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ORIGINAL ARTICLE

Progress of Clinical Studies Targeting Claudin18.2 for the Treatment of Gastric Cancer

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Abstract

Claudin18.2 is a tight junction protein, highly selective, generally expressed only in normal gastric mucosal epithelial cells, which can effectively maintain the polarity of epithelial and endothelial cells, thus effectively regulating the permeability and conductance of the paracellular pathway. Abnormal expression of Claudin18.2 can occur in various primary malignant tumors, especially gastrointestinal tumors, and even in metastatic foci. It regulates its expression by activating the aPKC/MAPK/AP-1 pathway, and therefore, the Claudin18.2 protein is a pan-cancer target expressed in primary and metastatic lesions in human cancer types. Zolbetuximab (IMAB362), an antibody specific for Claudin18.2, has been successfully tested in a phase III clinical trial, and the results of the study showed that combining Zolbetuximab with chemotherapy notably extends patients' survival and is expected to be a potential first-line treatment for patients with Claudin18.2(+)/HER-2(−) gastric cancer. Here, we systematically describe the biological properties and oncogenic effects of Claudin18.2, centering on its clinical-pathological aspects and the progress of drug studies in gastric cancer, which can help to further explore its clinical value.

Keywords Claudin18.2 · Molecular biomarker · Diagnosis · Targeted therapy · Clinical trial

Introduction

Gastric cancer is one of the most common cancers in the world, with more than one million new cases in 2020, the fifth highest incidence rate, and the fourth highest mortality rate in the world [1]. The main treatment for early gastric cancer is endoscopic resection or cured by radical gastrectomy, but about 50% of the patients will recur and most of the patients are already in the advanced stage when they are found, so comprehensive treatment is mainly adopted. Currently, fluorouracil combined with platinum is the first-line chemotherapy for advanced gastric cancer, but chemotherapy has the disadvantages of low efficiency, high toxicity and side effects, and easy drug resistance. With the deepening of gastric cancer research, immunotherapy and targeted drugs have significantly improved the survival rate of advanced gastric cancer and are gradually becoming an important means to improve the overall survival (OS) and progression-free survival (PFS) of gastric cancer patients. Unfortunately, only HER-2-targeted drugs (trastuzumab) [2] or immune checkpoint inhibitors combined with chemotherapy have shown high remission rates and have become the standard first-line therapies for advanced GC (Gastric Cancer) [3, 4]. However, the prognosis of patients with advanced gastric cancer is still unsatisfactory. In recent years, the newly discovered target Claudin18.2 (CLDN18.2) may become a new option for targeted therapy of gastric cancer. Studies have shown that abnormal expression of Claudin18.2 protein leads to the disruption of tight junction structure and function, activates the corresponding signaling

Wu-mei Jin and Yan Zhu represents the common one and their contributions are the same.

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pathway, and promotes the proliferation of tumor cells. Currently, most of the clinical studies have been conducted to explore the correlation between CLDN18.2 and the clinicopathological features of gastric cancer through immunohistochemical staining (IHC, Immunohistochemistry) of the tissue samples to determine its protein expression, and have conducted drug clinical trials, among which Zolbetuximab has made the fastest progress in the study and has already completed the phase III clinical study. Therefore, clarifying the biology of Clausin18.2 and understanding the molecular mechanisms and clinical features in tumors are essential for the development of drugs targeting Claudin18.2.

Biological Characterization of Claudin18.2

Claudins Protein

Claudins, a tetrameric transmembrane protein encoded by the multigene family CLDN, was first identified in chicken liver by Furuse [5] and is a key protein in the composition of tight junctions. Tight junctions are an essential component of maintaining normal epithelial intercellular adhesion function by mechanically connecting cells to form an epithelial barrier. Claudins (CLDNs) are about 20–34 kDa in size and consist of the N-terminal region of the cytoplasm, two extracellular loops, four transmembrane structural domains, and the C-terminal tail of the cytoplasm [6, 7]. Claudins are generally localized in the apical region of the cell membrane and form cell–cell adhesions, which can maintain cell polarity, function as tight junction barriers and selective permeability and thus effectively regulate paracellular permeability and conductance [8–12]. Claudin-mediated dysfunction is a precursor to the pathogenesis of many human diseases [13], and it is also involved in the regulation of tumor proliferation and differentiation [14]. Currently, several Claudins family members have been reported to be aberrantly expressed in tumor tissues and to promote tumorigenesis and metastasis.

Claudin18 Protein

Claudin18 (CLDN18) is a protein encoded by the human CLDN18 gene, which was first identified in 2001 as a downstream target gene of the T/EBP/NKX2.1 homology domain transcription factor [15]. Claudin18 is located on chromosome 3q22 and has a molecular size of about 30 KD, containing six exons and five introns. The alternate splicing of the first exon divides it into Claudin18.1 (CLDN18.1) and Claudin18.2 (CLDN18.2) [16], which have highly similar amino acid sequences and the differences are mainly concentrated in the first extracellular loop (Fig. 1). It was reported that paracellular tight junctions and selective ion permeability were associated with the first extracellular loop, thus

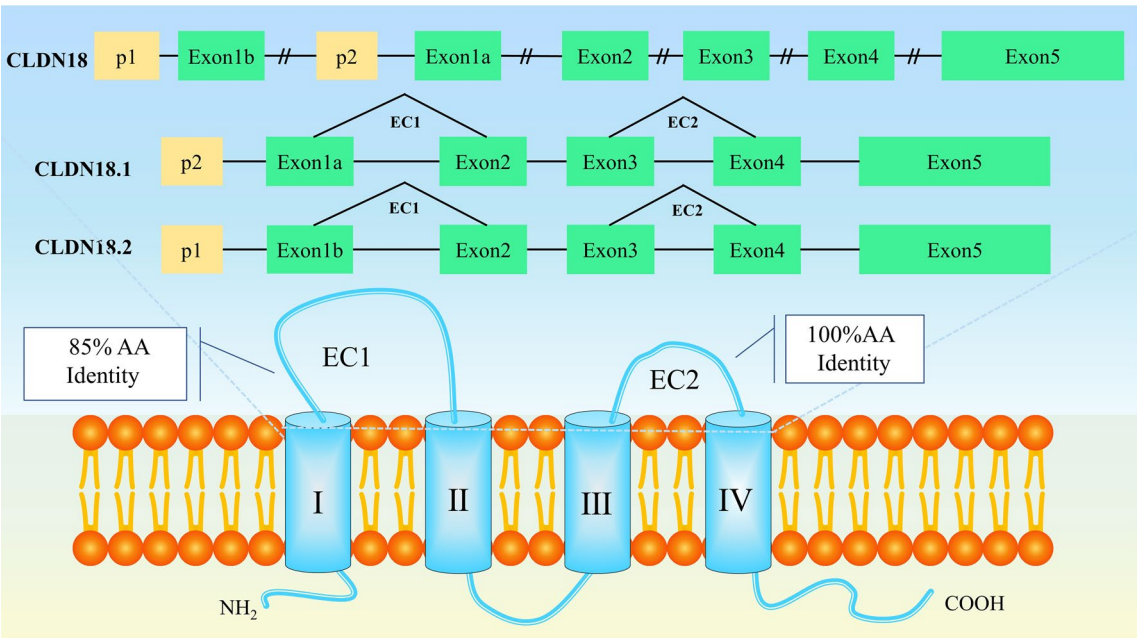

Fig. 1 The upper part belongs to Schematic representation of human CLDN18 transcript variants. CLDN18 contains two kinds of exons (exon 1a and exon 1b). p1 indicates the promoter of Claudin18.2, while p2 indicates the promoter of Claudin18.1. The lower half belongs to the schematic of predicted membrane topology of claudins, noting the cytosolic NH2 (N) and COOH (C) termini and the first (1) and second (2) extracellular domains. Claudin18.1 differs from Claudin18.2 by 8 amino acid residues only in the 1st extracellular structural domain

CLDN18.1 differed from CLDN18.2 in selective ion permeability [17].

Claudin18.1 is predominantly expressed in the lungs is essential for lung development and maintenance of lung cellular architecture and is required for normal airway epithelial permeability [18]. Deficiency can lead to lung hypoplasia and lung damage [19]. Zhou et al. found that abnormal expression of Claudin18.1 could also lead to lung cancer using mice in an in vitro study [20]. Furthermore, it has been shown that claudin18 suppresses tumor progression by inhibiting the PI3K/PDK1/Akt signaling pathway [21].

Claudin18.2 is a gastric-specific isoform that can participate in the regulation of ions, which is conducive to the maintenance of the gastric mucosal barrier function and prevents the infiltration of H^+ from gastric acid via the paracellular pathway [22, 23], and Claudin18.2 deficiency leads to neutrophils recruitment and inflammation development [24]. Claudin18.2 is normally buried in tightly linked complexes under normal conditions, making it difficult to come into contact with antibodies in the bloodstream. However, the loss of cell polarity during malignant tumorigenesis, the exposure of CLDN18.2 to the surface of tumor cells [23], and Sahin's discovery that Claudin18.2 is a highly selective molecule that is widely expressed only in cancer cells [25] are unique features that make it an ideal tumor target. The main types of drugs targeting Claudin18.2 for the treatment of solid tumors are monoclonal antibodies (Zolbetuximab), ADCs, CAR-T, and bispecific antibodies. However, only Zolbetuximab has completed phase 3 clinical studies [26].

Fundamental Research Concerning Claudin18.2's Carcinogenic Properties

Claudin18.2 Tumorigenicity

Claudins are adhesion molecules located at tight junctions between epithelial cells. A series of studies have reported aberrant expression of Claudin proteins during tumor transformation, suggesting their role in tumorigenesis. However, the mechanism of Claudin18.2 in tumorigenesis is still not well understood, and it is currently believed that it affects paracellular tight junctions, ion permeability, and certain signaling molecules in oncogenic pathways.

Claudins are key proteins of tight junctions and their aberrant expression leads to the loss of tight junctions, which mainly serve to maintain cell polarity and paracellular pathways to regulate ion permeability. The PDZ domain at the carboxyl-terminal end of the Claudins structure binds to ZO-1 [27] and thus promotes the interaction of intracellular actin cytoskeleton in the tight junction domain; therefore, the Claudins may affect cell polarity through cytoskeletal rearrangements, thereby promoting tumor proliferation and invasion [28]. As mentioned previously, Claudin18 is divided into two isoforms, Claudin18.1 and Claudin18.2, of which Claudin18.1 is mainly expressed in the lungs. Clauidn18.2 is normally expressed only in the epithelial cells of the gastric mucosa, but in malignant tumors it is retained both in gastric cancer and its metastases, as well as in other tumors, such as pancreatic, esophageal, and cholangiocarcinoma. Studies have shown that Claudin18 gene amplification occurs predominantly in squamous cell carcinoma of the lung, cervix, esophagus, head and neck, and ovary, while gene fusion is predominant in gastric cancer [29]. The CLDN18-ARHGAP26 fusion gene is one of the most common somatic genomic rearrangements in gastric cancer, and fusion-positive epithelial cells exhibit epithelial–mesenchymal transition (EMT), impaired cellular barriers, and inhibition of the RHOA pathway, which may lead to H^+ leakage, contributing to tumor aggressiveness [30]. Claudin18.2 was shown to correlate with overall survival and lymph node metastasis in intra-biliary cholangiocarcinoma, which is absent in normal gallbladder epithelial cells, and by knocking down Claudin18 expression, researchers found that it could reduce the proliferation of biliary adenocarcinoma cells, and further studies showed that the overexpression of EGFR resulted in the activation of downstream RAS/RAF/MEK/ERK cascade reaction, which induced Clauidn18 expression, and the overexpression of Claudin18 induces further activation of ERK1/2, forming positive feedback and promoting cancer [31]. Biljiana et al. found that Claudin18 protein was largely absent from normal esophageal squamous epithelium (SqE) and highly expressed in Barrett's esophagus (BE) columnar epithelium (SCE) and showed that Claudin18 is the major compact protein in SCE TJ, which, by reducing the permeability of H^+ in the tight junctions, allows BE to have a stronger by decreasing the H^+ permeability of tight junctions, resulting in greater acid resistance of BE and thus promoting tumorigenesis [32]. In addition, Claudin18.2 expression has been associated with integrin αvβ5, EpCAM extracellular structural domain EpEX, and lysozyme [33], and these molecules have been shown to regulate the cell growth cycle and promote cell migration and proliferation; thus, Claudin18.2 could promote tumor growth in this cell-dependent manner [34, 35].

Claudin18.2 downregulation can also lead to tumorigenesis, especially in gastric cancer. In a mouse model infected with Helicobacter pylori (HP) constructed by HAGEN et al., it was found that HP-infected mice reduced CLDN18 expression and progressively decreased it over time, whereas deletion of CLDN18 in the stomach resulted in gastrointestinal intraepithelial neoplasia even in the absence of HP infection. This suggests that HP infection is required to attenuate Claudin18.2 expression, but cancer progression can occur independently once Claudin18.2 is lost. In addition, the investigators found that Claudin18 activates

the corresponding cellular signaling pathways, including Wnt/β-linker downstream effectors (CD44, EFNB1, EFNB2, and EPHB2) and the HIPPO/YAP1 signaling pathways [36], thereby promoting cell proliferation, cancer stem cell development, and tumorigenesis. Furthermore, it has been found that downregulation of Claudin18.2 expression leads to paracellular H^+ leakage, inflammatory cell infiltration, and the development of precancerous lesions in the gastric mucosa by electrophysiology and H^+ titration and that during gastric tumorigenesis in Claudin18 knockout mice, expression levels of C-X-C motif chemokine 5 (CXCL5), Toll-like receptor 2 (TLR2), and CD44 splice variants [24], a feature similar to the oncogenic effects associated with HP infection. Sanada et al. [37] found that Claudin18.2 was down-regulated in intestinal (type I) gastric cancer by quantitative RT-PCR analysis, speculated that the disappearance of claudin18 (Claudin18.2) might be related to gastrointestinal metaplasia, and suggested that this change occurs in the early stages of gastric carcinogenesis. In addition, the level of claudin18.2, the invasive front of submucosal invasive GCs, was found to be negatively correlated with Ki-67 positivity in early GC tissues resected by endoscopic mucosal or submucosal resection, and Claudin18.2 was down-regulated in GCs belonging to differentiated adenocarcinomas as compared to the surrounding normal mucosa of gastric and intestinal metaplasia, again suggesting that the downregulation of Claudin18.2 expression could promote early GC of cancer invasion [38]. Therefore, the deletion of claudin18.2 may be a key factor mediating the biological behavior of type I GC. It was mentioned above that Claudin18 is abnormally activated in malignant tumors, so whether the Claudin18 gene is a tumor suppressor gene also needs further verification.

Regulation of Claudin18.2 Expression

Claudin18.2 expression in tumor cells is regulated by multiple mechanisms. It was found that PMA promotes Claudin18.2 mRNA transcription and protein translation by phosphorylating activated AP-1 through inducing PKC as well as the ERK/MAPK pathway. Research indicates that PMA treatment increases the mRNA and protein levels of claudin18.2 in pancreatic and gastric cancer cell lines [39, 40]. They found that the use of PKC inhibitors, MAPK/ERK (MEK) inhibitors, and ERK inhibitor II abrogated PMA-stimulated Claudin18a2 promoter activity, and PMA has been shown to activate PKC, which in turn mediates signaling to MAPK and thus Claudin18a2 promoter activity can be regulated through both the PKC and ERK-MAPK pathways. Furthermore, it was shown that the synergistic effect of AP-1 binding sites is essential for PMA to stimulate the promoter activity of claudin18.2 to increase its transcriptional activity, whereas the PKC and ERK-MAPK pathways can increase the activation of AP-1 to enhance mRNA transcription and protein translation of Claudin18.2. In addition, Sun et al. also reported that Claudin18.2 expression in gastric cancer cells was up-regulated through the aPKC/MAPK/AP-1-dependent pathway [41].

Hypomethylation of CpG islands in the promoter region is associated with transcriptional regulation of Claudin18.2, with the involvement of the transcription factor CREB. Methylation of the promoter region CpG has been reported in the literature as a mechanism for ectopic activation of genes in cancer [42]. Sahin et al. [23] found by sequencing the Claudin18.2 promoter that methylation of the CpG island in the promoter region of the binding site prevents the transcription factor CREB from binding to it, which represses the expression of Claudin18.2, but escapes repression in malignant tumors, which leads to tumorigenesis. In addition, a negative correlation between miR1303 and claudin18 expression has been reported [43] in GC tissues, and miR1303 can significantly attenuate the expression of claudin18 (Claudin18.2) by binding to the CLDN18 mRNA 3′-UTR fragment, which therefore helps us to carry out new therapeutic strategies for GC.

Expression of Claudin18.2 in Patients with Gastric Cancer

Claudin18.2 Protein Method of Detection

Presently, immunohistochemical staining (IHC) stands as the predominant technique for identifying CLDN18.2 expression. Quantitative scoring of CLDN18.2 expression is generally based on the staining intensity and the percentage of stained tumor-positive cells. In contrast, some studies have taken the product of the sum of the percentages of tumor cells with different staining intensities and the respective staining intensities for scoring purposes [44, 45]. The detection antibodies taken for most of the research generally fall into two categories: a CLAUDETECTTM18.2 Diagnostic Kit (Clone43-14A) and Abcam Cambridge (EPR19202) used in the FAST study. However, when the two antibodies were applied to the same tissue sample, the positive detection rate of the Clone43-14A antibody was slightly higher than that of EPR19202 [46, 47]. Clone43-14A antibody only recognizes Claudin18, so it caused the study to need to increase the definition value of Claudin18.2 expression in the clinical enrollment group to screen a more suitable population. Therefore, there is a need to establish a uniform standard for the detection reagents and the criteria for determining positivity among clinical studies, which is essential for the comparability of data. In addition, due to the high amino acid sequence similarity between CLDN18.1 and CLDN18.2, a molecular beacon (MB) [48] for CLDN18.2

has been designed for the identification of CLDN18.2 RNA, which can be used not only for rapid and precise identification of Claudin18.2 but also for the detection of circulating tumor cells (CTC).

Distribution of Claudin18.2 Expression

CLDN18.2 is normally expressed only in gastric mucosal epithelial cells and PAN cells of the duodenum, but it is now believed to be commonly expressed in malignant tumors as well, especially in gastric cancers, and ectopic activation of CLDN18.2 has also been detected in pancreatic ductal carcinoma [25], NSCLC [49], esophageal adenocarcinoma [50], and ovarian mucinous neoplasms [23]. Among them, it was reported in research on pancreatic ductal carcinoma [25] and cervical gastric-type carcinoma [51] that Claudin18 could be used as an aid in staging and early diagnosis. Claudin18.2 expression is not only limited to primary lesions but also highly expressed in metastatic foci [44, 52], which suggests that Claudin18.2 may be involved in malignant tumor cell proliferation and invasiveness, and also implies that Claudin18.2 is an ideal target for tumor therapy. In addition, the correlation between the positivity rate of Claudin18.2 in gastric cancer and clinical case characteristics varied in different studies due to the different types or concentrations of antibodies detected, different IHC interpretation criteria, intra-tumor variability, and limited sample size, as well as the different ethnic composition of the cohort (Table 1) and therefore, a more rigorous approach is needed for more clinical studies. However, the positive rate of Claudin18.2 reached 40% and some patients showed high expression, suggesting that Claudin18.2 may be the second most important target in gastric cancer after HER-2.

Correlation Between Claudin18.2 Expression and Clinicopathological Features of Gastric Cancer

Retrospective clinical studies as well as analysis of clinical data with larger sample sizes suggest that there are certain molecular pathological features of Claudin18.2 expression. Several investigations have shown [33, 44, 53–56] that Claudin18.2 expression in EBVaGC (EBV virus-positive gastric cancer) is significantly higher than that in EBV virus-negative gastric cancer patients, which may be related to the fact that EBVaGC originates from low-differentiated cells. In addition, CLDN18.2 expression was found to be negatively correlated with perineural infiltration in the dataset of one study [57]. Downregulation of CLDN18 (Claudin18.2) has also been shown to be a feature of GC in various previous studies [15, 33, 36, 37, 43, 58, 59] and CLDN18.2 downregulation has been observed to be associated with poorer survival. However, most of the current retrospective studies indicated that CLDN18.2 expression status was not associated with patients' overall survival. Due to the presence of too many intervening factors in the populations included in the studies, which have received different combinations of treatments, the relationship of CLDN18.2 on prognosis is still unclear and further studies are needed.

However, probably due to the highly heterogeneous nature of the GC microenvironment, the relationship between CLDN18.2 expression and some of the clinicopathological features is controversial and has not yielded consistent results. Some researchers state that CLDN18.2 expression does not significantly correlate with Lauren typing [33, 46, 53], but others have shown that CLDN18.2 expression correlates with Lauren typing and is higher in the diffuse type [37, 44, 52, 60]. In addition, Baek et al. found higher expression in HER-2-positive (HER-2 2+ or 3+) gastric cancer when exploring the expression of CLDN18.2 in gastric cancer in Koreans [60]. However other investigations have not found an association between them. However, more studies have found that the percentage of CLDN18.2 and HER-2 co-expression population is roughly the same as the number of HER-2-positive population. This offers the possibility of a dual-targeting strategy for subsequent patients with Claudin18.2 and HER-2 co-expression. In addition, most studies concluded that there was no association between CLDN18.2 expression and dMMR, PD-L1, p53, or E-calmodulin, but CLDN18.2-positive patients existed in the overlap of these biomarkers (Table 2), and further investigation of combination therapy with these molecular targets is needed in future. The combination of anti-Claudin18.2 antibodies and immunotherapy is currently the focus of clinical research, and the association between CLDN18.2 expression and immunotherapy outcomes has not been concluded. A negative correlation between CLDN18.2 expression and the prognosis of anti-PD-1/PD-L1 therapy was first reported in an experiment using immunohistochemistry to study the correlation between Claudin18.2-positive tumors and the outcome of immunotherapy [56], suggesting that CLDN18.2-positive patients with gastric cancer are unlikely to benefit from PD-1/PD-L1 inhibitors. This is consistent with a previous report in which it was suggested that targeting CLDN18.2 may theoretically improve the efficacy of immune checkpoint inhibitors [61], as well as a study reporting that there was no statistically significant difference between CLDN18.2 expression on the efficacy of current first-line chemotherapy as well as anti-PD-1 therapy for gastric cancer and that Claudin18.2 was not a predictive factor for chemotherapy or checkpoint inhibition [62]. Accordingly, there is still a need for large samples to be studied for the relationship between Claudin18.2 expression and clinicopathological features and prognosis.

Frequent fusion genes have now been shown to participate in tumorigenesis and progression as driver events. In 2014, the Cancer Genome Atlas Research Network

Table 1 Expression of Claudin18/Claudin18.2 in different studies of gastric cancer

Tumor	Country	Clone	Stage (TNM)	Case	Expression rate of CLDN18.2		Definition of high expression	Clinicopathological characteristic	
					Expression rate	High expression		Correlation	No correlation
GC and GEJC [79]	Several countries	VENTANA CLDN18 [43-14A] RxDx Assay	All	2004	–	42.0	≥2 + SI and ≥75%TCs	–	HER-2, PD-L1
GC and GEJC [82]	Several countries	VENTANA CLDN18 [43-14A] RxDx Assay	–	2104	–	38.4	≥2 + SI and ≥75%TCs	–	HER-2, PD-L1
GC and GEJC [80]	Several countries	–	–	351	–	36.8	≥2 + SI and ≥75%TCs	–	–
GC and GEJC [62]	Japan	Clone 43-14A	–	408	–	24.0	≥2 + SI and ≥75%TCs	Borrmann type 4, KRAS amplification, low CD16, and high CD68 expression	OS, MMR, EBV, HER-2, PD-L1
GC [56]	China	–	All	80	–	52.5	≥2 + SI and ≥40%TCs	Stage (III–IV), poor tumor differentiation, poor OS, the prognosis of anti-PD-1/PD-L1 therapy	HER-2 status, PD-L1 expression score, MMR status
GC [60]	South Korea	Abcam Cambridge (1:75)	I–III	367	74.4	29.4	≥2 + SI and a percentage of staining score of 3 (51–100)	Lauren phenotype, HER-2 status	Tumor location, OS and stage
GC [77]	Several countries	Clone 43-14A, CLAUDETECT™	III–III/IV	686	–	36.3	≥2 + SI and ≥70% TCs	–	–
GC and GEJC [76]	Several countries	anti-claudin18.2 rabbit antiserum	–	261	–	14.4	≥2 + SI and ≥70% TCs	–	–
GC and GEJC [53]	Italy	Clone 43-14A, CLAUDETECT™	I–IV	350	70.6	33.4	≥2 + SI and ≥75%TCs	Stage (III–IV), liver metastatic, peritoneal involvement, EBV status	Primary resection, histology, grading, Lauren, HER-2, PD-L1, MMRd, p53, E-cadherin
GC [52]	Japan	Clone 43-14A, CLAUDETECT™	All	262 (PT) 135 (LMN)	87.0 (PT) 80.0 (LMN)	52.0 (PT) 45.0 (LMN)	≥2 + SI and ≥40% TCs	Lauren type, grading	Stage
GC and GEJC [33]	Germany	Clone EPR19202, Abcam Cambridge (1:2000)	I–III/IV	481	42.2	10.0	≥2 + SI and ≥40% TCs	Mucin phenotype, EBV status, αvβ5 integrin, EpEX, and lysozyme	Lauren phenotype, MSI status, HER-2, MET status, αvβ3 integrin, EpICD, E-cadherin

Table 1 (continued)

Tumor	Country	Clone	Stage (TNM)	Case	Expression rate of CLDN18.2		Definition of high expression	Clinicopathological characteristic	
					Expression rate	High expression		Correlation	No correlation
GC and GEJC [46]	Germany	clone43-14A (1:1)	All	381	53.1	17.1	IRS > 8	–	OS, any clinicopathological characteristic
Advanced gastric SRCC [57]	China	Abcam (1:800)	III–IV	105	95.2	64.8	≥ 2 + SI and ≥ 40% TCs	DFS, GRIN2A mutation	OS, gender, age, stage
GC and GEJC [44]	Italy	Clone 34H14L15 (1:200)	I–IV	510	61.6 (PT) 55.3 (LMN)	29.3 (PT) 55.3 (LMN)	H-score > 51	Lauren type, tumor site, EBV status	HER-2 status, p53 status, p16 status, PD-L1 status, MMRd status, staging, grading, Ming classification, prognosis
GC and GEJC [105]	Several countries	$_{\text{CLAUDETECT}}^{\text{TM}}$	–	286	–	30.0	≥ 2 + SI and ≥ 75% TCs	–	–
GC [45]	America	anti-hCLDN18.2 antibody, anti-CLDN-mIgG1	–	236	44.0	16.0–23.0	H-score > 100	–	–
GC [23]	Germany	Mouse anti-CLDN18.2 monoclonal antibody	–	66	77.0	56.0	≥ 2 + SI and ≥ 60% TCs	–	–

PT primary tumor, *LNM* lymph node metastasis, *GC* gastric cancer, *GEJC* gastroesophageal junction cancer, *GEC* gastroesophageal cancer, *PC* pancreatic cancer, *SI* staining intensity, *TCs* tumor cells, *IRS* percentage scoring of stained tumor cells (0 = 0%, 1 = 1% ~ 25%, 2 = 26% ~ 50%, 3 = 51% ~ 75%, 4 = 76% ~ 100%) × staining intensity (score 0–3 = no staining to strong staining), *OS* overall survival, *H-score* sum of percentage of tumor cells with different staining intensities × respective staining intensities, *DFS* disease free survival, *MMR* mismatch repair, *EBV* Epstein–Barr virus, *HER-2* human epidermal growth factor receptor 2, *PD-L1* programmed death-ligand 1

Table 2 Summary of biomarker overlap with CLDN 18.2 in GC/GEJC

References	Definition of Claudin18.2 (+)	Biomarker overlap with CLDN18.2 (+) (%)			
		HER-2 (+)	PD-L1 CPS ≥ 5	dMMR	P53 (+)
[79]	≥ 2 + SI and ≥ 75%TCs	–	13	–	–
[82]	≥ 2 + SI and ≥ 75%TCs	–	22	–	–
[62]	≥ 2 + SI and ≥ 75%TCs	15.3	41.9	5.1	–
[56]	≥ 2 + SI and ≥ 40%TCs	21.4	57.1	14.3	–
[60]	≥ 2 + SI and a percentage of staining score of 3 (51–100)	25.9	–	–	–
[77]	≥ 2 + SI and ≥ 40% TCs	12.0	–	–	–
[53]	≥ 2 + SI and ≥ 75%TCs	4.9	6.0	4.3	16.3
[33]	Membranous staining was present	23.5	–	–	–
[46]	IRS > 8	10.3	–	28.9	
[44]	Membranous staining was present	23.8 (PT) 0.0 (LMN)	–	33.6 (PT) 31.6 (LMN)	31.2 (PT) 25.0 (LMN)

PT primary tumor, *LNM* lymph node metastasis, *GC* gastric cancer, *GEJC* gastroesophageal junction cancer, *SI* staining intensity, *TCs* tumor cells, *IRS* = percentage scoring of stained tumor cells (0 = 0%, 1 = 1% ~ 25%, 2 = 26% ~ 50%, 3 = 51% ~ 75%, 4 = 76% ~ 100%) × staining intensity (score 0–3 = no staining to strong staining), *HER-2* human epidermal growth factor receptor 2, *dMMR* mismatch repair deficient, *PD-L1* programmed cell death-ligand 1, *CPS* combined positive score, *p53* tumor protein 53

(TCGA) detected the CLDN18-ARHGAP26/6 fusion for the first time in GC and showed that this isoform is the most common (15%) among genome-stable phenotypes [63] and can direct loss of epithelial phenotype, epithelial–mesenchymal transition, and inhibition of the RHOA signaling pathway, which can contribute to the invasive and migratory capacity of gastric cancer cells [30, 64]. The current findings revealed a correlation between the CLDN18-ARHGAP fusion and clinicopathological features. Shu et al. [65] as well as Japanese studies [66, 67] demonstrated that the CLDN18-ARHGAP fusion gene was associated with age, gender, indolent cell carcinoma content, and TNM stage and was significantly enriched in female patients, younger patients, and patients with diffuse and more advanced tumor stage according to Lauren's classification (TNM stage), but was not associated with the location of the primary tumor. They also reported that the CLDN18-RHGAP26/6 fusion was a risk factor for overall survival and that this group of patients did not derive a survival benefit from 5-FU/oxaliplatin-based chemotherapy, which may also explain the poorer prognosis of diffuse gastric carcinoma compared to intestinal gastric carcinoma [68]. A 2018 retrospective study similarly supports this view [65]. Yet, no studies have analyzed the relationship between the CLDN18-ARHGAP26 fusion gene and therapeutic sensitivity to chemotherapeutic agents. Although Yan et al. established a cancer organoid model that can be used to assess the efficacy of chemotherapy [69]. Unfortunately, no patients with CLDN18-ARHGAP26 fusion were found in their cancer organoid library. Therefore, we need to further investigate the mechanism of this unique fusion of CLDN18-ARHGAP in GC and the drugs targeting this fusion.

Claudin18.2 Drug Mechanism of Action and Clinical Test

The high selectivity of Claudin18.2 makes it an ideal target for tumor therapy. Different therapeutic agents targeting Claudin18.2 have been developed, among which IMAB362 (Zolbetuximab) is the most intensively studied and has completed phase III clinical studies. In this review, the latest clinical trial results of drugs targeting Claudin18.2 are summarized in focus.

Monoclonal Antibody Therapies

IMAB362 (Zolbetuximab)

Claudin18.2 was first reported as a therapeutic target for mAb (monoclonal antibody) in 2008 [23], and Zolbetuximab was the first drug developed against the CLDN18.2 target, and it is also the fastest progressing drug in research. IMAB362 is a novel IgG-1 antibody that binds to CLDN18.2 [70]. It is shown that IMAB362 exerts its killing effect by inducing antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). Also, in combination with chemotherapy, CLDN18.2 enhances T-cell infiltration and induces pro-inflammatory cytokines [12]. In addition, it inhibits cell proliferation and induces apoptotic effects [71]. The role of IMAB362 has been studied in a

variety of solid tumors, including advanced gastric cancer [72], pancreatic cancer [73], non-small cell lung cancer [49], and gastric cancer of the gastroesophageal junction [74], with the field of gastric cancer being the most extensively studied. The clinical trials of CLDN18.2 with currently disclosed results are shown in Table 3.

In a Phase I IMAB362 dose escalation study published in 2009, it was shown that IMAB362 was generally well tolerated in humans, predominantly causing nausea and vomiting, and it also showed that the Phase II multidose trial used 600 mg/m^2 doses, which prompted follow-up studies of IMAB 362 [70]. Subsequently, a phase I clinical trial "PILOT" study was conducted on a limited number of patients to evaluate the safety and efficacy of IMAB362 in combination with zoledronic acid (ZA) and interleukin-2 (IL-2) in the treatment of advanced gastroesophageal junction adenocarcinoma [75], confirming that Zolbetuximab has a favorable antitumor effect (OS: 40 weeks, PFS: 12.7 weeks) and also verified that IMAB362 can be safely combined with ZA/IL-2. Zolbetuximab monotherapy in relapsed or refractory progressive gastric adenocarcinoma or low-grade esophageal cancer was shown to be well tolerated in a phase II clinical trial called MONO [76], which demonstrated an objective remission rate (ORR) of 9%, a disease control rate (DCR) of 30% and a positive correlation with CLDN18.2 expression in patients with CLDN18.2-positive expression of ≥ 70% of tumor cells had an ORR of up to 14%. Meanwhile, in another work, chemotherapeutic agents such as gemcitabine were found to enhance IMAB362-induced ADCC and EC50 effects by upregulating Claudin18.2 expression [71]. This was confirmed by subsequent trials, in which enrolled patients receiving IMAB362 combination chemotherapy (EOX: epirubicin + oxaliplatin + capecitabine) significantly prolonged the survival of patients with progressive gastric cancer or gastroesophageal conjugate tumors compared with chemotherapy alone (mOS: 13 months vs 8.3 months, mPFS: 7.5 months vs 5.3 months) and was more effective in patients with ≥ 70% of expressed cells (mPFS: 9.0 vs 5.7 months, mOS: 16.5 vs 8.9 months) [77]. In addition, it has been reported that the OS of patients in the FAST trial did not differ significantly from that of HER-2-targeted therapy (FAST vs. ToGA: 13.0 months vs. 13.8 months) [78], this also provides a solid foundation for large-scale Phase III clinical studies. These studies all suggested that monoclonal antibody therapy was well tolerated and also found a correlation between Claudin18.2 expression and therapeutic benefit, with patients with a high degree of expression experiencing a more pronounced effect of use. Therefore, the inclusion criteria for both large phase III studies conducted in 2018 were subjects with CLDN18.2 ≥ 2 + by IHC and ≥ 75% of expressed cells.

The SPOTLIGHT study [79] was a multicenter, randomized, double-blind phase III trial to evaluate the efficacy of zolbetuximab in combination with mFOLFOX6 (5-fluorouracil + calcium folinic acid + oxaliplatin) for the first-line treatment of CLDN18.2-positive/HER-2-negative locally advanced (LA) unresectable or metastatic gastric cancer or gastroesophageal junction (mG/ GEJ) adenocarcinoma patients, data analysis indicated that a significant reduction in the risk of death was achieved in the Zolbetuximab-treated group, with a statistically significant improvement in the primary study endpoint of PFS and the secondary endpoint of OS compared to the placebo group (mPFS: 10.61 vs. 8.67 months, and mOS: 18.23 vs. 15.54 months) and a statistically significant improvement in the class of longest mOS observed in a Phase III trial. Notably, PD-L1 CPS ≥ 5 was observed in 41 of 311 evaluable patients (13%), and the trial of zolbetuximab combination chemotherapy plus anti-PD-1 antibody in the ILUSTRO Phase II study is currently underway, with promising results. Furthermore, the efficacy of zolbetuximab in combination with mFOLFOX6 in the first-line treatment of a Claudin18.2 high-expressing population was evaluated in Cohort 2 of the ILUSTRO Phase II study [80], with a DCR of 100% for disease control, an ORR of 71.4% for objective remission, and an mPFS of 17.8 months confirming the SPOTLIGHT study's Results. Nevertheless, a 2023 article reported that ZOL-FO (zolbetuximab plus mFOLFOX6) is unlikely to be cost-effective as a first-line treatment option for CLDN18.2-positive, HER-2-negative advanced G/GEJ adenocarcinomas from the perspective of the Chinese healthcare system [81]. Another China-led GLOW study [82], a clinical trial of Zolbetuximab in combination with CAPOX (cisplatin + pemetrexed + oxaliplatin) for the first-line treatment of advanced gastric cancer, demonstrated that real-world data showed that mPFS and mOS were significantly prolonged by the addition of Zolbetuximab to CAPOX (mPFS: 8.21 vs. 6.8 months, mOS: 14.39 vs. 12.16 months). 14.39 vs 12.16 months). Since the GLOW study is focused on gastric cancer, which is a highly prevalent cancer in China, it is an important guide for our clinic. The success of the SPOTLIGHT trial and the GLOW trial confirms that treatment targeting Claudin18.2 is feasible. Differences between the phase I/II/III studies may be related to the different degrees of clinical benefit and treatment efficacy observed due to differences in chemotherapy regimens, population distribution, and number of enrollments. It has also been noted that gastrointestinal adverse effects have been observed with all targeted therapies using IMAB362, with vomiting being the most common [12]. Thus, management of gastrointestinal toxicity remains a challenge. In addition, for CLDN18.2-positive/HER-2-negative patients, chemotherapy in combination with immune checkpoint inhibitors is currently the standard first-line treatment for advanced HER-2-negative gastric cancer. For CLDN18.2-positive and HER-2-negative patients, is chemotherapy combined with CLDN18.2 monoclonal

Table 3 CLDN18.2 clinical trial with disclosed results

NCT Number	Clinical trial	Phase	No of patients	Design	Cut-off value of Claudin18.2	Outcome			Adverse effect
						mOS	mPFS	ORR	
NCT03504397	SPOTLIGHT [79]	III	2004	mFOL-FOX6 + IMAB362 vs Placebo + mFOL-FOX6	≥ 2 + staining intensity and ≥ 75% tumor cells	18.23 vs 15.54 months	10.61 vs 8.67 months	61% vs 62%	Nausea, vomiting
NCT03653507	GLOW [82]	III	2104	IMAB362 + CAPOX vs Placebo + CAPOX	≥ 2 + staining intensity and ≥ 75% tumor cells	14.39 vs 12.16 months	8.21 vs 6.8 months	42.5% vs 40.3%	Nausea, vomiting
NCT03505320	ILUSTRO [80]	II	351	Cohort1A: IMAB362; Cohort2: mFOL-FOX6 + IMAB362; Cohort 3A: Pembrolizumab + IMAB362	≥ 2 + staining intensity and ≥ 75% (Cohort 1A, 2, 3A); ≥ 2 + staining intensity and 50–75% (Cohorts 3A)	Cohort1A: 5.62 months	1.54 vs 17.8vs 2.96 months	0% vs 71.4% vs 0%	Nausea, vomiting
NCT01630083	FAST [77]	IIb	246	EOX vs. IMAB362 + EOX	≥ 2 + staining intensity and ≥ 40% tumor cells	5.3 vs 7.5 months	8.3 vs 13 months	25% vs 39%	Nausea, vomiting
NCT01197885	MONO [76]	IIa	268	Multiple dose study of IMAB362 as monotherapy	≥ 2 + staining intensity and ≥ 50% tumor cells	24.5 weeks	–	19%	Nausea, vomiting, fatigue
NCT00909025	–[70]	I	15	Single-dose escalation study; evaluating safety and tolerability	–	–	–	–	Nausea, vomiting
NCT01671774	PILOT [75]	I	32	IMAB362 + ZA + IL-2	–	12.7 weeks	12.7 weeks	–	Nausea, vomiting
NCT03528629	[106]	I	71	IMAB362 (Safety part arm A and Expansion: 800 mg/m^2 on cycle 1 + 600 mg/m^2 (Q3W); Safety part arm B: 800 mg/m^2 on cycle 1 + 1000 mg/m^2 (Q3W))	Safety part: ≥ 1 + staining intensity Expansion part: ≥ 2 + staining intensity and ≥ 75% tumor cells	Safety part: arm A 4.4 months, arm B 6.4 months Expansion part: 4.4 months	Safety part: arm A 2.6 months, arm B 1.7 months Expansion part: 2.6 months	–	Gastrointestinal adverse reactions

Table 3 (continued)

NCT Number	Clinical trial	Phase	No of patients	Design	Cut-off value of Claudin18.2	Outcome			Adverse effect
						mOS	mPFS	ORR	
NCT03874897	[92]	I	70	CAR-T	≥ 2 + staining intensity and ≥ 40% tumor cells	–	3.7 months, GC patients: 4.2 months	48.6%, GC patients: 57.1%	Grade 3 or higher hematologic toxicity: leukopenia,, neutropenia, anemia, thrombocytopenia; Grade 1 or 2 (CRS)
NCT03159819	[107]	I	11	CAR-T	–	–	130 days	33%	Lymphocytes, neutrophils, and white blood cells decreased

GC gastric cancer, *IMAB362* zolbetuximab, *mOS* median survival, *mPFS* median progression-free survival, *ORR* objective response rate, *ZA* zoledronic acid, *IL-2* interleukin-2, *EOX* Epirubicin + Oxaliplatin + Capecitabine, *mFOLFOX6* modified folinic acid + Fluorouracil + Oxaliplatin, *CAPOX*: *CRS* Capecitabine + Oxaliplatin; cytokine release syndrome

antibody or chemotherapy combined with immunotherapy better or worse? Is chemotherapy combined with CLDN18.2 monoclonal antibody and immunotherapy more effective? These questions need to be further explored, and we need to further investigate the correlation between CLDN18.2 levels and PD-L1.

TST001 (Osemitamab)

Claudin18.2 expression subgroup analysis showed that Zolbetuximab treatment was difficult to cover the low and medium Claudin18.2 expression population, so the newly developed TST001, a humanized monoclonal antibody targeting Claudin18.2, binds to Claudin18.2-expressing cells with high affinity, and this class of drugs reduces the Fc-terminal fucoidan content and further enhanced binding to Fc receptors on NK cells, resulting in enhanced ADCC activity. In the presence of human PBMC and NK cells, TST001 showed antitumor activity against gastric cancer cells expressing moderate to low CLDN18.2 [83].

Transtar102/TST001-1002 is a Phase I/IIa study with Cohort C evaluating the efficacy and safety of TST001 in combination with CAPOX chemotherapy for the first-line treatment of gastric cancer in both dose escalation and dose expansion components. Expanding the beneficiary population compared to the IMAB362 study, whose inclusion criteria were the inclusion of patients exhibiting mild (≥ 1 +) or greater intensity of CLDN18.2 membrane staining in ≥ 10% of tumor cells as detected by immunohistochemistry for LDT. At 11.3 months of follow-up [84], the cohort had a median duration of remission (DoR) of 12.7 months, an estimated median progression-free survival of 14 months, and an overall survival rate of 88.9% (95% CI: 74.2, 95.4) for the 64 patients in Cohort C. The most common adverse reactions were nausea, vomiting, and hypoalbuminemia, most of which were grade 1 or 2 TEAE (Treatment Emergency Adverse Event) and occurred 2 weeks ago and did not result in a grade 4 TEAE, which can be managed or prevented in the clinic in patients with adverse reaction symptoms. Furthermore, preclinical findings indicated a notable increase in PD-L1 expression in gastric cancer cells due to Osemitamab [85], and the enhanced cancer-fighting effectiveness of Osemitamab combined with nivolumab, a PD-L1 antibody, and chemotherapy over Osemitamab alone or nivolumab with chemotherapy in the experimental mouse model, thereby supporting the practicality of using Osemitamab in combination with nivolumab and chemotherapy as a first-line therapeutic regimen for CLDN18.2-positive adenocarcinoma at the stomach/gastroesophageal junction.

Other Monoclonal Antibodies

AB011 [86] is a monoclonal antibody against Claudin 18.2 independently developed in China. Preclinical studies have shown good safety and efficacy, and single-agent incremental and dose amplification studies have been completed. Furthermore, phase I or II studies of ASKB589 [87], ZL-1211 [88], and MIL93 [89] are in progress, with previously revealed data indicating effective results. The most recent findings regarding the main objectives of these studies are consolidated in Table 4, anticipating additional clinical data for future reference.

Chimeric Antigen Receptor T-Cell Immunotherapy (CAR-T)

CAR-T has made significant progress in hematologic malignancies in recent years and has also shown good results in some advanced solid tumors [90], including in Claudin18.2-positive gastric cancer. A 2018 study [91] using both a mouse gastric cancer cell line model and a Claudin18.2-positive human-derived tumor xenograft (PDX) model of gastric cancer found that CAR-T cells were effective at infiltrating into the tumor tissue without causing damage to normal gastric tissue or organs. In addition, two clinical phase I trials have now disclosed results for CT041 (Table 2). The results

Table 4 Ongoing clinical trial of CLDN18.2

NCT Number	Country	Tumor	Type of drug	Phase	Drug	Experiment subject	Latest disclosure of primary endpoint
NCT04632108 [87]	China	Advanced solid tumors	mAb	I/II	ASKB589	51	DLT: not observed MTD: not reached AEs: nausea, vomiting, hypoalbuminemia, granulocytopenia, and hypoleukemia
NCT04495296 [84]	China	Advanced solid tumors	mAb	I/IIa	TST001-1002	64	AEs: nausea, vomiting, hypoalbuminemia DoR: 12.7months mPFS: 14months
NCT05065710 [88]	United States	Advanced solid tumors	mAb	I/II	ZL-1211	19	DLT: not observed AEs: nausea, vomiting, and abdominal pain ORR: –
NCT04671875 [89]	China	Advanced solid tumors	mAb	I	MIL93	30	MTD: not reached DLT: observed in one patient at 30 mg/kg AEs: nausea, hypoalbuminemia, vomiting, anemia et
NCT04400383 [86]	China	Solid tumor, GC, PC	mAb	I	AB011	59	DLT: observed in one patient at 30 mg/kg AEs: neutrophil count decreased, anemia, hypoalbuminemia, nausea, and vomiting
NCT04856150 [108]	China	Advanced solid tumors	BsAb	I	Q-1802	9	MTD: not reached AEs: gastrointestinal AE and IRR
NCT04805307 [101]	China	Advanced solid tumors	ADC	I	CMG901	113	MTD: not reached AEs: vomiting, anemia, hypoalbuminemia, ORR: 32.6% mPFS: 4.76 months
NCT05009966 [102]	China	Advanced solid tumors	ADC	I	SYSA-1801	33 (17GC)	AEs: nausea, vomiting, dry eye syndrome and anemia ORR: 38.1% (47.1%), DCR: 57.1% (64.7%)

mAb monoclonal antibody, *BsAbs* bispecific antibody, *ADC* antibody–drug conjugate, *GC* gastric cancer, *PC* pancreas cancer, *ORR* objective response rate, *AE* adverse event, *DLT* dose-limiting toxicity, *MTD* maximum tolerated dose, *DCR* disease control rate

of a phase 1 study of CT041 in patients with CLDN18.2-positive gastrointestinal cancers showed an mPFS of 4.2 months and an ORR of 57.1% for objective remission in China [92]. The results of the phase Ia clinical study of IBI345 were presented at European Society for Medical Oncology (ESMO) 2023 [93], demonstrating that one of the four efficacious patients achieved PR and two achieved SD, illustrating the manageable safety and preliminary efficacy of IBI345 in CLDN18.2-positive solid tumors. In terms of additional information, LY011 [94] has entered a Phase I clinical trial to determine its safety and efficacy and is currently completing the DLT observation phase. All of these results show the effectiveness of CAR-CLDN18.2 T-cell therapy in Claudin18.2 tumors and are expected to be a therapeutic strategy for Claudin18.2-positive gastric cancer or other solid tumors. However, the majority of these studies recruited post-operative patients, and drug efficacy studies are now being recruited primarily in patients with inoperable solid tumors to make up for the prior shortfall.

Bispecific Antibody (BsAb)

BsAb is antibodies with two specific antigen-binding sites, targeting one antigen-binding site to immune cells (e.g., T cells) and the other to target cells (e.g., cancer cells), which can redirect T cells to tumor-targeting antigens and activate T-cell-mediated cytocidal effects [95]. PD-L1/Claudin18.2 bispecific antibody is a hotspot of present research, and the results of the first clinical trial of PD-L1/Claudin18.2 bispecific antibody-SPX301 were published in 2020, which demonstrated that it could effectively inhibit CLDN18.2-positive tumors with a favorable safety profile [96]. Q-1802, which was developed in China, is also a bi-characteristic antibody against PD-L1 and CLDN18.2, and single-agent dose escalation dosing has been completed in China, with dose expansion studies still underway. In addition, CD3/Claudin18.2 bispecific antibodies are also the most developed drugs. Data from Zhu et al. showed that targeting CD3/Claudin18.2 could effectively inhibit the growth of GC cells, and the safety and efficacy were verified in an in vitro animal live model [45]. The announcement at the European Society for Medical Oncology (ESMO) in 2020 of the trial of AMG-910, a CD3/Claudin18.2 bispecific antibody, which is currently in Phase I clinical trial (NCT04260191) phase [97]. Yet, some studies [98] have shown that CD3BsAb has systemic side effects and can cause severe cytokine release syndromes, so further studies are needed to investigate the safety of Claudin18.2BsAb application. In addition to this, Liang et al. [99] designed a bispecific antibody to CD28/CLDN18.2 which was also found to reduce immunosuppression in tumor tissues and thus play a role in killing tumor cells in their study.

Antibody-Coupled Drugs (ADC)

Many researchers have indicated that antibody-coupled drugs (ADCs) are effective therapeutic approaches for the treatment of GC [45]. Antibody-coupled drugs make use of chemical connectors to couple monoclonal antibodies and cytotoxic drugs, so that they have both the specific binding characteristics of antigen–antibody and the high antitumor activity of cytotoxic drugs and achieve specific killing of tumor cells through endocytosis release and the "bystander effect" [100]. At present, CMG901 is the fastest growing drug among ADCs targeting Claudin18.2. Preclinical studies have shown that CMG901 can effectively kill gastric cancer cells and exhibit good tolerability and safety, in which the ORR value of Claudin18.2-positive GC/GEJ patients ($n=89$) was 32.6%, and in the 5.98 months of follow-up, the mPFS was 4.76 months, and OS has not yet been achieved [101]. Also entering clinical phase I are the drugs SYSA-1801 and RC118 [94], with SYSA-1801 now announcing preliminary results from the dose escalation phase. Among the 17 GC-assessable sites, the ORR and DCR were 47.1% and 64.7%, respectively, indicating that SYSA-1801 has a well-tolerated safety profile in drug-resistant/refractory solid tumors expressing CLDN18.2 [102]. All of the studies of ADCs for the treatment of CLDN18.2-positive gastric cancer are still ongoing, with unpublished results, and their safety and efficacy have yet to be verified.

Other Applications

With the in-depth study of Claudin18.2, molecularly targeted probes are of guiding significance for patient stratification and treatment. Zhao et al. [103] explored an antibody-dependent molecular imaging strategy based on the CLDN18.2-specific antibody 5C9 for the detection of Claudin18.2 antibodies and for guiding the surgery of Claudin18.2-positive tumors. Furthermore, a fundamental trial in 2023 [104] demonstrated that Jian Excel Yang Zheng Tang (JPYZ) had an inhibitory effect on GC growth and metastasis, which may be due to increased CLDN18.2 expression in GC cells and significant rescue of CLDN18.2 loss-induced GC cell proliferation, suggesting that a larger number of patients may benefit from the combination therapy of JPYZ and the upcoming CLDN18.2-targeting drug combination therapy.

Conclusion

Addressing advanced gastric cancer remains a complex task, as detailed research in targeted therapy and genotyping has led to the emergence of targeted therapy as a novel approach for personalized, all-encompassing cancer

treatment offering an innovative blend of chemotherapy, radiotherapy, and immunotherapy. Presently, Claudin18.2 stands out as a prime therapeutic target for gastric cancer, owing to its specific targeting in tumor tissues and its notably high expression rate among gastric cancer patients. In addition, available clinical study data show that monoclonal antibodies, bispecific antibodies, antibody-coupled drugs, and CAR-T cellular immunotherapy targeting Claudin18.2 have demonstrated good efficacy and safety, in which the CLDN18-ARHGAP fusion gene was identified in anti-Claudin18.2 antibody drug development and GS and is expected to become a new therapeutic target. Moreover, some studies have identified an overlap of Clauidn18.2 with other biomarkers, providing additional combination therapy options.

However, the impact of Claudin18.2 on patient prognosis is still unclear, the testing reagents used in various clinical studies and the criteria for determining positivity need to be established as a unified standard; secondly, the differences in the positive expression rate of Claudin18.2 in different ethnic populations need to be further evaluated, thus we are still faced with a huge uncharted territory to be continually explored.

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Declarations

Competing interests The authors declare that they have no competing interests.

References

1. Sung H, Ferlay J, Siegel RL et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *A Cancer J Clin.* 2021;71:209–249.
2. Joshi SS, Badgwell BD. Current treatment and recent progress in gastric cancer. *A Cancer J Clin.* 2021;71:264–279.
3. Shitara K, Cutsem EV, Bang YJ et al. Efficacy and safety of pembrolizumab or pembrolizumab plus chemotherapy vs chemotherapy alone for patients with first-line, Advanced Gastric Cancer: The KEYNOTE-062 phase 3 randomized clinical trial. *J JAMA Oncol.* 2020;6:1571–1580.
4. Kohei S, Mustafa Ö, Yung JB et al. Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial. *J Lancet.* 2018;392:123–133.
5. Furuse M, Fujita K, Hiiragi T et al. Claudin-1 and -2: novel integral membrane proteins localizing at tight junctions with no sequence similarity to occludin. *J Cell Biolog.* 1998;141:1539–1550.
6. Lal-Nag M, Morin PJ. The claudins. *J Genome Biol.* 2009;10:235.
7. Tabaries S, Siegel PM. The role of claudins in cancer metastasis. *J Oncogene.* 2017;36:1176–1190.
8. Turner JR, Buschmann MM, Romero-Calvo I et al. The role of molecular remodeling in differential regulation of tight j unction permeability. *Sem Cell Dev Biol.* 2014;36:204–212.
9. Hu Y-J, Wang Y-D, Tan F-Q et al. Regulation of paracellular permeability: factors and mechanisms. *Mol Biol Rep.* 2013;40:6123–6142.
10. Ding L, Lu Z, Lu Q et al. The claudin family of proteins in human malignancy: a clinical perspec tive. *Cancer Manag Res.* 2013;5:367–375.
11. Gyõrffy H, Holczbauer A, Nagy P et al. Claudin expression in Barrett's esophagus and adenocarcinoma. *Virchows Archiv* 2005;447:961–968.
12. Singh P, Toom S, Huang Y. Anti-claudin 182 antibody as new targeted therapy for advanced gastric cancer. *J Hematol Oncol.* 2017;10:105.
13. Zihni C, Mills C, Matter K et al. Tight junctions: from simple barriers to multifunctional molecular gates. *Nat Rev Mol Cell Biol.* 2016;17:564–580.
14. Swisshelm K, Macek R, Kubbies M. Role of claudins in tumorigenesis. *Adv Drug Deliv Rev.* 2005;57:919–928.
15. Niimi T, Nagashima K, Ward JM et al. Claudin-18, a novel downstream target gene for the T/EBP/NKX2.1 homeod omain transcription factor, encodes lung- and stomach-specific isoform s through alternative splicing. *Mol Cell Biol.* 2001;21:7380–90.
16. Türeci O, Koslowski M, Helftenbein G et al. Claudin-18 gene structure, regulation, and expression is evolutionary conserved in mammals. *Gene.* 2011;481:83–92.
17. Angelow S, Yu ASL. Structure-function studies of claudin extracellular domains by cystein e-scanning mutagenesis. *J Biol Chem.* 2009;284:29205–29217.
18. Sweerus K, Lachowicz-Scroggins M, Gordon E et al. Claudin-18 deficiency is associated with airway epithelial barrier dys function and asthma. *J Allergy Clin Immunol.* 2017;139:72–81.
19. LaFemina MJ, Sutherland KM, Bentley T et al. Claudin-18 deficiency results in alveolar barrier dysfunction and impa ired alveologenesis in mice. *Am J Respir Cell Mol Biol.* 2014;51:550–558.
20. Casadevall A, Jackson S, Semenza GL et al. The Journal of Clinical Investigation in the time of COVID-19. *J Clin investig.* 2021;131:e156409.
21. Shimobaba S, Taga S, Akizuki R et al. Claudin-18 inhibits cell proliferation and motility mediated by inhibition of phosphorylation of PDK1 and Akt in human lung adenocarcinoma A 549 cells. *Biochimica et Biophysica Acta.* 2016;1863:1170–8.
22. Iwaya M, Hayashi H, Nakajima T et al. Colitis-associated colorectal adenocarcinomas frequently express claud in 18 isoform 2: implications for claudin 18.2 monoclonal antibody the rapy. *Histopathology.* 2021;79:227–237.
23. Sahin U, Koslowski M, Dhaene K et al. Claudin-18 splice variant 2 is a pan-cancer target suitable for therap eutic antibody development. *Clin Cancer Res.* 2008;14:7624–7634.
24. Hayashi D, Tamura A, Tanaka H et al. Deficiency of claudin-18 causes paracellular H+ leakage, up-regulation of interleukin-1β, and atrophic gastritis in mice. *Gastroenterology.* 2012;142:292–304.

25. Tanaka M, Shibahara J, Fukushima N et al. Claudin-18 is an early-stage marker of pancreatic carcinogenesis. *J Histochem Cytochem.* 2011;59:942–952.
26. Al-Batran S-E, Schuler MH, Zvirbule Z et al. FAST: An international, multicenter, randomized, phase II trial of epi rubicin, oxaliplatin, and capecitabine (EOX) with or without IMAB362, a first-in-class anti-CLDN18.2 antibody, as first-line therapy in patients with advanced CLDN18.2+ gastric and gastroesophageal junction (GE J) adenocarcinoma. *J Clin Oncol.* 2016;34:LB4001.
27. Stiffler MA, Chen JR, Grantcharova VP et al. PDZ domain binding selectivity is optimized across the mouse proteome. *Science.* 2007;317:364–9.
28. Bhat AA, Uppada S, Achkar IW et al. Tight junction proteins and signaling pathways in cancer and inflammat ion: A functional crosstalk. *Front Physiol.* 2019;9:1942.
29. Li J, Zhang Y, Hu D et al. Analysis of the expression and genetic alteration of CLDN18 in gastric cancer. *Aging.* 2020;12:14271–14284.
30. Yao F, Kausalya JP, Sia YY et al. Recurrent fusion genes in gastric cancer: CLDN18-ARHGAP26 induces loss of epithelial integrity. *Cell Rep.* 2015;12:272–285.
31. Takasawa K, Takasawa A, Osanai M et al. Claudin-18 coupled with EGFR/ERK signaling contributes to the malignant potentials of bile duct cancer. *Cancer Lett.* 2017;403:66–73.
32. Jovov B, Van Itallie CM, Shaheen NJ et al. Claudin-18: a dominant tight junction protein in Barrett's esophagus and likely contributor to its acid resistance. *Am J Physiol-Gastrointest Liver Physiol.* 2007;293:G1106–G1113.
33. Dottermusch M, Krüger S, Behrens H-M et al. Expression of the potential therapeutic target claudin-18.2 is frequently decreased in gastric cancer: results from a large Caucasian cohort study. *Virchows Archiv.* 2019;475:563–571.
34. Liang K-H, Tso H-C, Hung S-H et al. Extracellular domain of EpCAM enhances tumor progression through EGFR signaling in colon cancer cells. *Cancer Lett.* 2018;433:165–175.
35. Lu Z, Kim DH, Fan J et al. A non-tight junction function of claudin-7-Interaction with integrin signaling in suppressing lung cancer cell proliferation and detachment. *Mol Cancer.* 2015;14:120.
36. Hagen SJ, Ang L-H, Zheng Y et al. Loss of tight junction protein Claudin 18 promotes progressive neoplas ia development in mouse stomach. *Gastroenterology.* 2018;155:1852–1867.
37. Sanada Y, Oue N, Mitani Y et al. Down-regulation of the claudin-18 gene, identified through serial analysis of gene expression data analysis, in gastric cancer with an intestinal phenotype. *J Pathol.* 2006;208:633–642.
38. Oshima T, Shan J, Okugawa T et al. Down-regulation of claudin-18 is associated with the proliferative and invasive potential of gastric cancer at the invasive front. *PloS ONE.* 2013;8:e74757.
39. Ito T, Kojima T, Yamaguchi H et al. Transcriptional regulation of claudin-18 via specific protein kinase C signaling pathways and modification of DNA methylation in human pancr eatic cancer cells. *J Cell Biochem.* 2011;112:1761–1772.
40. Yano K, Imaeda T, Niimi T. Transcriptional activation of the human claudin-18 gene promoter through two AP-1 motifs in PMA-stimulated MKN45 gastric cancer cells. *Am J Physiol-Gastrointest Liver Physiol.* 2008;294:G336–G343.
41. Sun H, Cui C, Xiao F et al. miR-486 regulates metastasis and chemosensitivity in hepatocellular ca rcinoma by targeting CLDN10 and CITRON. *Hepatol Res.* 2015;45:1312–1322.
42. Koslowski M, Bell C, Seitz G et al. Frequent nonrandom activation of germ-line genes in human cancer. *Cancer Res.* 2004;64:5988–5993.
43. Zhang S-J, Feng J-F, Wang L et al. miR-1303 targets claudin-18 gene to modulate proliferation and invasion of gastric cancer cells. *Dig Dis Sci.* 2014;59:1754–1763. https://doi.org/10.1007/s10620-014-3107-5.
44. Coati I, Lotz G, Fanelli GN et al. Claudin-18 expression in oesophagogastric adenocarcinomas: a tissue mi croarray study of 523 molecularly profiled cases. *Br J Cancer.* 2019;121:257–263.
45. Zhu G, Foletti D, Liu X et al. Targeting CLDN18.2 by CD3 bispecific and ADC modalities for the treatments of gastric and pancreatic cancer. *Sci Rep.* 2019;9:8420.
46. Arnold A, Daum S, van Winterfeld M et al. Prognostic impact of Claudin 18.2 in gastric and esophageal adenocarcinomas. *Clin Transl Oncol.* 2020;22:2357–2363.
47. Kyuno D, Takasawa A, Takasawa K et al. Claudin-18.2 as a therapeutic target in cancers: cumulative findings from basic research and clinical trials. *Tissue Barriers* 2022;10:1967080.
48. Fan L, Chong X, Zhao M et al. Ultrasensitive gastric cancer circulating tumor cellular CLDN18.2 RNA Detection based on a molecular beacon. *Anal Chem.* 2021;93:665–670.
49. Micke P, Mattsson JSM, Edlund K et al. Aberrantly activated claudin 6 and 18.2 as potential therapy targets in non-small-cell lung cancer. *Int J Cancer.* 2014;135:2206–2214.
50. Moentenich V, Gebauer F, Comut E et al. Claudin 18.2 expression in esophageal adenocarcinoma and its potential impact on future treatment strategies. *Oncol Lett.* 2020;19:3665–3670.
51. Kiyokawa T, Hoang L, Pesci A et al. Claudin-18 as a promising surrogate marker for endocervical gastric-type carcinoma. *Am J Surg Pathol.* 2022;46:628–636.
52. Rohde C, Yamaguchi R, Mukhina S et al. Comparison of Claudin 18.2 expression in primary tumors and lymph node metastases in Japanese patients with gastric adenocarcinoma. *Japanese J Clin Oncol.* 2019;49:870–876.
53. Pellino A, Brignola S, Riello E et al. Association of CLDN18 protein expression with clinicopathological features and prognosis in advanced gastric and gastroesophageal junction A denocarcinomas. *J Pers Med.* 2021;11:1095.
54. Yang J, Liu Z, Zeng B et al. Epstein-Barr virus-associated gastric cancer: A distinct subtype. *Cancer Lett.* 2020;495:191–199.
55. Shinozaki A, Ushiku T, Morikawa T et al. Epstein-Barr virus-associated gastric carcinoma: a distinct carcinoma of gastric phenotype by claudin expression profiling. *J Histochem Cytochem* 2009;57:775–785.
56. Jia K, Chen Y, Sun Y, et al. Multiplex immunohistochemistry defines the tumor immune microenvironme nt and immunotherapeutic outcome in CLDN18.2-positive gastric cancer. *BMC Med.* 2022;20.
57. Xu B, Liu F, Liu Q et al. Highly expressed Claudin182 as a potential therapeutic target in advanced gastric signet-ring cell carcinoma (SRCC). *J Gastrointest Oncol.* 2020;11:1431–1439.
58. Matsuda Y, Semba S, Ueda J et al. Gastric and intestinal claudin expression at the invasive front of gastric carcinoma. *Cancer Sci.* 2007;98:1014–1019.
59. Jun K-H, Kim J-H, Jung J-H et al. Expression of claudin-7 and loss of claudin-18 correlate with poor pro gnosis in gastric cancer. *Int J Surg.* 2014;12:156–162.
60. Baek JH, Park DJ, Kim GY et al. Clinical implications of Claudin18.2 expression in patients with gastric cancer. *Anticancer Res.* 2019;39:6973–6979.
61. Zhang J, Dong R, Shen L. Evaluation and reflection on claudin 18.2 targeting therapy in advanced gastric cancer. *Chin J Cancer Res* 2020;32:263–270.
62. Kubota Y, Kawazoe A, Mishima S et al. Comprehensive clinical and molecular characterization of claudin 18.2 expression in advanced gastric or gastroesophageal junction cancer. *ESMO Open.* 2023;8:100762.
63. Cancer Genome Atlas Research N. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature.* 2014;513:202–209.

64. Yang H, Hong D, Cho SY et al. RhoGAP domain-containing fusions and PPAPDC1A fusions are recurrent and prognostic in diffuse gastric cancer. *Nat Commun.* 2018;9:4439.
65. Shu Y, Zhang W, Hou Q et al. Prognostic significance of frequent CLDN18-ARHGAP26/6 fusion in gastric signet-ring cell cancer. *Nat Commun.* 2018;9:2447.
66. Nakayama I, Shinozaki E, Sakata S et al. Enrichment of CLDN18-ARHGAP fusion gene in gastric cancers in young adults. *Cancer Sci.* 2019;110:1352–1363.
67. Tanaka A, Ishikawa S, Ushiku T et al. Frequent CLDN18-ARHGAP fusion in highly metastatic diffuse-type gastric cancer with relatively early onset. *Oncotarget.* 2018;9:29336–29350.
68. Cheng X, Yu S, Wang Y et al. The role of oxaliplatin in the adjuvant setting of different Lauren's type of gastric adenocarcinoma after D2 gastrectomy: a real-world study. *Gastric Cancer.* 2019;22:587–597.
69. Yan HHN, Siu HC, Law S et al. A comprehensive human gastric cancer organoid biobank captures tumor subtype heterogeneity and enables therapeutic screening. *Cell Stem Cell.* 2018;23:882–897.
70. Sahin U, Schuler M, Richly H et al. A phase I dose-escalation study of IMAB362 (Zolbetuximab) in patients with advanced gastric and gastro-oesophageal junction cancer. *Eur J Cancer.* 2018;100:17–26.
71. Türeci Ö, Mitnacht-Kraus R, Wöll S et al. Characterization of zolbetuximab in pancreatic cancer models. *Oncoimmunology.* 2018;8:e1523096.
72. Lordick F, Shitara K, Janjigian YY. New agents on the horizon in gastric cancer. *Ann Oncol.* 2017;28:1767–1775.
73. Wöll S, Schlitter AM, Dhaene K et al. Claudin 182 is a target for IMAB362 antibody in pancreatic neoplasms. *Int J Cancer.* 2014;134:731–9.
74. Lyons TG, Ku GY. Systemic therapy for esophagogastric cancer: targeted therapies. *Chin Clin Oncol.* 2017;6:48–48.
75. Sahin U, Al-Batran S-E, Hozaeel W et al. IMAB362 plus zoledronic acid (ZA) and interleukin-2 (IL-2) in patients (pts) with advanced gastroesophageal cancer (GEC): clinical activity and safety data from the PILOT phase I trial. *J Clin Oncol.* 2015;33:e15079.
76. Türeci O, Sahin U, Schulze-Bergkamen H et al. A multicentre, phase IIa study of zolbetuximab as a single agent in pa tients with recurrent or refractory advanced adenocarcinoma of the sto mach or lower oesophagus: the MONO study. *Ann Oncol.* 2019;30:1487–1495.
77. Sahin U, Türeci Ö, Manikhas G et al. FAST: a randomised phase II study of zolbetuximab (IMAB362) plus EOX v ersus EOX alone for first-line treatment of advanced CLDN18.2-positive gastric and gastro-oesophageal adenocarcinoma. *Ann Oncol.* 2021;32:609–619.
78. Bang Y-J, Van Cutsem E, Feyereislova A et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet.* 2010;376:687–697.
79. Shitara K, Lordick F, Bang Y-J et al. Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-ne gative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicen tre, randomised, double-blind, phase 3 trial. *Lancet.* 2023;401:1655–1668.
80. Klempner SJ, Lee K-W, Shitara K et al. ILUSTRO: Phase II multicohort trial of zolbetuximab in patients with advanced or metastatic Claudin 182–positive gastric or gastroesophagea l junction adenocarcinoma. *Clin Cancer Res.* 2023;29:3882–3891.
81. Huang Y, You M, Wu Q et al. Cost-effectiveness analysis of zolbetuximab plus mFOLFOX6 as the first -line treatment for CLDN182-positive, HER2-negative advanced gastric or gastroesophageal adenocarcinoma. *Front Pharmacol.* 2023;14:1238009.
82. Shah MA, Shitara K, Ajani JA et al. Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophage al junction adenocarcinoma: the randomized, phase 3 GLOW trial. *Nat Med.* 2023;29:2133–2141.
83. Teng F, Gu Y, Chai H et al. Abstract 5183: The preclinical characterization of TST001, a novel humanized anti-claudin18.2 mAb with enhanced binding affinity and anti-tumor activity. *Cancer Res.* 2020;80:5183–5183.
84. Shen L, Liu D, Li N et al. 1524P First-line TST001 plus capecitabine and oxaliplatin (CAPOX) for advanced G/GEJ cancer with CLDN18.2 positive overall survival data fro m study transtar102-Cohort C. *Ann Oncol.* 2023;34:S858–S859.
85. Qian X, Teng F, Guo H et al. 1560P Osemitamab (TST001): An ADCC enhanced humanized anti-CLDN18.2 ma b, demonstrated improved efficacy in combination with anti-PD-L1/PD-1 mab and oxaliplatin/5-FU in preclinical tumor models. *Ann Oncol.* 2023;34:S873.
86. Li J, Pan H, Liu T et al. A multicenter, phase 1 study of AB011, a recombinant humanized anti-CL DN18.2 monoclonal antibody, as monotherapy and combined with capecitabine and oxaliplatin (CAPOX) in patients with advanced solid tumors. *J Clin Oncol.* 2023;41:391–391.
87. Zhang M, Gong J, Wang J et al. A phase I/II study of ASKB589 (anti-claudin 18.2 [CLDN18.2] monoclonal antibody) in patients with solid tumors. *J Clin Oncol.* 2023;41:397–397.
88. Sharma S, Starodub A, Xu N et al. Preliminary results of a phase 1/2, first-in-human, open-label, dose escalation study of ZL-1211 (anti-Claudin 18.2 mAb) in patients with un resectable or metastatic solid tumors. *J Clin Oncol.* 2023;41:2537–2537.
89. Huang J, Zhang B, Wang Y et al. Safety and preliminary efficacy of MIL93 in patients with advanced sol id tumors: The monotherapy part of a phase 1 trial. *J Clin Oncol.* 2023;41:798–798.
90. Grosser R, Cherkassky L, Chintala N et al. Combination immunotherapy with CAR T cells and checkpoint blockade for the treatment of solid tumors. *Cancer Cell.* 2019;36:471–482.
91. Jiang H, Shi Z, Wang P et al. Claudin18.2-specific chimeric antigen receptor engineered T cells for the treatment of gastric cancer. *J Natl Cancer Inst.* 2019;111:409–418.
92. Qi C, Gong J, Li J et al. Claudin18.2-specific CAR T cells in gastrointestinal cancers: phase 1 trial interim results. *Nat Med.* 2022;28:1189–1198.
93. Qin S, Tian W, Li M et al. 1054P A phase Ia study to evaluate the safety, tolerability, pharmacok inetics and preliminary efficacy of a modular CLDN18.2-targeting PG CA R-T therapy (IBI345) in patients with CLDN182+ solid tumors. *Ann Oncol.* 2023;34:S638.
94. Cao W, Xing H, Li Y et al. Claudin182 is a novel molecular biomarker for tumor-targeted immunotherapy. *Biomark Res.* 2022;10:38.
95. NS NSRR, AD ADSS, SH S-hCC, et al. An anti-B cell maturation antigen bispecific antibody for multiple myeloma. 2015;5288–5291.
96. Zhu G, Ye J, Ma J, et al. Abstract 534: Discovery of an anti-claudin182/anti-PD-L1 bispecific a ntibody SPX-301 in the SMARTOPTM format. *Cancer Res*. 80:534–534.
97. Lordick F, Chao J, Buxò E et al. 1496TiP Phase I study evaluating safety and tolerability of AMG 910, a half-life extended bispecific T cell engager targeting claudin-18.2 (CLDN18.2) in gastric and gastroesophageal junction (G/GEJ) adenocarcinoma. *Ann Oncol.* 2020;31:S928–S929.

98. Wu Z, Cheung NV. T cell engaging bispecific antibody (T-BsAb): From technology to thera peutics. *Pharmacol Ther.* 2018;182:161–175.
99. Liang J, Zhang H, Huang Y et al. A CLDN182-targeting bispecific t cell co-stimulatory activator for cancer immunotherapy. *Cancer Manag Res.* 2021;13:6977–6987.
100. Peters C, Brown S. Antibody-drug conjugates as novel anticancer chemotherapeutics. *Biosci Rep.* 2015;35:e00225.
101. Xu R-H, Ruan D-Y, Zhang D-S et al. A phase 1 trial of claudin 182-specific antibody-drug conjugate CMG90 1 in patients with advanced gastric/gastroesophageal junction cancer. *J Clin Oncol.* 2023;41:434420.
102. Wang Y, Gong J, Lin R et al. First-in-human dose escalation and expansion study of SYSA1801, an antibody-drug conjugate targeting claudin 182 in patients with resistant/refractory solid tumors. *J Clin Oncol.* 2023;41:3016.
103. Zhao C, Rong Z, Ding J et al. Targeting Claudin 18.2 using a highly specific antibody enables cancer diagnosis and guided surgery. *Mol Pharm.* 2022;19:3530–3541.
104. Xu X, Li Y, Zhang R et al. Jianpi Yangzheng decoction suppresses gastric cancer progression via m odulating the miR-448/CLDN18.2 mediated YAP/TAZ signaling. *J Ethnopharmacol.* 2023;311:116450.
105. Moran D, Maurus D, Rohde C. Prevalence of CLDN182, HER2 and PD-L1 in gastric cancer samples. *Ann Oncol* 2018;29:32.
106. Shitara K, Kawazoe A, Hirakawa A. Phase 1 trial of zolbetuximab in Japanese patients with CLDN18.2+ gastric or gastroesophageal junction adenocarcinoma. *Cancer Sci* 2023;14:1606–1615.
107. Zhan X, Wang B, Li Z et al. Phase I trial of Claudin 18.2-specific chimeric antigen receptor T cel ls for advanced gastric and pancreatic adenocarcinoma. *J Clin Oncol.* 2019;37:2509–2509.
108. Gong J, Shen L, Hou J et al. Safety results of Q-1802, a Claudin18.2/PD-L1 bsABs, in patients with relapsed or refractory solid tumors in a phase 1 study. *J Clin Oncol.* 2022;40:2568–2568.