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Molecular characteristics, regulatory mechanisms, and targeted therapeutic strategies of Claudin18.2 in pancreatic cancer

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive malignancy with a rising incidence and a poor five-year survival rate. Current therapeutic strategies provide only limited survival benefit, underscoring the urgent need for novel therapeutic targets. The tight junction protein Claudin18.2 (CLDN18.2) is highly expressed in PDAC, presenting on tumor cell surfaces as a promising tumor-associated antigen with restricted expression in normal tissues. This review highlights the molecular characteristics, regulatory mechanisms, and targeted therapeutic developments of CLDN18.2 in PDAC, discussing the clinical progress and limitations of monoclonal antibodies (mAbs), bispecific antibodies (BsAbs), chimeric antigen receptor T-cell therapy (CAR-T cell therapy), and antibody-drug conjugates (ADCs), as well as future prospects for combination strategies and next-generation agents.

Keywords: Claudin18.2, PDAC, Targeted therapy, Biomarkers

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most prevalent and lethal malignancies worldwide, with a steadily rising incidence. According to the most recent epidemiological statistics, the global incidence and mortality rates of pancreatic carcinoma are approximately 6.22 and 5.74 per 100,000, respectively. Pancreatic cancer is expected to become the second leading cause of cancer-related death in the United States by 2030[1]. Due to the low rates of early diagnosis, rapid disease progression, and poor prognosis, the majority of PDAC patients are already at an advanced stage when diagnosed. By the time of diagnosis, curative options are often limited, and the five-year survival rate for pancreatic cancer remains approximately 13%[2–5]. Invasive growth, early metastasis, and a dense desmoplastic stroma are biological characteristics of PDAC that impede drug delivery and promote immune evasion[3]. Current systemic therapy for PDAC remains largely dependent on cytotoxic chemotherapy. Although FOLFIRINOX and gemcitabine plus albumin-bound paclitaxel are established treatment options, the survival gains remain limited[4,5]. Similarly, immune checkpoint blockade has produced little benefit in unselected PDAC, with activity largely confined to the rare microsatellite instability-high/deficient mismatch repair (MSI-H/dMMR) subgroup[6,7]. These clinical limitations highlight the need for druggable molecular targets that combine tumor selectivity with biomarker value for patient selection.

As one of the members of the tight junction protein family, claudins maintain the integrity of epithelial tight junctions by regulating paracellular permeability, ion homeostasis, and intercellular junction polarity. The family includes at least 27 members in mammals and exhibits highly tissue-specific expression patterns. Cancer cells frequently express altered forms of these proteins to promote tumor proliferation, invasion, and metastasis[8]. Among these, Claudin18.2 (CLDN18.2) is a stomach-specific isoform of Claudin18 (CLDN18) that is restrictedly expressed in normal tissues but aberrantly activated in several malignancies, particularly PDAC[9]. Importantly, during malignant transformation, loss of cell polarity exposes the CLDN18.2 epitope on the tumor cell surface, making it accessible to targeted therapies[10–13]. CLDN18.2 positivity in PDAC varies between 60%–90%, correlating with tumor differentiation[11]. Recent findings indicate that CLDN18.2 may serve both as a biomarker and a therapeutic target, with clinical trials already showing encouraging results for strategies such as monoclonal antibodies (mAbs) and antibody-drug conjugates (ADCs)[10].

Although Tojjari et al. provided a valuable overview of CLDN18.2 as an emerging therapeutic target in gastric cancer (GC) and pancreatic cancer, including CLDN18.2-directed therapies, resistance mechanisms, and toxicity management[10], their review primarily adopted a broad gastrointestinal cancer perspective. Consequently, several issues that are particularly relevant to PDAC remain insufficiently explored, including pancreatic cancer-specific biology, CLDN18.2 expression heterogeneity, assay standardization, microenvironmental barriers, and clinical translation strategies[14–18]. To address this gap, this review takes a PDAC-centered approach and systematically summarizes the current status of CLDN18.2 research in PDAC, including its molecular characteristics, regulatory mechanisms, and functional significance. Particular emphasis is placed on bridging recent molecular biology findings with current standard-of-care strategies and on highlighting innovative approaches to the challenges of clinical translation.

Structure of CLDN18.2

At least 27 claudin family members have been found in mammals, and their expression patterns are highly tissue-specific. The CLDN18 gene is located at 3q22.1 and has a length of about 35 kb. It comprises six exons and five introns. Alternative splicing of the first exon generates two isoforms with similar sequences, CLDN18.1 and CLDN18.2[12]. Although both isoforms are derived from the same gene, they differ markedly in tissue distribution and biological significance.

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CLDN18.2 is a 264-amino acid protein with a molecular weight of approximately 27 kDa and belongs to the claudin family of tetraspan transmembrane proteins. It consists of four transmembrane domains, two extracellular loops (extracellular loop 1 and extracellular loop 2), one intracellular loop, and cytoplasmic N- and C-terminal regions[19]. The extracellular loop 1 (ECL1), has significantly different sequences from CLDN18.1 and contains a disulfide bond essential for structural stability[20]. This region serves as the primary epitope for therapeutic antibodies, including zolbetuximab, to target CLDN18.2-positive cells selectively. Additionally, the extracellular loop 2 (ECL2) contains a hydrophobic amino acid sequence that can form dimers with claudin proteins on adjacent cells, thereby promoting intercellular adhesion[21] (Fig. 1).

CLDN18.2-expressing cells and expression profile in PDAC

CLDN18.1 and CLDN18.2 display markedly distinct tissue distribution patterns. This tissue-specific expression is caused by distinct promoter regions. CLDN18.2 has a gastric-specific promoter and is expressed at low levels in most non-gastric tissues through epigenetic silencing mechanisms[22]. Under physiological conditions, CLDN18.2 expression is largely restricted to the tight junctions of differentiated gastric epithelial cells, with little to no detectable expression in most healthy non-gastric tissues[12,13].

In PDAC, by contrast, CLDN18.2 may be aberrantly expressed in tumor epithelial cells, where it is predominantly detected as membranous staining. This pattern contrasts with its restricted distribution in normal gastric mucosa and is thought to involve the reprogramming of gastric lineage-related gene expression during pancreatic tumorigenesis[22], though the precise regulatory mechanisms remain incompletely understood. Because CLDN18.2 expression is largely absent from healthy non-gastric tissues, its ectopic activation in PDAC provides a favorable therapeutic window with limited on-target toxicity, establishing the biological rationale for CLDN18.2-directed therapy.

IHC remains the primary method for evaluating CLDN18.2 expression in PDAC, directly visualizing protein distribution in tumor tissue and providing a basis for identifying candidates for CLDN18.2-targeted therapy. Current data indicate that approximately 60%–90% of PDAC cases are CLDN18.2-positive, though staining intensity and distribution vary considerably among individual patients[12,23–25].

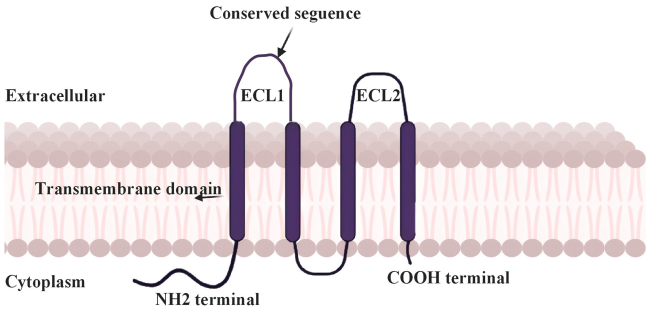

Fig. 1 The protein structure and function of CLDN18.2. CLDN18.2 contains four transmembrane domains, two extracellular loops (ECL1 and ECL2), one intracellular loop, and cytoplasmic N- and C-terminal regions. ECL1 contains major epitopes recognized by therapeutic antibodies, while ECL2 contributes to claudin-claudin interactions and intercellular adhesion.

A real-world German study used an antibody similar to the ones in the SPOTLIGHT and GLOW trials and applied the same IHC scoring criteria, where CLDN18.2 positivity was defined as moderate-to-strong membranous staining in ≥ 75% of tumor cells. The positive rate of CLDN18.2 in 309 patients with resectable PDAC was 30.4%[14]. CLDN18.2 expression appears to remain stable during pancreatic cancer progression, with consistent positivity observed in primary tumors, regional lymph nodes, and distant metastases[15]. Another study using the same detection system reported a 92.5% concordance rate for CLDN18.2 expression between biopsy and surgical resection specimens, among 211 resected, 133 biopsy, and 60 recurrent samples. However, the sensitivity of biopsy alone was only 54.6%, indicating a risk of underdetection. Concordance between primary and recurrent lesions was 83.3%, although reduced expression was observed in some local recurrences and liver metastases[16]. Given the considerable intratumor heterogeneity in PDAC, biopsy alone provides an initial assessment of CLDN18.2 expression, but incorporating surgical resection specimens improves the identification of patients likely to benefit from CLDN18.2-targeted therapy. CLDN18.2 expression has also been detected in PDAC precursor lesions, including pancreatic intraepithelial neoplasia (PanIN) and intraductal papillary mucinous neoplasm (IPMN)[17,18,26]. Collectively, these findings reinforce the need for a standardized CLDN18.2 testing protocol in PDAC.

The prognostic significance of CLDN18.2 expression in PDAC remains inconclusive. While some studies have reported that CLDN18.2 positivity correlates with prolonged overall survival[8, 21, 27,28], others have not reached similar conclusions[11]. Clinicopathological correlations have also been inconsistent. In some cohorts, CLDN18.2 expression has been associated with better tumor differentiation and lower rates of regional lymph node metastasis[11, 29]. However, one study reported a higher incidence of distant lymph node metastasis in CLDN18-positive cases[11]. This seemingly contradictory finding may reflect differences in nodal staging criteria, cohort composition, sample size, or the distinction between regional and distant nodal disease, and should therefore be interpreted with caution. In addition, CLDN18.2 expression has not shown a consistent association with human epidermal growth factor receptor 2 (HER2) expression or mismatch repair (MMR) status[9], suggesting that it should be evaluated as an independent biomarker. Overall, current evidence supports CLDN18.2 more strongly as a therapeutic biomarker than as an established prognostic marker in PDAC.

Several technical challenges hinder the clinical implementation of standardized CLDN18.2 testing in pancreatic cancer. Chief among these is the lack of a standardized immunohistochemistry (IHC) scoring system. Inconsistent positivity thresholds have substantially limited inter- and intra-laboratory comparability. Many early PDAC studies adopted positivity criteria originally derived from GC clinical trials. In the phase II FAST trials, positivity was defined as moderate-to-strong (≥ 2+ or 3+) membranous staining greater than 40% positive cancer cells; whereas the phase III SPOTLIGHT and GLOW trials adopted a stricter ≥ 75% standard[8]. While a lower positivity threshold may expand the population eligible for CLDN18.2-targeted therapy, it also risks increasing false positives and reducing the precision of patient selection. Although FAST, SPOTLIGHT, and GLOW were conducted in gastric or gastroesophageal junction adenocarcinoma (G/GEJ adenocarcinoma) rather than PDAC, they provide clinically validated models for linking antibody clones, assay platforms, scoring criteria, and positivity thresholds to treatment selection. In PDAC, these trials should therefore be used as methodological references for CLDN18.2 testing, rather than as directly transferable diagnostic standards.

A second challenge relates to the variable sensitivity and specificity across different CLDN18.2 antibody clones. Cross-study comparisons are further complicated by inconsistent reporting of key methodological details, including antibody clone, staining platform, detection system, and positivity threshold[12,14]. Future PDAC studies should provide complete assay information and adopt transparent reporting standards. Dedicated PDAC-specific validation studies are needed to define clinically meaningful cutoffs, improve inter-study reproducibility, and establish a reliable framework for CLDN18.2 assessment[17].

The role of CLDN18.2 in different cells and its function in PDAC

CLDN18.2 has context-dependent biological significance. In differentiated gastric epithelial cells, it is located within tight junction complexes and contributes to epithelial barrier function, cell polarity, and intercellular adhesion. In this physiological setting, its extracellular epitopes are relatively inaccessible to circulating antibodies, which may partly support the therapeutic selectivity of CLDN18.2-directed strategies[10,22]. During malignant transformation, loss of epithelial polarity and disruption of tight junction integrity can expose CLDN18.2 epitopes on the tumor cell surface, rendering them accessible to therapeutic agents. Therefore, the therapeutic value of CLDN18.2 depends not only on its expression level, but also on its membrane localization and epitope accessibility.

In PDAC, CLDN18.2 is best regarded as a tumor-associated membrane antigen with potential biological and therapeutic relevance. Recent studies suggest that CLDN18.2 may influence T-cell infiltration, ERK1/2 activation, tumor progression, metastasis, and sensitivity to CLDN18.2-targeted therapy[20, 30,31]. These findings indicate that CLDN18.2 may have broader biological significance beyond serving as a surface marker, although its direct role as an oncogenic driver in PDAC remains unclear.

Collectively, the restricted expression of CLDN18.2 in most healthy non-gastric tissues, combined with its aberrant membranous expression in PDAC, provides the rationale for developing mAbs, ADCs, bispecific antibodies (BsAbs), and chimeric antigen receptor T-cell therapy (CAR-T)[32–34].

Regulation of CLDN18.2

The regulation of CLDN18.2 expression in PDAC involves the interplay of multiple mechanisms, including promoter methylation, activation of signaling pathways, microRNA-mediated regulation, and remodeling of the immune microenvironment. Dysregulation of these mechanisms collectively contributes to the aberrant expression of CLDN18.2 in pancreatic cancer and shapes its functional roles (Fig. 2).

At the epigenetic level, promoter methylation is a key determinant of CLDN18.2 transcriptional activity. In the gastric epithelium, the methylation status of CpG islands within the CLDN18 gene promoter is inversely correlated with CLDN18.2 expression. Promoter methylation impedes transcription factor binding, thereby suppressing gene transcription and resulting in CLDN18.2 downregulation[35]. During pancreatic carcinogenesis, aberrant DNA methylation patterns disrupt this silencing mechanism, contributing to the ectopic expression of CLDN18.2 in PDAC[36].

Beyond epigenetic regulation, specific transcription factors also directly drive CLDN18.2 expression. Cellular studies have identified ZIC2 as a transcriptional activator of CLDN18.2, which binds to cis-regulatory elements in the CLDN18.2 promoter, elevates CLDN18.2 protein levels, and in turn activates the ERK1/2 pathway, ultimately promoting pancreatic cancer cell growth and metastasis[30].

At the post-transcriptional level, CLDN18.2 expression is further modulated by microRNAs. In several tumor types, miR-1303 and miR-767-5p have been found to interact with the 3' UTR of CLDN18.2 mRNA, reducing its stability or inhibiting its translation, thereby lowering CLDN18.2 protein levels[37]. Alterations in microRNA expression profiles in PDAC may similarly modulate CLDN18.2 abundance, though the specific regulatory mechanisms in this context remain to be fully characterized.

In addition to transcriptional control, CLDN18.2 is further regulated by post-translational modifications. A recent study demonstrated that O-GlcNAcylation at T204 in the cytoplasmic domain is associated with reduced expression level of CLDN18.2 in cancer cells. This not only reduces its potential as a therapeutic target but also decreases its binding efficiency with protein tyrosine phosphatase 1B (PTP1B) through reduced binding affinity. Concurrently, phosphorylated CLDN18.2 recruits and activates Src kinase *via* binding with its Src homology 2 (SH2) domain, thereby promoting migration, invasion, and distant metastasis of pancreatic cancer cells. Notably, treatment with low-dose KRAS G12D inhibitors can reduce CLDN18.2 O-GlcNAcylation and restore its membrane localization, supporting the rationale for combining KRAS-targeted agents with CLDN18.2-directed therapy[31].

Beyond its direct effects on tumor cells, CLDN18.2 also participates in shaping the immune microenvironment through a distinct mechanism. Zhou et al.[38] found that pancreatic cancer cells transferred membrane-bound CLDN18.2 to $CD8^+$ T cells *via* ALCAM-CD6-mediated trogocytosis, inducing T-cell metabolic dysregulation and functional exhaustion through β-catenin-dependent glucose metabolic reprogramming. These CLDN18.2-'dressed' $CD8^+$ T cells subsequently home to the bone marrow through the CXCL12-CXCR4 axis, where they release IL-1α to induce the differentiation of hematopoietic stem cells (HSCs) into immunosuppressive myeloid cells, thereby driving systemic immune senescence and promoting tumor growth. Blocking the interaction between CLDN18.2 and β-catenin using PC18.1 was shown to restore T-cell function, identifying CLDN18.2 as a mediator of systemic immunosuppression in PDAC.

Taken together, CLDN18.2 expression and function in PDAC are governed by a multilayered regulatory network spanning epigenetic, transcriptional, post-transcriptional, and post-translational mechanisms, as well as indirect effects on the immune microenvironment. A deeper understanding of these regulatory processes may reveal additional therapeutic vulnerabilities and inform strategies to enhance the efficacy of CLDN18.2-targeted therapies, several of which are discussed in the following section.

Therapeutic strategies

Due to its preferential expression in tumor tissues and restricted distribution in normal tissues, CLDN18.2 represents an attractive therapeutic target in pancreatic cancer[39]. At present, several CLDN18.2-targeted therapeutic strategies are under clinical investigation, including mAbs, BsAbs, CAR-T cell therapies, ADCs, and combination therapies. This section summarizes the clinical progress, challenges, and future prospects for these strategies in pancreatic cancer. The mechanisms of CLDN18.2-targeted therapies are shown in Fig. 3. An overview of ongoing trials is provided in Table 1 and Fig. 4.

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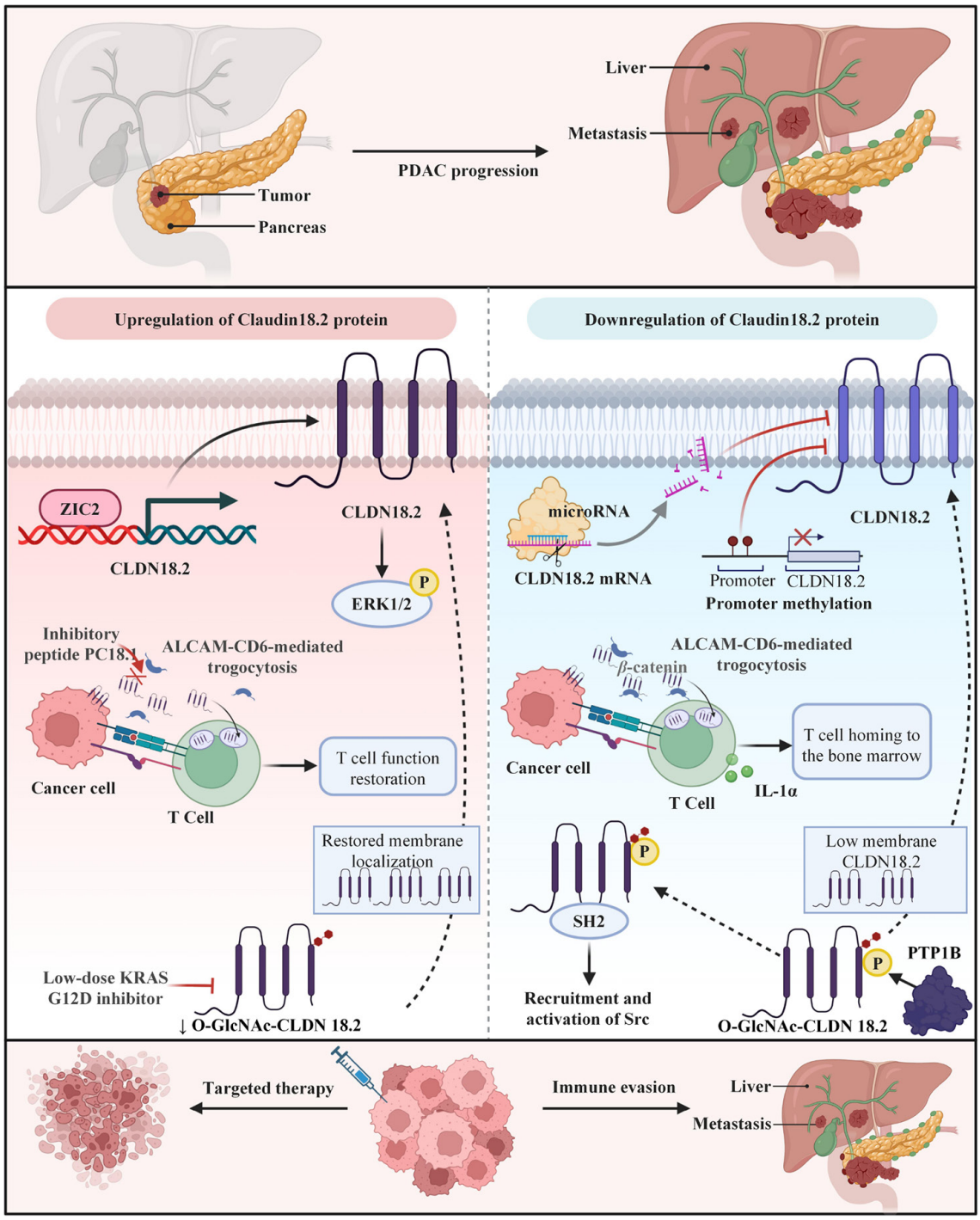

Fig. 2 Regulatory mechanisms of CLDN18.2 expression in PDAC. CLDN18.2 in pancreatic ductal adenocarcinoma (PDAC) is regulated by promoter methylation, ZIC2/ERK1/2 signaling, microRNAs, O-GlcNAcylation, and immune-mediated remodeling. O-GlcNAcylation at T204 reduces membrane CLDN18.2, weakens protein tyrosine phosphatase 1B (PTP1B) binding, increases phosphorylation, and promotes Src recruitment, thereby enhancing invasion, metastasis, and treatment resistance. KRAS G12D inhibition may reverse this process by reducing O-GlcNAcylation and restoring membrane localization. CLDN18.2 can also be transferred from tumor cells to $CD8^+$ T cells through ALCAM-CD6-mediated trogocytosis, driving β-catenin-dependent metabolic reprogramming, T-cell dysfunction, systemic immunosenescence, and tumor progression. PC18.1 may restore T-cell function by blocking CLDN18.2-β-catenin interaction.

Monoclonal antibodies (mAbs)

Monoclonal antibodies represent the earliest established CLDN18.2-targeted therapy. By binding to ECL1 of CLDN18.2, mAbs block intercellular signal transmission and inhibit tumor cell proliferation and survival. Simultaneously, the Fc region can mediate antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), recruiting natural killer cells (NK cells), macrophages, and other immune effectors to induce tumor cell apoptosis and promote antigen presentation[10].

Among CLDN18.2-targeted therapeutic strategies, mAbs represent the most clinically validated approach, although their value in PDAC remains uncertain. Zolbetuximab, formerly known as IMAB362, is a chimeric IgG1 antibody that has provided the clearest clinical proof of concept in G/GEJ adenocarcinoma. In the phase III

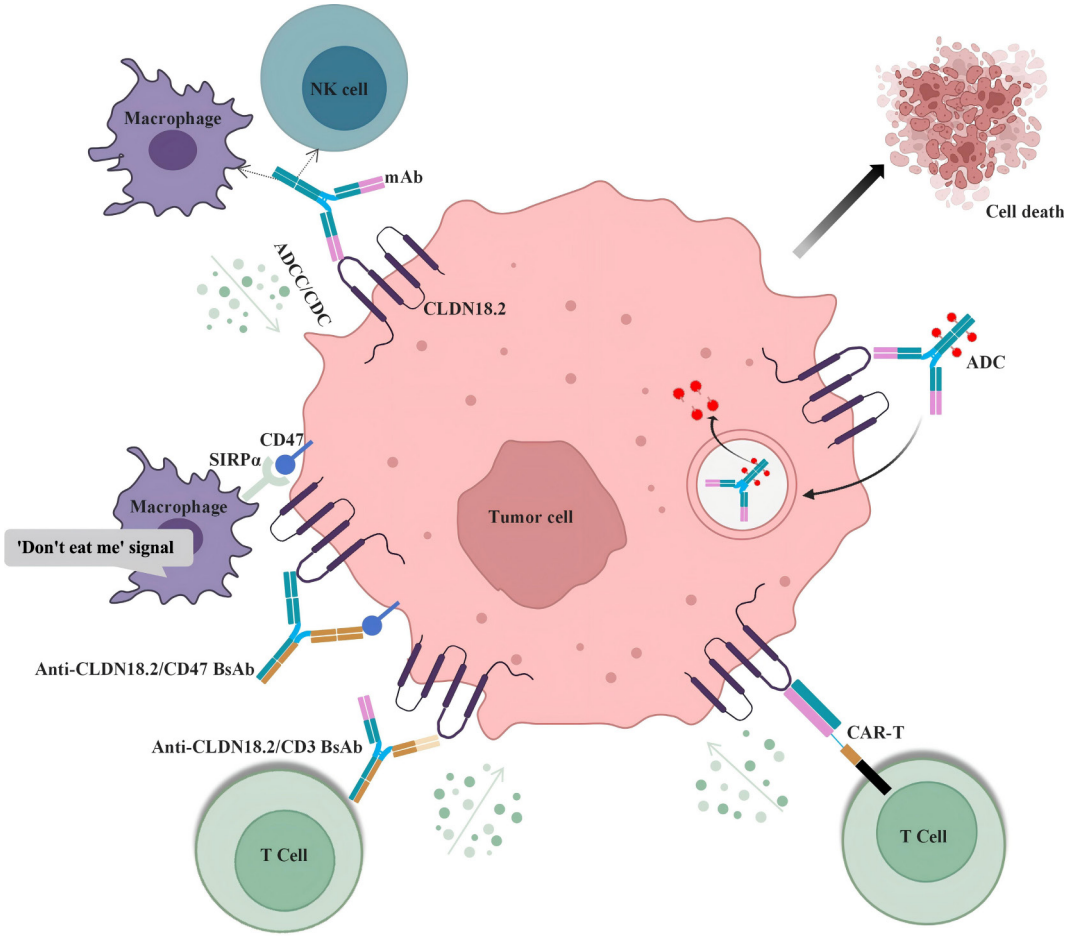

Fig. 3 The mechanisms of CLDN18.2-targeted therapies. Multiple therapeutic modalities are shown: (1) monoclonal antibodies (mAbs), which mediate tumor cell killing mainly through antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC); (2) antibody-drug conjugates (ADCs), which bind CLDN18.2 and deliver cytotoxic payloads to CLDN18.2-expressing tumor cells; (3) bispecific antibodies (BsAbs), including CLDN18.2/CD3 T-cell engagers that redirect T cells toward CLDN18.2-positive tumor cells and CLDN18.2/CD47 BsAbs that block the CD47-SIRPα 'don't eat me' axis to enhance macrophage-mediated phagocytosis; and (4) chimeric antigen receptor T-cell (CAR-T cell) therapy, which uses engineered T cells to recognize CLDN18.2-positive tumor cells and induce cytotoxic killing.

SPOTLIGHT and GLOW trials, zolbetuximab combined with first-line chemotherapy improved progression-free survival (PFS) and overall survival (OS) compared with chemotherapy alone, although no significant improvement in objective response rate (ORR) was observed[40,41]. This suggests that the clinical benefit may derive more from prolonged disease control than from rapid tumor shrinkage. The same strategy has shown limited efficacy in PDAC. The randomized phase II GLEAM trial (NCT03816163) evaluated zolbetuximab plus gemcitabine and nab-paclitaxel (GnP) as first-line therapy for CLDN18.2-positive metastatic PDAC, with positivity defined as moderate-to-strong membranous staining in ≥ 75% of tumor cells. Only approximately 27.7% of screened patients met this criterion, and the trial failed to meet its prespecified primary endpoint of overall survival. These findings indicate that the CLDN18.2-targeted treatment model established in GC cannot be directly transferred to PDAC.

Next-generation CLDN18.2-targeted mAbs are being developed to overcome some of these limitations. FG-M108 is an Fc-engineered anti-CLDN18.2 antibody designed to enhance ADCC and NK cell recruitment[42]. Updated data presented by the American Society of Clinical Oncology (ASCO) in 2025 showed encouraging activity for FG-M108 at 300 mg·m^{-2} in combination with GnP as first-line therapy for locally advanced unresectable or metastatic CLDN18.2-positive PDAC. Among 32 evaluable patients with moderate-to-high CLDN18.2 expression, ORR was 53.1%, the disease control rate (DCR) was 100%, the median progression-free survival (mPFS) was 9.9 months, and the estimated median overall survival (mOS) was 17.4 months, although the overall survival data remained immature. AB011, a recombinant humanized anti-CLDN18.2 mAb, has also shown preliminary activity in a phase I study of advanced solid tumors[43]. TST001 is designed with reduced fucosylation to enhance natural killer cell-mediated ADCC and has shown activity in tumors with moderate-to-low CLDN18.2 expression[44]. CLDN18.2-307-mAb is another preclinically validated candidate, with substantially higher binding affinity for endogenous CLDN18.2-expressing cells than zolbetuximab[45].

Overall, these agents suggest that CLDN18.2-targeted mAbs are evolving from simple target recognition toward optimized antibody engineering. However, these agents still face multiple barriers in PDAC. Their efficacy depends on sufficient membranous CLDN18.2 expression, antibody penetration through the dense stroma, and preserved Fc-mediated immune effector function. The negative result of the GLEAM trial further suggests that CLDN18.2 positivity alone may be insufficient to identify patients likely to benefit. Future clinical trials of mAbs should incorporate antigen density, spatial heterogeneity, Fc-effector function, and microenvironmental features into study design.

Table 1. Ongoing trials of anti CLDN18.2 in PDAC*.

Mechanism	Drug	Trial ID	Phase	Enrollment	Condition	Status	Treatment regimen	Line of setting	Primary endpoint
mAb	Zolbetuximab	NCT06396091	1	12	PC	Active_not_recruiting	Zolbetuximab+mFFX	1L metastatic	AE, DLT, ECOG PS
	Zolbetuximab	NCT03816163	2	393	PC	Active_not_recruiting	Zolbetuximab+AG	1L metastatic	AE, DLT, OS, ECOG PS
	FG-M108	NCT07383922	3	524	PC	Not_yet_recruiting	FG-M108+AG	1L LA/metastatic	OS
	TST001	NCT04396821	1/2	150	PC, GC, GEJ	Active_not_recruiting	TST001+AG	1L LA/metastatic	AE, MTD, DLT
	FG-M108	NCT04894825	1	152	Solid tumors	Unknown	FG-M108 monotherapy	LA/metastatic	AE, MTD
	TORL-2-307-MAB	NCT05159440	1	70	Solid tumors	Active_not_recruiting	TORL-2-307-MAB monotherapy	LA/metastatic	AE, MTD, RP2D
	AB011	NCT04400383	1	62	Solid tumors	Completed	AB011 monotherapy, AB011+AG	≥ 2L metastatic	AE, DLT
BsAb	ANO31905	NCT07444541	1/2	84	PC	Not_yet_recruiting	ANO31905+AG	1L LA/metastatic	DLT, ORR
	ASP2138	NCT07024615	1	25	PC	Recruiting	Neoadjuvant ASP2138 monotherapy	Neoadjuvant	AE, ECOG PS
	QLS31905	NCT07079228	3	602	PC	Recruiting	QLS31905+AG	1L LA/metastatic	OS
	ASP2138	NCT05365581	1	398	PC, GC, GEJ	Recruiting	ASP2138 monotherapy, ASP2138+mFFX	LA/metastatic	AE, DLT, ECOG PS
	AZD5863	NCT06005493	1/2	280	PC, GC, GEJ, EC	Recruiting	AZD5863 monotherapy	≥ 2L metastatic	AE, DLT, ORR
	PT886	NCT05482893	1/2	258	PC, GC, GEJ, BTC	Recruiting	PT886+AG, PT886+FOLFIRINOX/mFFX	≥ 2L metastatic	MTD, DLT
	IBI389	NCT05164458	1	320	Solid tumors	Unknown	IBI389 monotherapy, IBI389+ IBI308	LA/metastatic	AE, DLT
CAR-T	CLDN18.2 CAR-T	NCT07416240	Early_1	10	PC	Recruiting	Claudin 18.2 CAR-T monotherapy	≥ 3L metastatic	AE
	LY011	NCT04966143	Early_1	30	PC	Unknown	LY011 monotherapy	≥ 2L metastatic	ORR
	CT041	NCT05911217	1	20	PC	Recruiting	CT041 injection after adjuvant chemotherapy	Adjuvant	DFS
	Mesothelin and CLDN 18.2 CAR-T	NCT07066995	1/2	60	PC	Recruiting	Mesothelin and Claudin 18.2 CAR-T monotherapy	≥ 2L metastatic	DLT, MTD
	CBG131	NCT07394205	Early_1	18	PC, GC	Not_yet_recruiting	CBG131 monotherapy	≥ 2L metastatic	AE, DLT, MTD, RP2D
	CBG131	NCT05620732	1	20	PC, GC	Recruiting	CBG131 monotherapy	≥ 3L metastatic	AE
	HEC-016	NCT05277987	Early_1	18	PC, GC, GEJ	Unknown	HEC-016 monotherapy	≥ 2L metastatic	DLT
	CT048	NCT05393986	1	63	PC, GC, GEJ	Unknown	CT048 monotherapy	≥ 2L metastatic	DLT, MTD
	IMC002	NCT05472857	1	30	PC, GC, GEJ, AOC	Recruiting	IMC002 monotherapy	1L LA/metastatic	AE, MTD, DLT
	LB1908	NCT05539430	1	56	PC, GC, GEJ, EC	Active_not_recruiting	LB1908 monotherapy	≥ 2L metastatic	RDE, RP2D
	KD-496	NCT05583201	1	18	Solid tumors	Recruiting	KD-496 monotherapy	≥ 2L metastatic	TEAE, DLT, CAR-T cells
	KD-496	NCT06134960	1	12	Solid tumors	Not_yet_recruiting	KD-496 monotherapy	≥ 3L metastatic	AE, DLT
	CT041	NCT04404595	1/2	110	PC, GC	Active_not_recruiting	CT041 monotherapy	≥ 2L metastatic	AE, DLT, MTD/MAD, ORR
	CT041	NCT04581473	1/2	192	PC, GC, GEJ	Active_not_recruiting	CT041 monotherapy	≥ 2L metastatic	AE, MTD, PFS
ADC	LM-302	NCT07108504	2	30	PC	Not_yet_recruiting	LM-302+GEM	2L metastatic	ORR
	IBI343	NCT06770439	2	64	PC	Recruiting	IBI343+AG	LA/metastatic	AE, ORR
	IBI343	NCT07415525	2	40	PC	Not_yet_recruiting	IBI343+AG	Neoadjuvant	EFS
	IBI343	NCT07066098	3	201	PC	Recruiting	IBI343 monotherapy	≥ 3L metastatic	OS
	DA-3501	NCT07481357	1	51	PC, GC, GEJ	Not_yet_recruiting	DA-3501 monotherapy	LA/metastatic	MTD, ORR
	IBI343	NCT05458219	1	470	Solid tumors	Recruiting	IBI343 monotherapy, IBI343+FOLFIRINOX/mFFX	LA/metastatic	AE, DLT, ORR
	TORL-2-307-ADC	NCT05156866	1	163	Solid tumors	Active_not_recruiting	TORL-2-307-ADC monotherapy	LA/metastatic	AE, MTD, RP2D
	AZD0901	NCT04805307	1	176	Solid tumors	Completed	AZD0901 monotherapy	≥ 2L metastatic	AE, MTD, ORR
	LM-302	NCT05001516	1	17	Solid tumors	Completed	LM-302 monotherapy	≥ 2L metastatic	AE, DLT
	XNW27011	NCT06792435	1/2	240	PC, NSCLC, OC, CRC, BTC, GC, GEJ	Recruiting	XNW27011 monotherapy	≥ 2L metastatic	ORR, MTD, RP2D
	AZD4360	NCT06921928	1/2	117	PC, GC, GEJ, BTC	Recruiting	AZD4360 monotherapy	≥ 2L metastatic	AE, MTD
	AZD0901	NCT06219941	2	224	PC, GC, GEJ, BTC	Recruiting	AZD0901 monotherapy, AZD0901+AG/FOLFIRINOX	LA/metastatic	AE, ORR
	IBI343	NCT07483554	2	389	PC, GC, GEJ	Not_yet_recruiting	IBI343+AG	LA/metastatic	AE, ORR

* This information is available on https://clinicaltrials.gov/, accessed on 21 March 2026.

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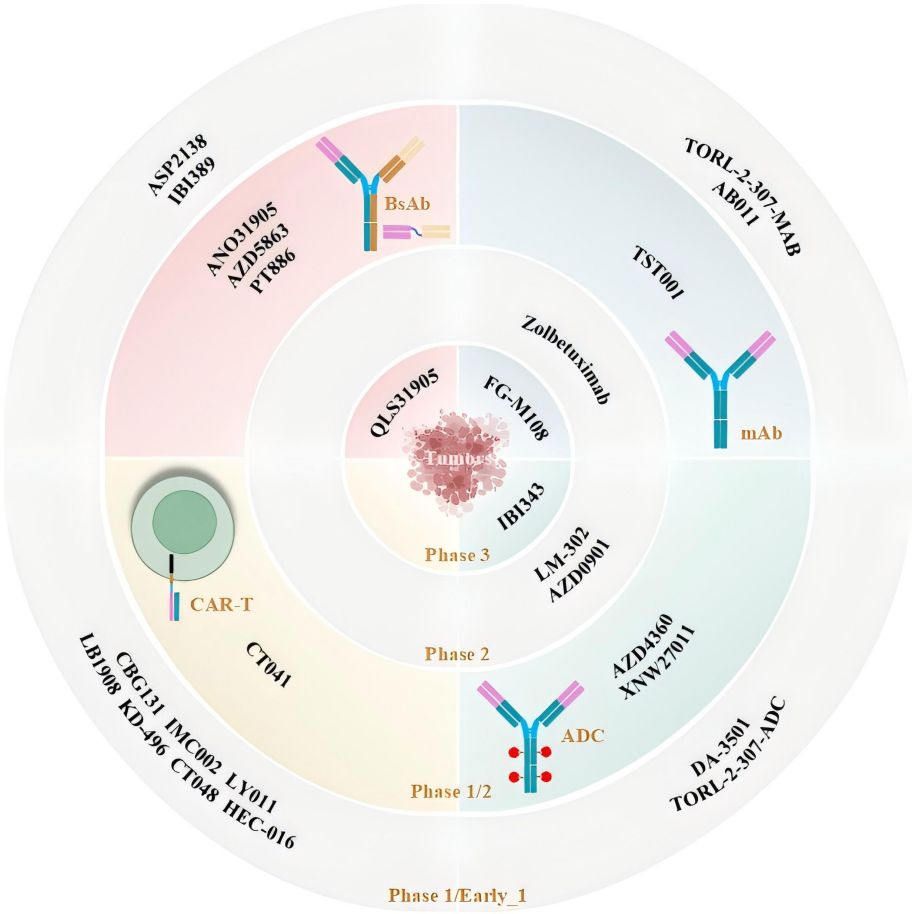

Fig. 4 CLDN18.2-targeted therapies for PDAC.

Bispecific antibodies (BsAbs)

To engage the tumor-immune microenvironment more effectively, BsAbs have been proposed as a promising therapeutic strategy. Using chemical conjugation or recombinant DNA engineering, researchers can create BsAbs that simultaneously bind CLDN18.2 on tumor cells and immune cell antigens such as CD3 on T cells. The dual-targeting strategy actively redirects effector cells to the tumor site and boosts the anti-tumor response. This approach is particularly relevant for pancreatic cancer, which is typically characterized by insufficient effector T-cell infiltration and poor responsiveness to immunotherapy[46].

Among these, one actively investigated strategy involves CLDN18.2/CD3-targeting BsAbs. IBI389, a BsAb developed by Innovent Biologics, targets both CLDN18.2 and CD3. A phase I clinical trial (NCT05164458) evaluated the safety and preliminary efficacy of IBI389 in patients with advanced PDAC. A total of 64 CLDN18.2-positive PDAC patients were enrolled. As of the data cutoff date of January 31, 2024, among the 23 efficacy-evaluable patients, ORR was 30.4%, and DCR was 69.6%. Overall, safety was generally manageable, although one treatment-related fatal adverse event was reported[47,48]. QLS31905 is another CLDN18.2/CD3-targeting BsAb with lower *in vitro* cytokine release than the comparable agent AMG910, suggesting a potentially improved safety profile[19, 32]. Phase I data presented at the 2025 ASCO meeting reported that, among 12 patients with pancreatic cancer, ORR was 25.0%, DCR was 91.67%, mPFS was 3.94 months, and mOS had not yet been reached. Notably, cytokine release syndrome (CRS) was observed in some patients but was fully treated with no treatment-related deaths[49].

ASP2138 is also an IgG-based BsAb that targets both CLDN18.2 and CD3. Preclinical studies have shown that ASP2138 can increase the cytotoxicity of CLDN18.2-expressing tumor cells and promote the secretion of interferon-γ, along with the expression of T cell activation markers[19]. The results of a phase I clinical trial (NCT05365581) of ASP2138 monotherapy in previously treated patients with locally advanced unresectable or metastatic G/GEJ adenocarcinoma and pancreatic cancer were reported at the 2025 ESMO meeting, which showed immune activation, increased $CD8^+$ T cell infiltration, and increased PD-L1 expression in the tumor microenvironment (TME) during treatment. Moreover, a phase I clinical study (NCT07024615) is ongoing in patients with resectable PDAC, using a strategy of preoperative ASP2138 injection combined with standard postoperative chemotherapy.

Beyond CD3-engaging strategies, simultaneously target CLDN18.2 and immune checkpoints represents another promising strategy. Spevatamig (PT886) is a BsAb targeting both CLDN18.2 and CD47, thereby enhancing the phagocytosis of tumor cells and offering the dual advantages of precise targeting and immune modulation[48]. Preliminary data from the phase I/II TWINPEAK study (NCT05482893), presented at the 2026 ASCO Annual Meeting, showed that among 15 treatment-naïve patients with metastatic PDAC, first-line therapy with spevatamig at 2 $mg{\cdot}kg^{-1}$ in combination with chemotherapy achieved a DCR of 93%, with varying degrees of improvement observed in ORR, mPFS, and mOS. Notably, spevatamig retains activity against tumor cells with CLDN18.2 expression as low as 10%. In addition, owing to its unique molecular design, spevatamig effectively mitigates the hematologic off-target toxicity caused by the high expression of CD47 on erythrocytes and

platelets, and the incidence of thrombocytopenia in the combination-therapy group was even lower than that in the chemotherapy-alone group[50].

Despite these advances, currently available BsAbs still face several limitations, including structural heterogeneity, short half-life, and the need for continuous infusion. Their efficacy may also be limited in advanced disease due to increased fibrosis and reduced T-cell infiltration. Ongoing optimized strategies, including trispecific T-cell engagers such as DR30318[51], conditional activation *via* STING agonists[18], dual-epitope binding designs, and BiTE-armed oncolytic viruses[52] may reduce toxicity and enhance therapeutic efficacy.

CAR-T cell therapy

CAR-T cell therapy uses viral vector–mediated genetic engineering to introduce chimeric antigen receptors (CARs) into a patient's autologous T cells, enabling specific recognition of tumor-associated antigens (TAA). The CAR construct comprises an extracellular single-chain variable fragment (scFv) for antigen recognition, the transmembrane domain for membrane anchoring, and an intracellular signaling domain for signal transduction[53]. After *in vitro* expansion, CAR-T cells are infused back into the pretreated patients, where they can specifically recognize and kill tumor cells, with the potential to form durable immunological memory.

CT041 is one of the most advanced CLDN18.2-targeted CAR-T therapies in clinical exploration. In a phase Ib study (NCT05911217), an infusion of 250×10^6 CT041 cells was administered to CLDN18.2-positive PDAC patients at high risk of postoperative recurrence, following three months of standard adjuvant chemotherapy. Most patients showed marked reductions in CA19-9 levels, with encouraging long-term survival trends[54]. Previously, a pooled analysis of two phase I/Ib studies showed that CT041 had promising efficacy in previously treated patients with CLDN18.2-positive metastatic pancreatic cancer, with an ORR of 16.7% and a DCR of 70.8%. Patients who achieved disease control also had longer survival, supporting the potential of CT041 in the later-line setting. Adverse events were predominantly grade 1–2 CRS, which occurred in 97% of patients and was manageable with tocilizumab[33]. In addition, a minority experienced gastric mucosal injury-related symptoms (e.g., upper gastrointestinal symptoms or bleeding) or grade ≥ 3 conditioning-related hematologic toxicity; however, none of these events led to serious adverse consequences[34].

Beyond CT041, next-generation CAR-T cell therapy candidates targeting CLDN18.2 are also under development. One example is KJ-C1807 (CT048), which is currently being evaluated in a clinical trial (NCT05393986) for patients with GC and pancreatic cancer[22]. Another CAR-T therapeutic candidate for solid tumors that merits attention is KD-496, the world's first dual-target CAR-T therapy directed against CLDN18.2 and NKG2DL. Compared with other CAR-T approaches, KD-496 is engineered to confer dual-target recognition, thereby effectively reducing off-target effects. An investigator-initiated trial (IIT, NCT06134960) showed that 50% (1/2) of pancreatic cancer patients in the intermediate-dose group achieved an objective response. Notably, one patient maintained a stable partial response (PR) at the eight-month follow-up after infusion, suggesting a definite and durable antitumor effect. Subsequent studies will further explore the safety and efficacy of high-dose KD-496 therapy.

CAR-T cell therapy in solid tumors such as PDAC still faces multiple barriers, including a complex manufacturing process, gastric on-target off-tumor toxicity, tumor antigen heterogeneity, T-cell exhaustion, insufficient *in vivo* persistence, and an inhibitory microenvironment shaped by factors such as TGF-β and cancer-associated fibroblasts (CAFs)[55,56]. To address these limitations, a series of optimization strategies based on synergistic mechanisms has been explored including a truncated epidermal growth factor receptor (tEGFR) safety switch to control off-tumor toxicity[2], signal-transducing activator receptor T cells (STAR-T) to reduce off-target toxicity[55], interleukin-15 (IL-15) incorporation to enhance cellular persistence[10], CLDN18.2 CAR-T cell-derived small extracellular vesicles (CAR-sEVs)[5], fibroblast activation protein (FAP)-targeting combinations to reduce CAF recruitment[57,58], nanobody-based antigen-binding domains such as IMC002[59], CXCR4 co-expression to enhance T-cell infiltration[60], and combined FNDC4 targeting to remodel the immune microenvironment[61]. Among these, armored CLDN18.2 CAR-T therapies, such as AZD6422[62] and RD07[63], represent a key strategy for improving efficacy in solid tumors. Most of these strategies remain at the preclinical stage, and none has yet been validated in phase III trials. Their clinical translational value, therefore, still requires further systematic investigation[48].

Antibody-drug conjugates (ADCs)

ADCs represent another major area of investigation in pancreatic cancer therapy. ADCs consist of three components: a mAb targeting a tumor-associated antigen, a highly potent cytotoxic payload, and a linker. This dual mechanism confers both selectivity and potent antitumor activity, making ADCs well-suited for patients with advanced pancreatic cancer who are not candidates for surgical resection[44]. Compared with CAR-T cell therapy, ADCs are smaller in size and therefore exhibit superior tumor penetration. In addition, their cytotoxic payloads can exert a bystander effect, thereby effectively eliminating neighboring antigen-negative tumor cells and compensating for the limitations of antibody monotherapy. In the field of CLDN18.2-targeted therapy, several ADCs have already entered clinical investigation and have shown preliminary potential.

Currently, based on the cytotoxic payloads, CLDN18.2-targeted ADCs can be broadly divided into two major categories: topoisomerase I inhibitors (TOPO1is) and microtubule inhibitors such as monomethyl auristatin E (MMAE). IBI343, which carries a TOPO1i payload, is currently the most advanced candidate and the first CLDN18.2-targeted ADC to demonstrate breakthrough efficacy in pancreatic cancer. In addition, IBI343 has been granted Breakthrough Therapy designation or Fast Track designation by the China NMPA and the U.S. Food and Drug Administration (FDA). Using site-specific conjugation technology, IBI343 precisely links the topoisomerase I inhibitor exatecan to a CLDN18.2 mAb at a drug-to-antibody ratio (DAR) of 4. Following receptor-mediated endocytosis, the ADC enters lysosomes and is cleaved, and the released exatecan subsequently induces apoptosis through DNA damage. Notably, this agent incorporates an Fc-silencing design that eliminates ADCC activity, thereby reducing gastrointestinal toxicity mediated by immune effector cells, while optimized linker cleavage kinetics limit systemic payload exposure[48]. These safety-optimization strategies have been validated in both GC and pancreatic cancer cohorts. Phase I study presented at the 2025 ASCO Annual Meeting confirmed very low gastrointestinal toxicity in pancreatic cancer, with no cases of grade ≥ 3 nausea or vomiting. Among CLDN18.2-positive pancreatic cancer patients with target expression ≥ 60% who had received at least one prior line of therapy ($n = 44$), those treated with 6 mg·kg^{-1} achieved an ORR of 22.7%, a DCR of 81.8%, a mPFS of 5.4 months, and a mOS of 8.5 months. Subgroup analysis further suggested that patients who had received only one prior line of therapy ($n = 17$) had a longer mOS of 12.1 months, compared with 9.1 months in those who had received two prior lines of therapy ($n = 18$), supporting earlier use of this agent[64]. Although the prespecified statistical endpoint was not met, IBI343 nearly doubled overall

survival compared with the current mOS of less than six months in the later-line treatment setting for pancreatic cancer.

In contrast to IBI343, which uses a TOPO1i as its payload, another important strategy is to employ microtubule inhibitors, such as MMAE, as the cytotoxic payload. Representative agents in this category include AZD0901, LM-302[65], CLDN18.2-307-ADC[45] and SYSA1801[22]. AZD0901, formerly known as CMG901, consists of the anti-CLDN18.2 antibody CM311, a cleavable linker, and an MMAE payload[44]. The high affinity of the CM311 antibody for CLDN18.2, together with the potent bystander effect of MMAE, confers distinct advantages in the setting of heterogeneous antigen expression in pancreatic cancer. But this benefit is offset by greater hematologic toxicity[66]. The differentiated benefit-risk profiles of TOPO1i-based and MMAE-based ADCs may serve as a reference for patient stratification: IBI343 may be preferred in patients with poor gastrointestinal tolerance, while MMAE-based agents may be more suitable for patients with high tumor burden seeking rapid remission.

Combination strategies represent the most active area of CLDN18.2-targeted ADC development. Combining ADCs with PD-1/PD-L1 inhibitors may activate innate immunity, reshape the TME, and convert immunologically 'cold' tumors into 'hot' ones[10, 19]. Another promising strategy is target-target combination therapy. In a preclinical study, low-dose KRAS G12D inhibition enhances response to CLDN18.2-targeted therapy by restoring CLDN18.2 membrane localization. This provides a mechanistic rationale for combining these two targets[31]. Antiangiogenic agents might also boost ADC delivery through vascular normalization. The DCR of IBI343 combined with bevacizumab in GC was 93.3%, which was better than that of monotherapy, and no toxic overlap was observed[67]. Its cost-effectiveness and clinical feasibility make this combination a candidate for consideration in future practice guidelines.

Despite this progress, CLDN18.2 ADC development has faced inherent challenges. The concealed nature of the CLDN18.2 epitope in normal gastric mucosa introduces the inherent risk of on-target off-tumor toxicity. In pancreatic cancer, multiple barriers, including low expression of tumor-specific antigens, stromal barriers, resistance mechanisms, and dose-limiting toxicities, have further constrained the clinical translation of earlier ADCs. As a result, most candidates have failed to advance into late-stage clinical development due to insufficient efficacy or safety concerns[65]. Future efforts should focus on optimizing the molecular design of antibodies, linkers, and cytotoxic payloads, advancing combination strategies, and establishing precise patient selection systems to improve both efficacy and safety.

Discussion

Taken together, the clinical data reviewed above underscore both the promise and the limitations of CLDN18.2 as a therapeutic target in PDAC. In the broader oncology landscape, CLDN18.2 IHC has already been incorporated into pre-treatment biomarker assessment for G/GEJ adenocarcinoma, helping to identify HER2-negative, CLDN18.2-positive patients with locally advanced unresectable or metastatic disease[40]. This experience provides a valuable framework for CLDN18.2-guided diagnosis and treatment in PDAC. Nevertheless, pancreatic cancer presents greater heterogeneity, and the clinical value of this approach will need to be confirmed in prospective studies[68]. At present, CLDN18.2 is better viewed as a therapeutic biomarker and targetable membrane antigen rather than a classical immune checkpoint or a confirmed oncogenic driver in PDAC. Its main clinical value lies in helping to identify patients who may benefit from CLDN18.2-directed therapy[8,17].

Therapeutically, CLDN18.2 can be targeted through mAbs, BsAbs, ADCs, and CAR-T cell therapy, each offering a distinct mechanism of action and facing different barriers in the PDAC microenvironment. Zolbetuximab has established a clinical precedent for CLDN18.2-directed mAb therapy in G/GEJ adenocarcinoma, and related strategies are now being explored in phase II studies for PDAC. These antibodies act mainly through ADCC and CDC, with nausea, vomiting, and decreased appetite representing key gastrointestinal safety concerns[40,41]. BsAbs provide an immune-redirection strategy for CLDN18.2-targeted therapy. CLDN18.2/CD3 BsAbs bridge T cells and CLDN18.2-expressing tumor cells, enhancing T cell-mediated cytotoxicity. However, their efficacy in PDAC may be constrained by the dense stromal barrier, limited T-cell infiltration, and the strongly immunosuppressive TME[32,51,52]. ADCs such as IBI343 deliver cytotoxic payloads to CLDN18.2-expressing tumor cells, making them less dependent on endogenous immune effector activity. Early PDAC data point to a possible advantage with earlier-line use, while gastrointestinal toxicity appears manageable, with no reported grade ≥ 3 nausea or vomiting[64]. These early findings suggest that ADCs may provide a comparatively tolerable CLDN18.2-targeted option, particularly relative to earlier agents associated with more prominent gastrointestinal toxicity. Although CAR-T cell therapy may enhance local antitumor immunity, its application in PDAC remains limited by poor tumor infiltration, T-cell dysfunction, and CRS. Whether these approaches can produce durable clinical benefit remains to be confirmed in prospective studies[33,34,55,62,63]. The dense desmoplastic stroma and immunosuppressive microenvironment of PDAC remain major obstacles to effective CLDN18.2-targeted therapy. Target positivity alone is therefore insufficient. Drug penetration and microenvironmental remodeling are equally important for improving therapeutic response.

Antigen heterogeneity is a major contributor to resistance. In PDAC, the proportion of CLDN18.2-positive tumors varies substantially depending on the IHC cutoff applied, and discordance between primary and metastatic lesions may further complicate patient selection[14–17]. In addition, treatment pressure may favor the emergence of antigen-low tumor clones, while adaptive signaling changes could further drive acquired resistance. Safety also remains a concern, as CLDN18.2 is physiologically expressed in gastric mucosa. Fc-enhanced formats may therefore carry a higher risk of gastrointestinal toxicity[31].

Looking forward, standardizing CLDN18.2 testing will be a priority, with validated antibody clones, clinically meaningful cutoffs, and assays capable of distinguishing CLDN18.2 from other CLDN18 isoforms. Combining CLDN18.2-targeted therapy with KRAS pathway inhibition and stromal remodeling strategies should be explored in biomarker-driven clinical trials. At present, CLDN18.2 should not be adopted as a routine screening biomarker in all PDAC patients. Its clinical benefit requires validation in randomized controlled trials.

Conclusions

In summary, CLDN18.2, owing to its specific expression pattern and unique molecular characteristics, represents a promising tumor-specific biomarker with significant diagnostic and therapeutic value in pancreatic cancer. Current CLDN18.2-targeted therapies, including mAbs, BsAbs, CAR-T cell therapies, and ADCs, have demonstrated favorable safety profiles and preliminary efficacy across multiple clinical settings. However, several key challenges remain, including incompletely understood resistance mechanisms, the absence of standardized detection protocols, and pronounced

intratumoral expression heterogeneity. Establishing unified CLDN18.2 testing criteria, refining patient selection, and optimizing combination strategies are therefore priorities for the field. With continued research, diversification of therapeutic approaches, and refinement of combination strategies, these limitations may be gradually overcome. Looking ahead, CLDN18.2-targeted therapy holds the potential to improve individualized treatment and extend survival for patients with PDAC.

Ethical statements

Not applicable.

Author contributions

The authors confirm contributions to the work as follows: manuscript conception and design: Ying J; draft manuscript preparation: Pan X, Cao X, Ni J. All authors reviewed the results and approved the final version of the manuscript.

Data availability

Data sharing is not applicable to this review as no datasets were generated or analyzed.

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Conflict of interest

The authors declare that they have no conflict of interest.

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