–7	SD ≥18 wks	Range: 18–56

MMRp, mismatch repair proficient.

Time on treatment and clinical activity (monotherapy cohorts ≥1 mg/kg)

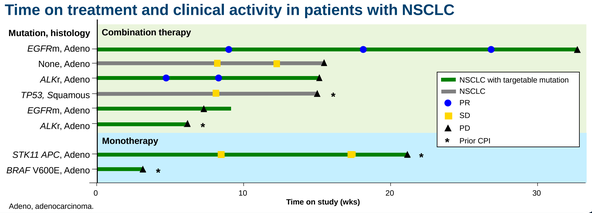


Carc, carcinoma; Sarc, sarcoma.
[a]Patient maintained CR after study treatment discontinuation. [b]Rectal squamous cell carcinoma.

Efficacy in NSCLC (monotherapy and combination cohorts)

- 8 of the 11 patients with NSCLC were RECIST evaluable; of these, 6 had oncogenic mutations
  - 3 of the 6 patients with oncogenic mutations experienced clinical benefit
    - 2 PRs and 1 SD lasting >18 weeks

Time on treatment and clinical activity in patients with NSCLC



Adeno, adenocarcinoma.

SAFETY

- CLN-619 was well tolerated in combination with pembrolizumab and as monotherapy
  - No AEs met protocol-defined DLT criteria
  - Most treatment-emergent adverse events (TEAEs) were grade 1/2

Overview of TEAEs

Overview	CLN-619 + pembrolizumab (n=22)		CLN-619 monotherapy (n=42)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any TEAE	21 (95.5)	10 (45.5)	41 (97.6)	16 (38.1)
Any treatment-related AE[a]	13 (59.1)	2 (9.1)	30 (71.4)	6 (14.3)
Any-grade TEAEs in ≥15% of patients or grade ≥3 TEAEs[b] in ≥5% of patients in either group				
Fatigue	8 (36.4)	0	10 (23.8)	0
Nausea	5 (22.7)	1 (4.5)	8 (19.0)	1 (2.4)
Constipation	5 (22.7)	0	4 (9.5)	0
IRR	4 (18.2)	0	12 (28.6)	0
Anemia	4 (18.2)	1 (4.5)	5 (11.9)	3 (7.1)
Back pain	4 (18.2)	1 (4.5)	5 (11.9)	0
Headache	4 (18.2)	0	2 (4.8)	0
Hyponatremia	4 (18.2)	0	1 (2.4)	0
Abdominal pain	3 (13.6)	0	10 (23.8)	2 (4.8)
AST increased	2 (9.1)	0	4 (9.5)	3 (7.1)
Hypertension	2 (9.1)	2 (9.1)	0	0
Pyrexia	0	0	8 (19.0)	0

Values are number of patients (%).
AST, aspartate aminotransferase; GERD, gastroesophageal reflux disease.
[a]AEs considered related to treatment with CLN-619 and/or pembrolizumab.
[b]One case of grade 3 laryngeal edema in the setting of IRR occurred at the monotherapy 10 mg/kg dose level in the absence of mandated steroid premedication (not captured in the table).

Treatment-related AEs

- Treatment-related AEs reported in ≥10% of patients were IRRs (combination: 18.2%; monotherapy: 28.6%) and fatigue (combination: 18.2%; monotherapy: 9.5%)
- The only grade ≥3 treatment-related AE reported in >5% of patients in any group was increased AST (combination: 0%; monotherapy: 7.1%)
- One patient in each cohort discontinued study treatment due to a treatment-related AE (combination: 4.5% [1/22]; monotherapy: 2.4% [1/42])
- IRRs are the most frequent treatment-related AEs with CLN-619
  - With administration of prophylactic premedications, most IRRs were grade 1 or 2 and occurred on Day 1 of Cycle 1
- There were no treatment-related deaths

REFERENCES
1. Whalen KA, et al. mAbs. 2023;15(1):2208697.
2. Wang JS , et al. J Clin Oncol. 2023;41(S16):2532.

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