Claudin-18.2: Molecular mechanisms to clinical translation in solid tumors (Review)

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Abstract. Claudin 18.2 (CLDN18.2) is a functional subtype generated by alternative splicing of the CLDN18 gene. It is aberrantly overexpressed in a variety of gastrointestinal solid tumors such as gastric cancer and pancreatic cancer, and has emerged as a promising target for tumor targeted therapy. To date, zolbetuximab, a monoclonal antibody targeting CLDN18.2, has demonstrated survival benefits in phase III clinical trials. Antibody-drug conjugates, bispecific antibodies and chimeric antigen receptor T cell therapies also exhibit favorable application potential. Nevertheless, multiple challenges remain in this field. Distinction between CLDN18.1 and CLDN18.2 subtypes is often ambiguous, and the lack of unified immunohistochemistry testing criteria, including antibody selection and specimen types, leads to conflicting findings on prognostic research. Additionally, intratumoral heterogeneity, differential functions across tumor types and tumor microenvironment limitations further compromise the efficacy of targeted therapy. As a narrative review, this article systematically elaborates the molecular structure, expression regulatory mechanisms and clinicopathological value of CLDN18.2. Based on the data of 58 global clinical trials, it analyzes the current status, existing problems in testing standardization and drug development. Future directions are proposed, including standardizing detection protocols, developing differentiated drugs, optimizing combination regimens and overcoming drug resistance, aiming to provide references for the clinical translation and standardized application of CLDN18.2-targeted therapies.

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Contents

1. Introduction

Claudin 18.2 (CLDN18.2) is a subtype produced by alternative splicing of the CLDN18 gene and belongs to the claudin family. Under physiological conditions, it is specifically localized at the tight junctions of gastric mucosal epithelial cells, maintaining cell polarity and barrier function (1). During malignant transformation, the loss of cell polarity and disruption of tight junctions expose the extracellular epitopes of CLDN18.2, converting it into a tumor-associated antigen amenable to targeted therapy. This process is regulated by the protein kinase C (PKC) and ERK/MAPK pathways, which in turn activate the MAPK and PI3K/AKT pro-survival signaling cascades (2).

CLDN18.2 is abnormally expressed in multiple solid tumors. Its positive rate is ~35% in gastric cancer and reaches 60-90% in pancreatic ductal adenocarcinoma; overexpression is also observed in colorectal cancer and lung cancer (3-5). Notably, CLDN18.2-positive tumors often exhibit specific clinicopathological features: Patients are mostly <70 years old, Epstein-Barr virus-positive, diagnosed at an advanced stage and have a lower incidence of liver metastasis (6). Globally, >1 million new cases of gastric cancer and 500,000 new cases of pancreatic cancer occur annually, with a 5-year survival rate for advanced patients of <10% (7).

Since the first CLDN18.2-targeting monoclonal antibody, zolbetuximab, entered clinical trials in 2016, research in this field has experienced explosive growth (8,9). Zolbetuximab, a chimeric IgG1 monoclonal antibody, exerts its anti-tumor effects through antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity (6). Two Phase III clinical trials, SPOTLIGHT and GLOW, confirmed that in HER2-negative patients with advanced gastric or gastroesophageal junction adenocarcinoma with high CLDN18.2 expression (≥75% of tumor cells with intensity ≥2+), Zolbetuximab combined with fluoropyrimidine-based chemotherapy significantly prolonged progression-free survival (PFS) and overall survival (OS) (10,11). Current CLDN18.2-targeting strategies are diversifying: Besides monoclonal antibodies, they include antibody-drug conjugates (ADCs), bispecific antibodies and chimeric antigen receptor (CAR)-T cell therapies (12). Particularly noteworthy is that the ADC CMG901 showed a 33% objective response rate even in patients with lower CLDN18.2 expression levels (≥20% of tumor cells with intensity ≥2+), which may be related to the bystander effect of ADCs (13).

Despite the promising prospects, this field still faces numerous challenges: Standardization of detection methods [different studies use expression thresholds ranging from 40 to 75% (11,14)], optimal biomarker combination strategies [co-expression patterns of CLDN18.2 with programmed cell death ligand 1 (PD-L1) and HER2] (15) and optimization of treatment sequences are key issues that need urgent resolution (5). This article integrates recent basic and clinical evidence, focusing on translational medicine challenges and systematically elaborates on the research progress of CLDN18.2 from molecular mechanisms to clinical translation.

This is a narrative review and no systematic literature screening or statistical meta-analysis was performed.

2. Molecular biological basis of CLDN18.2

Prior to the discussion, it is necessary to clarify the key terms involved. The CLDN18 gene generates two protein isoforms via alternative splicing: CLDN18.1 and CLDN18.2. CLDN18.1 is predominantly expressed in pulmonary epithelial cells, while CLDN18.2 is specifically distributed at the tight junctions of gastric epithelial cells and serves as the core target of this review (16). When interpreting published literature, it should be noted that results obtained using pan-CLDN18 antibodies (recognizing both isoforms) reflect the overall characteristics of CLDN18 rather than a single subtype. Only assays employing isoform-specific antibodies or probes can be attributed to CLDN18.1 or CLDN18.2, respectively. For instance, Zolbetuximab specifically binds to CLDN18.2 rather than CLDN18, whereas transcriptional regulation studies on the CLDN18 promoter generally target the whole gene. Furthermore, the two isoforms differ greatly in biological functions: CLDN18.1 mainly acts as a tumor suppressor in lung adenocarcinoma, while CLDN18.2 frequently exerts z effects in gastrointestinal cancers (17). These differences highlight the necessity of accurate isoform discrimination.

Molecular structure and function. CLDN18.2 belongs to the tight junction protein family, which consists of at least 27 transmembrane proteins and is a crucial component and functional structure of tight junctions, forming the paracellular barrier to control molecular flow between cells (4). Under normal physiological conditions, CLDN18.2 is specifically localized at the tight junctions of gastric mucosal epithelial cells, maintaining cell polarity, forming the paracellular barrier and regulating ion-selective permeability (18,19).

In terms of molecular structure, CLDN18.2 is a transmembrane protein with four transmembrane domains, two extracellular loops (ECL1 and ECL2), and N and C termini located in the cell (20). Its first extracellular loop (ECL1) is the key region for targeted drug binding. For example, Zolbetuximab specifically binds to an epitope on the first extracellular loop of CLDN18.2, located within the C-terminal domain (3). This structural feature determines its 'targetability'.

During malignant transformation, loss of cell polarity leads to abnormal exposure of CLDN18.2 epitopes on the cell membrane surface, a process involving regulation by PKC and ERK/MAPK signaling pathways (2). Functionally, CLDN18.2 is associated with anion permeability and barrier function, and its loss is related to atrophic gastritis and tumorigenesis (21,22). In the tumor microenvironment, CLDN18.2 promotes malignant phenotypes such as proliferation, invasion, angiogenesis and anti-apoptosis of tumor cells by activating RAS-RAF-MEK-ERK and PI3K-PDK1-AKT-mTOR signaling pathways (23,24). Furthermore, exposed CLDN18.2 can mediate adhesion between gastric cancer cells and cancer-associated fibroblasts (CAFs). This interaction is driven by the CAF marker S100A4, leading to the aggregation of cancer cells and stromal cells into clusters, forming tumor thrombi, thereby significantly increasing the risk of metastasis and embolic death (25).

Regulatory mechanisms of tumor expression. The regulation of CLDN18.2 expression in tumors is a complex process involving multiple levels and pathways, and its aberrant expression is a key event during malignant transformation.

Transcriptional and signaling pathway regulation. In normal gastric mucosa, CLDN18.2 expression may decrease due to *Helicobacter pylori* infection, leading to H+ paracellular leakage, upregulation of pro-inflammatory cytokines (including IL-1β) and neutrophil infiltration, ultimately causing chronic atrophic gastritis (26). At the signaling pathway level, the PKC pathway and the ERK/MAPK pathway are involved in regulating CLDN18.2 expression. Studies show that treatment with phorbol esters upregulates CLDN18.2 mRNA and protein expression in pancreatic and gastric cancer cell lines, while PKC inhibitors completely suppress this induction, indicating PKC pathway involvement in regulating CLDN18.2 expression during carcinogenesis (27,28). The HER2/HER3 signaling pathway is also associated with claudin-18 expression. IL-1β can inhibit claudin-18 protein expression and membrane localization by activating HER2/HER3-related signaling pathways, and this effect can be blocked by the HER2 inhibitor lapatinib (29).

Epigenetic regulation. Methylation of CpG islands in the promoter region is an important epigenetic mechanism regulating CLDN18.2 expression. The methylation status can completely prevent the transcription factor cAMP

responsive element binding protein 1 (CREB1) from binding to the CLDN18.2 promoter region, and CREB activation is necessary for CLDN18.2 transcription (1), ultimately leading to gene silencing (18,30).

Post-transcriptional regulation by microRNAs (miRNAs). miRNAs, as important molecules for post-transcriptional regulation of gene expression, regulate CLDN18.2 expression by binding to the 3'-UTR of CLDN18.2 mRNA. For example, miR-1303 and miR-767-3p can bind to CLDN18 mRNA, leading to translational inhibition or mRNA degradation (31).

Functional heterogeneity in malignant transformation. The function of CLDN18.2 may differ across cancer contexts. In gastric cancer, CLDN18.2 expression is significantly reduced in tumor tissue compared to surrounding normal mucosa or intestinal metaplasia, and its downregulation may promote cell proliferation and invasion (25,32). By contrast, downregulating CLDN18.2 inhibits the proliferation, invasion and tumorigenic capacity of cholangiocarcinoma cells. Specifically, in cholangiocarcinoma cell lines, the EGFR pathway and activated RAS can induce claudin-18 expression by activating ERK1/2, and the enhanced claudin-18 expression subsequently reactivates ERK1/2, forming a positive feedback loop that plays a promoting role in cholangiocarcinoma malignancy (24,33).

CLDN18 expression has a dual role in different tumor types: CLDN18.2 acts as a tumor suppressor in gastric cancer but an oncogene in esophageal cancer, pancreatic cancer, colorectal cancer and cholangiocarcinoma. Lung cancer mainly expresses CLDN18.1 instead of CLDN18.2, resulting in functional discrepancies between the two isoforms (2,18). This cancer-promoting function may be closely related to its remodeling of the tumor microenvironment. CLDN18.2-positive gastric cancer exhibits unique microenvironment characteristics: On one hand, it is significantly associated with higher PD-L1 expression [especially combined positive score (CPS) ≥5] and activation of immune-inflammatory-related pathways; on the other hand, its microenvironment shows strong stromal remodeling and fibrosis features, with highly active stromal-related signaling pathways such as TGF-β/bone morphogenetic protein (34). These immune-activated but fibrosis-rich microenvironment features shaped by CLDN18.2 expression may collectively form the basis for tumor progression and potential treatment resistance.

3. Clinicopathological value: Controversies and consensus

Contradictory evidence on prognostic value. Conflicting conclusions regarding the prognostic value of CLDN18.2 in gastric cancer mainly stem from systemic discrepancies in detection and interpretation protocols. First, the positive staining cut-off value is a major source of divergence. The phase III SPOTLIGHT and GLOW trials defined CLDN18.2 positivity as ≥75% tumor cells with moderate to strong staining (10,11), while the earlier phase II FAST trial adopted a cut-off of 40% positive tumor cells (15). A high cut-off of 75% can select patients with the optimal response to Zolbetuximab, but excludes potential beneficiaries with lower expression. Therefore, the selection of cut-off values requires a balance between maximizing therapeutic efficacy and expanding the eligible patient population. Second, intratumoral heterogeneity cannot be ignored. CLDN18.2 presents a heterogeneous distribution within tumors, and relevant studies have shown that only 46.7% of samples yield consistent results when detected with two different antibodies (5). Furthermore, tumor type differences further aggravate inconsistent research findings. In gastric cancer, CLDN18.2 downregulation promotes cell proliferation and invasion; in cholangiocarcinoma, reduced CLDN18.2 expression inhibits cell growth and tumorigenesis. Such functional heterogeneity across tumors indicates that its prognostic value cannot be generalized and must be interpreted based on specific cancer types.

Established role as a predictive biomarker. Despite controversies over its prognostic value, the role of CLDN18.2 as a predictive biomarker has been clearly validated through key Phase III clinical trials. Its core value lies in predicting patient response to CLDN18.2-targeted therapy.

Studies show that in patients with gastric cancer receiving chemotherapy, high CLDN18.2 expression is associated with treatment resistance. More importantly, CLDN18.2-targeted therapy has shown significant efficacy in CLDN18.2-positive patients. Two Phase III studies (SPOTLIGHT and GLOW) confirmed that in patients with CLDN18.2-positive (defined as ≥75% of tumor cells with expression intensity ≥2+), HER2-negative advanced gastric or gastroesophageal junction adenocarcinoma, adding the monoclonal antibody Zolbetuximab to standard chemotherapy significantly improved PFS and OS (10,11). The two global phase III double-blind trials (SPOTLIGHT: 565 cases; GLOW: 507 cases) indicated the following: i) In the SPOTLIGHT trial, Zolbetuximab plus modified FOLFOX (mFOLFOX) achieved mPFS of 10.61 vs. 8.67 months [hazard ratio (HR)=0.75] and mOS of 18.23 vs. 15.54 months (HR=0.75); ii) in the GLOW trial, Zolbetuximab plus capecitabine and oxaliplatin (CAPOX) achieved a median (m)PFS of 8.21 vs. 6.80 months (HR=0.687) and mOS of 14.39 vs. 12.16 months (HR=0.771) (12). These data establish CLDN18.2 as a predictive biomarker guiding targeted therapy selection.

Furthermore, CLDN18.2 expression overlaps with and complements other known biomarkers. Research found that among patients with HER2-negative, PD-L1 CPS 0 and mismatch repair-proficient status, more than half (54%) of tumors still express CLDN18.2. By testing biomarkers including CLDN18.2, HER2, PD-L1 and mismatch repair (MMR), at least one targeted therapy option can be identified for 93% of patients with gastric and gastroesophageal junction adenocarcinoma (15). This highlights the indispensable role of CLDN18.2 testing in achieving precision therapy for gastric cancer and expanding the beneficiary population.

4. Detection standardization: Core bottlenecks and breakthroughs

Major discrepancies in immunohistochemistry (IHC) detection

Antibody variability. Antibody selection is the primary factor leading to heterogeneous IHC results for CLDN18.2. The commercially available VENTANA CLDN18 (43-14A) companion diagnostic kit has excellent specificity. However, research antibodies such as clone EPR19202 have unstable performance. Several studies have reported weak staining in

normal pancreatic tissues, while others detected no expression, leading to inconsistent and incomparable data (4).

Membrane vs. cytoplasmic staining. As a tight junction protein, functional CLDN18.2 positivity is defined as linear membrane staining. Cytoplasmic staining is regarded as non-specific background or protein internalization and shall not be included in scoring. Cytoplasmic interference frequently causes assessment bias in clinical practice (35). Therefore, establishing unified criteria focusing on membrane staining and excluding cytoplasmic signals is essential to improve detection reliability.

Discrepancy between biopsy and surgical specimens. Different specimen types lead to systematic detection bias. One representative cohort study focusing on pancreatic ductal adenocarcinoma show that the positive rate of fine-needle aspiration biopsy samples (67.71%) is significantly higher than that in surgical specimens (34.29%), which is mainly attributed to poor tissue fixation (4). For patients with unresectable advanced tumors who are only diagnosed by biopsy, the CLDN18.2 expression levels may be overestimated. Poorly fixed surgical specimens may produce false-negative results and deprive patients of targeted treatment opportunities.

Discordance between primary and metastatic lesions. Spatial expression heterogeneity exists between primary tumors and metastatic foci. A large-scale cohort study on metastatic gastric cancer indicated that the inconsistency rate of CLDN18.2 expression among different metastatic lesions reaches 20 to 40% (17). Single-site biopsy of either primary or metastatic tumors cannot reflect the overall CLDN18.2 expression status of systemic tumors, thus reducing the accuracy of patient screening.

Inter-observer variability. CLDN18.2 IHC scoring relies on visual evaluation by pathologists and is highly subjective. CLDN18.2 exhibits an intratumoral heterogeneous distribution, with positive and negative regions coexisting in the same tissue (36). Such heterogeneity complicates the assessment of positive cell proportion and staining intensity. Disagreements on staining grade (weak, moderate, strong) and positive cell ratio are common among observers, especially when the staining intensity is close to the positive cut-off value. Standardized training, digital pathology and artificial intelligence-assisted interpretation can reduce human errors and improve result consistency.

Clinical impact of cut-off values. The selection of positive cut-off values directly determines the eligibility and therapeutic outcomes of patients. The phase III SPOTLIGHT and GLOW trials defined CLDN18.2 positivity as ≥75% tumor cells with moderate to strong staining (2+/3+). This high cut-off identifies patients with the optimal response to Zolbetuximab (10,11). The phase II FAST trial adopted a relatively lenient cut-off of 40% positive cells and also achieved definite therapeutic benefits. In addition, ADCs exert anti-tumor activity via the bystander effect and remain effective even in patients with as low as 20% positive cells (14).

The selection of cut-off values represents a trade-off between maximizing efficacy and expanding the patient population. Differentiated cut-offs should be formulated according to the mechanisms of monoclonal antibodies, ADCs and CAR-T cell therapies. H-score and other continuous scoring systems are recommended to replace single percentage cut-offs for refined patient stratification. Uniform testing criteria and interpretation guidelines are critical to resolve the above discrepancies.

5. Current status of clinical research and development

All interventional clinical trials targeting CLDN18.2 were retrieved via the Citeline Trialtrove clinical intelligence platform (https://clinicalintelligence.citeline.com) on January 1, 2026, with the single search term 'claudin 18.2'. This database exclusively archives standardized registered clinical trial protocols without preclinical data, observational trials or duplicate entries. All 58 retrieved interventional trial records obtained from this database were fully incorporated into subsequent analysis, and no records were excluded after retrieval. Trials were stratified by phase, geographic region, tumor type, therapeutic modality and sponsor category following the official classification rules of this platform for subsequent analysis. A categorized overview of these trials is presented in Table I, and full individual trial data including official registry numbers are listed in Table SI; landmark trials such as the phase III SPOTLIGHT trial (NCT03504397) and negative phase II GLEAM pancreatic adenocarcinoma trial (NCT05910405) are elaborated on below to dissect translational discrepancies across tumor types (2).

Systematic analysis of the 58 trials revealed the current landscape: More than half of the trials are phase I studies focusing on safety exploration; Asia is the dominant region for clinical research; monoclonal antibodies, ADCs and CAR-T cell therapies are the three major research directions. CLDN18.2-targeted therapy is currently in the transition period from proof-of-concept to pivotal clinical validation.

Highly concentrated research activities in Asia. A total of 48 trials were conducted in Asia, far exceeding 6 trials in the Americas and 4 trials in Europe. This regional disparity is jointly determined by epidemiological characteristics and industrial development. Gastric cancer and pancreatic cancer have a higher incidence and heavier disease burden in Asian populations, leading to large unmet clinical needs (37). Meanwhile, the biopharmaceutical industry in Asia has developed rapidly in the fields of solid tumor targeted therapy and cell therapy. Supported by innovative drug policies, a research boom driven by clinical demands and industrial capabilities has been formed.

Although European and American institutions initiated the pivotal phase III trials of Zolbetuximab, they launched fewer follow-up studies, which mainly focused on mechanistic research and small-scale cross-tumor exploration. Most clinical evidence is generated from Asian populations. Additional real-world data across different ethnic groups are required to verify the efficacy and safety for global application.

Development led by a broad range of industrial forces. Small and medium-sized biopharmaceutical companies (all other pharma, Table SI) sponsored 39 trials, while academic institutions launched 6 trials and top global pharmaceutical enterprises (Top 20 pharma, Table SI) only participated in 4 trials. At present, small and medium-sized biotech companies take the lead in this field, while global pharmaceutical giants

Table I. Distribution of global claudin 18.2-targeted clinical trials.

Category/subgroup	Number of trials
Trial phase	
I	28
I/II	10
II	15
III	5
Geographic region	
Asia (including China)	48
Americas	6
Europe	4
Tumor type	
Gastric/gastroesophageal junction cancer	32
Pancreatic cancer	12
Biliary tract cancer	6
Other solid tumors	8
Therapeutic class	
Monoclonal antibody	12
Antibody-drug conjugate	18
Bispecific antibody	10
CAR-T cell therapy	15
Sponsor type	
Pharmaceutical companies (other enterprises)	42
Academic institutions	6
Top-tier global pharmaceutical enterprises	10
Start year	
2020 and earlier	12
2021	9
2022	10
2023	9
2024 (peak)	18

CAR T-cells, chimeric antigen receptor T-cells.

remain cautious. For small biotechs, CLDN18.2 is a mature target with validated phase III efficacy and relatively low research and development (R&D) risks, leading to a crowded pipeline (2). By contrast, leading pharmaceutical companies hold a wait-and-see attitude due to unresolved issues such as inconsistent detection standards, limited cross-tumor efficacy and gastrointestinal toxicity. Academic trials focus on basic translational research and biomarker analysis, which complement commercial studies.

Clinical trial phase skewed towards early stages. More than 60% of all trials are at phase I or I/II stages, while only 5 trials have entered phase III. Most candidate agents are still in the early clinical exploration stage. A large number of homogeneous early-phase products face high elimination risks without differentiated advantages, while a few mature candidates have advanced to pivotal studies and become the first-tier pipelines.

Diversified therapeutic modalities. Four major therapeutic modalities are currently under clinical development, covering monoclonal antibodies, ADCs, CAR-T cell therapies and bispecific antibodies.

Monoclonal antibodies account for 12 trials in total. Zolbetuximab serves as the representative agent with the most robust clinical evidence and official clinical approval for gastric and gastroesophageal junction cancer. It is supported by two positive global phase III pivotal trials, the SPOTLIGHT and GLOW studies (10,11). However, the phase II GLEAM trial investigating Zolbetuximab combined with chemotherapy for metastatic pancreatic cancer failed to meet its primary efficacy endpoint (38), which reveals obvious tumor-type discrepancies in therapeutic response.

ADCs occupy the largest number of ongoing trials (18 items), making them the most vibrant research branch. Benefiting from the unique bystander effect, ADCs can exert potent anti-tumor activity even in tumors with low CLDN18.2 expression, effectively expanding the pool of eligible patients.

CAR-T cell therapies are being evaluated across 15 trials and represent a promising hotspot for solid tumor immunotherapy, while their clinical application is still hampered by systemic immunosuppressive microenvironments and inadequate tumor infiltration capacity.

Bispecific antibodies correspond to 10 registered trials. This modality works by linking tumor cells and immune effector cells to amplify anti-tumor immune responses, accompanied by a favorable safety profile.

Overall, these four therapeutic approaches develop in parallel with distinct advantages, forming a differentiated pipeline layout to target CLDN18.2-positive malignancies.

Recent surge in clinical development activity. The number of newly initiated trials was 12 (in 2020 and earlier), 9 (in 2021), 10 (in 2022), 9 (in 2023) and peaked at 18 in 2024. The positive results of the SPOTLIGHT and GLOW trials published in 2023 greatly boosted industrial confidence and triggered a surge of new projects. In the next 2-3 years, competition will intensify and the research focus will shift from project initiation to differentiated value verification.

Indication layout. Trials are highly concentrated on gastric/gastroesophageal junction cancer (32 trials), followed by pancreatic cancer (12 trials) and biliary tract cancer (6 trials), with only 8 trials for other solid tumors. Gastric cancer is the priority indication with sufficient clinical evidence. Pancreatic and biliary cancers have high CLDN18.2 expression but poor response to monoclonal antibodies due to fibrotic and immunosuppressive microenvironments, thus serving as secondary exploratory indications. Cross-tumor expansion requires more preclinical and clinical evidence.

Monotherapy and combination therapy. Most phase I trials adopt single-agent regimens for safety evaluation. Combination regimens dominate phase II studies. Combining CLDN18.2-targeted agents with conventional chemotherapy follows the proven therapeutic paradigm established by zolbetuximab in gastroesophageal cancer (10,11). Combinations with programmed cell death 1/PD-L1 inhibitors are also widely explored, given the immune-activated features of

CLDN18.2-positive tumors. However, most combination regimens are empirically designed. Further stratified studies are needed to clarify optimal drug combinations, dosages and administration sequences.

In summary, global CLDN18.2-targeted research is in a period of rapid development and fierce competition. Asia leads clinical research and industrial companies dominate R&D. Major challenges include detection heterogeneity, limited cross-tumor efficacy and homogeneous pipelines. More phase III studies and technical optimizations are required to promote standardized and individualized clinical application.

6. Future directions

CLDN18.2 is a promising therapeutic target for gastrointestinal solid tumors. Current research features diversified pipelines and global layout. Nevertheless, inconsistent detection standards, tumor heterogeneity, variable cross-tumor efficacy and drug resistance restrict its clinical application (5).

Precision and standardization of biomarkers. It is urgent to promote the formulation of international multi-center guidelines to unify companion diagnostic antibodies, specimen handling and membrane-based interpretation criteria. Differentiated IHC cut-offs shall be formulated for monoclonal antibodies, ADCs and CAR-T therapies. H-score and other continuous scoring systems are recommended to quantify intratumoral heterogeneity and replace single percentage cut-offs. Liquid biopsies such as circulating tumor DNA and exosomes can be applied for dynamic monitoring and early relapse prediction (39). Combined multi-biomarker panels integrating CLDN18.2, HER2, PD-L1 and MMR are also worthy of exploration to expand the beneficiary population.

In-depth exploration of combination therapy strategies. Homogenization is prominent among current drug pipelines. Differentiated development based on drug mechanisms is critical: Optimize monoclonal antibody structure to reduce gastrointestinal off-target toxicity; improve ADC linkers and payloads to enhance activity in low-expression tumors; modify CAR-T cells to overcome the immunosuppressive microenvironment via chemokine engineering; develop bispecific antibodies targeting CLDN18.2 plus immune checkpoints. In addition, novel agents with high selectivity for CLDN18.2 over CLDN18.1 can be developed to reduce cross-reactivity (2,5).

Optimization of combination therapy based on tumor microenvironment. Single-agent therapy has limited efficacy. Most existing combination regimens are empirically designed without sufficient mechanistic guidance (34,38). CLDN18.2-positive gastric cancers present an immune-activated phenotype, while pancreatic and biliary cancers are characterized by severe fibrosis and immune suppression (34). Combination strategies should be tailored to tumor types: Prioritize immunotherapy combinations for gastric cancer; combine stroma-modulating and anti-angiogenic agents for fibrotic tumors.

The phase II open-label randomized GLEAM trial evaluated the combination of Zolbetuximab plus gemcitabine and nab-paclitaxel as first-line systemic treatment for patients with unresectable metastatic CLDN18.2-positive pancreatic ductal adenocarcinoma. Unlike Zolbetuximab's positive survival benefits validated in gastric and gastroesophageal junction carcinoma pivotal trials, this pancreatic-focused study was only presented as an abstract poster at the 24th European Society for Medical Oncology Congress held in September 2024 (38), and no full peer-reviewed journal manuscript has been published to date. The trial failed to meet its predefined primary endpoint of prolonged OS, confirming that chemotherapy regimens effective in CLDN18.2-positive upper gastrointestinal malignancies cannot be directly copied for pancreatic tumors. The underlying cause is the unique pathological feature of pancreatic lesions: Abundant dense fibrotic stroma creates a physical barrier to block drug penetration and immune cell infiltration, forming a strongly immunosuppressive microenvironment that blunts the anti-tumor activity of antibody-mediated cytotoxicity. Therefore, simple chemotherapy combinations matched for gastric cancer cannot achieve equivalent efficacy in pancreatic cancer. Future research should carry out prospective stratified controlled trials to screen optimal drug doses, treatment cycles and sequential administration schedules specifically for pancreatic CLDN18.2-positive populations (38).

Mechanisms and management of drug resistance. Primary and acquired resistance are inevitable obstacles for targeted therapy. Known resistance mechanisms include target loss, compensatory pathway activation and microenvironment remodeling (6). Future research shall profile resistance patterns based on clinical samples and organoid models, develop novel agents targeting alternative epitopes or bypass pathways and screen predictive biomarkers for early intervention.

Expansion to new indications. Current trials mainly focus on gastric and gastroesophageal junction cancer (14). Pancreatic and biliary cancers have high CLDN18.2 expression but unsatisfactory clinical outcomes (40), and other solid tumors remain in the exploratory stage (41). Indication expansion shall follow a stratified strategy based on inter-tumor functional heterogeneity. Tumors with similar biological features to gastric cancer should be prioritized, and microenvironment and resistance problems clarified before expanding to refractory malignancies. Subgroup analysis across regions and ethnicities is also required.

Personalized treatment and comprehensive management. CLDN18.2 is physiologically expressed in normal gastric mucosa, which easily causes gastrointestinal adverse reactions. ADCs and CAR-T therapies may induce cytokine release syndrome and hematological toxicity (14). Two complementary strategies can mitigate these toxic risks: optimizing drug structures to enhance tumor-targeting specificity and off-target toxicity reduction, and establishing standardized protocols for adverse event surveillance and clinical management. Multi-omics and clinical data should be integrated to build individualized treatment systems.

7. Conclusion

In conclusion, CLDN18.2 has become a valuable targeted agent for gastrointestinal solid tumors. The clinical success of Zolbetuximab has opened a new era for gastric cancer targeted

therapy. Globally, monoclonal antibodies, ADCs, bispecific antibodies and CAR-T cell therapies form diversified pipelines, with Asia as the core research region. At present, the confusion of CLDN18 isoforms, inconsistent IHC criteria and cut-offs, inter-tumor functional heterogeneity, homogeneous R&D pipelines, drug resistance and off-target toxicity remain major obstacles. In the future, international detection guidelines, differentiated drug design and microenvironment-adapted combination regimens shall be promoted. Combined with resistance research and standardized safety management, CLDN18.2-targeted therapies will benefit more patients with solid tumors and further improve the precision treatment system for gastrointestinal malignancies.

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Authors' contributions

XY and NL contributed to study conception. MZ and DW were the major contributors in writing the manuscript. YT retrieved, sorted and analyzed clinical trial data, and wrote the relevant sections. All authors participated in critical revision of intellectual content. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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