Zolbetuximab + pembrolizumab and chemotherapy as first-line treatment for patients with CLDN18.2-positive, HER2-negative, PD-L1-positive locally advanced unresectable or metastatic G/GEJ adenocarcinoma: Phase 3, double-blind, randomized trial (LUCERNA)

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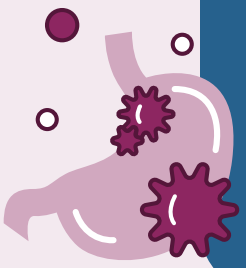
Key Summary

The LUCERNA clinical trial is recruiting patients with previously untreated advanced gastric or gastroesophageal junction cancer to evaluate the effectiveness and safety of the triplet therapy combination of zolbetuximab, pembrolizumab, and chemotherapy



Two different combination approaches demonstrated a treatment benefit

in patients with HER2–, LA unresectable or mG/GEJ adenocarcinoma whose tumors were either CLDN18.2+ or PD-L1+

Zolbetuximab plus chemotherapy
demonstrated longer PFS and OS versus placebo plus chemotherapy in patients with CLDN18.2+ tumors (defined as those with ≥ 75% of tumor cells demonstrating moderate-to-strong membranous CLDN18 staining using the VENTANA CLDN18 [43-14A] RxDx Assay)[1-3]

Pembrolizumab plus chemotherapy
demonstrated longer OS versus placebo plus chemotherapy in patients with PD-L1+ tumors (defined as those with a CPS ≥ 1)[4]

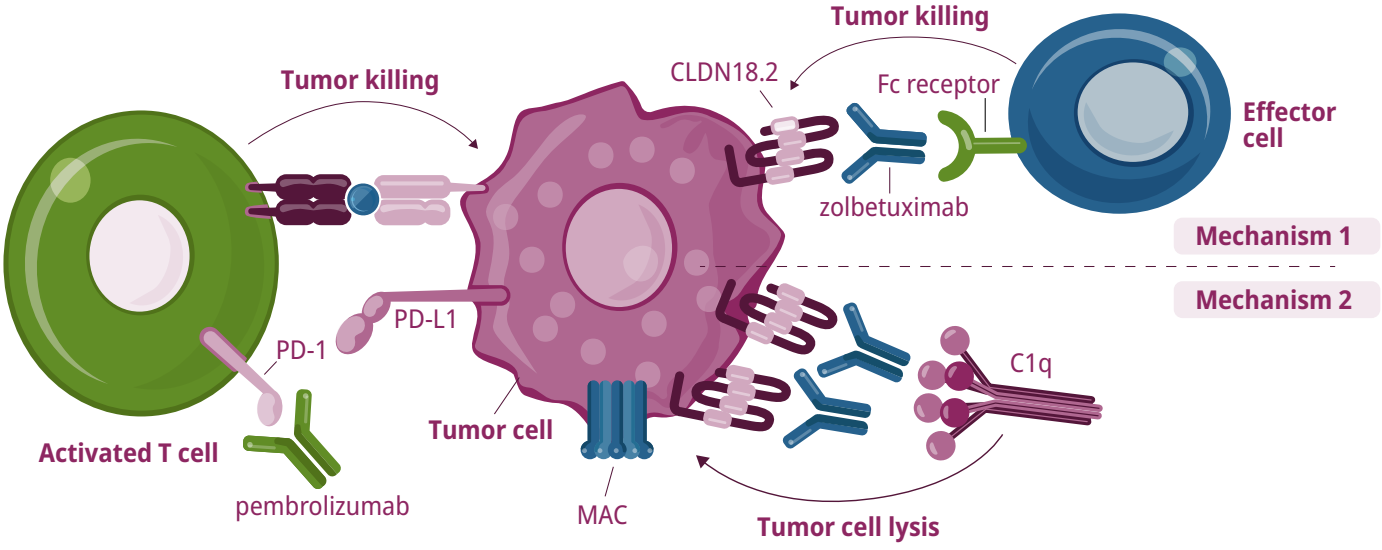
Interim results from the phase 2 ILUSTRO trial

demonstrated promising antitumor activity with zolbetuximab plus pembrolizumab or zolbetuximab plus chemotherapy and nivolumab in patients with LA unresectable or mG/GEJ adenocarcinoma with CLDN18.2+ tumors[5,6]

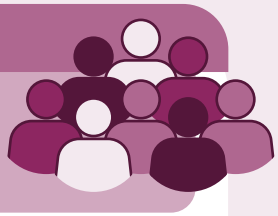
For patients with LA unresectable or mG/GEJ adenocarcinoma, current evidence suggests a combination of treatments may **improve patient survival**

The phase 3 LUCERNA trial (NCT06901531)

is evaluating the effectiveness and safety of using anti-CLDN18.2 and anti-PD-1 therapies simultaneously



LUCERNA: A global, double-blind, randomized, phase 3 trial



Patients with previously untreated LA unresectable or mG/GEJ adenocarcinoma (N ≈ 500)

CLDN18.2+ | **HER2–** | **PD-L1+**

Patients cannot have had prior treatment with chemotherapy, immunotherapy, or anti-CLDN18.2 therapy

Randomly assigned 1:1

Stratified by:
Region (Asia vs non-Asia)
PD-L1 CPS (≥ 1 to < 10 vs ≥ 10)

Placebo, pembrolizumab, and chemotherapy (n ≈ 250)	Zolbetuximab, pembrolizumab, and chemotherapy (n ≈ 250)
	
Cycles 1–4 (42 days/cycle)	**Cycles 1–4 (42 days/cycle)**
Placebo IV Q2W or Q3W	Zolbetuximab IV 800 mg/m² Cycle 1 Day 1 → 400 mg/m² Q2W or 600 mg/m² Q3W
Pembrolizumab IV 200 mg Q3W or 400 mg Q6W	Pembrolizumab IV 200 mg Q3W or 400 mg Q6W
CAPOX[a] / mFOLFOX6[b]	CAPOX[a] / mFOLFOX6[b]

Patients can continue beyond Cycle 4 with zolbetuximab plus pembrolizumab or placebo plus pembrolizumab; and either capecitabine, or folinic acid and fluorouracil, at the discretion of the treating physician

Primary endpoint	Secondary endpoints	Exploratory endpoints
• OS	• PFS[c] • DOR[c] • Safety • ORR[c] • PK • Immunogenicity	• HRQoL • PFS2 • Biomarkers

The results of this trial will provide insight into the therapeutic potential of the triplet combination of CLDN18.2 targeting with zolbetuximab, PD-1 blockade with pembrolizumab, and chemotherapy

[a]Oral capecitabine 1000 mg/m² twice daily on Days 1–14 and 22–35, and IV oxaliplatin 130 mg/m² Q3W; [b]Folinic acid 400 mg/m², fluorouracil 400 mg/m² bolus followed by 2400 mg/m², and oxaliplatin 85 mg/m², IV Q2W; [c]Per RECIST version 1.1 by investigator assessment.

References: 1. Shitara K et al. *Lancet.* 2023;401(10389):1655-68; **2.** Shah MA et al. *Nat Med*. 2023;29(8):2133-41; **3.** Shitara K et al. *N Engl J Med*. 2024;391(12):1159-62; **4.** Rha SY et al. *Lancet Oncol*. 2023;24(11):1181-95; **5.** Klempner SJ et al. *Clin Cancer Res*. 2023;29(19):3882-91;**6.** Shitara K et al. Presented at ASCO GI 2026. Abstract LBA284.

Abbreviations: C1q, complement component 1q; CAPOX, capecitabine and oxaliplatin regimen; CLDN18.2, claudin 18 isoform 2; CPS, combined positive score; DOR, duration of response; G/GEJ, gastric or gastroesophageal junction; HER2, human epidermal growth factor receptor 2; HRQoL, health-related quality of life; IV, intravenous; LA, locally advanced; MAC, membrane attack complex; mFOLFOX6, modified folinic acid, fluorouracil, and oxaliplatin regimen; mG/GEJ, metastatic gastric or gastroesophageal junction; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PFS2, PFS after subsequent anticancer therapy; PK, pharmacokinetics; Q2W, every 2 weeks; Q3W, every 3 weeks; Q6W, every 6 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.