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# *Research Progress of CLDN18.2 in Gastric Cancer*

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***Abstract.*** Gastric cancer, as a globally prevalent malignancy with poor prognosis, exhibits limited efficacy to conventional therapies in advanced stages, necessitating novel therapeutic targets and strategies. CLDN18.2, a member of the Claudin protein family, is predominantly expressed in gastric mucosal epithelial cells under normal conditions, but is aberrantly overexpressed in malignancies such as gastric cancer. Its expression is closely associated with tumor invasion, metastasis, and poor prognosis, making it a highly promising therapeutic target. This paper elucidates the protein structure and biological functions of CLDN18.2, as well as its expression characteristics in gastric cancer. It systematically reviews clinical trial progress of various CLDN18.2-targeted agents, including monoclonal antibodies such as zolbetuximab, antibody-drug conjugates (ADCs) such as CMG901 and LM-302, bispecific antibodies such as Q-1802 and AMG910, and CAR-T cell therapies such as CT041. The efficacy and safety data of these agents in existing studies are analyzed. Furthermore, challenges in current research, including drug resistance, management of adverse effects, and precise patient selection, are discussed. Finally, future directions for optimizing drug design and exploring combination therapy strategies are proposed, providing a reference for the development of CLDN18.2-targeted therapies and the treatment of gastric cancer.

***Keywords:*** CLDN18.2, Gastric Cancer, Targeted Therapy

## 1. Introduction

Gastric cancer is one of the malignant tumors that pose a serious threat to human health worldwide, with relatively high incidence and mortality rates among various cancers. In 2022, there were 9.7 million cancer-related deaths globally, with gastric cancer accounting for 6.8%, ranking third among causes of cancer-related mortality, and it is the fifth most common cancer worldwide [1]. Although certain advances have been made in diagnostic technologies and therapeutic approaches, the 5-year survival rate of patients with advanced gastric cancer remains low, and the prognosis is generally poor. Conventional treatment methods, such as surgical resection, chemotherapy, and radiotherapy, have very limited efficacy for advanced or metastatic gastric cancer [1,3], and are often accompanied by significant adverse effects, severely impacting patients' quality of life. Therefore, identifying novel therapeutic targets and developing more effective treatment strategies have become critical tasks in gastric cancer research. With the rapid development of molecular biology

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techniques, the molecular mechanisms underlying tumorigenesis and progression have gradually been elucidated, providing a theoretical basis for targeted therapies. Claudin18.2 (CLDN18.2), a protein aberrantly expressed in tumor cells, has gradually emerged as a research hotspot in the field of gastric cancer therapy. CLDN18.2 exhibits highly specific expression in normal tissues, being mainly restricted to gastric mucosal epithelial cells; however, its expression is significantly upregulated in gastric cancer and other malignancies [2], and is closely associated with tumor invasion, metastasis, and poor prognosis. This characteristic makes CLDN18.2 a highly promising therapeutic target, and targeted therapies against CLDN18.2 are expected to offer new hope for patients with gastric cancer. In recent years, research on CLDN18.2 has deepened, covering multiple aspects including its basic biological characteristics, clinical diagnostic value, and therapeutic applications. Numerous studies have shown that CLDN18.2-targeted treatments—such as monoclonal antibodies, antibody-drug conjugates (ADCs), bispecific antibodies, and CAR-T cell therapies—demonstrate certain efficacy in clinical trials, opening new avenues for gastric cancer treatment. Nevertheless, significant challenges remain, such as drug resistance, management of adverse effects, and precise patient selection [3]. This paper aims to summarize the clinicopathological and microenvironmental features related to CLDN18.2, review the progress of its clinical trials, and provide reference for the development of related therapeutics.

## 2. Structure, biological function, and expression of CLDN18.2 in gastric cancer

### 2.1. The Claudin protein family

The Claudin protein family is a key component of tight junctions (TJs), playing an essential role in maintaining cell polarity, regulating paracellular permeability, and mediating intercellular signal transduction. To date, this family is known to comprise 27 members. The classical tight junction proteins include Claudins 1–10, 14, 15, 17, and 19, while the non-classical tight junction proteins include Claudins 11–13, 16, 18, and 20–24. Generally, Claudins 2, 7, 10, 15, and 16 enhance paracellular cation permeability by forming gaps in tight junctions, whereas Claudins 4, 5, 8, 11, 14, and 18 function as sealing proteins [4]. Structurally, these proteins share significant similarity; all are transmembrane proteins containing four transmembrane domains, two extracellular loops (ECL1 and ECL2), and intracellular N- and C-termini (Figure 1) [5].

CLDN18, as a member of the Claudin family, is encoded by a gene located at the 3q22 region of human chromosome 3, spanning approximately 35 kb. The CLDN18 gene produces two main isoforms—CLDN18.1 and CLDN18.2—through alternative splicing. These isoforms exhibit high homology in their amino acid sequences but differ markedly in tissue-specific expression. CLDN18.1 is specifically expressed in lung tissue, whereas CLDN18.2 is predominantly expressed in gastric mucosal epithelial cells, including the chief cells, parietal cells, and endocrine cells of the gastric glands [6]. Under normal physiological conditions, CLDN18.2 localizes to the apical membrane of gastric mucosal epithelial cells, forming tight junctions that contribute to the barrier function of the gastric mucosa [7]. This prevents the intrusion of harmful substances while regulating the transport of ions and small molecules in the paracellular space.

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## 2.2. Differences between CLDN18.1 and CLDN18.2

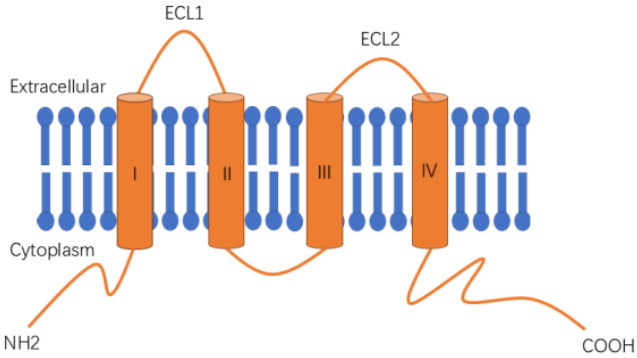


Figure 1. Molecular structure of CLDN18.2 [5]

CLDN18.1 and CLDN18.2 share high homology in their amino acid sequences, with 91% of residues being identical. However, they differ markedly in tissue-specific expression. CLDN18.1 is predominantly and specifically distributed in lung tissue, whereas CLDN18.2 is mainly localized to the gastric mucosa, including normal gastric glands, chief cells, parietal cells, and endocrine cells, as well as Paneth cells in the duodenum. Notably, regions harboring gastric stem cells do not express CLDN18.2 [6,9]. Structurally, the primary difference between the two isoforms lies in the first extracellular loop (ECL1), which contains 69 differing amino acids [8]. Additionally, the distribution and number of charged residues in ECL1 differ significantly. Since the first extracellular loop of Claudin proteins is closely associated with paracellular tight junctions and selective ion permeability, CLDN18.1 and CLDN18.2 exhibit differences in their paracellular cation permeability [9]. Current research generally suggests that CLDN18.2 is involved in regulating the permeability of cations such as $H^+$ and $Na^+$. Loss of CLDN18.2 expression can trigger the aggregation of neutrophils in the gastric submucosa and induce inflammatory responses. Regarding intracellular distribution, CLDN18 expressed in parietal cells is arranged along the basolateral membrane in discontinuous tight junction strands that fully encircle the parietal cells; in chief cells, the spacing between junction strands is relatively wider [9]. This observation indicates that CLDN18.2 may regulate paracellular cation permeability through specific structural constraints [9].

## 2.3. Expression of CLDN18.2 in gastric cancer

In normal gastric mucosal tissue, the expression of CLDN18.2 is strictly regulated, being primarily restricted to specific regions of gastric mucosal epithelial cells and generally at low levels. However, during the development and progression of gastric cancer, the expression of CLDN18.2 undergoes significant alterations. Numerous studies have demonstrated that CLDN18.2 is highly expressed in gastric cancer tissues, with positive expression rates ranging from 40% to 95%, depending on the study cohort and detection methods employed.

High expression of CLDN18.2 is associated with various clinicopathological features of gastric cancer. In terms of tumor staging, elevated CLDN18.2 expression is often linked to advanced gastric cancer, suggesting a potential role in tumor progression [10]. Regarding lymph node metastasis, studies have reported that patients with CLDN18.2-positive gastric cancer are more prone to lymph node involvement, with expression levels positively correlating with both the number and extent of affected lymph nodes. Furthermore, high CLDN18.2 expression is closely associated with poor

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prognosis in gastric cancer patients, with those exhibiting high expression demonstrating significantly lower survival rates compared to patients with low expression.

## 3. Summary of rapidly advancing CLDN18.2-targeted clinical drugs

### 3.1. Monoclonal antibodies

Zolbetuximab is currently the most extensively studied monoclonal antibody targeting CLDN18.2. It is a chimeric IgG1 monoclonal antibody that specifically binds to the CLDN18.2 protein and exerts antitumor effects through antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) [11]. Numerous clinical trials have evaluated the efficacy and safety of zolbetuximab. In the FAST study, a randomized controlled phase II trial, 246 patients with CLDN18.2-positive advanced gastric, gastroesophageal junction (GEJ), or esophageal adenocarcinoma (≥18 years old; CLDN18.2 expression in ≥40% of tumor cells with moderate-to-strong signal) were enrolled and divided into three cohorts. The latest data indicated that zolbetuximab combined with EOX chemotherapy further prolonged progression-free survival (PFS) and overall survival (OS) compared to EOX alone. In the subgroup of patients with >70% CLDN18.2-positive tumor cells, the median PFS and OS were 9.0 months and 16.5 months, respectively, whereas the placebo plus EOX group showed 5.7 months and 8.9 months, respectively. Among 15 patients with measurable lesions who had undergone at least one prior tumor assessment, according to RECIST 1.1 criteria, the best overall response included 11 patients (73.3%) achieving partial response (PR) and 4 patients (26.7%) maintaining stable disease (SD), yielding a disease control rate (DCR) of 100% [12].

On September 16, 2024, the New England Journal of Medicine published an article summarizing final survival and safety data from two global multicenter phase III trials (SPOTLIGHT and GLOW) [13]. Both studies were randomized, double-blind, placebo-controlled, global multicenter phase III trials, enrolling a total of 1,072 patients with CLDN18.2-positive, HER2-negative locally advanced unresectable or metastatic gastric and gastroesophageal junction adenocarcinoma [14]. Patients were randomized to receive either zolbetuximab plus chemotherapy or placebo plus chemotherapy, with the SPOTLIGHT study using the mFOLFOX6 regimen and the GLOW study using the CAPOX regimen [14]. Pooled analysis showed that compared with placebo plus chemotherapy, zolbetuximab combined with chemotherapy significantly prolonged PFS and OS in HER2-negative, CLDN18.2-positive advanced gastric cancer patients [14]. The median PFS in the treatment and placebo groups was 9.2 months and 8.2 months, respectively, with a 29% reduction in the risk of disease progression (HR=0.71; 95% CI: 0.61–0.83) [14]. Regarding key secondary endpoints, zolbetuximab plus chemotherapy also significantly improved OS: the median OS was 16.4 months in the treatment group versus 13.7 months in the placebo group, corresponding to a 23% reduction in the risk of death (HR=0.77; 95% CI: 0.67–0.89), and the 2-year survival rate in the treatment group was double that of the control group [14]. Based on the favorable efficacy demonstrated in these two pivotal phase III trials, the zolbetuximab plus chemotherapy regimen has been approved by Japanese regulatory authorities for the treatment of CLDN18.2-positive, unresectable, or advanced gastric cancer patients and has also been submitted for approval in China, the United States, and Europe.

### 3.2. Antibody-Drug Conjugate (ADC) drugs

ADCs combine the targeting specificity of monoclonal antibodies with the potent cytotoxicity of chemotherapeutic drugs [15]. By linking the two via a cleavable linker, ADCs can deliver cytotoxic

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agents precisely to tumor cells, enhancing therapeutic efficacy while reducing adverse effects. Significant progress has been made in the development of CLDN18.2-targeted ADCs.

CMG901 (AZD0901) is the world's first CLDN18.2-targeted ADC to enter clinical trials. It was jointly developed by Keymed Biosciences (Chengdu) Co., Ltd., LaNova Medicines (Shanghai) Limited, and AstraZeneca [16]. This drug links an anti-CLDN18.2 monoclonal antibody to monomethyl auristatin E (MMAE) via a cleavable linker. In November 2023, Professor Ruihua Xu's team at the Sun Yat-sen University Cancer Center published the results of a phase I clinical trial of CMG901 in patients with advanced solid tumors. The study included 27 patients with advanced solid tumors (13 with gastric/GEJ adenocarcinoma and 14 with pancreatic cancer) in the dose-escalation phase, and 107 patients with advanced gastric or GEJ adenocarcinoma in the dose-expansion phase, all of whom had failed multiple lines of standard therapy. Among 109 evaluable gastric/GEJ adenocarcinoma patients, the objective response rate (ORR) was 29%, and the confirmed disease control rate (DCR) was 65%. In 89 patients with high CLDN18.2 expression (defined as ≥20% of tumor cells showing staining intensity ≥2+), the confirmed ORR was 35%, and the confirmed DCR was 70%. For all patients with high CLDN18.2 expression, the median PFS was 4.8 months and the median OS was 11.8 months. The recommended dose of CMG901 was established as 2.2 mg/kg. During the dose-expansion phase, although 68% of patients experienced treatment-emergent adverse events (TEAEs) of grade ≥3, the most common grade ≥3 TEAEs were neutropenia (21%), anemia (14%), and vomiting (10%). CMG901 is currently undergoing an international, multicenter phase III study (NCT06346392) to compare the efficacy and safety of CMG901 monotherapy with investigator's choice of standard therapy in patients with CLDN18.2-expressing advanced solid tumors [16].

LM-302 is a CLDN18.2-targeted ADC independently developed by LaNova Medicines (Shanghai) Limited. Its structure consists of a CLDN18.2-specific antibody, a cleavable linker, and the cytotoxic payload MMAE. Preclinical studies have demonstrated that LM-302 exhibits good safety and activity both in vitro and in vivo. The drug has received three orphan drug designations from the U.S. FDA for pancreatic cancer, gastric and gastroesophageal junction (G/GEJ) adenocarcinoma, and cholangiocarcinoma. In a multicenter, two-stage, randomized phase Ib/II clinical trial for cholangiocarcinoma, six patients received LM-302 in combination with cadonilimab. The results showed that three patients (with CLDN18.2 expression rates of 30%, 40%, and 80%, respectively) achieved a partial response (PR). In a phase I/II clinical study targeting gastric/G/GEJ adenocarcinoma, as of November 15, 2023, among 36 evaluable G/GEJ adenocarcinoma patients who had received at least two prior systemic therapies, 11 patients achieved PR and 16 patients maintained stable disease (SD), yielding an objective response rate (ORR) of 30.6% and a disease control rate (DCR) of 75%. The progression-free survival (PFS) was 7.16 months, while overall survival (OS) had not yet been reached [17].

IBI343 is a CLDN18.2-targeted ADC developed by Innovent Biologics (Suzhou) Co., Ltd. It exerts antitumor effects through CLDN18.2-dependent internalization and bystander killing. Data reported in Nature Medicine and at ASCO in 2025 showed that, in patients with advanced gastric/gastroesophageal junction (G/GEJ) adenocarcinoma, the 6 mg/kg high-expression cohort achieved a confirmed objective response rate (ORR) of 29.0% and a disease control rate (DCR) of 90.3%, with a median overall survival (OS) of 10.8 months. Among high-expression pancreatic cancer patients, the ORR was 22.7%, DCR 81.8%, and median OS 9.1 months. Safety was primarily characterized by hematologic toxicity, with relatively low gastrointestinal toxicity. In 2024, the drug received breakthrough therapy designation from the CDE for advanced G/GEJ adenocarcinoma, and

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in 2025 it received a breakthrough therapy designation for pancreatic cancer. International, multicenter phase III studies for gastric and pancreatic cancer are currently underway.

ATG-022 is a CLDN18.2-targeted ADC independently developed by Antengene Corporation Limited. Its structure comprises an anti-CLDN18.2 monoclonal antibody, a apoptosis-inducing cytotoxic payload, and a linker that is cleaved only intracellularly, enabling bystander killing. The drug exhibits low nanomolar affinity for CLDN18.2 and demonstrates potent antitumor activity both in vitro and in vivo. At the 2024 ASCO Annual Meeting, AutekBio reported data from a phase I multicenter, open-label, dose-escalation study of ATG-022 in patients with advanced solid tumors. Among the seven enrolled gastric cancer patients, three were confirmed as CLDN18.2-positive: one patient receiving 0.9 mg/kg maintained stable disease with tumor shrinkage for over six months, confirming the tolerability of ATG-022; in the 1.8 mg/kg cohort, one gastric cancer patient (CLDN18.2 expression status pending) achieved a partial response (PR). Notably, in the 2.4 mg/kg cohort, one gastric cancer patient with CLDN18.2-negative expression achieved a complete response (CR).

### 3.3. Bispecific antibodies

Bispecific antibodies can simultaneously bind two different antigen epitopes, offering unique advantages in tumor therapy. Currently, research and development of CLDN18.2-targeted bispecific antibodies are actively underway.

Q-1802, developed by Qure Biotechnology, is a humanized bispecific antibody targeting the tumor-specific antigen CLDN18.2 and the immune checkpoint PD-L1. Preliminary phase I clinical data were presented at the 2022 ASCO Annual Meeting [18]. In an international, multicenter phase I clinical trial (NCT04260191), AMG910, a T-cell engager developed based on half-life extension technology, has two ends that can respectively recognize and bind CLDN18.2 on cancer cells and CD3 on T cells. This enables the formation of close connections between cancer cells and functional T cells, thereby triggering targeted immune responses [19]. The trial results showed that among 36 subjects with measurable tumor lesions, 31 experienced varying degrees of tumor shrinkage, yielding an objective response rate (ORR) of 48.6% and a disease control rate (DCR) of 73.0%. Among all gastric cancer patients, the ORR was 57.1%. Subgroup analysis of baseline characteristics in 28 patients with gastric/Gastroesophageal Junction (G/GEJ) adenocarcinoma indicated that even in patients with poor prognostic factors—such as prior failure of PD-(L)1 inhibitors, presence of peritoneal metastasis, or signet-ring cell carcinoma histology—the ORR remained at or above 50%.

### 3.4. CAR-T cell therapy

CAR-T cell therapy has emerged as a significant advance in tumor immunotherapy in recent years. It involves genetically modifying a patient's own T cells to express a chimeric antigen receptor (CAR) that can specifically recognize tumor antigens, thereby enabling T cells to selectively target and kill tumor cells. In gastric cancer treatment, CLDN18.2-targeted CAR-T therapy has shown promising potential.

CT041 is an autologous CAR-T candidate targeting CLDN18.2, independently developed by CARsgen Therapeutics. It is expected to become the world's first therapy of its kind, applicable for treating CLDN18.2-positive solid tumors, such as gastric/gastroesophageal junction (G/GEJ) cancer and pancreatic cancer. At the 2021 European Society for Medical Oncology (ESMO) Annual Meeting, study data were presented showing that, as of April 8, 2021, 37 patients with digestive

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system tumors had received CT041 infusions, with a median follow-up of 7.6 months (95% CI: 5.6–8.6). The overall ORR for all enrolled patients was 48.6% (95% CI: 31.9%–65.6%), with gastric cancer patients achieving an ORR of 57.1% (95% CI: 37.2%–75.5%). Among 18 gastric cancer patients who had failed at least two prior lines of therapy (44% previously received PD-1/PD-L1 immunotherapy), the overall ORR was 61.1%, progression-free survival (PFS) was 5.4 months, and overall survival (OS) was 9.5 months. Regarding safety, the most common grade ≥3 adverse events (AEs) were hematologic toxicities, which resolved within two weeks. No immune effector cell-associated neurotoxicity, treatment-related deaths, or grade ≥3 cytokine release syndrome events were observed.

Professor Lin Shen's team at Peking University Cancer Hospital conducted further in-depth studies on CT041, with results published in the internationally renowned journal Nature Medicine. This was a single-center, open-label, single-arm phase I study involving patients with CLDN18.2-positive advanced gastrointestinal tumors (defined as ≥40% of tumor cells with membrane staining intensity ≥2+). As of January 26, 2024, the median follow-up since the first infusion of CT041/satri-cel was 32.4 months. Among 98 patients, 90 had target lesions, of which 70 experienced tumor regression. The overall ORR was 42.2% and the DCR was 91.1%. Among GC/GEJ patients receiving CT041/satri-cel monotherapy (59 patients), 51 had target lesions, with ORR and DCR of 54.9% (28/51) and 96.1% (49/51), respectively, and a median duration of response (DOR) of 6.4 months. The median PFS and OS for these 59 patients were 5.8 months and 9.0 months, respectively. Subgroup analysis indicated that among GC/GEJ patients treated with CT041/satri-cel monotherapy, patients with high CLDN18.2 expression (≥70% of tumor cells with membrane staining intensity ≥2+) had superior PFS compared with low/medium expression patients (7.1 months vs. 4.2 months, P = 0.00257). Patients with liver metastases (3.9 months vs. 7.1 months, P = 0.0327) or bone metastases (3.1 months vs. 7.5 months, P = 0.0009) exhibited significantly shorter PFS. CLDN18.2-high patients without liver or bone metastases showed markedly superior PFS (8.4 months vs. 3.7 months, P = $0.00\times10^{-5}$) and OS (13.1 months vs. 6.3 months, P = 0.0028) [20]. The study also explored the feasibility and clinical value of "early leukapheresis" during first-line treatment. Among GC/GEJ patients receiving monotherapy, compared with the conventional leukapheresis cohort (48 patients), the early leukapheresis cohort showed numerically longer PFS (7.1 months vs. 5.5 months, P = 0.8912) and OS (10.2 months vs. 8.8 months, P = 0.6683). On March 3, 2025, CT041 was included by the Center for Drug Evaluation (CDE) of the National Medical Products Administration (NMPA) as a breakthrough therapy for treating CLDN18.2-positive advanced gastric/G/GEJ adenocarcinoma patients who had failed at least two prior lines of therapy.

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## 4. Summary of phase III CLDN18.2 clinical drugs

Table 1. Phase III CLDN18.2 clinical drugs

| Drug Name | Development Code | Drug Type | Company | Indication |
|---|---|---|---|---|
| Osemitamab | MSB-018; TST-001 | Monoclonal antibody (ADCC-enhanced) | Suzhou Transcenta Holding Limited, Hangzhou HJB Biologics Co., Ltd. | Solid tumors, cholangiocarcinoma, esophageal cancer, gastric cancer, pancreatic cancer, tumor, lung cancer, gallbladder cancer |
| IBI-343 | IBI-343; IBI343 | ADC (TOP1i toxin) | Innovent Biologics (Suzhou) Co., Ltd. | Solid tumors, esophageal cancer, gastric cancer, pancreatic cancer, tumor |
| LM-302 | LM-302; TPX-4589; BMS-986476 | ADC (MMAE payload) | LaNova Medicines (Shanghai) Limited | Solid tumors, gastric cancer, esophageal cancer, pancreatic cancer, tumor, gastrointestinal cancers |
| SYSA-1801 | SYSA-1801; SYSA1801; CPO-102; EO-3021 | ADC (MMAE payload) | CSPC Pharmaceutical Group Limited | Solid tumors, gastric cancer, esophageal cancer, pancreatic cancer, tumor, digestive system tumors, gastrointestinal cancers |
| SHR-A-1904 | SHR-A-1904; SHR-A1904 | ADC (TOP1 inhibitor) | Shanghai Hengrui Pharmaceutical Co., Ltd. | Cystic lymphangioma, solid tumors, esophageal cancer, gastric cancer, pancreatic cancer |
| M-108 | M108;M-108 | Monoclonal antibody (ADCC-enhanced) | FutureGen Biopharmaceutical (Beijing) Co., Ltd. | Solid tumors, esophageal cancer, gastric cancer, pancreatic cancer |
| CMG-901 | CMG-901; CMG901; AZD-0901; AZD0901 | ADC (world's first CLDN18.2-targeted ADC, MMAE) | Keymed Biosciences (Chengdu) Co., Ltd. | Solid tumors, cholangiocarcinoma, esophageal cancer, gastric cancer, pancreatic cancer, pancreatic ductal carcinoma |
| ASKB-589 | ASKB-589 | Monoclonal antibody (combined with chemotherapy) | Aosaikang Pharmaceutical (Jiangsu) Co., Ltd., AskGene Pharma Inc | Solid tumors, esophageal cancer, gastric cancer, pancreatic cancer, adenocarcinoma |

Currently, multiple drugs targeting CLDN18.2 have entered phase III clinical trials. These drugs are developed by different companies and have distinct development codes. Their indications are broad, primarily focusing on solid tumors and digestive system cancers (Table 1).

### 4.1. Osemitamab (MSB-018; TST-001)

Osemitamab is jointly developed by Suzhou Transcenta Holding Limited and Hangzhou HJB Biologics Co., Ltd. It is one of the leading CLDN18.2-targeted antibody therapy candidates worldwide, developed using the Immune Tolerance Breakthrough (IMTB) technology platform. The drug exhibits high affinity for CLDN18.2 and can effectively recognize and kill CLDN18.2-expressing tumor cells through ADCC and CDC mechanisms. Its fucosylation level is significantly reduced during production, further enhancing NK cell-mediated ADCC activity. Preclinical studies have shown that Osemitamab, when combined with anti-PD-L1/PD-1 antibodies and oxaliplatin/5-fluorouracil, demonstrates good antitumor efficacy in tumor models. The U.S. FDA has granted it orphan drug designation for the treatment of patients with gastric or gastroesophageal junction adenocarcinoma and pancreatic cancer. Ongoing clinical trials (Transtar101, Transtar102) are being

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conducted in the U.S. and China, targeting advanced gastric/gastroesophageal junction cancer, advanced pancreatic cancer, and other late-stage solid tumors, aiming to evaluate safety, tolerability, pharmacokinetics, and preliminary efficacy.

### 4.2. IBI-343

IBI-343, developed by Innovent Biologics (Suzhou) Co., Ltd., is a recombinant human anti-CLDN18.2 ADC. It binds to CLDN18.2-expressing tumor cells and undergoes CLDN18.2-dependent ADC internalization. After lysosomal processing, the active payload (TOP1i) is released, causing DNA damage and ultimately inducing tumor cell apoptosis. The free drug also exerts a "bystander killing effect," spreading to eliminate neighboring tumor cells. Preliminary phase I results in patients with advanced pancreatic cancer were reported at the 2024 ASCO Annual Meeting. In the 6 mg/kg dose group, among 10 evaluable CLDN18.2-positive (1/2/3+ ≥60%) pancreatic cancer patients, the overall ORR was 40%. The U.S. FDA has granted it Fast Track designation for the treatment of patients with advanced unresectable or metastatic pancreatic cancer. The China National Medical Products Administration (NMPA) has also granted breakthrough therapy designation for the treatment of CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma. A multicenter phase III trial for this indication is currently in preparation.

### 4.3. LM-302 (LM-302; TPX-4589; BMS-986476)

Developed by LaNova Medicines (Shanghai) Co., Ltd., LM-302 is currently undergoing clinical trials targeting CLDN18.2-positive advanced solid tumors, including gastric cancer, gastroesophageal junction (GEJ) cancer, esophageal cancer, colorectal cancer, ovarian cancer, pancreatic cancer, gastrointestinal tumors, and cholangiocarcinoma. The drug is administered via intravenous infusion and consists of a CLDN18.2-specific antibody conjugated to the cytotoxic payload MMAE through a cleavable vc-pab linker. Preclinical studies demonstrated favorable safety and in vitro/in vivo activity. The U.S. FDA has granted three Orphan Drug Designations for pancreatic cancer, gastric and gastroesophageal junction cancer, and cholangiocarcinoma. In a multicenter, two-stage, randomized phase Ib/II clinical trial for cholangiocarcinoma, partial responses were observed in some patients. Phase I/II clinical studies for gastric/GEJ adenocarcinoma are also underway.

### 4.4. SYSA-1801 (SYSA-1801; SYSA1801; CPO-102; EO-3021)

Developed by CSPC Jishi Biological Pharmaceutical Co., Ltd., SYSA-1801 is designed for the treatment of solid tumors, gastric cancer, esophageal cancer, pancreatic cancer, gastrointestinal tumors, and digestive system malignancies. As an anti-CLDN18.2-MMAE ADC, it targets tumor cells via an anti-CLDN18.2 antibody after intravenous administration, followed by internalization, delivering the MMAE toxin into tumor cells to exert its therapeutic effect. Although large-scale clinical data are currently lacking, its ADC mechanism indicates the potential for precise targeting of tumors with high CLDN18.2 expression to inhibit tumor growth. The development is based on accurate targeting of CLDN18.2, and subsequent clinical studies will focus on evaluating efficacy and safety across different tumor types.

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### 4.5. SHR-A-1904 (SHR-A-1904; SHR-A1904)

Developed by Hengrui Pharmaceuticals Co., Ltd. (Shanghai), SHR-A-1904 is an ADC drug targeting CLDN18.2. Its active indications include gastric adenocarcinoma, CLDN18.2-positive gastroesophageal junction adenocarcinoma, and CLDN18.2-positive gastric cancer, with ongoing clinical trials for solid tumors, advanced malignant solid tumors, and advanced pancreatic cancer at various stages. Results from a phase I clinical study (NCT04877717) presented at the 2024 ESMO conference demonstrated certain efficacy in 73 patients with CLDN18.2-positive gastroesophageal junction cancer or gastric cancer. The drug exerts its antitumor effect by conjugating a cytotoxic agent to an anti-CLDN18.2 antibody for targeted delivery. Future studies will further investigate its efficacy across different stages and metastatic statuses, as well as its potential in combination therapy.

### 4.6. M-108 (M108; M-108)

Developed by FutureGen Biopharmaceutical (Beijing) Co., Ltd., M-108 primarily targets solid tumors, esophageal cancer, gastric cancer, and pancreatic cancer. Publicly available information is currently limited; however, it is hypothesized that the agent may act by specifically binding CLDN18.2, thereby activating host immune responses or blocking tumor cell–associated signaling pathways. In preclinical studies it may have demonstrated inhibitory effects against CLDN18.2-positive tumor cells in cell-based assays and animal models. As the program advances into Phase III trials, study efforts will focus on assessing safety and efficacy across different dose regimens and tumor types, optimizing dosing strategies, and exploring potential synergistic effects when combined with conventional therapies.

### 4.7. CMG-901 (CMG-901; CMG901; AZD-0901; AZD0901)

Developed by Keymed Biosciences (Chengdu) Co., Ltd., CMG-901 is an antibody-drug conjugate (ADC) in which an anti-CLDN18.2 monoclonal antibody is conjugated to MMAE via a cleavable linker. According to the results of a Phase I clinical trial released in November 2023, among 109 evaluable patients with gastric cancer or gastroesophageal junction adenocarcinoma, the objective response rate (ORR) was 29%, and the confirmed disease control rate (DCR) was 65%. In the subgroup of 89 patients with high CLDN18.2 expression, the confirmed ORR reached 35%, and the confirmed DCR was 70%. The median progression-free survival (PFS) for all patients with high CLDN18.2 expression was 4.8 months, and the median overall survival (OS) was 11.8 months. The recommended dose was determined to be 2.2 mg/kg. An international, multicenter Phase III trial is currently underway to compare the efficacy and safety of CMG-901 monotherapy versus investigator’s choice of standard treatment in patients with advanced solid tumors expressing CLDN18.2.

### 4.8. ASKB-589

Jointly developed by Aosaikang Pharmaceutical (Jiangsu) Co., Ltd. and AskGene Pharma Inc, ASKB-589 is intended for the treatment of solid tumors, esophageal cancer, gastric cancer, pancreatic cancer, and adenocarcinomas. Although publicly available information regarding its mechanism of action and clinical data remains limited, targeting CLDN18.2 suggests a potential mode of action by blocking CLDN18.2-associated signaling pathways to inhibit tumor cell proliferation, migration, and invasion. Preclinical studies likely included preliminary assessments of

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safety and efficacy. As the program progresses to Phase III clinical trials, researchers will closely monitor efficacy and safety parameters across different dosing regimens and tumor types, including objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). In addition, the optimal combination strategies with other therapies will be explored to enhance therapeutic outcomes in various tumor indications.

## 5. Summary and outlook

As an emerging target in the treatment of gastric cancer, CLDN18.2 has achieved remarkable progress in both basic research and clinical applications in recent years. From a deeper understanding of its protein structure and biological function to the development and clinical testing of multiple targeted therapies, CLDN18.2 has brought new hope to patients with gastric cancer, particularly those who are CLDN18.2-positive.

At present, several drugs targeting CLDN18.2—such as the monoclonal antibody zolbetuximab, antibody-drug conjugates CMG901, LM-302, IBI343, and ATG-022; bispecific antibodies Q-1802 and AMG910; and the CAR-T cell therapy CT041—have demonstrated varying degrees of efficacy in clinical trials. Among them, zolbetuximab has been approved for marketing in Japan and filed for approval in multiple countries and regions, becoming an important therapeutic option for patients with advanced CLDN18.2-positive gastric cancer. Other drugs at various stages of development are also under continuous exploration and optimization, with the potential to bring further breakthroughs in gastric cancer treatment.

Nevertheless, some challenges remain. First, although therapies targeting CLDN18.2 have shown promising results in some patients, a proportion of patients still fail to respond or develop resistance. This highlights the need for deeper studies into resistance mechanisms and strategies to overcome them. Second, the safety and toxicity of these drugs are also areas of concern. For example, ADCs may cause hematologic toxicity, while bispecific antibodies and CAR-T therapies may trigger immune-related adverse events. Further optimization of drug design and treatment regimens is needed to improve patient tolerability and quality of life. In addition, precise identification of patients who can benefit from CLDN18.2-targeted therapies remains a crucial issue. More accurate biomarkers and diagnostic methods are needed to achieve truly personalized treatment.

Looking forward, with the continuous advancement of research on CLDN18.2, it is expected that more efficient and low-toxicity targeted therapies will be developed. On the one hand, drug development will focus on further optimizing the structures and mechanisms of existing agents, such as improving the linkers and cytotoxic payloads of ADCs, enhancing the targeting specificity and affinity of bispecific antibodies, and refining the design of CAR-T cells. On the other hand, combination therapy strategies are likely to become a major focus. Integrating CLDN18.2-targeted therapies with conventional treatments such as chemotherapy, immunotherapy, and radiotherapy—or combining different targeted agents may improve therapeutic efficacy and help overcome drug resistance. Meanwhile, the ongoing advancement of emerging technologies, including gene-editing and single-cell sequencing, will facilitate a deeper understanding of the role of CLDN18.2 in tumorigenesis and progression, thereby providing a theoretical foundation for the development of novel therapeutic approaches. Furthermore, the application of artificial intelligence in drug development and clinical decision-making is expected to bring new opportunities for CLDN18.2-targeted therapy. Through big data analysis and machine learning, it will become possible to more precisely select patients, predict treatment outcomes, and optimize therapeutic regimens.

It is believed that in the future, with the integration of multiple disciplines and continued research, CLDN18.2-targeted therapy will play an increasingly important role in the treatment of

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gastric cancer, significantly improving patient prognosis and quality of life and bringing new hope for overcoming this challenging disease.

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