Abstract # 374

Phase 1 study of LB1908, an autologous claudin 18.2-targeted chimeric antigen receptor T-cell product, in subjects with advanced gastroesophageal adenocarcinoma

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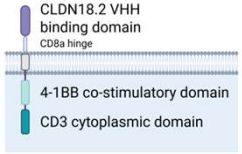
Clinicaltrials.gov no. NCT05539430

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 gastrointestinal (GI) cancers. We present 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

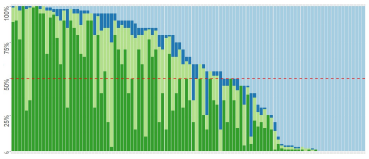
Methods

- This is an ongoing, open-label, multicenter phase 1 dose-escalation/expansion trial
- Enrolling subjects with locally advanced/unresectable or metastatic GC (n=5), GEJC (n=6), or EC (n=6)
  - ≥ 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 are to evaluate safety, tolerability, pharmacokinetics (PK) and preliminary antitumor activity of LB1908
- Dose-escalation design using modified 3+3 evaluating 3 dose levels (DLs): 0.5, 1.5, and 3 x 10^6 CAR+ T cells/kg
- LB1908 administered as a single infusion after 3 days of lymphodepletion with cyclophosphamide (300mg/m^2/dose) and fludarabine (30 mg/m^2/dose)
- Bridging therapy allowed between leukapheresis and lymphodepletion/LB1908 infusion

Claudin 18.2 Expression

- Potential subjects are screened for tumor CLDN18.2 expression by an immunohistochemistry assay (Ventana 43-14A antibody), performed centrally
- 1+ expression in ≥50% of tumor cells is considered positive (red dotted line in **Figure 2**)
- 64% (67 of 104 patients tested) had tumors that were CLDN18.2 positive at this threshold

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



Results

Subject Demographics and Baseline Characteristics

As of 15 Dec 2025, 17 subjects had received LB1908: n=6 at dose level 1 (DL1); n=3 at DL2; n=8 at DL3, with a median post-infusion follow-up of 2.9 months.

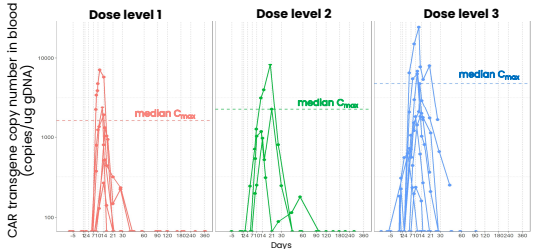
Table 1. Patient Baseline and Demographic Characteristics

	DL1 0.5x10^{6}CAR+ T cells/kg (N=6)	DL2 1.5x10^{6}CAR+ T cells/kg (N=3)	DL3 3.0x10^{6}CAR+ T cells/kg (N=8)	Overall (N=17)
Median age (years)	53.0	58.0	62.5	58.0
Sex, male	5 (83.3)	3 (100)	6 (75)	14 (82.4)
ECOG score at baseline				
0	2 (33.3)	0	3 (37.5)	5 (29.4)
1	4 (66.7)	3 (100)	5 (62.5)	12 (70.6)
Primary Tumor Type				
GC	2 (33.3)	0	3 (37.5)	5 (29.4)
GEJC	1 (16.7)	1 (33.3)	4 (50)	6 (35.3)
EC	3 (50)	2 (66.7)	1 (12.5)	6 (35.3)
Metastatic sites, median (range)	3 (2-5)	3 (2-3)	2.5 (1-5)	3 (1-5)
Selected sites of metastatic disease				
Liver	4 (66.7)	2 (66.7)	4 (50)	10 (58.8)
Peritoneum	4 (66.7)	1 (33.3)	3 (37.5)	8 (47.1)
Lung	1 (16.7)	0	3 (37.5)	4 (23.5)
Bone	1 (16.7)	1 (33.3)	0	2 (11.8)
Prior therapies				
Prior LOTs, median (range)	2 (1-2)	4 (2-8)	3.5 (1-6)	2 (1-8)
≥2 prior LOT	5 (83.3)	3 (100)	7 (87.5)	15 (88.2)
Prior CLDN18.2-directed therapy	0	0	1 (12.5)	1 (5.9)
CLDN 18.2 expression, median (range)				
H score	263 (218-282)	288 (181-299)	167 (115-295)	245 (115-299)
Overall % expression ≥1%	96 (90-98)	98 (88-100)	75 (55-100)	95 (55- 100)

Note: all values are number (%), unless otherwise noted.

Pharmacokinetics

Figure 3. Peripheral CAR-T Cell Expansion



CAR-T expansion was observed in all subjects and appears dose-dependent

Table 2. PK Parameters

	DL1 (N=6)	DL2 (N=3)	DL3* (N=7)	Overall (N=16)
C_{max} (copies/µg gDNA)	1594 (264-6922)	2211 (1172-8124)	4693 (233-23991)	2048 (233-23991)
T_{max} (days)	14 (11-15)	20 (13-21)	11 (10-13)	13 (10-21)
T_{last} (days)	16 (13-28)	30 (27-55)	21 (14-41)	21 (13-55)
AUC_{last} (copies*day/µg gDNA)	7667 (1182-37122)	19641 (11339-68760)	36296 (1160-189942)	13366 (1160-189942)

Note: all values median (range)
*1 DL3 subject with incomplete PK data due to recent dosing was excluded from analysis

Safety

Safety Summary

- All but 1 subject (16/17; 94.1%) experienced at least 1 grade ≥3 treatment-emergent adverse event (TEAE)
- The most common grade ≥3 TEAEs were hematologic and mostly attributable to the lymphodepletion regimen
- The only non-hematologic grade ≥3 TEAE considered LB1908-related occurring in >1 subject was gastritis/gastric mucosal injury, including 1 DLT at DL1
- No AE-related deaths

Upper Gastrointestinal Toxicity

- Gastritis or gastric mucosal lesions occurred in 10 subjects (grade 2: n=2; grade 3: n=8) and were considered an on-target/off-tumor toxicity
  - Median time to onset was 9 days (range 2-50)
  - 6/8 grade 3 events resolved/resolved with sequelae, in a median 12 days (2 are ongoing at the time of the data cut)
- A mitigation strategy including non-absorbable (beclomethasone) and systemic steroids ameliorated the incidence, severity, and duration of upper GI events (see Table 3)

CAR-T Cell Toxicities

- Cytokine release syndrome (CRS) occurred in 13/17 (76.5%) subjects; only 1 grade 3 event (at dose level 3)
  - Median time to onset: 6 days (range 1-10)
  - Median duration: 6 days (range 2-9)
  - Treatment:
    - Tocilizumab: 8 subjects (47%)
    - Steroids: 1 subject
    - ICU care: none
- No Immune effector cell-associated neurotoxicity syndrome (ICANS) observed
- One grade 2 IEC-HS event in the subject with grade 3 CRS

Table 3. Grade ≥3 TEAEs Occurring in ≥ 10% of Subjects

	DL1 (N=6)	DL2 (N=3)	DL3 (N=8)	Overall (N=17)
Any TEAE Grade 3 or higher	6 (100)	3 (100)	7 (87.5)	16 (94.1)
Non-hematologic TEAEs				
Gastritis/gastric mucosal lesion	3 (50)	3 (100)	2 (25)	8 (47.1)
Nausea	1 (16.7)	0	1 (12.5)	2 (11.8)
Fatigue	0	0	2 (25)	2 (11.8)
Pneumonia	0	0	2 (25)	2 (11.8)
Hyperglycemia	1 (16.7)	1 (33.3)	0	2 (11.8)
Hypocalcemia	1 (16.7)	1 (33.3)	0	2 (11.8)
Hematologic TEAEs				
Anemia	5 (83.3)	1 (33.3)	2 (25)	8 (47.1)
Neutrophil count decreased	5 (83.3)	1 (33.3)	2 (25)	8 (47.1)
Lymphocyte count decreased	4 (66.7)	2 (66.7)	0	6 (35.3)
White blood cell count decreased	5 (83.3)	1 (33.3)	0	6 (35.3)
Platelet count decreased	1 (16.7)	1 (33.3)	2 (25)	4 (23.5)

Note: all values are number (%)

Antitumor Activity

Table 4. Summary of Antitumor Activity

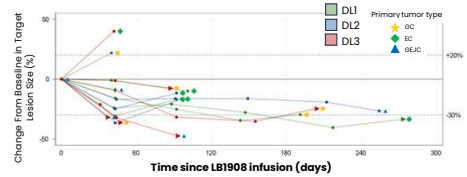
	DL1 (N=6)	DL2 (N=3)	DL3 (N=8)	Overall (N=17)
Objective response rate (PR)	1 (16.7)	1 (33.3)	4 (50)	6 (35.3)
Disease control rate (PR+SD)	2 (33.3)	3 (100)	5 (62.5)	10 (58.8)

Note: all values are number (%). Response assessment based on RECIST v1.1.

Figure 4. Best Change from Baseline in Target Lesion Size and Response

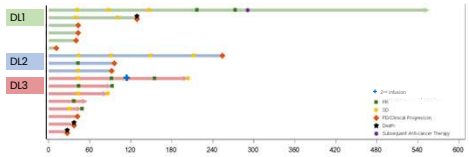
Note: 2 subjects with clinical progression without post-infusion radiographic assessment not displayed

Figure 5. Change in Target Lesion Size Over Time



Note: 2 subjects with clinical progression without post-infusion radiographic assessment not displayed

Figure 6. Response and Durability by Dose Level



Conclusions

- LB1908, a CLDN18.2-targeted autologous CAR-T product, demonstrated encouraging antitumor activity in heavily pre-treated subjects with GC, GEJC, or EC
- Durable dose-dependent antitumor activity was observed, with deepening responses over time in multiple subjects
- CAR-T expansion was associated with dose and detected in all subjects
- Upper GI toxicity (manifesting as gastritis/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: Study is funded by Legend Biotech USA Inc. We would like to thank subjects, families, and caregivers for their participation