J Gastric Cancer. 2026 Jan;26(1):127-145
https://doi.org/10.5230/jgc.2026.26.e10
pISSN 2093-582X·eISSN 2093-5641

Journal of Gastric Cancer

Review Article

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CLDN18.2 in Gastric Cancer: Current Therapeutic Landscape and Future Perspectives

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OPEN ACCESS

Received: Dec 9, 2025
Revised: Dec 18, 2025
Accepted: Dec 18, 2025
Published online: Dec 31, 2025

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

ABSTRACT

Claudin 18.2 (CLDN18.2), a tight junction protein selectively expressed in normal gastric epithelium and widely retained during carcinogenesis, has emerged as a promising therapeutic target for advanced gastric cancer (AGC). SPOTLIGHT and GLOW trials evaluated the anti-CLDN18.2 monoclonal antibody (mAb) zolbetuximab in combination with first-line chemotherapy, and established CLDN18.2 as a therapeutic target, initiating a paradigm shift toward a biomarker-driven treatment approach in AGC. In addition, from zolbetuximab to a diverse pipeline of promising high-affinity mAbs, bispecific antibodies, antibody-drug conjugates and chimeric antigen receptor T cells, this target has established a new and highly effective therapeutic avenue for CLDN18.2-expressing AGC. Therefore, as research progresses, CLDN18.2-targeted therapy is poised to become a cornerstone of treatment across multiple disease stages and cancer types. This review describes the biological role of CLDN18.2 in normal gastric epithelium and gastric carcinogenesis and summarizes the current therapeutic landscape and future perspectives targeting CLDN18.2 in AGC.

Keywords: Claudins; Gastric cancer; Targeted therapy; Biomarker

INTRODUCTION

Gastric cancer (GC) is the fifth leading causes of cancer-related death worldwide [1,2]. For years, treatment for advanced GC (AGC) relied heavily on systemic chemotherapy, typically a fluoropyrimidine plus a platinum agent, with human epidermal growth factor receptor 2 (HER2)-targeted therapy (trastuzumab) being the major biomarker-driven option for a relatively small subset (~20%) of patients [1]. Based on the success of CheckMate-649, KEYNOTE-859 and RATIONALE-305, immune checkpoint inhibitor (ICI) combined with chemotherapy has been established as standard of care for treating patients with microsatellite instability-high, or HER2-negative and programmed cell death ligand 1 (PD-L1) combined positive score (CPS) ≥1 tumors [3-5]. Subsequently, ICI with chemotherapy plus trastuzumab was approved for HER2-positive and PD-L1 CPS ≥1 AGC [6,7]. Although recent advances

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Author Contributions
Conceptualization: Z.F., N.I., S.K.; Investigation: Z.F., O.U., N.I.; Supervision: N.I., S.K.; Visualization: Z.F., O.U.; Writing - Z.F., O.U., N.I.; Writing - review & editing: N.I, S.K.

have improved treatment options, the prognosis still remains poor, with a median overall survival (OS) ≤20 months [1]. Therefore, identifying novel and promising targets suitable for molecularly targeted therapies is essential to further improve treatment outcomes.

The establishment of claudin 18.2 (CLDN18.2) as a novel and optimal target has revolutionized the treatment landscape. CLDN18.2, a tight-junction protein predominantly expressed in normal stomach epithelial mucosa, is widely retained during tumorigenesis [8]. During malignant transformation, it becomes accessible on the tumor surface through cellular disruption, making it an attractive target for therapies such as monoclonal antibodies (mAbs) [8,9]. Two global randomized phase III (SPOTLIGHT and GLOW) trials have demonstrated improved clinical outcomes and manageable safety profiles of zolbetuximab plus chemotherapy as first-line therapy in HER2-negative and CLDN18.2-positive AGC [10-12]. Furthermore, various novel anti-CLDN18.2 mAbs, bispecific antibodies (BsAbs), antibody-drug conjugates (ADCs), and chimeric antigen receptor T (CAR-T) cells have also demonstrated promising anti-tumor activity in early phase clinical trials [13-16].

In this review, we describe the biological role of CLDN18.2 in normal gastric epithelium and gastric carcinogenesis, and also summarize the current therapeutic landscape and future perspectives considering the targeting of CLDN18.2 in treating AGC.

BIOLOGICAL ROLE OF CLDN18.2 IN NORMAL GASTRIC EPITHELIUM

Human CLDN18 is located on chromosome 3q22, with a total length of approximately 35 kb consisting of 6 exons and 5 introns [17,18]. CLDN18 has 2 alternative splicing variants: CLDN18.1 and 18.2 [19]. Under physiological conditions, CLDN18.2 is tightly buried within the paracellular space between gastric epithelial cells and is not readily exposed on the cell surface (**Fig. 1**) [17,19].

CLDN18.2 has a structure with 4 transmembrane domains that anchor it to the cell membrane. Both its amino- and carboxyl-termini are located in the cytoplasm, whereas the 4 transmembrane helical regions form 2 extracellular loops that play crucial roles in maintaining the stability and selective barriers of intercellular tight junctions [17-19]. Tight sealing between gastric epithelial cells serves as a protective barrier that is essential for maintaining the health and integrity of the stomach wall [20]. CLDN18.2 plays a key gatekeeping role in regulating the highly selective permeability between the apical and basal sides of epithelial cells. Given the highly acidic environment of the gastric lumen, gastric lineage-specific claudins are indispensable for sustaining epithelial barrier function [21].

BIOLOGICAL ROLE OF CLDN18.2 IN GASTRIC CARCINOGENESIS

Considering its physiological role, CLDN18.2 does not directly participate in the signal transduction pathways that drive cell proliferation or survival. Therefore, unlike epidermal growth factor receptor, HER2, and KRAS proto-oncogene, it is not considered a conventional oncogenic driver [22]. Few studies suggest that CLDN18.2 may engage in protumorigenic signaling, including the mitogen-activated protein kinase/extracellular signal-regulated

https://doi.org/10.5230/jgc.2026.26.e10

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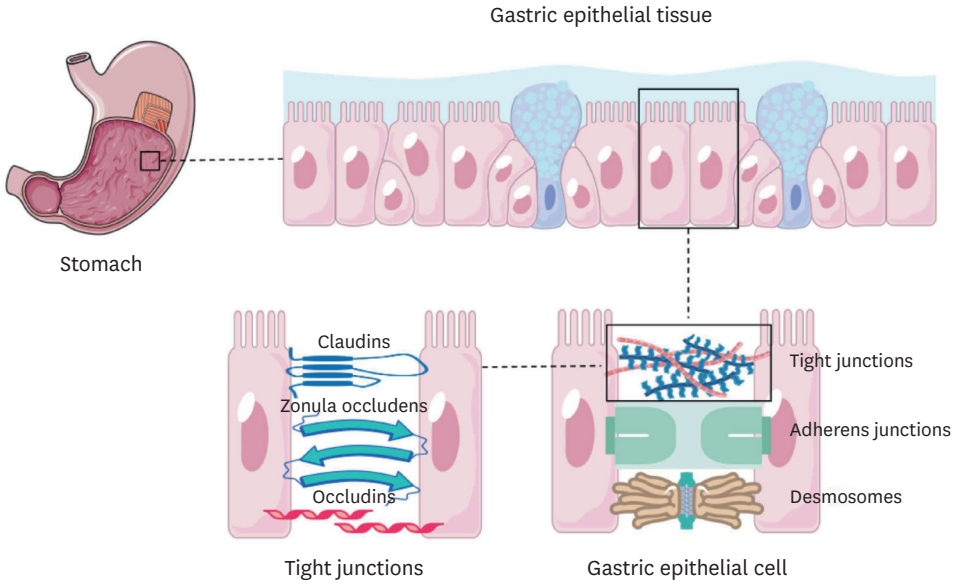

Fig. 1. Expression patterns of CLDN18.2. CLDN18.2 is highly selectively expressed in the nonmalignant gastric epithelial tissue and tightly buried within the tight junctions and is not readily exposed on the cell surface, which helps maintain the health and integrity of the stomach wall.
CLDN18.2 = claudin 18.2.

kinase and phosphoinositide 3-kinase/protein kinase B pathways, but the strength and consistency of these effects remain unclear [22,23]. Loss of CLDN18.2 disrupts the tight junction structure and immediately induces severe gastritis in mouse models; however, carcinogenesis additionally requires aberrant activation of oncogenic pathways such as Wnt/β-catenin signaling [21]. Similar to other cell adhesion molecules (such as cadherins), downregulation of CLDN18.2 may contribute to increased cellular motility and invasive potential [24-27]. However, additional genetic events are required to overcome anoikis and enable malignant progression. Conversely, the mechanisms underlying tumorigenesis in CLDN18.2-maintaining or overexpressing cancers remain poorly understood [24,28,29].

Recurrent CLDN18–ARHGAP26/6 fusions, particularly those enriched in diffuse-type GC, disrupt the C-terminal intracellular domain of CLDN18.2, likely impairing tight junction assembly and enhancing cell migration [25,30-34].

Taken together, CLDN18.2 dysregulation appears relevant to the multistep process of gastric carcinogenesis, but is unlikely to function as a primary oncogenic driver [22,24,25]. Instead, it facilitates tumor progression when combined with other molecular alterations [22].

From a therapeutic perspective, malignant transformation results in loss of epithelial polarity and exposure of CLDN18.2 on the tumor cell surface, making it readily targetable by intravenously administered agents [25-27,29]. Moreover, its restricted expression in normal tissues underscores its value as a tissue-associated antigen in GC [22,23].

CURRENT THERAPEUTIC LANDSCAPE

The success of zolbetuximab, the first-in-class mAb targeting CLDN18.2, has transformed CLDN18.2 from preclinical curiosity into a clinically validated therapeutic target [10-12].

https://doi.org/10.5230/jgc.2026.26.e10

jgc Journal of Gastric Cancer

The approval of zolbetuximab accelerated the adoption of biomarker-driven treatment strategies for AGC. Currently, comprehensive biomarker testing for HER2, DNA mismatch repair (MMR), PD-L1, and CLDN18.2 is essential for optimal patient selection in the first-line setting [1,22]. New modalities—including next-generation mAbs, BsAbs, and ADCs—may extend clinical benefit to patients with lower CLDN18.2 expression than that required for zolbetuximab (≥75% tumor cells with moderate to strong staining) [13-15].

As a tissue-associated antigen with restricted normal tissue distribution, CLDN18.2 also represents a promising target for innovative cell-based therapies such as CAR-T cells [16]. Altogether, targeting CLDN18.2 is a strategy that can expand the therapeutic landscape beyond classical oncogenic drivers.

mAbs Targeting CLDN18.2

The breakthrough: zolbetuximab

Sahin et al. [19] and Türeci et al. [18] first discovered CLDN18.2 as a pan-cancer target. They attempted to identify lineage-specific targets, such as CD19 or CD20, using an in silico screen. Therefore, similar to conventional oncogenic drivers, this therapeutic target lacks biological relevance in treating cancer. Subsequently, they developed zolbetuximab (IMAB362), a mouse chimeric immunoglobulin G1 (IgG1) mAb with splice variant specificity and initiated the first-in-human study [9]. Preclinical data showed that upon binding, zolbetuximab initiates an immune attack against cancer cells through antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) in CLDN18.2-expressing GC cells [35]. Patients with CLDN18.2-expressing tumors were enrolled in a phase I dose-escalation study [36]. Consequently, the recommended phase II dose of zolbetuximab was determined to be 300–600 mg/m^2 every 2 weeks, and gastrointestinal (GI) toxicities were the most common adverse events (AEs) [36]. Consistent with its proposed mechanism of action, zolbetuximab induced robust ADCC and CDC activities in patient samples collected during the phase I study [36]. The single-arm, multi-cohort phase IIa MONO study evaluated zolbetuximab 300 mg/m^2 (cohort 1) or 600 mg/m^2 (cohort 2) as second-line or later-line therapy for patients with CLDN18.2-positive (defined as ≥2+ on ≥50% of tumor cells), gastric, gastroesophageal junction (G/GEJ) or esophageal adenocarcinoma [37]. The objective response rate (ORR) was 9% and disease control rates (DCR) was 23%. In patients with high CLDN18.2 expression (≥2+ in ≥70% of tumor cells), the ORR and DCR increased to 14% and 31%, respectively. The most common grade 3–4 treatment emergent AEs (TEAEs) included vomiting (22%), nausea (15%), and dyspnea (11%) [37]. Subsequently, a combination of cytotoxic chemotherapy was evaluated in the randomized phase II FAST study (NCT01630083) in patients with moderate-to-strong CLDN18.2 expression [38]. Zolbetuximab plus epirubicin, oxaliplatin, and capecitabine (EOX) demonstrated significantly improved progression free survival (PFS) (hazards ratio [HR], 0.44; 95% confidence interval [CI], 0.29–0.67; P<0.0005) and OS (HR, 0.55; 95% CI, 0.39–0.77; P<0.0005) compared with EOX alone. Patients with high CLDN18.2 expression (≥70% tumor cells with ≥2+ staining) derived the greatest benefit, with improved PFS (HR, 0.38) and OS (HR, 0.50). In contrast, the Kaplan–Meier curves for patients with moderate expression (40%–69%) were nearly identical between the zolbetuximab and placebo arms [38]. The international randomized phase III SPOTLIGHT (zolbetuximab + modified FOLFOX6 vs. placebo + modified FOLFOX6) and GLOW (zolbetuximab + capecitabine and oxaliplatin [CAPOX] vs. placebo + CAPOX) studies were independently performed to elucidate the efficacy and safety of zolbetuximab in combination with chemotherapy as a first-line treatment for HER2-negative, CLDN18.2-positive unresectable locally advanced

https://doi.org/10.5230/jgc.2026.26.e10

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or metastatic G/GEJ adenocarcinoma [10,11]. The cutoff value for CLDN18.2-positivity was set at 75%, corresponding to 70% in previous studies. Compared to the control group, the addition of zolbetuximab to chemotherapy (modified folinic acid, fluorouracil, oxaliplatin [mFOLFOX6]/CAPOX) significantly improved median PFS and OS. However, no significant difference was observed in the ORRs between the zolbetuximab-arm and placebo-arm [10-12]. Consistent with previous results, nausea, vomiting, and anorexia were the most common and severe AEs associated with zolbetuximab combination treatment [10-12]. Based on the positive results from the SPOTLIGHT and GLOW trials, zolbetuximab combined with chemotherapy has been established as a standard of care for patients with previously untreated HER2-negative, CLDN18.2-positive (≥2+ in ≥75% of tumor cells) metastatic G/GEJ adenocarcinoma. This led to the regulatory approval of zolbetuximab in Japan, Europe, the United Kingdom, the United States, South Korea, and China. Several clinical practice guidelines, including the Korean Gastric Cancer Treatment Guidelines, now recommend chemotherapy regimens incorporating zolbetuximab for patients with HER2-negative and CLDN18.2-positive metastatic G/GEJ adenocarcinoma [39,40].

Furthermore, Cohort 4 of the ILUSTRO study investigated the efficacy and safety of zolbetuximab in combination with mFOLFOX6 and nivolumab [41]. The currently ongoing international randomized phase III LUCERNA study (NCT06901531) evaluates the addition of zolbetuximab to pembrolizumab plus chemotherapy in treatment-naïve patients with HER2-negative, proficient MMR, CLDN18.2-positive disease and PD-L1 CPS ≥1. In addition, early onset GI toxicities occasionally lead to early discontinuation of treatment. Managing GI toxicity is critical for implementing zolbetuximab in routine clinical practice. The use of multiple antiemetic agents and step-up dosing strategies are currently recommended. A randomized phase II GENTLE-Z trial (jRCTs031240347) is currently underway to evaluate whether omitting a high loading dose (800 mg/m^2) in the initial infusion can mitigate GI toxicities without compromising efficacy [42].

Other novel mAbs beyond zolbetuximab

In addition to zolbetuximab, several other mAbs targeting CLDN18.2 are also under clinical investigation (**Table 1**). Osemitamab (TST001, a IgG1 high-affinity humanized mAb targeting CLDN18.2 by binding Fc to FcγRIIIa) [13], ASKB589 (a humanized IgG1 mAb targeting CLDN18.2 with high affinity and enhanced ADCC activity) [43,44], MIL93 (a recombinant humanizerd mAb specifically targeting CLDN18.2, and with enhanced ADCC activity via engineered Fc segment for better binding to natural killer [NK] cells) [45], AB011 [46], ZL-1211 [47], and DR30303 (a Fc-engineered, humanized mAb) alone or in combination with chemotherapy have also been shown to have promising results and are well tolerated in specified populations. However, relevant clinical trials have just been initiated recently, and detailed data remain limited at this moment. Furthermore, the efficacy and safety of SPX-101 (NCT05231733) and FL-301 (NCT05153096) have been investigated in patients with AGC in phase I clinical trials, particularly for recurrent and refractory diseases.

ADCs Targeting CLDN18.2

ADCs are an important class of targeted therapies for AGC that are highly specific, particularly in targeting HER2 and the newly emerging target CLDN18.2 [1,48]. ADCs are like "precision missiles" for cancer cells. They consist of 3 essential parts: an antibody designed to recognize a specific protein (target) on cancer cells, a potent cytotoxic drug (payload) that kills cancer cells, and a linker that connects the antibody and payload, designed to be stable in the bloodstream but release the payload inside the target cells. This design allows for

https://doi.org/10.5230/jgc.2026.26.e10

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https://doi.org/10.5230/jgc.2026.26.e10

Table 1. Summary of phase I/II trials targeting CLDN18.2 for gastric/gastroesophageal junction cancer

NCT	Phase	Line	Treatment	Agent type	No.	ORR	mPFS	mOS	Representative toxicity		Reference
									TRAEs ≥ Gr1	TRAEs ≥ Gr3	
NCT04495296*	I/IIa	1 L	Osemitamab + CAPOX + Nivo	mAb	82	68.0% (M/H, n=26) 55.3% (L, n=40)	16.6 mo (H, n=26) 7.1 mo (L, n=40)	21.7 mo (H, n=26) 18.6 mo (L, n=40)	Nausea (67%), vomiting (60%), hypoalbuminemia (70%)	Nausea (4%), vomiting (2%)	[13]
NCT05632939	I/II	1 L	ASKB589 + CAPOX + PD-1 inhibtor*	mAb	100	76.1% (6 mg/kg, M/H, n=46) 81.8% (6 mg/kg, H, n=33)	12.45 mo (6 mg/kg, M/H, n=47) 15.28 mo (6 mg/kg, H, n=34)	-	Nausea (69.6%), vomiting (53.6%), hypoalbuminemia (64.3%)†	Nausea (0%), vomiting (7.1%), hypoalbuminemia (1.8%)†	[42]
NCT4631208	I/II	2 L	ASKB589 + PTX ASKB589 + DTX ASKB589 + CPT-11	mAb	47	34.2% (M/H, n=38) 31.1% (+PTX, n=35)	5.3 mo (total, n=47) 4.6 mo (+PTX, n=35)	11.14 mo (total, n=47) 13.73 (+PTX, n=35)		Neutrophil count decreased (42.6%) White blood cell count decreased (17%)	[41]
NCT04400383	I	1 L	AB011 + CAPOX	mAb	24	65.2%		-			[44]
NCT04805307	I	≥2 L	CMG901 (AZD0901) (MMAE)	ADC (MMAE)	113	28% (total, n=113) 33% (H, n=93)	3.7 mo (total, n=113) 4.8 mo (H, n=93)	10.1 mo (total, n=113) 11.8 mo (H, n=93)	Nausea (56%), vomiting (57%), hypoalbuminemia (61%), ILD (6%)‡	Nausea (10%), vomiting (4%)§	[15]
NCT05458219	I	≥2 L	IBI343	ADC (TOP1 INH)	116	32.3% (6 mg/kg, H, n=31) 47.1% (8 mg/kg, H, n=17)	5.5 mo (6 mg/kg, H, n=31) 6.8 mo (8 mg/kg, H, n=19)	10.8 mo (6 mg/kg, H, n=31) NR (8 mg/kg, H, n=19)	Nausea (41.4%), vomiting (25.0%), hypoalbuminemia (37.9%), ILD (0%)	Nausea (1.7%), vomiting (2.6%)	
NCT04877717	I	≥2 L	SHR-A1904	ADC (TOP1 INH)	95	26.7% (6 mg/kg, M/H, n=30) 26.7% (8 mg/kg, M/H, n=34)	5.6 mo (6 mg/kg, M/H, n=32) 5.5 mo (8 mg/kg, M/H, n=36)	6-mo OS rate 71.9% 12-mo OS rate 29.8%	Nausea (64.2%), vomiting (55.8%), hypoalbuminemia (67.4%), ILD (0%)	Nausea (5.3%), vomiting (4.2%)	
NCT06038396	I/II	≥2 L	RC118 + RC148	ADC (MMAE)	21	57.1%	7.9 mo	-	Nausea (42.9%), vomiting (23.8%)	Nausea (0%), vomiting (4.8%)	
	I/II	≥2 L	RC118 + toripalimab	ADC	21	33.3%	4.3 mo	-	Nausea (42.0%), vomiting (19.0%)	Nausea (0%), vomiting (0%)	
NCT05161390	I/II	≥2 L	LM302	ADC (MMAE)	59	32.7% (n=52)	4.9 mo (1.8 mg/kg)	10.9 mo (1.8 mg/kg)	Vomiting (41.2%), nausea (41.8%)	Vomiting (3.3%)	

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Journal of Gastric Cancer

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https://doi.org/10.5230/jgc.2026.26.e10

Table 1. (Continued) Summary of phase I/II trials targeting CLDN18.2 for gastric/gastroesophageal junction cancer

NCT	Phase	Line	Treatment	Agent type	No.	ORR	mPFS	mOS	Representative toxicity		Reference
									TRAEs ≥ Gr1	TRAEs ≥ Gr3	
CTR20231735	I/II	≥2 L	XNW27011	ADC (TOP1 INH)	84	82.8% (2.4 mg/kg, n=29) 87.1% (3.0 mg/kg, n=31) 88.9% (3.6 mg/kg, n=18)	-	-	Nausea (59.5%), vomiting (40.5%)	-	
NCT05365581	I	≥2 L	ASP2138 monotherapy	BsAb (CD3)	36	14.3% (n=21)	-	-	Nausea (27.8%), vomiting (11.1%), gastritis (2.8%), CRS (5.6%)	Nausea (0%), vomiting (0%), gastritis (0%), CRS (0%)	[58]
		1 L	ASP2138 + pembro/FOLFOX	BsAb (CD3)	39	62.5% (n=24)	-	-	Nausea (53.8%), vomiting (17.9%), gastritis (5.1%)	Nausea (5.1%), vomiting (2.6%)	[58]
		2 L	ASP2138 + ram/PTX	BsAb (CD3)	41	37.5% (n=24)	-	-	Nausea (43.9%), vomiting (17.1%), gastritis (29.3%)	Nausea (2.4%), gastritis (9.8%)	[58]
NCT05164458	I	≥2 L	IBI389	BsAb (CD3)	120	30.8% (n=26) (IHC 2/3+ ≥10%, n=26)	3.5 mo (IHC 2/3+ ≥10%, n=27)	-	Pyrexia (46%), nausea (37%), vomiting (23%), CRS (33%)	Nausea (1%), vomiting (3%), CRS (1%)	[59]
NCT05839106	I/II	≥2 L	PM1032	BsAb (4-1BB)	30	20% (n=10)			Nausea (20%), aspartate transaminase increase (16.7%)		[60]
NCT04856150	I		Q1802	BsAb (PD-L1)	29	66.6% (n=9)			Nausea (62.1%), vomiting (62.1%), abdominal pain (27.6%)	Nausea/vomiting (10.3%)	[14]
NCT04900818	Ib	≥2 L	Givastomig	BsAb	43§	16% (n=43)	1.7 mo	-	Nausea (21.3%), vomiting (12%)	Nausea (0%), vomiting (0%)	[61]
	Ib	1 L	Givastomig + FOLFOX + Nivo	BsAb	17	71.6% (n=17)	-	-	Nausea (53%), vomiting (35%)	Nausea (0%), vomiting (0%)	[61]
NCT04581473	II	≥2 L	CT041	CAR-T	104	22.1% (n=104)	3.25 mo	7.92 mo	Nausea (73%), vomiting (63%), CRS (95.6%)	Nausea (3%), vomiting (5%), CRS (4.5%)	[16]

CLDN18.2 = claudin 18.2; ORR = overall response rate; mPFS = median progression-free survival; mOS = median overall survival; TRAE = treatment-related adverse event; Gr = grade; L = CLDN18.2 expression low; CAPOX = capecitabine and oxaliplatin; Nivo = nivolumab; mAb = monoclonal antibody; M = CLDN18.2 expression moderate; H = CLDN18.2 expression high; PD-1 = programmed cell death protein 1; PTX = paclitaxel; DTX = docetaxel; CAR-T = chimeric antigen receptor-T; ADC = antibody-drug conjugate; MMAE = monomethyl auristatin E; ILD = interstitial lung disease; OS = overall survival; TOP1 = DNA topoisomerase 1; INH = inhibitor; NR = not reached; pembro = pembrolizumab; BsAb = bi-specific antibody; ram = ramucirumab; CRS = cytokine release syndrome.
*Marketed PD-1 inhibitors for gastric cancer in China including tislelizumab and sintilimab.
†Dose expansion cohort (n=56).
‡Dose expansion cohort (n=107).
§Efficacy-evaluable patients with CLDN18.2+ gastroesophageal carcinoma, safety set (n=75).

Journal of Gastric Cancer

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highly specific delivery of chemotherapy, aiming to maximize the killing of tumor cells while minimizing damage to healthy tissues [49,50]. ADCs such as trastuzumab and deruxtecan (an HER2-targeted ADC) have had significant success, even in patients with low levels of HER2 expression, changing the treatment landscape for this subgroup and opening a new avenue for drug development paradigms [51,52]. Recent positive data on CLDN18.2-targeted ADCs represent a significant advancement of targeted therapy options (**Table 1**).

CMG901 (also known as AZD0901) is a CLDN18.2-targeted ADC consisting of a humanized IgG1 anti-CLDN18.2 antibody conjugated to an monomethyl auristatin E (MMAE) payload via a protease-cleavable linker with a drug-to-antibody ratio (DAR) of approximately 4 and has shown promising results in clinical trials for advanced G/GEJ adenocarcinoma. The phase I KYM901 study (NCT04805307) established the foundation for AZD0901's development, demonstrating its efficacy and safety in heavily pretreated patients. In a cohort of patients with CLDN18.2-high expressing tumors, the drug showed strong anti-tumor activity [15]. The confirmed ORR was 35% across 3 dose levels. In the 2.2 mg/kg dose group (the recommended phase III dose), the confirmed ORR was higher at 48%, DCR was 70%, and median OS was 11.8 months in the CLDN18.2-high expression group. In addition, this therapy has a manageable and tolerable safety profile. Most treatment-related AEs (TRAEs) can be controlled with supportive care, allowing patients to continue the treatment. The most common side effects include hematological issues such as anemia and neutropenia, as well as GI symptoms such as nausea and vomiting. Based on the positive phase I results, a pivotal phase III multi-center randomized trial named CLARITY-Gastric 01 (NCT06346392) is currently actively recruiting participants with the objective of comparing the efficacy between AZD0901 monotherapy and the treatment option chosen by the investigator, in patients with CLDN18.2-positive advanced G/GEJ adenocarcinoma who had undergone at least one prior line of therapy.

IBI343 is another novel CLDN18.2-targeted ADC comprising a humanized anti-CLDN18.2 mAb conjugated to a DNA topoisomerase I inhibitor (exatecan) via a cleavable linker with a DAR of approximately 4. Its mechanism includes a bystander effect, enabling the killing of adjacent cancer cells, which is beneficial for tumors with heterogeneous target expression, thereby demonstrating promising efficacy and manageable safety profile in a phase I clinical trial (NCT05458219) for those with advanced CLDN18.2-high expression (defined as ≥75% of tumor cells with staining intensity ≥2+) G/GEJ adenocarcinoma, who had experienced treatment failure after at least 2 prior systemic therapies [53]. The confirmed ORR, DCR, and median PFS were 32.3%, 90.3%, and 5.5 months, respectively, at a dose of 6 mg/kg (RP2D), and 47.1%, 88.2%, and 6.8 months, respectively, at a dosage of 8 mg/kg. The most common TRAEs were hematologic, including decreased white blood cell count (67.2%), anemia (64.7%), and decreased neutrophil count (58.6%). Importantly, no interstitial lung disease was reported at any grade, and severe (grade ≥3) GI toxicities, such as nausea, were rare (1.7%). RP2D was determined to be 6 mg/kg every 3 weeks. Although the 8 mg/kg dose showed a higher response rate, the 6 mg/kg dose was selected to achieve a better balance between efficacy and safety. Based on the positive phase 1 results, a global phase III multi-center randomized controlled trial (G-HOPE-001, NCT06238843) was initiated to further confirm the efficacy and safety of IBI343. This drug has also been granted a breakthrough therapy designation (BTD) in China for this indication.

SHR-A1904 is another promising CLDN18.2-targeted ADC, consisting of an antibody that targets the CLDN18.2 protein on cancer cells, a cytotoxic payload (a DNA topoisomerase I inhibitor), and a cleavable linker that connects them. A phase I trial published in July 2025 showed that

https://doi.org/10.5230/jgc.2026.26.e10

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SHR-A1904 is safe and encourages anti-tumor activity in previously treated patients [54]. A total of 95 patients with CLDN18.2-positive advanced G/GEJ adenocarcinoma who had prior treatment were enrolled; the confirmed ORRs were 24.2% and 25.0% at doses of 6.0 mg/kg (RP2D) and 8.0 mg/kg, respectively, and the median PFS were 5.6 and 5.8 months, respectively. In addition, deeper analysis showed that for patients with medium-to-high CLDN18.2 expression, the confirmed ORR was even higher at 26.7% and 26.5% for the 6.0 mg/kg and 8.0 mg/kg groups, respectively. Moreover, the drug showed activity in some patients who had previously received other CLDN18.2-targeted therapies, suggesting that it may help overcome resistance. Anemia (75.8%), nausea (67.4%), low albumin (64.2%), and decreased white blood cell count (58.9%) were the most common TEAEs. Based on the positive phase I results, researchers have initiated larger phase III clinical trials to further validate the efficacy and safety of the drug. These include a trial evaluating SHR-A1904 as a single agent in second-line treatment (NCT06649292) and another investigating its use in combination with chemotherapy as a first-line treatment (NCT06350006) for CLDN18.2-positive advanced solid tumors.

RC118 is a novel MMAE conjugated, CLDN18.2 specific ADC, with a DAR of approximately 4. It showed promising anti-tumor signals in advanced G/GEJ adenocarcinoma patients with CLDN18.2 immunohistochemistry (IHC) 2+/3+ ≥40%. Results from a multicenter phase I/II study showed that the ORR in intention-to-treat patients was 57.1% with RC118 plus RC148 (a novel IgG1 humanized BsAb that targets programmed cell death protein 1 (PD-1) and vascular endothelial growth factor, exerting its anti-tumor effects through the simultaneous inhibition of 2 critical signaling pathways) and 33.3% with RC118 in combination with toripalimab. The median PFS was 7.9 months for RC118 plus RC148 and 4.3 months for RC118 combined with toripalimab. In addition, patients who previously received PD-(L)1 therapy had ORR of 62.5% and 20.0%, and median PFS of 6.1 and 4.3 months in the 2 combination subgroups, respectively. Both combination therapies exhibited manageable safety profiles and comparable incidences of AEs, with a low rate of grade ≥3 AEs. However, the RC118 plus RC148 regimen was not associated with an increased risk of bleeding compared to the RC118 plus poripalimab regimen. A subsequent study evaluated RC118 combined with RC148 as first-line treatment for advanced CLDN18.2-positive G/GEJ adenocarcinoma [55].

LM302 (also known as tecotabart vedotin) is a novel ADC targeting CLDN18.2. In a Bayesian phase 1/2 clinical trial, 153 patients received LM302 (phase 1,38; phase 2,115). At higher doses, dose-limiting toxicities (DLTs) occurred in 5 patients. The maximum tolerated dose (MTD) was 2.4 mg/kg Q3W; recommended phase 2 doses were 1.8 mg/kg Q2W and 2.4 mg/kg Q3W. Among 52 evaluable patients with CLDN18.2-positive G/GEJ adenocarcinoma receiving 1.8 mg/kg Q2W, ORR was 32.7% (95% CI, 20.3–47.1), with median PFS of 4.9 months (95% CI, 2.7–6.9 months) and OS of 10.9 months (95% CI, 9.1–17.1 months). The AEs were manageable and consistent with those of the MMAE-based ADCs. Thus, LM302 demonstrated encouraging anti-tumor activity and safety in CLDN18.2-positive G/GEJ adenocarcinoma, supporting further clinical development [56].

XNW27011 is an investigational ADC composed of an mAb targeting CLDN18.2 conjugated to a potent proprietary topoisomerase I inhibitor. A dose-escalation study of XNW27011 demonstrated favorable safety, pharmacokinetics, and promising preliminary efficacy in advanced solid tumors. As of April 20, 2025, an ongoing phase I/II study had enrolled 84 patients with G/GEJ adenocarcinoma in the 2.4, 3.0, or 3.6 mg/kg dose groups. Efficacy was evaluated in 78 of the 84 patients. The median follow-up time was 8.4 months. The overall best of response was 51.3%, and the DCR was 85.9% in all patients [57]. The study

https://doi.org/10.5230/jgc.2026.26.e10

jgc Journal of Gastric Cancer

was expanded in patients with CLDN18.2-expressing advanced G/GEJ adenocarcinoma treated with XNW27011, which demonstrated promising anti-tumor activity and well-tolerated safety. These findings warrant further investigation. A randomized phase 3 clinical trial of XNW27011 monotherapy as ≥3L treatment versus chemotherapy in patients with previously treated locally advanced or metastatic G/GEJ adenocarcinoma has been planned.

EO3021 (also known as SYSA1801) is a high-affinity CLDN18.2-targeted ADC that uses MMAE as its payload and has a DAR of 2. However, as of March 2025, Elevation Oncology announced the termination of the EO3021 program based on updated data from the phase 1 trial showing a lower ORR of 22.2% in a larger set of 36 evaluable patients with G/GEJ adenocarcinoma with CLDN18.2-positive expression (≥20% of tumor cells with staining intensity 2+/3+) [58].

Meanwhile, other novel CLDN18.2-targeted ADCs have been investigated in clinical trials, including SOT102 (NCT05525286), ATG-022 (NCT05718895), TQB2103 (NCT05867563), and SKB315 (NCT05367635), which will help elucidate the application of CLDN18.2-targeted ADCs in advanced G/GEJ adenocarcinoma. In such cases, more attention should be paid to attain a balance between efficacy and safety. Future studies should focus on developing new strategies to enhance the specificity of the antibodies in the scenario of low CLDN18.2 expression.

BsAbs Targeting CLDN18.2

BsAbs are engineered antibodies that can simultaneously bind to 2 different epitopes or 2 distinct antigens. In the context of cancer, the most common format is bispecific T-cell engagement. These molecules have one arm that binds to a tumor-associated antigen (TAA; e.g., CLDN18.2) and another arm that binds to a T-cell activation marker (e.g., CD3 on T-cells). By physically linking a cancer cell to a T-cell, BsAbs bypass the normal major histocompatibility complex-restricted activation mechanism and trigger a potent, targeted T-cell response against the tumor, regardless of the native specificity of the T-cell. Compared to mAbs, BsAbs like T-cell engagers are significantly more potent. While mAbs (e.g., zolbetuximab) rely on secondary immune functions, such as ADCC, BsAbs directly activate and recruit the patient's own T-cells to become cytotoxic. BsAbs targeting CLDN18.2 represent a highly promising and competitive area of oncological drug development, particularly for patients with GC. They offer a different therapeutic approach compared to CAR-T cells, with distinct advantages and challenges (**Table 1**).

BsAbs Engaging T-Cell Engagers

ASP2138, a BsAb antibody and T-cell engager targeting CLDN18.2 and CD3, was designed to mitigate AEs, such as cytokine release syndrome (CRS), by minimizing systemic and off-tumor CD3 engagement and immune activation. Results from a phase I/Ib (NCT05365581) study showed that ASP2138 (420 μg, run-in 50 μg) monotherapy was optimal in patients with locally advanced unresectable or metastatic G/GEJ adenocarcinoma, based on emerging efficacy and safety data. TRAEs associated with ASP2138 monotherapy were generally of low severity. TRAEs included on-target AEs such as nausea and vomiting; 43.5% and 22.9% patients with locally advanced unresectable metastatic G/GEJ adenocarcinoma and metastatic prostate cancer (PC) experienced CRS, respectively. ASP2138 was tolerable, with manageable known T-cell engager and CLDN18.2-targeting therapy toxicity. Preliminary exploratory biomarker analysis supports the proposed mechanism of action of ASP2138 and the combination of ASP2138 with anti–PD-L1 therapy to maximize therapeutic benefit,

https://doi.org/10.5230/jgc.2026.26.e10

jgc Journal of Gastric Cancer

including in patients with low baseline PD-L1 expression. In addition, another phase I/Ib trial (NCT05365581) found that in patients with locally advanced unresectable or metastatic G/GEJ adenocarcinoma, TRAEs with subcutaneous ASP2138 alone or in combination with the current first-line chemotherapy were of low severity and included known T-cell engager-related (e.g., CRS) and CLDN18.2 targeting–related (e.g., nausea and vomiting) AEs, and the MTD was not reached. Subcutaneous administration of ASP2138 2,000 μg retained efficacy, demonstrated favorable safety and tolerability (CRS and gastric toxicity), and was more convenient compared to intravenous administration of 420 μg. Subcutaneous ASP2138 demonstrated clinically meaningful anti-tumor activity alone or in combination with the current first-line chemotherapy. Compelling responses have been observed in patients with both high and medium-to-low CLDN18.2 expression levels [59].

IBI389 is an anti-CLDN18.2/CD3 BsAb that induces immune synapse formations by linking CD3 molecules in T-cell receptor complexes and CLDN18.2 antigens on the membrane of tumor cells. The results of a phase I study (NCT05164458) showed that no DLTs were observed during dose escalation, and the MTD was not achieved. TEAEs occurred in 112 (98.2%) patients, including 76 (66.7%) patients with grade ≥3 TEAEs. TRAEs occurred in 111 (97.4%) patients, including 63 (55.3%) with grade ≥3 TRAEs. The most common grade ≥3 TRAEs (≥ 4%) were increased gamma-glutamyl transferase (21.9%), decreased lymphocyte count (13.2%), and nausea (4.4%). CRS-related AEs occurred in 65 (57.0%) patients, including 1 patient (0.9%) with grade 3 CRS and no grade 4 or 5 CRS. TEAEs leading to dose interruption and treatment discontinuation occurred in 44 (38.6%) and 8 (7.0%) patients. Preliminary efficacy of IBI389 was observed in patients with CLDN18.2 expression ≥10% (IHC 2+/3+). In G/GEJ adenocarcinoma patients with previous treatments including ≥2 lines administering IBI389 at various dose levels ranging from 10 μg/kg to 600 μg/kg (n=26), 8 patients had partial response (PR) and 11 patients had stable disease (SD). The ORR was 30.8% (95% CI, 14.3–51.8) and DCR was 73.1% (95% CI, 52.2–88.4). IBI389 showed a manageable safety profile in patients with advanced solid tumors and preliminary efficacy in CLDN18.2-positive patients with G/GEJ adenocarcinoma [60].

QLS31905 is another BsAb targeting both CD3 and CLDN18.2, and preliminary data from a completed phase Ib/II clinical trial (QLS31905-201) indicated an ORR of 18.18% and DCR of 87.88% in CLDN18.2-positive solid tumors treated with first line QLS31905 plus chemotherapy. Among these patients, the ORR was 15.8% for AGC and 25.0% for PC. The most common severe (grade ≥3) side effects included decreased lymphocyte count and elevated γ-glutamyltransferase [14]. A global phase III trial for advanced PC has begun, making this the first CLDN18.2/CD3 BsAb to reach this stage.

BsAbs Engaging 4-1BB

Givastomig (also known as TJ033721) is a BsAb that targets CLDN18.2 and conditionally activates local 4-1BB-expressing T cells. In another human phase I study, no DLTs were reported up to 18 mg/kg and the MTD was not reached. The most common TRAEs (in ≥10% of patients) were nausea, anemia, fatigue, decreased white blood cell count, vomiting, and increased alanine aminotransferase [61]. Givastomig exposure increased the dose proportionally, and soluble 4-1BB plateaud at doses >5 mg/kg. A dose of 12 mg/kg was selected for dose expansion. At doses >5 mg/kg (n=43), a 16% ORR was observed in CLDN18.2-positive GEJ adenocarcinoma. CLDN18.2 expression in responders, ranged from 11% to 100%. Givastomig had manageable safety profile, dose-dependent exposure, and anti-tumor activity in patients with advanced solid tumors, particularly CLDN18.2-positive GEJ adenocarcinoma.

https://doi.org/10.5230/jgc.2026.26.e10

jgc Journal of Gastric Cancer

A givastomig dose range of 5–12 mg/kg was chosen for combination with nivolumab and chemotherapy in Part 2 of a study on frontline metastatic GEJ adenocarcinoma [62].

PM1032 is an anti-CLDN18.2 and 4-1BB BsAb that activates immune cells, such as T cells and NK cells, via the CLDN18.2-mediated crosslinking of 4-1BB. The results of the first human phase I/II study (NCT05839106) demonstrated no DLTs in 30 patients who received PM1032 (18 during dose escalation and 12 during dose expansion). CLDN18.2 expression was evaluable in 80% of the patients, and 66.7% were positive. The most common tumor types were GI cancers, including 14 G/GEJ adenocarcinomas, 10 PC, and 5 other GI cancers. All patients had ≥1 line of prior therapy and 17 patients (56.7%) had prior immunotherapy. TRAEs occurred in 22 subjects (73.3%), and ≥ grade 3 TRAEs occurred in 3 subjects (10%). The most common TRAEs were nausea (20%) and increased aspartate transaminase (16.7%). Among 16 CLDN18.2+ patients enrolled at the 5, 8, and 12 mg/kg dose levels who completed at least one tumor evaluation, 2 patients achieved PR, 7 had SD, and 3 were non-complete response/non-progressive disease. Additionally, the ORR was 20% in 10 patients with measurable and evaluable CLDN18.2+ GC/GEJ. The longest treatment duration was 18 months and 5 patients had treatment durations ≥6 months. PM1032 was well tolerated up to 12 mg/kg Q2W and demonstrated preliminary anti-tumor activity in CLDN18.2+ tumors. Further development of PM1032 as a monotherapy and/or combination therapy for CLDN18.2-positive cancers is planned [63].

BsAbs Engaging Other Targets

PT886 is a first-in-class BsAb developed for treating GC and other solid tumors by simultaneously targeting 2 specific proteins on cancer cells, CDLN18.2 and CD47, and offers dual clinical advantages by not only engaging immune cells but also influencing immune escape pathways. A multi-center phase I/II clinical trial (the TWINPEAK study, NCT05482893) is ongoing in the United States to evaluate PT886 as a single agent in combination with pembrolizumab and/or chemotherapy. In addition, PT886 has entered clinical development in China. The first patient in the Chinese phase I study was treated in July 2024. Based on this, a phase II trial (CTR20252758) was approved and initiated in July 2025. This study, led by the Sun Yat-sen University Cancer Center, aimed to investigate the safety, tolerability, and anti-tumor activity of PT886 in combination with chemotherapy and/or a PD-1 inhibitor in patients with advanced G/GEJ adenocarcinoma and PC [64].

Moreover, the efficacy and safety of other novel BsAbs, including AZD5863 (targets CLDN18.2 and CD3, and NCT06005493), Q-1802 (targets CLDN18.2 and PD-L1, NCT04856150, and NCT05964543), and HC-2G4S (targets HER2 and CLDN18.2) as a single agent, or in combination with standard chemotherapy, are under investigation in patients with AGC, in phase I or II clinical trials, particularly in recurrent and refractory diseases.

In summary, BsAbs targeting CLDN18.2 are at the forefront of the next wave of immunotherapies for GC. They offer a potent and readily available alternative to CAR-T cells, with the potential to benefit a broader patient population.

CAR-T Cells Targeting CLDN18.2

The great success of CAR-T cells in advanced hematological malignancies has resulted in its application in treating solid tumors, including GI cancers. CLDN18.2-targeted CAR-T cells are highly personalized and promising immunotherapies in which a patient's own T cells are modified and engineered ex vivo to express a CAR that specifically targets CLDN18.2,

https://doi.org/10.5230/jgc.2026.26.e10

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enabling increased ability to recognize TAAs, leading to the activation of T lymphocytes, increased cell proliferation, cytotoxicity, and the transcription of genes encoding various cytokines, thereby strengthening anti-cancer activity (**Table 1**) [65].

Both preclinical and early phase clinical studies of CLDN18.2-targeted CAR-T cells (CAR-CLD18 T, a first-generation CAR T cell product, NCT03159819; CT041, a second-generation CAR T cell product, NCT03874897, and NCT04404595) have shown considerable efficacy and good tolerance in patients with advanced CLDN18.2-expressing gastric or pancreatic adenocarcinomas who failed previous therapies. In addition, the phase II trial CT041-ST-01 (NCT04581473, confirmatory study) randomly assigned 156 patients with CLDN18.2-positive (≥40% tumor cells with intensity ≥2+) advanced G/GEJ adenocarcinoma who failed ≥2 prior lines of therapy to receive either CT041 or a treatment of physician's choice (TPC; paclitaxel, or irinotecan). Patients in the TPC group were allowed to cross over to receive CT041 treatment upon disease progression. Compared to the TPC group, patients in the CT041 group had a favorable median PFS (3.25 vs. 1.77 months; HR, 0.37) and median OS (7.92 vs. 5.49 months; HR, 0.69). Furthermore, greater survival benefit could be achieved (median OS, 8.61 vs. 5.49 months; HR, 0.60) after statistical adjustment for crossover, and the ORR was significantly higher with CT041 (41% vs. 4%). Moreover, the safety profile of CT041 was manageable and consistent with the known effects of CAR-T cell therapy. The most common grade ≥3 TRAEs were hematologic, including decreased lymphocyte, white blood cell, and neutrophil counts. CRS occurred in 95% of patients, but only 4 cases were grade 3, with no grade 4 or 5 events reported. No immune effector cell-associated neurotoxicity was observed. This trial is considered a landmark achievement as it represents the first positive randomized controlled trial for CAR-T cell therapy in a solid tumor, supporting CT041 as a potential new standard of care for third-line treatment of CLDN18.2-positive G/GEJ adenocarcinoma [16]. CT041 has been granted BTD in China and Orphan Drug and Regenerative Medicine Advanced Therapy designations by the U.S. Food and Drug Administration for GC.

Besides, several other novel CAR-T cells products are under active investigation in early-phase clinical trials including 3 second-generation CAR-T cells (LB1908, NCT05539430; KD496, NCT05583201 and IMC002, NCT05946226, NCT05276310 and NCT05472857), one third-generation CAR-T cells (LY011, NCT04977193) and 2 fourth-generation CAR-T cells (RD07, NCT05284968 and CT048, NCT05393986), which would establish CLDN18.2-targeted CAR-T cells therapy as a promising therapeutic approach for patients with advanced CLDN18.2-positive GI cancers.

Although CAR-T cell therapy has emerged as a breakthrough treatment for hematologic malignancies, its efficacy remains limited to solid tumors, particularly GI cancers, even with repeated CAR-T cell infusions. Compared to ADCs and BsAb, the complex and time-consuming manufacturing process of CAR-T cell therapy is not yet justified by its current level of clinical efficacy in solid tumors. A deeper understanding of the interactions between CAR-T cells and the tumor microenvironment is essential to prevent T-cell exhaustion and achieve more durable clinical responses. The most compelling aspect of CAR-T cell therapy is that it harnesses living cells as a “drug,” offering inherent adaptability and the potential for sustained anti-tumor activity [63]. Despite the notable challenges, there remains substantial room for improvement in this field, and the emergence of innovative therapeutic strategies is highly anticipated.

https://doi.org/10.5230/jgc.2026.26.e10

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SAFETY MANAGEMENT OF CLDN18.2-TARGETED THERAPIES

Since CLDN18.2-targeted therapies have resulted in a paradigm shift in the comprehensive treatment of AGC, safety and tolerance have become major concerns. Safety management of CLDN18.2-targeted therapies primarily involves monitoring and managing GI AEs, which are among the most common and characteristic toxicities (**Table 1**).

Mechanically, GI toxicity is considered an "on-target, off-tumor" effect. Since CLDN18.2 is also present in the normal stomach lining, the drug can cause inflammation, leading to characteristic gastritis. Endoscopic exams reveal features like diffuse mucosal redness (100% of cases), white exudates (63.4%), and edema (28.8%). This inflammation is closely linked to symptoms, such as loss of appetite, and can lead to a significant drop in serum albumin levels. Thus, it is crucial to administer multiple prophylactic antiemetic agents, including 5-HT3 receptor antagonists, corticosteroids, aprepitant, and olanzapine, prior to each treatment cycle to minimize treatment interruptions and prevent early discontinuation. Moreover, most patients received proton pump inhibitors (PPIs). While the direct impact of PPIs on preventing this specific drug-induced gastritis has not been fully established, they are part of standard supportive care. Step-up dosing is also effective for managing GI toxicities. Before symptoms progress, a brief treatment interruption and the addition of supplemental antiemetic agents, such as dopamine receptor antagonists (such as prochlorperazine or metoclopramide), may help improve tolerability. Additionally, a recent preclinical study suggested that reduced affinity may mitigate GI toxicity [66].

Hypoalbuminemia has also been recognized as a relatively frequent AE following zolbetuximab use in clinical practice [67]. Recently, protein leakage from the stomach was detected using technetium-99m-labeled human serum albumin scintigraphy, supporting the concept of gastric mucosal injury-related protein loss in this setting [68]. Moreover, the patient's nutritional status and serum albumin levels should be closely monitored and albumin supplementation should be considered if necessary. Furthermore, GI AEs are most pronounced during the first infusion, and often become more manageable in subsequent cycles.

In addition, other TRAEs, including hematological toxicity and CRS, should be given more attention to make the application of CLDN18.2-targeted therapies safer in clinical practice.

FUTURE PERSPECTIVES

While CLDN18.2-targeted therapies have shown great promise, several challenges and future directions are emerging from research focusing on more sophisticated combination strategies, next-generation drug development, and refined patient selection to overcome the current challenges and benefit a broader patient population.

Next-Generation Agents and Combinations

The goal is to build on the success of first-generation mAbs (zolbetuximab), ADCs, and CAR-T cells. This is a strategic innovation because it avoids secondary resistance and offers a new option for patients who have failed prior treatment. Researchers are actively exploring combination therapies, particularly, immunotherapies. The rationale is that targeted cell killing by CLDN18.2 agents may help create a more immunogenic tumor microenvironment, potentially synergizing with PD-1/PD-L1 inhibitors to boost the overall anti-tumor response.

https://doi.org/10.5230/jgc.2026.26.e10

jgc Journal of Gastric Cancer

Precise Patient Selection

As not all patients with CLDN18.2-positive tumors respond to CLDN18.2-targeted therapies, future efforts should focus on refining the use of biomarkers. Critical challenges include determining the optimal level of CLDN18.2 expression required for a meaningful response, maximizing treatment benefit, avoiding unnecessary toxicity, and addressing tumor heterogeneity, where some areas of a tumor are CLDN18.2-positive while others are not. One promising approach to tackle heterogeneity is the development of novel antibodies that can simultaneously engage CLDN18.2 and another target, potentially improving tumor cell recognition and killing efficiency, which could help overcome primary and acquired resistance and expand treatment to tumors with heterogeneous or lower CLDN18.2 expression.

Integration Into the Broader Treatment Landscape

Accordingly, CLDN18.2-targeted therapy is poised to become a part of a multiplexed biomarker-guided treatment system alongside targets such as HER2 and PD-L1 CPS. Therefore, future first-line treatments for AGC will likely involve comprehensive biomarker testing to determine the best personalized therapy. Research will also focus on determining the optimal sequence for using these targeted and immunotherapeutic options.

In summary, the future of CLDN18.2-targeted therapies for AGC is promising, marked by more potent and specific drugs, smarter combination strategies, and more personalized treatment approaches. Ongoing and future clinical trials are crucial to define the best paths for improving the survival and quality of life of patients.

CONCLUSION

The emergence of CLDN18.2 as a target represents a paradigm shift in treating AGC. The approval of zolbetuximab has established a new standard of care for a large, molecularly defined subgroup. The pipeline is rich in next-generation modalities, such as new mAbs, BsAbs, ADCs, and CAR-T cells, which show promise, particularly in later-line settings and other cancer types. The future is bright and hinges on strategic combinations, refined biomarkers, safety management, and continued expansion of this powerful new class of oncology therapeutics.

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