State of the art and upcoming trends in claudin-directed therapies in gastrointestinal malignancies

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Purpose of review
Claudins, components of tight cell junctions in epithelial and endothelial cells, have emerged as a therapeutic target in gastrointestinal (GI) malignancies, particularly claudin 18.2 (CLDN18.2).

Recent findings
Zolbetuximab, a chimeric anti-CLDN18.2 monoclonal antibody (mAb), is currently under FDA review and may emerge as the first claudin targeted therapy approved. Phase 3 trials show that zolbetuximab in combination with front-line fluoropyrimidine plus oxaliplatin improves survival in advanced CLDN18.2 positive (≥75% of tumor cells) gastric adenocarcinoma (GAC) patients. Many other therapies (mAbs; CART; bispecific; ADCs) are under investigation.

Summary
CLDN18.2 will be an important target in GAC. Early understanding of how to target CLDN18.2 based on the level of expression (high, moderate, low) will be the key to success in this area. Studying these as separate entities should be considered. Resistance patterns, loss of CLDN18.2 expression, role in the refractory setting, and if any role in localized disease are questions that remain. Other targets for claudin that target claudin six and four are under investigation. Their role in GI malignancies will soon be further clarified.

Keywords
claudin 18.2, claudins, gastrointestinal malignancies, zolbetuximab

INTRODUCTION

Gastrointestinal (GI) malignancies are a heterogenous group of cancers consisting of commonly diagnosed tumors including colorectal cancer (CRC), pancreatic cancer (PDAC), gastric adenocarcinoma (GAC), esophageal cancer, and hepatocellular carcinoma (HCC) [1]. GI malignancies also include other rare tumors of the biliary tract, anus, gallbladder, appendix, and small bowels. Traditionally, targeted therapies in GI malignancies have involved targets such as: vascular endothelial growth factor (VEGF), human epidermal growth factor receptor-2 (HER2), epidermal growth factor receptor (EGFR), and protein kinase BRAF (BRAF) [2,3]. However, many GI cancer patients will lack any targeted therapy options. More approaches are needed for this diverse group of malignancies.

Claudins (CLDNs) have emerged recently as potential oncology targets [4–6]. CLDNs are major components of tight cell junctions in epithelial and endothelial cells which maintain cell-cell adhesion and control paracellular permeability. CLDNs and tight cell junctions additionally act as signaling hubs by binding multiple signaling pathways [7]. There are 27 CLDN transmembrane proteins, and altered function has been linked to various cancers including GI malignancies. Dependent on where the tumor originated, CLDNs can exert tumor suppressor or tumor promotor effects and activate signaling pathways associated with tumor progression and metastases [6,7]. Therefore, CLDNs are emerging as potential diagnostic, therapeutic, and/or prognostic markers [4–7].

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KEY POINTS

- Claudins, components of tight cell junctions, have emerged as potential therapeutic targets.
- Zolbetuximab, an anticlaudin 18.2 monoclonal antibody, has shown survival improvement in combination with front-line chemotherapy for advanced claudin18.2 positive gastric adenocarcinoma patients.
- Other agents that target claudin 18.2 are also currently under investigation.

CLAUDINS AND GASTROINTESTINAL MALIGNANCIES

Multiple CLDNs have now been linked to GI malignancies. CLDN1 promotes the growth and expression of various GI tumors including CRC, GAC, HCC, esophageal squamous cell carcinoma (ESCC), and PDAC [4]. In HCC, for example, CLDN1 activates the c-AbIRas-RAF-1-EKR1/2 signaling pathway. Although in CRC, studies link CLDN1 to many pathways (EGFR/PIKC/cludin-1 signaling, Wnt signaling, smad4 inhibition, and PI3K/AKT signaling) that promote invasiveness, metastases, and proliferation [4,7]. Upregulation of CLDN2 and CLDN3 look to play a role in CRC while downregulation of CLDN3 has a link with HCC [4]. CLDN4 dysregulation is seen in many cancers [4,6]. In GI tumors, CLDN4 upregulation activates the Wnt/b-catenin signaling and triggers HCC progression. CLDN6 has also been seen to be upregulated in HCC promoting cell migration, invasion, and proliferation via EGFR/AKT/mTOR signaling [4,6].

Currently for GI tumors, CLDN18.2 is the furthest along in becoming a therapeutic target. CLDN18 gene has two splice variants, CLDN18.1 which is specifically expressed in normal and lung cancer tissue while CLDN18.2 is expressed in normal gastric tissue and in GAC, PDAC, and esophageal adenocarcinoma (EAC) [5]. The expression of CLDN18.2 varies in GAC ranging from 24–87% depending on the level of expression (weak; moderate; strong) [7,8].

CLAUDIN 18.2 AND ZOLBETUXIMAB

Zolbetuximab, a chimeric anti-CLDN18.2 monoclonal antibody (mAb) has undergone phase 1, 2, and 3 explorations in advanced CLDN18.2 positive GAC tumors [9–12,13▪,14▪]. Phase 1 trials of zolbetuximab alone and in combination with zoledronic acid and interleukin-2 found zolbetuximab to be well tolerated in the GAC and gastroesophageal junction (GEJ) setting [9–10]. The MONO and FAST trials were phase 2 trials investigating zolbetuximab [11,12]. The MONO trial evaluated zolbetuximab monotherapy in advanced CLDN18.2 positive (≥50% CLDN18.2 tumor cell expression) GAC, GEJ, and EAC patients [11]. Overall response rate (ORR) was 9% ($n=4$) and 14% ($n=6$) had stable disease. In patients with CLDN18.2 expression in ≥70% of tumor cells showed an ORR of 14% and 17% had stable disease. The FAST trial administered zolbetuximab in combination with first line epirubicin, oxaliplatin, and capecitabine (EOX) compared to EOX alone in CLDN18.2 positive (≥40% CLDN18.2 expression) GAC, GEJ, and EAC patients [12]. EOX was given for a maximum of 8 cycles. Zolbetuximab was continued as maintenance therapy after EOX therapy. PFS and OS were improved with the zolbetuximab addition. Median PFS was 7.5 months in the zolbetuximab plus EOX arm compared to 5.3 months in the EOX arm, $P<0.0005$. Median overall survival (OS) was 13.0 months in the zolbetuximab plus EOX arm compared to 8.3 months in the EOX arm, $P<0.0005$. In those with 40–69% CLDN18.2 expression, PFS and OS were not statistically different. Whereas those with ≥70% CLDN18.2 positivity, median PFS was improved by ~3 months and median OS was improved by ~ 8 months with the addition of zolbetuximab. Discontinuation of zolbetuximab due to adverse events was rare. These early evaluations of zolbetuximab established dose and adverse events as traditional with early study but also shed light that zolbetuximab efficacy is more pronounced in combination with chemotherapy and in those with high CLDN18.2 positivity.

Spotlight was a phase 3 international multicenter double-blind randomized controlled trial of zolbetuximab (800 mg/m^2 loading dose followed by 600 mg/m^2 every 3 weeks) ($n=283$) or placebo ($n=282$) in combination with front-line oxaliplatin + 5-fluorouracil (5-FU) (FOLFOX) (every 2 weeks) [13▪]. The combination was given for four 42-day cycles. After these four cycles, patients without progression continued zolbetuximab or placebo ± 5-FU until disease progression. Patients were advanced treatment naïve GAC and GEJ adenocarcinoma patients with CLDN18.2 positive (≥75% CLDN18.2 expression). Patients were HER-2 negative. PFS and OS were improved. Median PFS was 10.61 months in the zolbetuximab group vs. 8.67 months in the placebo group, $P=0.0066$. Median OS was 18.23 months vs. 15.54 months in the placebo group, $P=0.0053$. ORR was not different amongst the two groups. The GLOW trial was an international multicenter phase 3 double-blind randomized trial of zolbetuximab (n = 254) or placebo ($n=253$) in combination with oxaliplatin and capecitabine (CapeOx) (every 3 weeks) [14▪]. Zolbetuximab was given at 800 mg/m^2 loading dose then 600 mg/m^2

every 3 weeks. After eight cycles of combination with CapeOx, patients continued zolbetuximab or placebo ± capecitabine until disease progression. Patients were advanced treatment naïve GAC or GEJ adenocarcinoma patients with CLDN18.2 positive (≥75% CLDN18.2 expression). Patients were HER-2 negative. PFS and OS were improved. Median PFS was 8.21 months in the zolbetuximab group vs. 6.8 months in the placebo group, $P = 0.0007$. Median OS was 14.3 months in the zolbetuximab group vs. 12.16 months in the placebo group, $P = 0.0118$. ORR was only marginally improved. Nausea and vomiting were the most common adverse events seen in both studies. SPOTLIGHT and GLOW revealed that zolbetuximab efficacy is more likely to provide disease stability vs. reduction and confirmed that it is most efficacious in combination with chemotherapy. There additionally is the potential role for maintenance therapy. Zolbetuximab is currently under FDA review for approval. We see it as a potential option for those advanced adenocarcinoma CLDN18.2 positive (≥75% CLDN18.2 expression) patients that are HER-2 negative in combination with front-line platinum plus fluoropyrimidine therapy.

Zolbetuximab in combination with antiprogrammed death-1 (anti-PD-1) immunotherapy is currently undergoing phase 2 study [15]. We believe this study will help shed light of how immunotherapy might augment the antibody dependent cellular toxicity of zolbetuximab in claudin positive patients. Additionally, these phase 2 results will help provide guidance on whether simultaneous or sequential use of anticlaudin and anti-PD-1 agents is more beneficial in those patients in the front-line setting who are claudin positive and PD-L1 positive (PD-L1 combined positive score ≥ 5) [3]. Future zolbetuximab treatment areas that still need addressed include (1) zolbetuximab's role in those with resectable GAC as retrospective review shows claudin positivity in these patients [16], (2) zolbetuximab impact those with *CLDN18-ARHGAP26* fusion [17], (3) combinations to improve efficacy in those with lower expression, and (4) evaluating resistance patterns. Zolbetuximab is also under phase 2 study in combination with front-line gemcitabine plus nab-paclitaxel in metastatic claudin 18.2 positive PDAC patients and we look forward to the outcomes reported [18].

CLAUDIN 18.2 AND CURRENT THERAPEUTIC PIPELINE

In addition to zolbetuximab, other agents are currently under investigation targeting CLDN18.2. Other CLDN18.2 mAbs examples include osemitamab (TST-001), ZL-1211, IBI360, AB011, NBL-015, SPX-101, MIL93, LM-102, among others [8,19▪▪]. Osemitamab in combination with front-line CapeOx was evaluated in a phase 1/2a multicenter study in China [20]. Patients had advanced GAC and GEJ patients. Patient had less CLDN18.2 staining (membranous staining ≥1 + intensity in ≥ 10% of tumor cells). Twenty-seven patients out of 40 patients had a partial response. The authors reported no obvious trends that with higher CLDN18.2 expression there was improved efficacy. With these encouraging results, there will be a planned phase 3 trial, the TranStar 301 global trial utilizing osemitamab in combination with chemotherapy and nivolumab [21].

CLDN18.2 antibody drug conjugates (ADCs) are also in the pipeline including BMS-986476, TPX4589, RC118, CMG901, IBI343, SOT102, TQB213, SYA1801, ATG-022, SHR-A1904, TORL-2-307 [8,19▪▪]. Phase 1 outcomes of CMG901, an anticlaudin ADC with monomethyl auristatin E (MMAE), showed an encouraging safety and efficacy profile in advanced GAC patients (claudin ≥2+ membrane staining in ≥5% tumor cells required for the expansion cohort) [22]. ORR was 32.6%, median PFS was 4.76 months, and median OS was 5.98 months. Combination trials are also underway as an example with RC118 with anti-PD-1 therapy in solid tumor basket trial (any claudin membrane staining) [23]. Other therapies such as bispecific antibodies targeting CLDN18.2 are also under development AMG910, ASP2138, Q-1802, TJ033721, and PT886 [8,15]. Interim results of phase 1 study with Q-1802, anticlaudin18.2 and PD-L1 bispecific antibody, have been reported in advanced solid tumors (claudin negative or positive expression) [24]. Out of nine claudin positive patients, six patients had either a partial response or stable disease showing encouraging data. Additionally, trials with chimeric antigen receptor T-cell therapy (CAR-T) for CLDN18.2 are underway. Examples include CT-041, LY011, LCAR-C18S, IMC002, TAC01-CLDN18.2, KD-496, IBI345, LB1908, IMC008, and BNT212 [8,19▪▪]. Results of Phase 1b ELIMYN18.2 (cohort A) of CT041, an autologous CAR-T against CLDN18.2 were recently presented [25]. Patients had advanced refractory CLDN18.2 positive (degree of positivity not specified) GAC, GEJ, or PDAC. With median follow up duration of 8.9 months, one patient with GAC/GEJ achieved a complete response and the confirmed ORR in GAC/GEJ patients was 42.9% with a median duration of response of 6.9 months. In the PDAC group, ORR was 16.7% with median duration of response of 3.4 months.

Table 1 outlines the current abundance of anti-CLDN18.2 agents and phase of study for these agents. The number of agents show the crowded and overlapping landscape targeting CLDN18.2. We believe

Table 1. Examples of anticlaudin 18.2 agents [8,19▪▪]

Claudin 18.2 agent	Drug classification
Zolbetuximab	mAb
Osemitamab	mAb
ZL-1211	mAb
IBI360	mAb
AB011	mAb
NBL-015	mAb
SPX-101	mAb
MIL93	mAb
LM-102	mAb
BMS-986476	ADC
TPX4589	ADC
RC118	ADC
CMG901	ADC
IBI343	ADC
SOT102	ADC
TQB213	ADC
SYA1801	ADC
ATG-022	ADC
SHR-A1904	ADC
TORL-2-307	ADC
AMG910	Bispecific
ASP2138	Bispecific
Q-1802	Bispecific
TJ033721	Bispecific
PT886	Bispecific
CT-041	CART
LY011	CART
LCAR-C18S	CART
IMC002	CART
TAC01-CLDN18.2	CART
KD-496	CART
IBI345	CART
LB1908	CART
IMC008	CART
BNT212	CART

ADC, antibody drug conjugate; CART, chimeric antigen receptor T-cell therapy; mAb, monoclonal antibody.

more translational research on how these agents impact specific solid tumors positive for CLD18.2 will lead to further success. As it is clear, that targeting CLDN18.2 differs in response based on tumor type (i.e. GAC vs. PDAC). Defining CLDN18.2 expression criteria and in turn having a universal acceptance of these established categories would allow for more clear understanding of the role of these agents and avoid the failure of medication success due to the lack of poor inclusion criteria. Additionally, studying these agents in the refractory setting following anti-CLDN18.2 agent exposure will help determine if patients with CLDN18.2 positivity will follow a different treatment pathway in GAC similar to that seen with HER-2 positive patients.

OTHER CLAUDIN TARGETS UNDER INVESTIGATION

Other CLDN agents targeting CLDN6 and CLDN4 are ongoing in solid tumors. DS-9606a, TORL-1–23, AMG794, BNT142 are being studied for CLDN6 positive solid tumors while ASP1002 is being investigated in CLDN4 positive tumors [26–30]. Whether these will have any role in GI tumors, particularly HCC, is too early to determine. These trials likely will reveal that targeting CLDN6 and CLDN4 for GI tumors might not align with how these agents work in other solid tumors under review such as ovarian, endometrial, and germ cell.

CONCLUSION

CLDNs have gained an enormous amount of oncology attention in recent years. The pipeline is vast with many agents currently undergoing investigation. We are at the beginning stages of understanding how these agents will have therapeutic potential. We look forward to the coming years to reveal outcomes of the current trials underway to better understand how each agent class will play a role.

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Conflicts of interest

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- ▪ of special interest
- ▪▪ of outstanding interest

1. Siegel RL, Giaqunto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin 2024; 71:12–49.
2. National Comprehensive Cancer Network. Colon cancer. Version 4. 2023. Available at: www.nccn.org [Accessed 26 January 2024].
3. National Comprehensive Cancer Network. Gastric cancer. Version 3. 2023. Available at: www.nccn.org [Accessed 26 January 2024].

4. Wang DW, Zhang WH, Danil G, *et al.* The role and mechanism of claudins in cancer. Front Oncol 2022; 12:1051497.
5. Hashimoto I, Oshima T. Claudins and gastric cancer: an overview. Cancers (Basel) 2022; 14:290.
6. Tao D, Guan B, Li H, *et al.* Expression patterns of claudins in cancer. Heliyon 2023; 9:e21338.
7. 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 2021; 10:1967080.
8. Inamoto R, Takahashi N, Yamada Y. Claudin 18.2 in advanced gastric cancer. Cancers (Basel) 2023; 15:5742.
9. Shain U, Schuler M, Richly H, *et al.* A phase I dose-escalation study of IMAB362. 2023; 15:5742.
10. Sahin U, Al-Batran SE, 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. 33(suppl):e.15079.
11. Tureci O, Shin U, Schulze-Bergkamen H, *et al.* A multicentre, phase IIa study of zolbetuximab as a single agent in patients with recurrent or refractory advanced adenocarcinoma of the stomach or lower oesophagus: the MONO study. Ann Oncol 2019; 30:1487–1495.
12. Sahin U, Tureci O, Manikhas G, *et al.* FAST: a randomised phase II study of zolbetuximab (IMAB362) plus EOX versus EOX alone for first-line treatment of advanced CLDN18.2-positive gastric and gastro-oesophageal adenocarcinoma. Ann Oncol 2021; 32:609–619.
13. ■ Shitara K, Lordick F, Bang YJ, *et al.* Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2 positive, HER-2 negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicentre, randomized, double-blind, phase 3 trial. Lancet 2023; 401:1655–1668.

Phase 3 trial of zolbetuximab.

14. ■ Shah MA, Shitara K, Ajani JA, *et al.* Zolbetuximab plus capeox in CLDN18.2 positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial. Nat Med 2023; 29:2133–2141.

Phase 3 trial of zolbetuximab.

15. Klempner SJ, Ajani JA, Al-Batran SE, *et al.* Phase II study of zolbetuximab plus pembrolizumab in claudin 18.2: positive locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma (G/GEJ)–ILUSTRO Cohort 3. J Clin Onc 2021; 39.
16. Kim HD, Choi E, Shin J, *et al.* Clinicopathologic features and prognostic value of claudin 18.2 overexpression in patients with resectable gastric cancer. Nature 2023; 13:20047.
17. Zhang WH, Zhang SY, Hou QQ, *et al.* The significance of the CLDN18-ARHGAP fusion gene in gastric cancer: a systematic review and meta-analysis. Front Oncol. 2022;10:1214.
18. Park W, O'Reilly EM, Furuse J, *et al.* Zolbetuximab plus gemcitabine and nab-paclitaxel (GN) in first-line treatment of claudin 18.2-positive metastatic pancreatic cancer (mPC): phase 2, open-label, randomized study. J Clin Onc 2022; 40.
19. ■■ Mullar A. Claudin 18.2 attracts the cancer crowd. Nat Rev Drug Discov 2023; 22:683–686.

Claudin options discussed.

20. Shen L, Liu D, Li Ning, *et al.* Osemitamab in combination with capecitabine and oxaliplatin (CAPOX) as a first line treatment of advanced G/GEJ cancer: Updated data of cohort C from a phase I/IIa, multicenter study (TranStar102/TST001-1002). J Clin Oncol 2023; 41:.
21. Clinical Trials Arena. FDA grants trascenta clearance for phase III trial of osemitamab. Available at: https://www.clinicaltrialsarena.com/news/fda-grants-trascenta-clearance-for-phase-iii-trial-of-osemitamab/?cf-view [Accessed 20 February 2024].
22. XU RH, Ruan DY, Zhang DS, *et al.* A phase 1 trial of claudin 18 2 specific antibody-drug conjugate CMG901 in patients with advanced gastric/gastroesophageal junction cancer 2023; 41:.
23. RemeGen Col, Ltd. A study of FC118 plus toripalimab in patients with locally advanced unresectable or metastatic solid tumors. In: ClinicalTrials.gov. National Library of Medicine (US). 2000 Available at: https://clinicaltrials.gov/study/NCT06038396. NLM Identifier: NCT06038396.
24. Wang YK, Gong J, Sun Y, *et al.* Interim results of a first-in-human phase 1 study of Q-1802, a CLDN18.2/PD-L1 bsABs, in patients with relapsed or refractory solid tumors. J Clin conOl 2023; 41:.
25. Botta GP, Kelly RJ, Jin Z, *et al.* CLDN18.2 chimeric antigen receptor T cell therapy for patients with advanced gastric and pancreatic adenocarcinoma. Results of ELIMYN18.2 phase 1b clinical trial. J Clin Onc 2024; 42.
26. Daiichi Sankyo. A study of DS-9606a in patients with advanced solid tumors. In: ClinicalTrials.gov. National Library of Medicine (US). 2000. Available at: https://clinicaltrials.gov/study/NCT05394675. NLM Identifier: NCT05394675.
27. TORL Biotherapeutics, LLC. First in human study of TORL-1-23 in participants with advanced cancer (TRI0049). In: ClinicalTrials.gov. National Library of Medicine (US). 2000. Available at: https://clinicaltrials.gov/study/NCT05103683. NLM Identifier: NCT05103683.
28. Amgen. A phase 1 safety, tolerability, and pharmacokinetics study of AMG 794 with claudin 6-positive nonsmall cell lung cancer, epithelial ovarian cancer, and other malignant solid tumor indications. In: ClinicalTrials.gov. National Library of Medicine (US). 2000. Available at: https://clinicaltrials.gov/study/NCT05317078. NLM Identifier: NCT05317078.
29. BioNTech SE. Safety and preliminary efficacy trial of BNT142 in patients with CLDN6-positive solid tumors. In: ClinicalTrials.gov. National Library of Medicine (US). 2000. Available at: https://clinicaltrials.gov/study/NCT05262530. NLM Identifier: NCT05262530.
30. Astellas Pharma Global Development, Inc. A study of ASP1002 in adults for treatment of solid tumors. In: ClinicalTrials.gov. National Library of Medicine (US). 2000. Available at: https://clinicaltrials.gov/study/NCT05719558. NLM Identifier: NCT05719558.