Abstract: 4022

Preliminary results of a phase 1 study of LB1908, an autologous Claudin 18.2-targeted chimeric antigen receptor T-cell product, in patients with advanced gastroesophageal adenocarcinoma

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Clinicaltrials.gov no. NCT05539430

Introduction

Claudin 18.2 (CLDN18.2) is expressed on most gastric, gastroesophageal, and esophageal adenocarcinomas (GC, GEJC, EC), with normal expression limited to the gastric epithelium. CLDN18.2 is a promising therapeutic target for multiple upper GI cancers. We present preliminary results of the Phase 1 dose-escalation trial of LB1908, a CLDN18.2-targeted autologous chimeric antigen receptor (CAR)-T cell product, in adults with GC, GEJC, or EC.

LB1908 Profile

Figure 1. LB1908 Structure

- Autologous CAR-T cell product
- VhH binding domain with high affinity and specificity for Claudin 18.2
- 4-1BB co-stimulatory domain

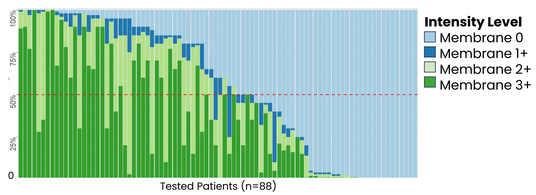
Methods

- This is an ongoing, open-label, multicenter phase 1 dose-escalation/expansion trial
- Enrolling patients with locally advanced/unresectable or metastatic GC, GEJC, or EC
  - ≥ 1 prior line of treatment
  - ECOG ≤1 & adequate organ function
  - CLDN18.2 expression of 1+ in ≥50% of tumor cells
  - Prior CLDN18.2-directed therapies allowable
- Primary objectives to evaluate safety, tolerability, pharmacokinetics (PK) and preliminary antitumor activity of LB1908
- Dose-escalation design using modified 3+3 evaluating up to 3 dose levels: 0.5, 1.5, and 3 x 10^6 CAR+ viable T cells/kg
- LB1908 administered as a single infusion after 3 days of lymphodepletion with cyclophosphamide (300 mg/m²/dose) and fludarabine (30 mg/m²/dose)
- Bridging therapy allowed between leukapheresis and lymphodepletion/LB1908 infusion

Claudin 18.2 Expression

- Potential patients are prescreened to determine tumor CLDN18.2 expression status based on centrally performed immunohistochemistry assay using Ventana 43-14A antibody
- 1+ expression in ≥50% of tumor cells is considered positive (red dotted line in **Figure 2**)
- 59% (52 of 88 patients tested) were CLDN18.2 positive at this threshold

Figure 2. Membrane Staining Intensity of CLDN18.2 in Tumor Biopsies from Patients



Results

Patient Demographics and Baseline Characteristics

As of the data cutoff of May 14, 2025, 9 patients had received LB1908, n=6 at dose level (DL) 1 (0.5x10^6 cells/kg) and n=3 at DL2 (1.5x10^6 cells/kg).

Table 1. Patient Baseline and Demographic Characteristics

	DL1: 0.5 × 10^6 CAR+ T cells/kg [N=6]	DL2: 1.5 × 10^6 CAR+ T cells/kg [N=3]	Overall [N=9]
Age (year), median	53	58	56
Sex: female	1 (16.7)	0	1 (11.1)
ECOG Performance Score at Baseline n(%)			
0	2 (33.3)	0	2 (22.2)
1	4 (66.7)	3(100)	7 (77.8)
Primary tumor type n (%)			
EC	3 (50.0)	2 (66.7)	5 (55.6)
GC	2 (33.3)	0	2 (22.2)
GEJC	1 (16.7)	1 (33.3)	2 (22.2)
Number of metastatic sites			
≤2	0	1 (33.3)	1 (11.1)
≥3	6 (100)	2 (66.7)	8 (88.9)
CLDN18.2 expression			
H score, median	263	288	269
% ≥1+, median	95	98	95
Prior lines of therapy n (%)			
1	1 (16.7)	0	1 (11.1)
≥2	5 (83.3)	3 (100)	8 (88.9)

Pharmacokinetics

- Expansion of CAR+ T cell cells (measured by qPCR) observed in all patients
- Preliminary evidence of dose-exposure relationship
- CAR-T expansion was preserved in patients receiving early/prophylactic steroids

Figure 2. Peripheral CAR-T Cell Expansion

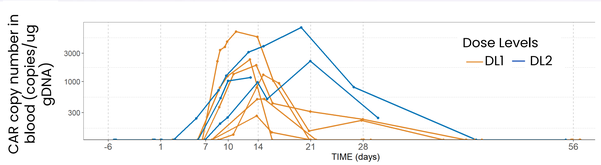
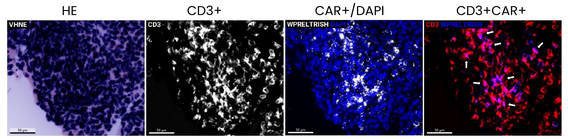


Table 2. PK Parameters

Dose levels (N)	DL1 (N = 6)	DL2 (N = 2*)	Overall (N = 8*)
C_{max} (copies/µg gDNA) Median (min, max)	1594 (264, 6922)	5167 (2211, 8124)	2048 (264, 8124)
T_{max} (days) Median (min, max)	14 (11, 15)	20 (20, 21)	14 (11, 21)
T_{last} (days) Median (min, max)	16 (13, 28)	28 (27, 30)	21 (13, 30)
AUC_{last} (copies*day/µg gDNA) Median (min, max)	7663 (1182, 37122)	44201 (19641, 68761)	10281 (1182, 68761)

*1 subject at DL2 has incomplete PK data (through day 14) due to recent dosing; PK parameters for this subject were not included in the analysis

Figure 3. Infiltration of Tumor Tissue by CD3+CAR+ T Cells (arrows)



Immunohistochemistry of FFPE sections (tissues collected at Day 10 post-infusion) with anti-human CD3 Ab and in situ hybridization with RNA probe for CAR transgene.
Scale bar=50 um

Safety

Safety Summary

- All patients experienced TEAEs, with at least 1 TEAE Grade ≥3
- The most common Grade ≥3 TEAEs were hematologic/cytopenias and attributed to the lymphodepletion regimen
- Of the 8 ≥Grade 3 non-hematologic TEAEs considered related to LB1908, only gastritis/gastric mucosal injury occurred in ≥2 patients (n=5)
  - Including 1 DLT of gastric mucosal injury in a patient in DL1
  - Three of the GI events have resolved; 1 is resolving and 1 is ongoing

Upper Gastrointestinal Toxicity

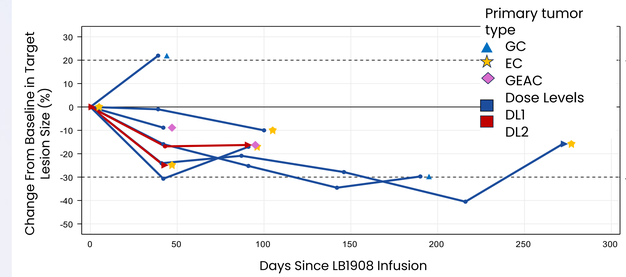
- Gastritis/gastric mucosal injury was observed in 5 patients (all Grade 3) and considered an on-target/off-tumor toxicity
- Initial symptoms arose within 2 weeks post-infusion
  - Endoscopic biopsies in some patients demonstrated infiltration of the gastric submucosa with T cells
- A mitigation strategy including non-absorbable (beclomethasone) and systemic steroids ameliorated the severity and duration of upper GI events

CAR-T Cell Toxicities

- CRS occurred in 7 patients (77.8%), all low-grade (no grade ≥3 events)
  - Median time to onset: 6 days (range: 4 to 10)
  - Median duration: 6 days (range: 4 to 9); all events resolved
  - Tocilizumab use: 3 (33.3%)
  - No patient required steroids or ICU admission
- No ICANS observed

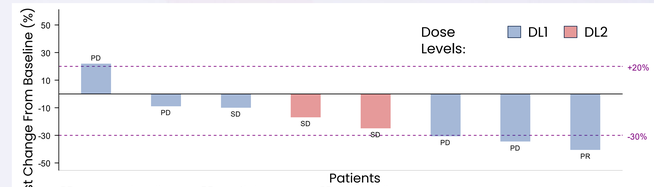
Antitumor Activity

Figure 4. Change in Target Lesion Size over Time



Note: 8 patients were response-evaluable; 1 patient did not have disease evaluation before data cutoff

Figure 5. Best Percent Change from Baseline in Sum of Target Lesion Measurements



PD, progressive disease; PR, partial response; SD, stable disease
Note: 8 patients were response-evaluable; 1 patient did not have disease evaluation before data cutoff

Table 3. Integrated Patient Summary

Dose Level	Patient #	Primary Disease	Number of Metastatic sites	Number of prior LOT	CLDN18.2 expression (1+/2+/3+)	LB1908 Cmax (copies/ug gDNA)	CRS (max grade)	Maximum Change in Sum of Target Lesions (BOR)
Dose Level 1 0.5x10^6 cells/kg	1	GC	3 (including liver)	2	5%/15%/70%	509	Grade 2	+21.9% (PD)
	2	EC	3 (including liver and bone)	1	2%/30%/65%	2359	Grade 2	-40.5% (PR)
	3	GC	4 (including liver)	2	0%/5%/90%	1886	Grade 2	-34.5% (PD)
	4	EC	4	2	2%/5%/90%	1303	Grade 2	-10.0% (SD)
	5	EC	6 (including liver)	2	5%/15%/78%	6922	Grade 2	-30.7% (PD)
	6	GEJ	3 (including liver)	2	12%/43%/40%	264	Grade 1	-8.9% (PD)
Dose Level 2 1.5x10^6 cells/kg	7	GEJ	1	2	10%/63%/15%	8124	Grade 1	-16.9% (SD)
	8	EC	3 (including liver)	8	2%/2%/94%	2211	none	-24.9% (SD)
	9	EC	3 (including liver and bone)	4	0%/1%/99%	Data Pending	None	Non-evaluable

BOR=best overall response; CRS=cytokine release syndrome; DL=dose level; LOT=line of therapy; PD=progressive disease; PR=partial response; SD=stable disease

Conclusions

- LB1908, a CLDN18.2-targeted autologous CAR-T product, demonstrated encouraging antitumor activity in heavily pre-treated patients with GC/GEJC/EC.
- Durable antitumor activity was observed even at lower dose levels.
- CAR-T expansion was detected in all treated patients, with preliminary evidence of a dose-exposure relationship.
- Upper GI toxicity (manifesting as gastric mucosal injury), consistent with an on-target/off-tumor effect of CLDN18.2-targeting, was mitigated with steroid prophylaxis without compromising CAR-T expansion or antitumor activity.

Acknowledgements and Disclosures:

This study was funded by Legend Biotech USA Inc. We would like thank patients, families, and caregivers for their participation.