

Review Article

Claudin 18.2-Targeted Therapies in Gastric and Gastroesophageal Junction Cancers: A Narrative Review of the Emerging Therapeutic Landscape

Lama K Wahb¹, Gehad Elsheikh¹, Mahmoud Sweid¹, Eman Gamal¹, Heba Shaheen¹.*1. Department of Clinical Oncology, Faculty of Medicine, Menoufia University, Shebin Elkom, Egypt*

Corresponding author: Corresponding author: Lama K Wahb, Assistant Lecturer, Department of Clinical Oncology, Menoufia University, Shebin Elkom, Egypt. Address: Yassin AbdelGhaffar Street, Shebin Elkom, PO 32511, Egypt. Email: lamakamalC3S@gmail.com

Received 20-6-2026

Revised 23-7-2026

Accepted 1-8-2026

Published 5-8-2026

DOI: 10.676G2/IODT.26.G635

How to cite: Lama K Wahb, Gehad Elsheikh, Mahmoud Sweid, Eman Gamal, Heba Shaheen. Claudin 18.2-Targeted Therapies in Gastric and Gastroesophageal Junction Cancers: A Narrative Review of the Emerging Therapeutic Landscape. Integr Oncol Diagn Treat. 2026;1(1):55-75. doi: 10.676G2/IODT.26.G635

Abstract

Objective: To survey the emerging therapeutic landscape of Claudin 18.2 (CLDN18.2)-directed agents in gastric and gastroesophageal junction (GEJ) cancers, encompassing CLDN18.2 biology, clinical evidence for approved and investigational therapies, biomarker-driven patient selection, resistance mechanisms, and a practical framework for integrating these agents into evolving treatment algorithms.

Data Sources: A narrative review of the published literature was conducted through searches of PubMed/MEDLINE, Embase, and the Cochrane Library from database inception to 31 May 2026, supplemented by hand-searching of reference lists, ClinicalTrials.gov, and abstracts from the ASCO, ESMO, and ASCO Gastrointestinal Cancers Symposium annual meetings (2022–2026). Search terms combined controlled vocabulary and free-text variants of "claudin 18.2", "CLDN18.2", "zolbetuximab", "gastric cancer", "gastroesophageal junction", "antibody-drug conjugate", "bispecific antibody", and "CAR-T". Sources further included pivotal phase II and III clinical trial data (FAST, SPOTLIGHT, GLOW, CT041-ST-01), phase I/II data for investigational agents, GLOBOCAN 2022 epidemiological data, The Cancer Genome Atlas molecular classification, and FDA regulatory documents pertaining to CLDN18.2-targeted therapies in gastric and GEJ cancers.

Data Summary: Zolbetuximab, a first-in-class anti-CLDN18.2 monoclonal antibody, demonstrated statistically significant improvements in progression-free and overall survival when added to first-line platinum-fluoropyrimidine chemotherapy in CLDN18.2-positive ($\geq 75\%$ viable tumor cells), HER2-negative advanced gastric/GEJ adenocarcinoma, supporting regulatory approval in the United States, Japan, and the European Union. An expanding pipeline of antibody-drug conjugates (IBI343, tecotabart vedotin), bispecific antibodies, and CAR-T cell therapies (CT041/satricabtagene autoleucel) is advancing through clinical development, employing lower IHC expression thresholds to broaden patient eligibility. Key challenges include intratumoral and temporal expression

heterogeneity, divergent IHC scoring criteria across trials, and resistance mechanisms including antigen downregulation and tumor microenvironment-mediated immune evasion.

Conclusions: CLDN18.2 represents a clinically validated therapeutic target in gastric and GEJ cancers. Harmonization of IHC scoring criteria, strategies to overcome expression heterogeneity and resistance, and rational sequencing of CLDN18.2-directed agents within multi-modal treatment algorithms are critical priorities to optimize patient outcomes.

Keywords: *Claudin 18.2; gastroesophageal junction cancer; zolbetuximab; antibody-drug conjugate; bispecific antibody*

1. Introduction

Gastric cancer and cancers of the gastroesophageal junction (GEJ) collectively represent the fifth most common malignancy and the fourth leading cause of cancer-related mortality worldwide, accounting for an estimated 968,000 new diagnoses and 660,000 deaths annually according to GLOBOCAN 2022 data [1]. Despite significant advances in molecular profiling and targeted therapy development over the past decade, the prognosis for patients with locally advanced unresectable or metastatic disease remains dismal, with a 5-year overall survival (OS) rate below 10% in most series [1]. The current standard-of-care first-line treatment for HER2-negative advanced gastric/GEJ adenocarcinoma consists of a fluoropyrimidine plus platinum doublet (mFOLFOX6 or CAPOX), with the addition of the anti-PD-1 antibody nivolumab for patients with a combined positive score (CPS) ≥ 5 based on CheckMate 649 data [2], or pembrolizumab for those with CPS ≥ 10 based on KEYNOTE-062 [3]. For the approximately 15–20% of patients with HER2-amplified disease, trastuzumab added to chemotherapy remains the cornerstone of first-line treatment based on the landmark ToGA trial [4], as reflected in current ESMO and NCCN treatment recommendations [27,28].

The molecular classification of gastric cancer established by The Cancer Genome Atlas (TCGA) Research Network identified four subtypes: Epstein-Barr virus (EBV)-positive, microsatellite instability-high (MSI-H), genomically stable (GS), and chromosomal instability (CIN) [5]. While this classification has deepened our understanding of gastric cancer biology, only MSI-H and EBV-positive subtypes—representing approximately 22% and 9% of cases, respectively, in the original TCGA cohort [5], with prevalence varying across geographical and ethnic populations in subsequent real-world series [6]—harbor actionable immune features. The majority of patients, particularly those with GS and CIN subtypes, lack currently approved targeted options beyond HER2 and PD-L1 [27,28], underscoring the critical unmet need for novel therapeutic targets [5,6].

Claudins are a family of approximately 27 tetra-spanning transmembrane proteins that constitute the structural backbone of epithelial and endothelial tight junctions, regulating paracellular permeability and contributing to cell polarity and barrier function [7]. The *CLDN18* gene on chromosome 3q22.3 produces two splice isoforms through alternative splicing of the first exon: CLDN18.1, predominantly expressed in lung alveolar epithelium, and CLDN18.2, which exhibits highly tissue-restricted expression in differentiated gastric mucosal cells [7,8]. In normal gastric epithelium, CLDN18.2 is sequestered within the tight-junction complex, rendering its extracellular loops inaccessible to circulating antibodies. However, during malignant transformation, disruption of epithelial polarity and tight-junction architecture exposes the first extracellular loop (ECL1) on the tumor cell surface, creating a tumor-restricted epitope that can be targeted therapeutically [8,9]. This differential accessibility between normal and malignant

tissue is the biological cornerstone of the favorable therapeutic index observed with CLDN18.2-directed agents.

CLDN18.2 is expressed at moderate-to-strong intensity by immunohistochemistry (IHC) in 60–80% of gastric/GEJ adenocarcinomas, making it one of the most prevalent targetable antigens in this disease [9,10]. Expression has also been documented in pancreatic ductal adenocarcinoma (50–70%), biliary tract cancers (40–60%), esophageal adenocarcinoma, ovarian cancer, and lung adenocarcinoma, raising the prospect of pan-tumor CLDN18.2 targeting [8,9]. A 2026 comprehensive review by Saviano et al. in *Nature Reviews Cancer* has further established the claudin protein family—and CLDN18.2 in particular—as a major emerging class of solid tumor targets with broad therapeutic implications [7].

A recent narrative review by Zhang et al. in the *Journal of Gastric Cancer* (2026) has similarly surveyed the CLDN18.2 therapeutic landscape [29]. The present review complements and extends that work with particular emphasis on biomarker standardization challenges, primary and acquired resistance mechanisms, real-world implementation barriers, and a practical clinical framework for treatment selection—dimensions critical for translating emerging CLDN18.2-directed therapies into routine oncology practice.

The aim of this review is to provide a comprehensive, clinician-focused synthesis of: (1) the molecular biology of CLDN18.2 as a therapeutic target; (2) the clinical evidence base for zolbetuximab, the first approved CLDN18.2-directed therapy; (3) the expanding pipeline of CLDN18.2-targeted ADCs, bispecific antibodies (BsAbs), and CAR-T cell therapies; (4) biomarker-guided patient selection strategies and their limitations; (5) primary and acquired resistance mechanisms; and (6) future directions for integrating CLDN18.2-directed therapy into multimodal treatment algorithms.

This article is a narrative rather than a systematic review; formal risk-of-bias assessment and quantitative synthesis were therefore not undertaken, and study selection reflects the authors' judgement of clinical relevance rather than a prespecified protocol. The search strategy is detailed in the Data Sources section of the Abstract.

2. Biology of Claudin 18.2 as a Therapeutic Target

2.1 Gene Structure and Protein Topology

The *CLDN18* gene is located on chromosome 3q22.3 and encodes a tight-junction protein belonging to the claudin superfamily. Alternative splicing of the first exon generates two distinct isoforms—CLDN18.1 and CLDN18.2—which differ in their N-terminal amino acid sequences and exhibit fundamentally different tissue distributions [7,8]. For clarity of nomenclature throughout this review, italicised *CLDN18* denotes the gene and its splice variants, whereas non-italicised "CLDN18.2" and the equivalent long form "Claudin 18.2" denote the protein isoform; the two protein designations are used interchangeably in accordance with prevailing usage in the clinical literature. CLDN18.2 is the gastric-restricted isoform, expressed selectively in differentiated gastric mucosal cells under homeostatic conditions, with no significant expression in other normal adult tissues [8,9]. The CLDN18.2 protein adopts a canonical claudin topology comprising four transmembrane (TM) domains, two extracellular loops (ECL1 and ECL2), a short intracellular N-terminus, and a longer intracellular C-terminus that interacts with PDZ-domain scaffolding proteins such as ZO-1, ZO-2, and ZO-3 [7]. ECL1, the larger of the two extracellular loops, spans approximately 53 amino acids and forms the primary antibody-binding epitope exploited by

therapeutic agents. The structure, topology, and differential surface accessibility of CLDN18.2 across normal and malignant contexts are illustrated in Figure 1.

2.2 Differential Accessibility in Malignant Transformation

In normal gastric epithelium, CLDN18.2 is incorporated into the tight-junction complex at the apical-lateral membrane interface, physically constraining ECL1 within the paracellular space and rendering it inaccessible to circulating macromolecules, including antibodies [8,9]. During malignant transformation, loss of epithelial polarity, disruption of cell-cell junctions, and cytoskeletal reorganization displace CLDN18.2 from the tight-junction complex to the free lateral and basolateral cell surface, where ECL1 becomes fully accessible to antibody binding [8]. This mechanism of target unmasking in cancer—absent in normal tissue—is the molecular basis for the favorable therapeutic index of CLDN18.2-directed therapies and distinguishes CLDN18.2 from most conventional tumor-associated antigens [7,9].

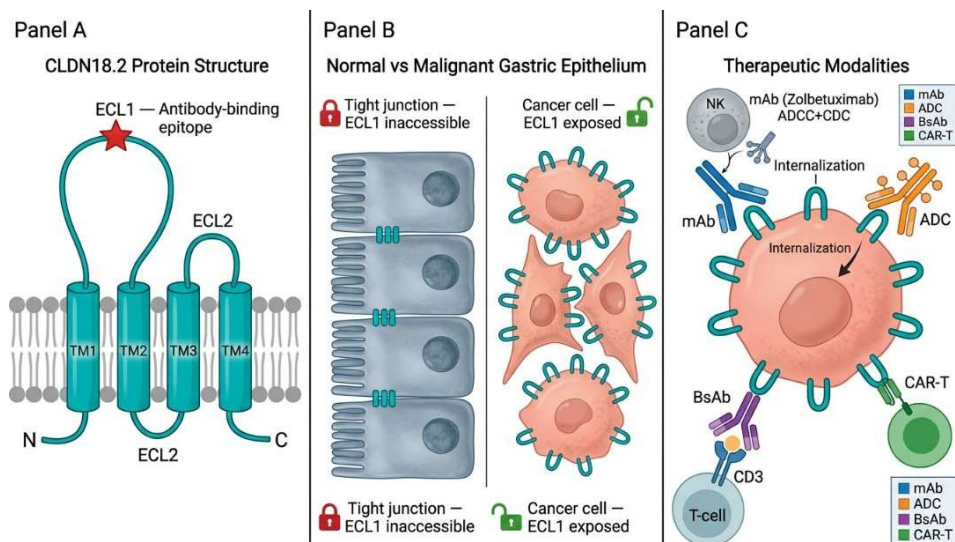


Figure 1. Structure and biology of Claudin 18.2 as a therapeutic target. **(A)** Schematic representation of the CLDN18.2 protein topology, comprising four transmembrane domains (TM1–TM4), two extracellular loops (ECL1 and ECL2), a short intracellular N-terminus, and a longer intracellular C-terminus. ECL1 is the primary epitope targeted by therapeutic antibodies. **(B)** Differential CLDN18.2 accessibility in normal versus malignant gastric epithelium. In normal gastric mucosa, CLDN18.2 is incorporated into the tight-junction complex at the apical-lateral membrane interface, with ECL1 sequestered within the paracellular space and inaccessible to circulating antibodies (left panel). In gastric cancer cells, disruption of tight-junction polarity displaces CLDN18.2 to the free lateral and basolateral cell surface, exposing ECL1 for antibody binding (right panel). **(C)** Binding sites and mechanisms of the four major therapeutic modalities targeting CLDN18.2: monoclonal antibody (mAb) binding to ECL1 with ADCC/CDC induction; ADC binding to ECL1 followed by internalization and intracellular payload release; bispecific antibody (BsAb) simultaneously binding ECL1 and engaging T cells via CD3; and CAR-T cell recognition of CLDN18.2 via the CAR scFv domain. Colour coding: mAb = blue; ADC = orange; BsAb = purple; CAR-T = green.

2.3 Expression Landscape Across Tumor Types

CLDN18.2 expression has been characterized by IHC across multiple solid tumor types. In gastric/GEJ adenocarcinoma, moderate-to-strong expression (2+/3+ IHC) is detected in 60–80% of tumors, with higher rates in both intestinal-type and diffuse-type histologies [9,10]. Pancreatic ductal adenocarcinoma demonstrates expression in approximately 50–70% of cases, and biliary tract cancers in 40–60% [8].

Additional expression has been documented in esophageal adenocarcinoma, ovarian serous carcinoma, and lung adenocarcinoma, though at lower frequencies [7,8]. Interstudy variability in antibody clones, scoring systems, and positivity thresholds has produced heterogeneous prevalence estimates, complicating cross-study comparisons [10].

2.4 Signalling and Oncogenic Implications

Beyond its structural role in tight junctions, CLDN18.2 participates in oncogenic signaling pathways. Its expression is regulated by transcription factors including CDX2, a master regulator of intestinal differentiation, which contributes to the enrichment of CLDN18.2 expression in intestinal-type gastric cancer [7]. CLDN18.2 has been shown to interact with components of the Wnt/ β -catenin pathway, with experimental evidence suggesting that its expression influences tumor cell proliferation through modulation of cell-cycle regulators including the minichromosome maintenance (MCM) complex proteins MCM2 and MCM5 [11]. These oncogenic functions suggest that CLDN18.2 is not merely a passive surface antigen but may actively contribute to tumor biology, further supporting its value as a therapeutic target [7,11].

3. Zolbetuximab: From Bench to Approval

3.1 Mechanism of Action

Zolbetuximab (zolbetuximab-clzb; Vyloy®) is a chimeric (human/mouse) IgG1 monoclonal antibody that binds with high affinity and specificity to ECL1 of CLDN18.2, engaging multiple effector mechanisms [12]. The primary cytotoxic mechanisms are antibody-dependent cellular cytotoxicity (ADCC), mediated by NK cells and macrophages engaging the Fc region of the bound antibody, and complement-dependent cytotoxicity (CDC), triggered by classical complement pathway activation [12]. The mechanisms of action of zolbetuximab and other CLDN18.2-directed therapeutic modalities are depicted in Figure 2. Secondary anti-proliferative effects arising from disruption of CLDN18.2-mediated tight-junction signaling have also been proposed [7]. Pharmacokinetically, zolbetuximab exhibits approximately dose-proportional exposure at the approved dose of 800 mg/m² on day 1 (cycle 1) followed by 600 mg/m² every three weeks, with a terminal half-life of approximately 12–16 days [12].

3.2 Pivotal Clinical Trials

FAST (Phase II). The FAST trial was a randomized phase II study evaluating zolbetuximab in combination with epirubicin, oxaliplatin, and capecitabine (EOX) versus EOX alone in patients with CLDN18.2-positive (IHC 2+/3+ in $\geq 40\%$ of tumor cells), HER2-negative advanced gastric/GEJ adenocarcinoma [13]. The trial demonstrated clinically meaningful improvements in median PFS (7.5 vs 5.3 months; HR 0.47; 95% CI 0.31–0.71) and median OS (13.0 vs 8.4 months; HR 0.56; 95% CI 0.39–0.83) in the high-expression subgroup (IHC 2+/3+ $\geq 70\%$), establishing proof of concept for CLDN18.2 targeting and informing the design of subsequent phase 3 trials [13].

Figure 2: Mechanisms of Action of CLDN18.2-Targeted Therapies

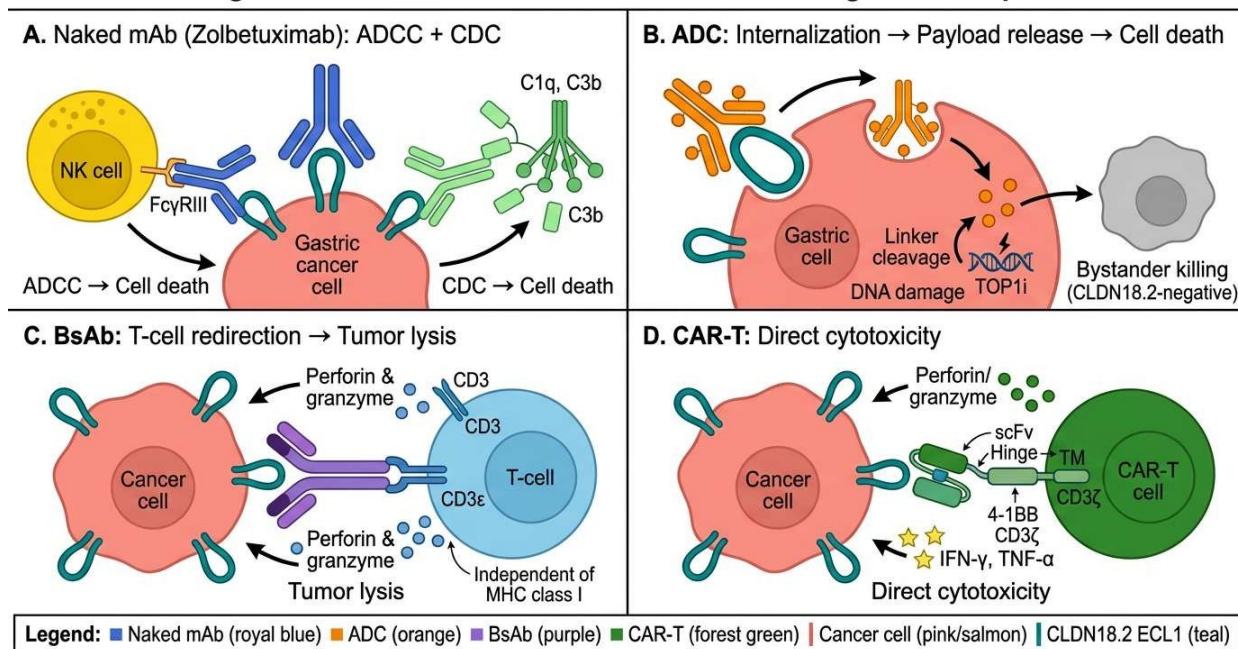


Figure 2. Mechanisms of action of CLDN18.2-targeted therapeutic modalities. Four-panel schematic illustrating the distinct cytotoxic mechanisms of each CLDN18.2-directed therapeutic class. **(A)** Naked monoclonal antibody (zolbetuximab): binding to CLDN18.2 ECL1 recruits NK cells and macrophages via FcγRIII (CD16), inducing ADCC, and activates the classical complement cascade, inducing CDC. **(B)** Antibody–drug conjugate (ADC): antibody binding to ECL1 undergoes receptor-mediated endocytosis; intracellular linker cleavage releases the cytotoxic payload (exatecan/TOP1i or MMAE), inducing DNA damage or microtubule disruption; released payload diffuses to neighboring cells mediating bystander killing. **(C)** Bispecific antibody (BsAb): simultaneously engages CLDN18.2 on the tumor cell and CD3ε on the T-cell receptor complex, forming an immunological synapse that activates cytotoxic T cells independent of MHC class I expression, leading to perforin/granzyme-mediated tumor lysis. **(D)** CAR-T cell: autologous T cells engineered with an anti-CLDN18.2 scFv-based CAR (incorporating 4-1BB co-stimulation and CD3ζ signaling) recognize CLDN18.2 on tumor cells, triggering direct cytotoxicity via perforin/granzyme and cytokine secretion (IFN-γ, TNF-α). Consistent colour coding throughout: mAb/zolbetuximab = blue; ADC = orange; BsAb = purple; CAR-T = green.

SPOTLIGHT (Phase III). SPOTLIGHT was a multicenter, randomized, double-blind, placebo-controlled phase 3 trial enrolling 565 patients with CLDN18.2-positive ($\geq 75\%$ of tumor cells with 2+/3+ IHC), HER2-negative, locally advanced unresectable or metastatic gastric/GEJ adenocarcinoma [14]. Patients were randomized 1:1 to zolbetuximab plus mFOLFOX6 versus placebo plus mFOLFOX6. The trial met its primary endpoint: median PFS was significantly improved with zolbetuximab (10.61 vs 8.67 months; HR 0.750; 95% CI 0.601–0.936; $p=0.0066$). Median OS was also significantly prolonged (18.23 vs 15.54 months; HR 0.750; 95% CI 0.601–0.936; $p=0.0053$). The most common grade ≥ 3 adverse events with zolbetuximab were nausea (9.0%), vomiting (8.5%), and decreased appetite (3.9%), predominantly occurring during the first infusion cycle and manageable with prophylactic antiemetics and dose modification [14].

GLOW (Phase III). GLOW was a similarly designed phase 3 trial in 507 patients randomized to zolbetuximab plus CAPOX versus placebo plus CAPOX, using an identical CLDN18.2 eligibility

criterion [15]. Zolbetuximab significantly improved median PFS (8.21 vs 6.80 months; HR 0.687; 95% CI 0.544–0.866; $p=0.0007$) and median OS (14.39 vs 12.16 months; HR 0.771; 95% CI 0.615–0.965; $p=0.0200$) [15]. Consistent with SPOTLIGHT, a subgroup analysis of Korean patients enrolled across both trials confirmed concordant efficacy and safety outcomes, reinforcing the generalizability of the clinical signal across ethnic populations and chemotherapy backbones [16]. Pivotal efficacy and safety data from FAST, SPOTLIGHT, and GLOW are summarized in Table 2.

Integrated safety profile. Across both phase 3 trials, the dominant toxicity of zolbetuximab was gastrointestinal, reflecting on-target effects on normal gastric mucosa. Nausea and vomiting were predominantly cycle 1 events, manageable with prophylactic 5-HT₃ antagonists and NK1 receptor antagonists, with rates declining substantially in subsequent cycles. This toxicity profile is distinct from and additive to the hematologic and neuropathic toxicities of platinum-fluoropyrimidine chemotherapy [12,14,15].

Table 2. Pivotal clinical trial results for zolbetuximab in advanced gastric and gastroesophageal junction adenocarcinoma.

Trial	Phase	N	Treatment Arms	CLDN18.2 Eligibility	Primary Endpoint	Median PFS (mo)	HR for PFS (95% CI)	Median OS (mo)	HR for OS (95% CI)	ORR (%)	Key Grade ≥3 AEs (%)
FAST	II (randomized)	161 (high-expression subgroup $p \sim 77$)	Zolbetuximab + EOX vs EOX alone	IHC 2+/3+ in ≥40% of tumor cells (primary analysis); high-expression subgroup ≥70% 2+/3+	PFS (investigator-assessed)	7.5 vs 5.3 (high-expression subgroup)	0.47 (0.31–0.71)	13.0 vs 8.4 (high-expression subgroup)	0.56 (0.39–0.83)	39% vs 25% (high-expression subgroup)	Nausea 58% (any grade); vomiting 50% (any grade); neutropenia ~30%
SPOTLIGHT	III (randomized, double-blind)	565	Zolbetuximab + mFOLFOX 6 vs Placebo + mFOLFOX 6	IHC 2+/3+ in ≥75% of viable tumor cells (VENTANA 43-14A RxDx Assay)	PFS (blinded independent central review)	10.61 vs 8.67	0.750 (0.601–0.936); $p=0.0066$	18.23 vs 15.54	0.750 (0.601–0.936); $p=0.0053$	60.7% vs 62.1%	Nausea 9.0%; vomiting 8.5%; decreased appetite 3.9%; peripheral neuropathy 6.5%
GLOW	III (randomized, double-blind)	507	Zolbetuximab + CAPOX vs Placebo + CAPOX	IHC 2+/3+ in ≥75% of viable tumor cells (VENTANA 43-14A RxDx Assay)	PFS (blinded independent central review)	8.21 vs 6.80	0.687 (0.544–0.866); $p=0.0007$	14.39 vs 12.16	0.771 (0.615–0.965); $p=0.0200$	54.5% vs 46.0%	Nausea 8.2%; vomiting 7.7%; decreased appetite 2.8%; thrombocytopenia 6.3%

Table 2 Footnotes: AE, adverse event; CAPOX, capecitabine plus oxaliplatin; CLDN18.2, claudin 18.2; EOX, epirubicin, oxaliplatin, and capecitabine; GEJ, gastroesophageal junction; HR, hazard ratio; IHC, immunohistochemistry; mFOLFOX6, modified folinic acid, fluorouracil, and oxaliplatin; ORR, objective response rate; OS, overall survival; PFS, progression-free survival. FAST trial data are reported for the high-expression subgroup ($\geq 70\%$ 2+/3+) which formed the basis for Phase III design. ORR for SPOTLIGHT and GLOW reflects investigator-assessed confirmed responses. Key grade ≥ 3 AEs are listed for the zolbetuximab arm only. Data from references [13–15].

3.3 Regulatory Milestones

Based on the SPOTLIGHT and GLOW data, zolbetuximab received U.S. Food and Drug Administration (FDA) approval in October 2024 for use in combination with fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumors are CLDN18.2-positive as determined by an FDA-approved companion diagnostic test [12]. Concurrent approval was granted for the VENTANA CLDN18 (43-14A) RxDx Assay (Roche Diagnostics) as the companion diagnostic, defining CLDN18.2 positivity as $\geq 75\%$ of viable tumor cells demonstrating moderate-to-strong (2+/3+) membranous staining [17]. The European Medicines Agency (EMA) and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) subsequently granted approval in 2024–2025, making zolbetuximab the first CLDN18.2-targeted therapy approved globally [12]. A comprehensive summary of all CLDN18.2-directed agents in clinical development is provided in Table 1.

Table 1. Summary of CLDN18.2-targeted agents in clinical development.

Agent Name	Developer	Modality	Target(s)	Payload / Format	Most Advanced Phase	Key Trial(s) (NCT#)	Tumor Type(s)	Notable Efficacy Signal	Status
MONOCLONAL ANTIBODIES									
Zolbetuximab (zolbetuximab-clzb; Vyloy®)	Astellas Pharma / Genentech	mAb (chimeric IgG1)	CLDN18.2 ECL1	ADCC, CDC	Approved (Phase 3 completed)	SPOTLIGHT (NCT03504397); GLOW (NCT03653507); FAST (NCT01630083)	Gastric, GEJ	SPOTLIGHT: PFS HR 0.750 (95% CI 0.601–0.936); OS HR 0.750. GLOW: PFS HR 0.687 (95% CI 0.544–0.866); OS HR 0.771	FDA/EMA/PM DA approved (1L gastric/GEJ, HER2-negative, CLDN18.2-positive)
ANTIBODY–DRUG CONJUGATES (ADCs)									
IBI343	Innovent Biologics (China)	ADC	CLDN18.2	Exatecan (TOP1i), site-specific cleavable glycol linker, DAR=4	Phase 1 (dose escalation/expansion completed; Phase 2 ongoing)	NCT05008848	Gastric, GEJ, pancreatic, other solid tumors	Phase 1 (N=127): DLTs at higher doses; objective responses in CLDN18.2-positive gastric/GEJ including post-zolbetuximab	Active enrollment; Phase 2 expansion ongoing

Agent Name	Developer	Modality	Target(s)	Payload / Format	Most Advanced Phase	Key Trial(s) (NCT#)	Tumor Type(s)	Notable Efficacy Signal	Status
LM-302 (tecotabart vedotin)	LaNova Medicines (China)	ADC	CLDN18.2	MMAE (microtubule inhibitor), cleavable linker	Phase 1/2 (Bayesian adaptive)	NCT04714710	Gastric, GEJ, pancreatic, other solid tumors	Phase 1/2: preliminary PK, safety, immunogenicity, and early antitumor activity reported	Active enrollment
SYSA1801	CSPC Pharmaceutical Group (China)	ADC	CLDN18.2	Payload not fully disclosed	Phase 1	NCT05184712	Gastric, pancreatic, other solid tumors	Comparative ADC/RDC preclinical analysis published; clinical data pending	Active enrollment
AZD0901	AstraZeneca	ADC	CLDN18.2	Payload not publicly disclosed	Phase 1	Not publicly disclosed	Solid tumors (gastric, pancreatic presumed)	No public clinical data available	Pipeline disclosure only
CMG901	Keymed Biosciences / Sino Biopharmaceutical (China)	ADC	CLDN18.2	Payload not publicly disclosed	Phase 1	NCT05001724	Gastric, GEJ, other solid tumors	No public clinical efficacy data	Active enrollment
BISPECIFIC ANTIBODIES (BsAbs)									
CLDN18.2 × CD3 bispecifics (multiple programs)	Various (academic and commercial)	BsAb (T-cell engager)	CLDN18.2 × CD3ε	BiTE, DVD-Ig, or IgG-like formats	Preclinical to Phase 1	Multiple NCTs	Gastric, GEJ, pancreatic	Preclinical: potent T-cell-mediated cytotoxicity; early clinical data emerging	Multiple programs in early development
CLDN18.2 × CD47 bispecifics	Various	BsAb	CLDN18.2 × CD47	Dual-target ADCP-enhancing format	Preclinical	N/A	Gastric, pancreatic (preclinical)	Preclinical: enhanced macrophage phagocytosis	Preclinical stage
CLDN18.2 × 4-1BB bispecifics	Various	BsAb	CLDN18.2 × 4-1BB (CD137)	Tumor-targeted co-stimulation format	Preclinical	N/A	Gastric, pancreatic (preclinical)	Preclinical: enhanced T-cell activation	Preclinical stage
CAR-T CELL THERAPIES									
CT041 (satricabtagene)	CARsgen Therapeutics (China)	CAR-T (autologous)	CLDN18.2	Anti-CLDN18.2 scFv, 4-	Phase 2 (randomized, completed)	CT041-ST-01 (NCT04404595)	Gastric, GEJ, pancreatic	Phase 2 randomized: clinically	Regulatory discussions ongoing;

Agent Name	Developer	Modality	Target(s)	Payload / Format	Most Advanced Phase	Key Trial(s) (NCT#)	Tumor Type(s)	Notable Efficacy Signal	Status
autoleucel; satri-cel)				1BB co-stimulation, CD3ζ				meaningful ORR and DCR vs TPC; manageable CRS; on-target gastric mucosal toxicity characterized	additional trials planned
Other CLDN18.2 CAR-T programs (allogeneic, armored, dual-target)	Various (China, USA, Europe)	CAR-T (autologous or allogeneic)	CLDN18.2 (± second antigen)	Various CAR constructs (CD28 or 4-1BB co-stimulation; armored with cytokines or checkpoint inhibitors)	Preclinical to Phase 1	Multiple NCTs	Gastric, GEJ, pancreatic, other solid tumors	Preclinical and early clinical data emerging; focus on antigen-escape prevention	Multiple programs in early development

Table 1 Footnotes: ADCC, antibody-dependent cellular cytotoxicity; ADC, antibody–drug conjugate; ADCP, antibody-dependent cellular phagocytosis; BiTE, bispecific T-cell engager; CAR-T, chimeric antigen receptor T cell; CDC, complement-dependent cytotoxicity; CLDN18.2, claudin 18.2; DAR, drug-to-antibody ratio; DCR, disease control rate; DLT, dose-limiting toxicity; DVD-Ig, dual-variable domain immunoglobulin; ECL1, first extracellular loop; EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; GEJ, gastroesophageal junction; HR, hazard ratio; IgG, immunoglobulin G; MMAE, monomethyl auristatin E; mAb, monoclonal antibody; NCT, ClinicalTrials.gov identifier; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RDC, radionuclide-drug conjugate; scFv, single-chain variable fragment; TPC, treatment of physician's choice; TOP1i, topoisomerase I inhibitor; 1L, first-line.

3.4 Positioning in Treatment Algorithms

In the current first-line treatment landscape, CLDN18.2 testing represents a third actionable biomarker alongside HER2 and PD-L1/CPS, and has been incorporated into contemporary ESMO and NCCN treatment recommendations for advanced gastric/GEJ adenocarcinoma [27,28]. Zolbetuximab is indicated exclusively in HER2-negative, CLDN18.2-positive tumors, creating a patient population distinct from the HER2-positive cohort [4,14]. The overlap between CLDN18.2-positive and PD-L1 CPS ≥ 5 populations is substantial (estimated 30–40%), and ongoing trials are evaluating zolbetuximab combined with anti-PD-1 agents and chemotherapy [14,18]. Critically, CLDN18.2 status should be assessed at the time of initial diagnosis for all patients with advanced gastric/GEJ adenocarcinoma, alongside HER2 IHC/FISH and PD-L1 CPS, to enable optimal treatment selection. Following progression on zolbetuximab-based first-line therapy, no approved CLDN18.2-directed second-line options currently exist, though ADCs and CAR-T cell therapies are under active investigation in this setting [18].

4. CLDN18.2-Targeted Antibody-Drug Conjugates

4.1 Rationale and Design Principles

The clinical success of HER2-directed ADCs such as trastuzumab deruxtecan (T-DXd) in previously treated HER2-positive gastric cancer has provided a compelling template for CLDN18.2-targeted ADC development [19]. ADCs exploit tumor surface antigen expression to deliver cytotoxic payloads selectively to cancer cells, combining the targeting precision of monoclonal antibodies with the potency of small-molecule chemotherapy. For CLDN18.2-directed ADCs, the surface accessibility of ECL1 on tumor cells enables efficient antibody binding, receptor-mediated endocytosis, and intracellular payload release [7]. The bystander killing effect—whereby released payload diffuses to kill neighboring antigen-negative cells—may additionally address the challenge of intratumoral CLDN18.2 heterogeneity, a key limitation of naked antibody approaches [19].

4.2 IBI343 (Innovent Biologics)

IBI343 is the most clinically advanced CLDN18.2-targeted ADC, comprising an anti-CLDN18.2 antibody conjugated to an exatecan derivative (a topoisomerase I inhibitor, TOP1i) via a site-specific, cleavable glycol linker, with a drug-to-antibody ratio (DAR) of 4 [20]. In a phase 1 dose-escalation and expansion trial enrolling 127 patients with advanced gastric/GEJ and other solid tumors, IBI343 demonstrated a manageable safety profile with dose-limiting toxicities observed at higher dose levels, primarily hematologic and gastrointestinal in nature [20]. Objective responses were observed in patients with CLDN18.2-positive gastric/GEJ adenocarcinoma, including those previously treated with zolbetuximab. The TOP1i payload class confers potent bystander activity and a favorable therapeutic window in tumors with heterogeneous antigen expression [20].

4.3 LM-302 / Tecotabart Vedotin (LaNova Medicines)

LM-302 (tecotabart vedotin) is an anti-CLDN18.2 ADC utilizing monomethyl auristatin E (MMAE), a microtubule-disrupting agent, as its cytotoxic payload via a cleavable linker [21]. A Bayesian adaptive phase 1/2 trial has reported preliminary pharmacokinetic characterization, safety data, immunogenicity assessment, and early antitumor activity signals in patients with CLDN18.2-positive advanced gastric/GEJ and other solid tumors [21]. The MMAE payload class is associated with peripheral neuropathy and neutropenia, though the bystander effect may be advantageous in heterogeneous tumors.

4.4 SYSA1801 (CSPC Pharmaceutical Group)

SYSA1801 is a CLDN18.2-directed ADC developed by CSPC Pharmaceutical Group. Comparative preclinical and early clinical analyses have evaluated SYSA1801 alongside radionuclide-drug conjugate (RDC) formats targeting CLDN18.2, exploring the relative merits of different conjugation strategies for this target [22]. Detailed clinical efficacy data are awaited from ongoing phase 1 studies.

4.5 AZD0G01 (AstraZeneca) and CMGG01 (Keymed Biosciences/Sino Biopharmaceutical)

AZD0901 (AstraZeneca) and CMG901 (Keymed Biosciences/Sino Biopharmaceutical) represent additional CLDN18.2-targeted ADC programs in early-phase development. Specific linker-payload details and clinical efficacy or safety data for both agents have not yet been publicly reported at the time of this review.

4.6 ADC-Class Toxicity Considerations

CLDN18.2-directed ADCs share class-specific toxicity risks with other ADC platforms. TOP1i-based ADCs (e.g., IBI343) carry risks of interstitial lung disease (ILD), hematologic toxicity, and gastrointestinal

adverse events, as observed with T-DXd [19,20]. MMAE-based ADCs (e.g., LM-302) are associated with peripheral neuropathy, neutropenia, and ocular toxicity [21]. The on-target gastric mucosal toxicity observed with zolbetuximab may be amplified with ADC payloads, necessitating careful monitoring of gastrointestinal adverse events in clinical trials and the development of standardized toxicity management guidelines specific to CLDN18.2-directed agents.

5. Bispecific Antibodies Targeting CLDN18.2

5.1 Rationale for Bispecific Approaches

Bispecific antibodies (BsAbs) offer a mechanistically distinct approach to CLDN18.2 targeting by simultaneously engaging the tumor antigen and an immune effector mechanism, thereby redirecting cytotoxic T cells, natural killer cells, or innate immune effectors to tumor cells [7]. Unlike naked monoclonal antibodies that rely on endogenous Fc-mediated effector recruitment, BsAbs can engage T cells independent of MHC class I expression—an advantage in tumors that downregulate antigen presentation machinery [7].

5.2 CLDN18.2 × CD3 T-Cell Engagers

CLDN18.2 × CD3 bispecific antibodies redirect cytotoxic T cells to CLDN18.2-expressing tumor cells by simultaneously binding CLDN18.2 on the tumor and CD3 ϵ on the T-cell receptor complex. Multiple formats are in development, including bispecific T-cell engager (BiTE) molecules, dual-variable domain immunoglobulin (DVD-Ig) constructs, and IgG-like bispecifics with extended half-life [7]. Preclinical studies have demonstrated potent T-cell-mediated cytotoxicity against CLDN18.2-positive gastric cancer cell lines and patient-derived tumor models. Early-phase clinical trials are underway for several programs. The primary safety concern is cytokine release syndrome (CRS), managed with established algorithms (tocilizumab, corticosteroids) analogous to those developed for CD19-directed BiTE therapies [7].

5.3 CLDN18.2 × CD47 and Innate Immune Engagers

CLDN18.2 × CD47 bispecific antibodies aim to simultaneously block CD47-mediated anti-phagocytic signaling and direct macrophage-mediated antibody-dependent cellular phagocytosis (ADCP) to CLDN18.2-positive tumor cells [7]. This approach exploits innate immune effector mechanisms potentially active in tumors with low T-cell infiltration, complementing T-cell-engaging strategies. These programs remain primarily in preclinical development.

5.4 Co-stimulatory Bispecifics: CLDN18.2 × 4-1BB

CLDN18.2 × 4-1BB (CD137) bispecifics aim to provide tumor-localized T-cell co-stimulation by crosslinking 4-1BB on T cells with CLDN18.2-expressing tumor cells, enhancing T-cell activation, proliferation, and persistence without systemic immune toxicity [7]. Preclinical data in gastric cancer models demonstrate enhanced antitumor T-cell responses compared to monotherapy with either component. Clinical development is in early stages.

5.5 Comparative Positioning

BsAbs offer potential advantages over zolbetuximab and ADCs including independence from Fc-mediated effector function, potential activity in Fc γ R-polymorphism-related resistance, and the ability to engage T cells directly. However, CRS risk, manufacturing complexity, and limited clinical data relative to

zolbetuximab mean that BsAbs currently occupy an investigational niche, most likely to emerge in the post-zolbetuximab setting or in combination strategies with checkpoint inhibitors.

6. CAR-T Cell Therapy Targeting CLDN18.2

6.1 Rationale and Challenges in Solid Tumors

Chimeric antigen receptor (CAR) T-cell therapy has transformed the treatment of hematologic malignancies but faces formidable barriers in solid tumors, including poor T-cell trafficking to the tumor microenvironment (TME), immunosuppression by regulatory T cells and myeloid-derived suppressor cells, and antigen heterogeneity [7,23]. CLDN18.2 represents a particularly attractive solid tumor CAR-T target given its high and relatively uniform expression in a substantial proportion of gastric/GEJ tumors, surface accessibility in malignant cells, and limited normal-tissue expression [23].

6.2 CT041 (Satricabtagene Autoleucel): Clinical Evidence

CT041 (satricabtagene autoleucel; satri-cel), developed by CARsgen Therapeutics, is the most clinically advanced CLDN18.2-directed CAR-T product, utilizing an autologous T-cell product engineered with an anti-CLDN18.2 single-chain variable fragment (scFv), 4-1BB co-stimulatory domain, and CD3 ζ signaling domain [23]. The pivotal CT041-ST-01 trial (NCT04404595) was a randomized, open-label phase 2 study comparing CT041 to treatment of physician's choice (TPC) in patients with previously treated advanced gastric/GEJ adenocarcinoma [23]. The trial demonstrated clinically meaningful improvements in objective response rate (ORR) and disease control rate (DCR) with CT041 versus TPC, with a manageable safety profile. CRS was the most common immune-related adverse event, predominantly grade 1–2. On-target, off-tumor gastric mucosal toxicity—including erosive gastritis and mucosal injury—was observed as a class effect of CLDN18.2-directed cellular therapies, reflecting expression of CLDN18.2 in normal gastric mucosa [23,24]. Immune effector cell-associated neurotoxicity syndrome (ICANS) was uncommon.

6.3 On-Target Off-Tumor Toxicity: Modeling and Mitigation

Computational and experimental modeling of on-target/off-tumor toxicity for CLDN18.2-directed immunotherapies has demonstrated that affinity modulation of the anti-CLDN18.2 binding domain can reduce gastric mucosal injury while preserving antitumor efficacy [24]. Reducing the binding affinity of the CAR or BsAb scFv such that it preferentially engages high-density tumor CLDN18.2 while sparing lower-density normal gastric mucosa represents a promising engineering strategy for next-generation CLDN18.2 cellular therapies [24].

6.4 Other CAR-T Programs and Next-Generation Approaches

Multiple additional CLDN18.2 CAR-T programs are in preclinical or early clinical development, employing CD28 co-stimulation, tandem CAR constructs co-targeting CLDN18.2 and a second antigen (e.g., PD-L1, EGFR) to address antigen escape, and armored CAR-T constructs secreting cytokines (e.g., IL-15, IL-21) to enhance persistence in the immunosuppressive TME. Allogeneic (off-the-shelf) CLDN18.2 CAR-T approaches are also under investigation to address the manufacturing constraints of autologous products [7,23].

6.5 Manufacturing and Logistical Considerations

Clinical implementation of autologous CAR-T therapy in gastric cancer is constrained by leukapheresis requirements, a 4–6 week manufacturing timeline, and the need for bridging therapy in patients with rapidly progressive disease. Antigen escape—CLDN18.2 downregulation or loss following CAR-T

infusion—has been documented in post-treatment biopsies and represents a mechanism of acquired resistance [23,25]. Combinatorial strategies pairing CAR-T with immune checkpoint inhibitors or local radiotherapy are under active investigation.

7. Biomarkers and Patient Selection

7.1 IHC-Based CLDN18.2 Assessment

The VENTANA CLDN18 (43-14A) RxDx Assay is the FDA-approved companion diagnostic for zolbetuximab, validated in SPOTLIGHT and GLOW tumor specimens [17]. The assay uses the 43-14A monoclonal antibody clone and defines CLDN18.2 positivity as $\geq 75\%$ of viable tumor cells demonstrating moderate-to-strong membranous staining (2+/3+), with analytical validation studies demonstrating high sensitivity and specificity and acceptable interobserver reproducibility among trained pathologists [17].

However, CLDN18.2 IHC assessment is complicated by intratumoral spatial heterogeneity and temporal heterogeneity, reflecting changes in expression between the primary tumor and metastatic sites, or before and after treatment [18,25]. Studies have documented secondary loss of CLDN18.2 expression in post-treatment biopsies from patients treated with zolbetuximab, suggesting that antigen downregulation may be a mechanism of acquired resistance [25]. Concordance between endoscopic biopsy specimens and surgical resection specimens has been variably reported, with meaningful discordance rates potentially affecting treatment eligibility [10,18].

7.2 Divergent Thresholds Across Trials

A critical challenge is the lack of harmonization in CLDN18.2 IHC scoring criteria across clinical trials. The FAST trial used a 40% positivity threshold (2+/3+ in $\geq 40\%$ of cells) [13], while SPOTLIGHT and GLOW adopted the more stringent $\geq 75\%$ threshold [14,15]. ADC trials, including IBI343 and LM-302, have employed varying thresholds as low as 1+ in $\geq 10\%$ of cells, reflecting potential activity of ADCs in lower-expressing tumors due to bystander effect [20,21]. CAR-T trials have similarly used heterogeneous criteria [23]. This divergence complicates cross-trial comparisons and creates uncertainty for clinicians regarding which patients benefit most from each modality (see Table 3).

7.3 Emerging Biomarker Strategies

Beyond IHC, liquid biopsy strategies using circulating tumor DNA (ctDNA) or circulating tumor cells (CTCs) may enable non-invasive, real-time monitoring of CLDN18.2 expression dynamics and resistance evolution, though validated assays for clinical use are not yet available [7]. RNA-based expression profiling has demonstrated discordance between mRNA and protein levels in some studies, suggesting that mRNA alone may not reliably predict IHC-based protein expression [7,10]. Co-expression profiling of CLDN18.2 with HER2, PD-L1, and FGFR2b is relevant for treatment sequencing and combination strategies [18,26].

7.4 Practical Clinical Framework

Based on current evidence, we propose the following framework: **all patients with newly diagnosed locally advanced unresectable or metastatic gastric/GEJ adenocarcinoma should undergo reflexive testing for HER2 (IHC/FISH), PD-L1 (CPS), and CLDN18.2 (IHC) simultaneously at the time of initial biopsy or resection.** This approach avoids sequential testing delays and enables comprehensive first-line treatment planning. For patients with CLDN18.2-low tumors (1+/2+ in $< 75\%$ of cells), enrollment in ADC or BsAb trials targeting lower expression thresholds should be considered [20,21].

Repeat biopsy at disease progression is recommended to characterize acquired resistance mechanisms, including CLDN18.2 expression changes, to guide subsequent therapeutic decisions [25].

Table 3. Comparison of CLDN18.2 immunohistochemistry scoring criteria across clinical trials.

Agent / Trial	Assay Platform	Antibody Clone	Positivity Definition	Threshold for Enrollment	Concordance Data (if available)
Zolbetuximab / FAST	Research-grade IHC (IMAB362 binding assay)	43-14A (research)	2+ or 3+ membranous staining	≥40% of tumor cells 2+/3+ (primary analysis); ≥70% 2+/3+ (high-expression subgroup)	Not formally reported; biopsy specimens used
Zolbetuximab / SPOTLIGHT	VENTANA CLDN18 (43-14A) RxDx Assay (Roche Diagnostics; FDA-approved)	43-14A	Moderate-to-strong (2+ or 3+) membranous staining	≥75% of viable tumor cells 2+/3+	Analytical validation: high sensitivity/specificity; interobserver concordance acceptable among trained pathologists; biopsy–resection concordance variable [10,18]
Zolbetuximab / GLOW	VENTANA CLDN18 (43-14A) RxDx Assay (Roche Diagnostics; FDA-approved)	43-14A	Moderate-to-strong (2+ or 3+) membranous staining	≥75% of viable tumor cells 2+/3+	Same as SPOTLIGHT; temporal heterogeneity documented in post-treatment biopsies [18,25]
IBI343 (ADC) / Phase 1	Local IHC (research-grade)	43-14A or equivalent	Any membranous staining (1+, 2+, or 3+)	≥10% of tumor cells 1+ (low threshold to capture broad expression range)	Not formally reported in Phase 1 publication [20]
LM-302 / tecotabart vedotin (ADC) / Phase 1/2	Local IHC	Anti-CLDN18.2 clone (not specified)	1+, 2+, or 3+ membranous staining	≥10% of tumor cells with any positive staining (1+/2+/3+)	Not formally reported [21]
CT041 (CAR-T) / CT041-ST-01	VENTANA CLDN18 (43-14A) or local IHC	43-14A	Moderate-to-strong (2+ or 3+) membranous staining	≥1+ in ≥1% of tumor cells (broad inclusion) or ≥2+ in ≥10% (varies by cohort)	Spatial and temporal heterogeneity with secondary antigen loss documented post-infusion [23,25]
SYSA1801 (ADC) / Phase 1	Local IHC	Anti-CLDN18.2 clone (not specified)	2+ or 3+ membranous staining	≥1% of tumor cells 2+/3+	Not reported [22]

Table 3 Footnotes: ADC, antibody–drug conjugate; CAR-T, chimeric antigen receptor T cell; CLDN18.2, claudin 18.2; IHC, immunohistochemistry; RxDx, regulatory diagnostic. **Clinical implication of divergent thresholds:** The use of heterogeneous IHC scoring criteria across CLDN18.2-directed clinical trials—ranging from ≥1% 1+ staining (ADC/CAR-T trials) to ≥75% 2+/3+ staining (zolbetuximab trials)—creates significant challenges for cross-trial comparisons, patient selection in clinical practice, and regulatory harmonization. Lower thresholds in ADC and CAR-T trials reflect the potential activity of these modalities in lower-expressing tumors through bystander killing and direct cellular cytotoxicity, respectively. Harmonization of CLDN18.2 IHC scoring criteria across trials is urgently needed and represents a priority for international consensus guidelines. Data from references [10,13–15,18,20–23,25].

8. Resistance Mechanisms and Strategies to Overcome Them

8.1 Primary Resistance

Primary resistance to CLDN18.2-targeted therapies is most commonly attributable to low or absent CLDN18.2 expression, affecting approximately 20–40% of gastric/GEJ tumors depending on the

positivity threshold applied [10,13]. Intratumoral spatial heterogeneity—where CLDN18.2-negative subclones coexist with positive subclones within the same tumor—may lead to incomplete tumor coverage even in nominally CLDN18.2-positive tumors, particularly with naked antibody approaches that lack bystander killing [18,25]. Primary resistance may also arise from tumor-intrinsic defects in ADCC effector cell recruitment or complement activation.

8.2 Acquired Resistance

Acquired resistance to zolbetuximab has been documented clinically and mechanistically. CLDN18.2 downregulation—through transcriptional silencing, epigenetic modification, or selection of pre-existing antigen-negative subclones—has been identified in post-progression biopsies from patients treated with zolbetuximab [25]. Splice-variant switching between CLDN18.2 and CLDN18.1 has been proposed as a resistance mechanism, though clinical evidence remains limited. Fc-mediated resistance, arising from FcγRIIIa (CD16) polymorphisms that reduce ADCC efficacy, may contribute to variable clinical outcomes with zolbetuximab [7]. Tumor microenvironment-mediated immune evasion—including PD-L1 upregulation, regulatory T-cell recruitment, and secretion of immunosuppressive cytokines—may attenuate CAR-T cell and BsAb efficacy [7,23]. Epithelial-to-mesenchymal transition (EMT) has been associated with CLDN18.2 downregulation in gastric cancer models, as EMT-associated transcriptional reprogramming reduces expression of epithelial tight-junction components [7].

8.3 Strategies to Overcome Resistance

Rational strategies under investigation to overcome primary and acquired resistance include: (1) combination with immune checkpoint inhibitors (anti-PD-1/PD-L1 or anti-CTLA-4) to relieve TME immunosuppression and enhance T-cell-mediated killing [18]; (2) ADC approaches with potent bystander killing payloads to overcome spatial heterogeneity [20,21]; (3) epigenetic modulation using DNA methyltransferase or histone deacetylase inhibitors to restore CLDN18.2 expression in silenced tumors, showing preclinical promise [7]; (4) dual-target CAR-T constructs co-targeting CLDN18.2 and a second antigen (e.g., PD-L1, EGFR, HER2) to prevent antigen escape [7,23]; and (5) affinity-tuned CAR-T and BsAb constructs designed to preferentially engage high-density tumor CLDN18.2 while sparing normal gastric mucosa [24].

G. Future Directions and Clinical Implications

G.1 Integration into Multimodal Treatment Algorithms

The approval of zolbetuximab establishes CLDN18.2 as the third major actionable biomarker in advanced gastric/GEJ adenocarcinoma. We propose a sequential testing and treatment decision framework (illustrated in Figure 3) integrating HER2, PD-L1/CPS, and CLDN18.2 at the time of initial diagnosis, consistent with the direction of current ESMO and NCCN guidance [27,28]. In this framework, HER2-positive patients receive trastuzumab-based regimens; HER2-negative patients with CPS ≥ 5 receive chemotherapy plus nivolumab or pembrolizumab; and among HER2-negative patients, those with CLDN18.2 positivity ($\geq 75\%$ 2+/3+) receive zolbetuximab plus chemotherapy. CLDN18.2-low patients without other actionable targets represent an unmet need for which ADC and BsAb trials should be prioritized. Dedicated investigation of triple combination strategies (zolbetuximab + anti-PD-1 + chemotherapy) is warranted in the substantial subgroup with CLDN18.2 positivity and CPS ≥ 5 [18].

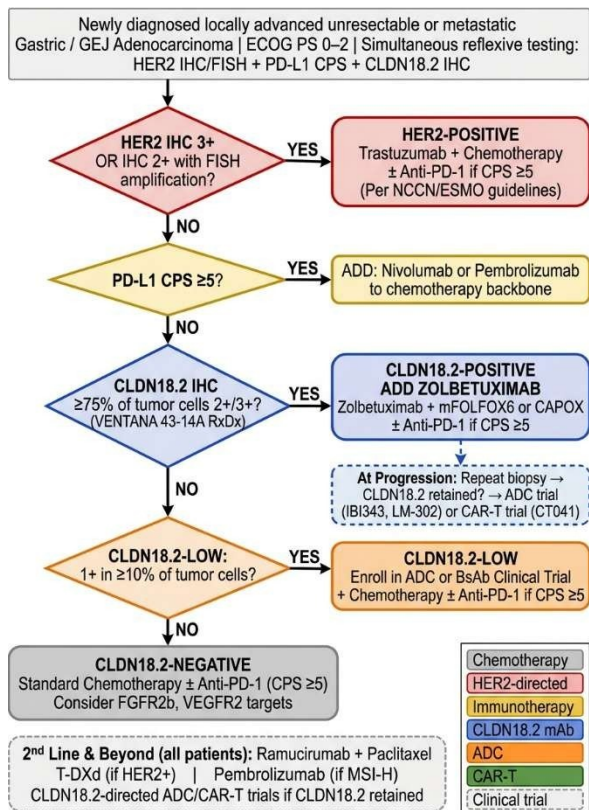


Figure 3. Proposed biomarker-guided treatment algorithm for newly diagnosed advanced/metastatic gastric and gastroesophageal junction adenocarcinoma. Clinical decision flowchart integrating HER2, PD-L1 combined positive score (CPS), and CLDN18.2 immunohistochemistry (IHC) for first-line treatment selection. Starting point (top): Newly diagnosed locally advanced unresectable or metastatic gastric/GEJ adenocarcinoma, performance status ECOG 0–2. Step 1 (HER2 testing): HER2 IHC 3+ or IHC 2+/FISH-amplified → trastuzumab-based first-line therapy (with or without anti-PD-1 based on CPS); HER2-negative → proceed to Step 2. Step 2 (PD-L1 CPS assessment): CPS ≥5 → add nivolumab or pembrolizumab to chemotherapy backbone; CPS <5 → chemotherapy backbone only; proceed to Step 3 in all HER2-negative patients. Step 3 (CLDN18.2 IHC): ≥75% of tumor cells 2+/3+ → add zolbetuximab to chemotherapy (± anti-PD-1 if CPS ≥5); CLDN18.2-low (<75% 2+/3+ but ≥10% 1+) → consider enrollment in ADC or BsAb clinical trials; CLDN18.2-negative → standard chemotherapy ± anti-PD-1 based on CPS. Second-line and beyond: For patients progressing on zolbetuximab-based therapy, consider CLDN18.2-directed ADC trials (e.g., IBI343, LM-302) or CAR-T trials (e.g., CT041) if CLDN18.2 expression is retained on repeat biopsy. Colour coding by treatment modality: chemotherapy = grey; trastuzumab/HER2-directed = red; anti-PD-1/immunotherapy = yellow; zolbetuximab/CLDN18.2 mAb = blue; ADC = orange; CAR-T = green; clinical trial = hatched border.

G.2 Expansion Beyond Gastric Cancer

The expression of CLDN18.2 in pancreatic ductal adenocarcinoma, biliary tract cancers, and other solid tumors creates opportunities for tumor-agnostic CLDN18.2-targeted strategies. Early-phase trials of IBI343, CT041, and other agents have enrolled patients with pancreatic and biliary cancers, with preliminary efficacy signals reported [20,23]. The development of CLDN18.2-directed therapies in these indications may substantially extend the clinical impact of this target class.

G.3 Earlier Disease Settings

The potential role of zolbetuximab and ADCs in the neoadjuvant and adjuvant settings for resectable gastric/GEJ cancer is under investigation. Neoadjuvant CLDN18.2 targeting could reduce tumor burden and potentially increase pathological complete response rates, while adjuvant therapy could eliminate minimal residual disease. Clinical trials exploring these settings are in early stages, and mature data are awaited.

G.4 Combinatorial Strategies and Platform Trials

The convergence of multiple CLDN18.2-directed modalities creates opportunities for rational combination and sequencing strategies. Zolbetuximab combined with anti-PD-1/PD-L1 agents aims to synergize ADCC/CDC with T-cell checkpoint reinvigoration. ADC plus ICI combinations leverage payload-induced immunogenic cell death to enhance tumor antigen presentation and T-cell priming. The need for head-to-head or adaptive platform trials comparing CLDN18.2 modalities—rather than sequential single-agent development—is increasingly recognized as essential for rational therapeutic sequencing.

G.5 Pharmacoeconomics and Global Access

The cost of CLDN18.2-targeted therapies, particularly CAR-T cell therapy, poses significant access challenges in low- and middle-income countries where gastric cancer incidence is highest. Implementation barriers including companion diagnostic availability, pathology infrastructure, and reimbursement frameworks must be addressed to ensure equitable access [27]. The establishment of an international CLDN18.2 registry to prospectively track biomarker dynamics, treatment outcomes, and resistance evolution in real-world populations would substantially accelerate the field.

10. Conclusions

The emergence of CLDN18.2 as a validated therapeutic target in gastric and GEJ adenocarcinoma represents one of the most significant advances in gastrointestinal oncology in recent years. Zolbetuximab, the first approved CLDN18.2-directed therapy, has demonstrated consistent and clinically meaningful improvements in PFS and OS when added to first-line chemotherapy in CLDN18.2-positive, HER2-negative advanced disease, establishing a new standard of care for a substantial proportion of patients. Beyond zolbetuximab, a diverse and rapidly expanding pipeline of ADCs, bispecific antibodies, and CAR-T cell therapies is advancing through clinical development, each offering mechanistically distinct approaches to CLDN18.2 targeting that may address the limitations of the approved agent—including antigen heterogeneity, Fc-mediated resistance, and the immunosuppressive tumor microenvironment.

The critical enabling technology for this therapeutic landscape is biomarker-guided patient selection. The VENTANA CLDN18 (43-14A) RxDx Assay provides a validated companion diagnostic for zolbetuximab, but the lack of harmonization in CLDN18.2 scoring criteria across the broader pipeline, combined with the challenges of intratumoral heterogeneity and temporal expression changes, demands urgent attention. Universal reflexive testing of CLDN18.2 alongside HER2 and PD-L1 at the time of initial diagnosis is now warranted for all patients with advanced gastric/GEJ adenocarcinoma.

Looking forward, the integration of CLDN18.2-directed therapies into multimodal treatment algorithms—combining with immune checkpoint inhibitors, sequencing across modalities, and expanding into earlier disease settings and other CLDN18.2-expressing tumor types—holds transformative potential. CLDN18.2 is emerging not only as a paradigm-shifting target in gastric cancer but as a founding member of a broader class of claudin-directed oncology therapeutics that may redefine the treatment of epithelial malignancies in the coming decade.

Declarations

Conflict of Interest: The authors declare no conflicts of interest.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical Approval: Not applicable.

Author Contributions:

- **Lama K Wabb** — Conceptualization; Supervision; Methodology; Formal analysis; Interpretation of results; Manuscript drafting; Critical revision; Project administration.
- **Gehad Elsheikh** — Literature search; Data extraction; Drafting selected sections; Manuscript editing.
- **Mahmoud Sweid** — Methodology; Data curation; Visualization; Manuscript review.
- **Eman Gamal** — Literature search; Data extraction; Quality assessment; Manuscript revision.

- **Heba Shaheen** — Conceptualization; Literature review; Drafting of manuscript; Critical revision.

Use of Artificial Intelligence: This article did not employ generative AI for content generation. Tables were visually formatted with AI-assisted tools; all written content remains fully human-authored. Grammar and language were reviewed using dedicated editing software. All references have been individually verified against primary source records (PubMed, CrossRef, and publisher websites) by the authors, and each cited DOI has been confirmed to resolve to the corresponding publication.

References

- [1] Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2024;74(3):229–263. <https://doi.org/10.3322/caac.21834>
- [2] Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *Lancet.* 2021;398(10294):27–40. [https://doi.org/10.1016/S0140-6736\(21\)00797-2](https://doi.org/10.1016/S0140-6736(21)00797-2)
- [3] Shitara K, Van Cutsem E, Bang YJ, et al. Efficacy and safety of pembrolizumab or pembrolizumab plus chemotherapy vs chemotherapy alone for patients with first-line, advanced gastric cancer (KEYNOTE-062): a phase 3 randomized clinical trial. *JAMA Oncol.* 2020;6(10):1571–1580. <https://doi.org/10.1001/jamaoncol.2020.3370>
- [4] Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet.* 2010;376(9742):687–697. [https://doi.org/10.1016/S0140-6736\(10\)61121-X](https://doi.org/10.1016/S0140-6736(10)61121-X)
- [5] Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature.* 2014;513(7517):202–209. <https://doi.org/10.1038/nature13480>
- [6] Lee YT, Lin SH, Yeh KT, et al. Prevalence of molecular subtypes of gastric cancer in Taiwan and the impact of high SLC25A22 expression on survival: a single-center experience. *Mol Carcinog.* 2026;65(6):770–776. <https://doi.org/10.1002/mc.70111>
- [7] Saviano A, Toso A, Klempner SJ, Baumert TF. Claudin proteins as emerging therapeutic targets for solid tumours. *Nat Rev Cancer.* 2026;26(5):178–197. <https://doi.org/10.1038/s41568-026-00913-3>
- [8] Sahin U, Koslowski M, Dhaene K, et al. Claudin-18 splice variant 2 is a pan-cancer target suitable for therapeutic antibody development. *Clin Cancer Res.* 2008;14(23):7624–7634. <https://doi.org/10.1158/1078-0432.CCR-08-1547>
- [9] Türeci Ö, Sahin U, Schulze-Bergkamen H, et al. A multicentre, phase IIa study of zolbetuximab as a single agent in patients with recurrent or refractory advanced adenocarcinoma of the stomach or lower oesophagus: the MONO study. *Ann Oncol.* 2019;30(9):1487–1495. <https://doi.org/10.1093/annonc/mdz199>

- [10] Fassan M, Chau I, Dasghaib H, Hill J, Pophale R, Shitara K. The prognostic role of Claudin 18.2 in advanced gastric or gastroesophageal junction adenocarcinoma: a systematic literature review. *ESMO Gastrointest Oncol.* 2025;9:100210. <https://doi.org/10.1016/j.esmogo.2025.100210>
- [11] Zheng B, Fu M, Lou F, et al. Claudin18.2 promote gastric cancer proliferation by activating MCM2/5. *Sci Rep.* 2026;16:10263. <https://doi.org/10.1038/s41598-026-39540-1>
- [12] Gorwitz GL, DeRemer DL. Zolbetuximab-clzb: targeting Claudin 18.2 in advanced gastric and gastroesophageal adenocarcinoma. *Ann Pharmacother.* 2025;59(7):700–712. <https://doi.org/10.1177/10600280251342801>
- [13] Sahin U, Türeci Ö, Manikhas G, et al. FAST: a randomised phase II study of zolbetuximab (IMAB362) plus EOX versus EOX alone for first-line treatment of advanced CLDN18.2-positive gastric and gastro-oesophageal adenocarcinoma. *Ann Oncol.* 2021;32(5):609–619. <https://doi.org/10.1016/j.annonc.2021.02.005>
- [14] Shitara K, Lordick F, Bang YJ, et al. Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicentre, randomised, double-blind, phase 3 trial. *Lancet.* 2023;401(10389):1655–1668. [https://doi.org/10.1016/S0140-6736\(23\)00620-7](https://doi.org/10.1016/S0140-6736(23)00620-7)
- [15] Shah MA, Shitara K, Ajani JA, et al. Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial. *Nat Med.* 2023;29(8):2133–2141. <https://doi.org/10.1038/s41591-023-02465-7>
- [16] Lee KW, Oh SC, Kim JG, Sym SJ, Shim BY, Kang SY, Kim IH, Kim JH, Chon HJ, Cho SH, Song EK, Oh DY, Kim JS, Park YI, Kang WK, Kim HD, Lee J, Yi M, Ryu MH. Zolbetuximab plus chemotherapy as first-line treatment in patients with Claudin 18.2-positive, HER2-negative, locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma: Korean population subgroup — combined efficacy and safety analysis from SPOTLIGHT and GLOW. *Cancer Res Treat.* Published online December 5, 2025. <https://doi.org/10.4143/crt.2025.935>
- [17] Stratton SP, Pang L, Pugh J, Kouzova M, Baldwin D, et al. Analytical and clinical performance of the VENTANA CLDN18 (43-14A) RxDx Assay in gastric and gastroesophageal junction adenocarcinoma tissue samples in SPOTLIGHT and GLOW. *Mod Pathol.* 2025;38(7):100844. <https://doi.org/10.1016/j.modpat.2025.100844>
- [18] Shreenivas A, Wright G, Vissers E, Ajani JA. Barriers to clinical implementation for novel therapies and biomarker testing in the community practice oncology setting: a CLDN18.2 case study. *Cancer Treat Res Commun.* 2026;47:101192. <https://doi.org/10.1016/j.ctarc.2026.101192>
- [19] Shitara K, Bang YJ, Iwasa S, et al. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. *N Engl J Med.* 2020;382(25):2419–2430. <https://doi.org/10.1056/NEJMoa2004413>

- [20] Liu J, Yang J, Sun Y, et al. CLDN18.2-targeting antibody-drug conjugate IBI343 in advanced gastric or gastroesophageal junction adenocarcinoma: a phase 1 trial. *Nat Med.* 2025;31(9):3028–3036. <https://doi.org/10.1038/s41591-025-03783-8>
- [21] Bai C, Zheng Y, Sun M, et al. Tecotabart vedotin in Claudin 18.2-positive advanced gastric/gastroesophageal junction cancer: a Bayesian phase 1/2 clinical trial. *Eur J Cancer.* 2025;230:115808. <https://doi.org/10.1016/j.ejca.2025.115808>
- [22] Du H, Hao XF, Lin BW, et al. Comparative analysis of the efficacy and safety of antibody-drug conjugates, radionuclide-drug conjugates and their combination targeting claudin 18.2 in gastric cancer treatment. *Oncol Rep.* 2025;55(1):9009. <https://doi.org/10.3892/or.2025.9009>
- [23] Qi C, Liu C, Peng Z, et al. Claudin-18 isoform 2-specific CAR T-cell therapy (satri-cel) versus treatment of physician's choice for previously treated advanced gastric or gastro-oesophageal junction cancer (CT041-ST-01): a randomised, open-label, phase 2 trial. *Lancet.* 2025;405(10494):2049–2060. [https://doi.org/10.1016/S0140-6736\(25\)00860-8](https://doi.org/10.1016/S0140-6736(25)00860-8)
- [24] Carstens EJ, Takahashi K, Sakamoto N, et al. Modeling and addressing on-target/off-tumor toxicity of claudin 18.2 targeted immunotherapies. *Nat Commun.* 2025;16(1):9651. <https://doi.org/10.1038/s41467-025-65148-6>
- [25] Morath O, Lindig U, Katenkamp K, et al. Diagnostic and therapeutic challenges in claudin 18.2-positive gastric cancer treated with zolbetuximab: inpatient heterogeneity or secondary loss of expression? *J Cancer Res Clin Oncol.* 2026;152(3):70. <https://doi.org/10.1007/s00432-026-06447-3>
- [26] Kwak Y, Kim TY, Lee HS, Nam SK, Oh HJ, Oh DY, Im SA. Comprehensive analysis of FGFR2b and its correlation with essential biomarkers, intratumoral heterogeneity, and survival in advanced gastric cancer. *Br J Cancer.* 2026;134(10):1429–1439. <https://doi.org/10.1038/s41416-026-03405-1>
- [27] Lordick F, Carneiro F, Cascinu S, et al. Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol.* 2022;33(10):1005–1020. <https://doi.org/10.1016/j.annonc.2022.07.004>
- [28] Ajani JA, D'Amico TA, Bentrem DJ, et al. Gastric Cancer, Version 2.2025, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw.* 2025;23(5):169–191. <https://doi.org/10.6004/jnccn.2025.0022>. Current online version: NCCN Clinical Practice Guidelines in Oncology: Gastric Cancer, Version 2.2026. Available at: <https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1434>.
- [29] Zhang F, Okazaki U, Nakayama I, Shitara K. CLDN18.2 in gastric cancer: current therapeutic landscape and future perspectives. *J Gastric Cancer.* 2026;26(1):127–145. <https://doi.org/10.5230/jgc.2026.26.e10>