Review Article

Evaluation and reflection on claudin 18.2 targeting therapy in advanced gastric cancer

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Abstract

Claudin 18.2 (CLDN18.2) is a tight-junction protein. CLDN18.2-targeting strategy has cut a striking figure in CLDN18.2 positive patients with advanced gastric cancer. Zolbetuximab, the CLDN18.2 antibody, obtained a better clinical benefit in patients compared with the controlled. In phase II trials, combination treatment of epirubicin, oxaliplatin and capecitabine (EOX) + zolbetuximab achieved the optimal effects of overall survival which extended to 13.2 months with tolerable safety events, indicating its greater potential playing the second promising target in gastric cancer. This review will reveal the definitive clinical benefit CLDN18.2-targeting therapies have achieved and update the highlighting development (like chimeric antigen receptor T-cell immunotherapy) to CLDN18.2 positive patients. We then focus on 10 questions arisen from recent progress and anticipate to provide a future perspective for novel cancer treatment.

Keywords: Claudin 18.2; gastric cancer; zolbetuximab; chimeric antigen receptor therapy

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Introduction

Gastric cancer, which ranks third in cancer-related mortality, is considered as one of the most incurable cancers worldwide (1). In patients with advanced or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma, the median overall survival (mOS) is no more than 10 months (2). Although human epidermal growth factor receptor-2 (HER-2) targeting therapy and immune checkpoint inhibitors (3) have brought the gospel to specific population, it's imperative to search for other targets in advanced gastric cancer, and here comes claudin 18.2 (CLDN18.2).

Claudins are a family of proteins acting to maintain the tight junction that controls the interchange of molecules between the cells. They prevalently distribute in gastric, pancreatic and lung tissues, which can be applied in diagnosis and therapy. The subtype CLDN18.2, which is a stomach specific-isoform, has emerged as an ideal target since Sahin has discovered it as a highly selective molecule that widely expresses only in cancer cells. This has paved the way for treatment of gastric/GEJ adenocarcinoma (4). CLDN18.2 is typically buried in gastric mucosa, largely inaccessible to monoclonal antibodies in normal tissues. It's malignant carcinogenesis that leads to disruptions in tight junctions, exposing CLDN18.2 epitopes on the surface of tumor cells to be specifically targeted. Thus, CLDN18.2 endows targeting therapy with specificity. Recent identified expression in pancreatic cancer (50%), esophagus cancer and lung cancers also indicated potentials for diagnosis (5) and treatment for other tumors (4).

Zolbetuximab (IMAB362, claudixmab), which is the first developmental drug aiming at the target, is a structurally chimeric IgG1 monoclonal antibody that specifically binds to CLDN18.2 on tumor cell surface, hence triggering antibody-dependent cellular cytotoxicity (ADCC),

complement-dependent cytotoxicity (CDC), apoptosis and inhibiting cell proliferation. Preclinical studies have successfully validated its potent ability to eliminate cancer cells and control diseases. Subsequently, clinical efficacy and toxicity have been assessed by several phase I/II trials.

CLDN18.2 targeting therapy

We reported the efficacy and safety of targeting therapies in CLDN18.2 positive patients. Data are summarized in *Table 1*, *2*.

The first-in-human study (NCT00909025) aimed at determining the maximum tolerated and recommended doses of the zolbetuximab in a dose-escalation cohort of 33–1,000 mg/m^2, and 15 patients with previously treated advanced gastric/GEJ adenocarcinoma entered into the evaluation. A 600 mg/m^2 dose was recommended for the following studies (6).

The phase IIa study (NCT01197885, MONO 2013) researched its efficacy and safety in 54 patients with refractory advanced or metastatic CLDN18.2 positive gastric adenocarcinoma. Patients with positive CLDN18.2 and Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 were eligible. Notably, positivity was defined as ≥2+ CLDN18.2 staining intensity in >50% of tumor cells. Median progression-free survival (mPFS) improved to 14.5 weeks. Those responded obtained median duration of response extended to 24.6 (range, 13.1–156.1) weeks. Ten patients achieved clinical benefit [partial response (PR) was presented in 4 (9%) patients and stable disease (SD) in 6 (14%)], among whom 90% had higher expression (7). Time to deterioration (TTD) for global health status was also elongated (11). Forty-four patients (82%) suffered treatment-related adverse events (TRAEs), most of which were grade 1 or 2. Nausea, vomiting, fatigue and decreased appetite emerged as the main events related to zolbetuximab in over 10% of the population. All serious TRAEs appeared in patients who received the 600 mg/m^2 dose. These could be resolved by pausing or slowing infusion of zolbetuximab. Moreover, 54% of patients in MONO study underwent prior gastrectomy. Patients without gastrectomy tended to have nausea and vomiting more often. Repeated zolbetuximab infusions could reduce the incidence (7).

A phase I trial (NCT01671774, PILOT 2014) investigated the safety of zolbetuximab in combination with zoledronic acid and interleukin-2 in chemo-refractory patients who progressed after chemotherapy regimens with CLDN18.2 positive gastroesophageal adenocarcinoma. mOS was observed to be 40 weeks. mPFS was 12.7 weeks. The TRAEs included nausea and vomiting mostly grades 1–3 and no adverse events led to study discontinuation. Thirteen of 15 patients experienced >1 TRAEs, with gastrointestinal disorders being most commonly reported (8).

The phase IIb study (NCT01630083, FAST 2015) evaluated zolbetuximab in coordination with first line epirubicin, oxaliplatin and capecitabine (EOX) chemotherapy in patients with advanced/recurrent gastric/GEJ cancer. Patients were eligible if their tumors expressed CLDN18.2 (defined as ≥2+ in ≥40% tumor cells detected by CLAUDETECT^{TM} 18.2 Kit) without HER-2. The inclusion criteria also included ECOG performance status of 0–1. Population positive rate reached to 48% (352/739). FAST study revealed an encouraging mPFS of 7.5 months in experimental groups and 5.3 months in the

Table 1 Efficacy of claudin 18.2 positive patients targeted regimen compared to alternative regimens

Trial name	NCT Trial No.	Phase	Sample size	Therapy	OS	mPFS	ORR
Sahin-2009 (6)	NCT00909025	I	15	Zolbetuximab (single-dose escalation)	–	–	–
MONO-2013 (7)	NCT01197885	IIA	43	Zolbetuximab	–	14.5 weeks	9%
PILOT-2014 (8)	NCT01671774	I	32	IMAB362 + zoledronic acid + IL-2	40 weeks	12.7 weeks	–
FAST-2015 (9)	NCT01630083	IIB	161	zolbetuximab + EOX *vs.* randomized EOX	13.2 months *vs.* 8.4 months	7.5 months *vs.* 5.3 months	39% *vs.* 25%
Zhan 2019 (10)	NCT03159819	I	12 (7)	Claudin 18.2-specific chimeric antigen receptor T cells	–	130 days	42.8%

OS, overall survival; mPFS, median progression-free survival; ORR, objective response rate; IL, interleukin; EOX, epirubicin, oxaliplatin and capecitabine.

Table 2 Ongoing clinical trials of targeted therapy

Title	NCT trial No.	Drug (s) tested	Sample size	Primary end point	Phase
A phase 2, open-label, randomized study to assess the antitumor activity and safety of zolbetuximab (IMAB362) in combination with nab-paclitaxel and gemcitabine (Nab-P+GEM) as first line treatment in subjects with claudin 18.2 (CLDN18.2) positive, metastatic pancreatic adenocarcinoma	NCT03816163	Zolbetuximab + nab-paclitaxel + gemcitabine	141	DLT, OS, AEs (SAE, TRAEs), ECOG	2
A phase 2 study of zolbetuximab (IMAB362) as monotherapy or in combination with mFOLFOX6 in subjects with metastatic or locally advanced unresectable gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors have high or intermediate claudin (CLDN) 18.2 expression	NCT03505320	Zolbetuximab + mFOLFOX6	102	ORR	2
A phase 3, global, multi-left, double-blind, randomized, efficacy study of zolbetuximab plus mFOLFOX6 compared with placebo plus mFOLFOX6 as first-line treatment of subjects with claudin 18.2-positive, HER2-negative, locally advanced unresectable or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma	NCT03504397	Zolbetuximab + mFOLFOX6	550	PFS	3
A phase 3, global, multi-left, double-blind, randomized, efficacy study of zolbetuximab (IMAB362) plus CAPOX compared with placebo plus CAPOX as first-line treatment of subjects with claudin (CLDN) 18.2-positive, HER2-negative, locally advanced unresectable or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma	NCT03653507	Zolbetuximab + CAPOX	500	PFS, PD	3
An open label, dose escalating/dose regimen finding clinical study to evaluate the safety, efficacy, and cytokinetics of autologous humanized anti-claudin 18.2 chimeric antigen receptor T cell in advanced solid tumor subjects	NCT03874897	CAR-CLDN18.2 T-cells	15	DLT, MTD	1
Clinical study of redirected autologous T cells with a claudin18.2-targeted chimeric antigen receptor in patients with advanced gastric adenocarcinoma and pancreatic adenocarcinoma	NCT03159819	CAR-CLDN18.2 T-cells	24	Safety, tolerability	–
A phase 1 study of LCAR-C182A cells in the treatment of advanced gastric cancer and pancreatic ductal adenocarcinoma	NCT03890198	CAR-CLDN18.2 T-cells LCAR-C182C Cells	18	AEs, transgene levels and cell concentration of LCAR-C82 CAR-T Cells, cytokine concentrations	1

DLT, dose-limiting toxicity; OS, overall survival; AE, adverse events/effect; SAE, serious adverse event; TRAE, treatment emergent adverse event; ECOG, Eastern Cooperative Oncology Group; ORR, objective response rate; PFS, progression-free survival; PD, progressive disease; MTD, maximum tolerated dose; mFOLFOX6 treatment includes oxaliplatin, leucovorin, fluorouracil; CAPOX contains capecitabine and oxaliplatin.

control [hazard ratio (HR)=0.44; 95% confidence interval (95% CI): 0.29, 0.67]. A 13.2 months OS benefit was retrieved in zolbetuximab plus EOX compared to 8.4 months in EOX alone (HR=0.56; 95% CI: 0.40, 0.79) along with a better objective response rate (ORR) (39% *vs*. 25%; P=0.022) (9). Eight patients (10.4%) gained complete response (CR), 22 (28.6%) patients obtained PR, and 34 (44.2%) had SD. PR, CR and SD were presented in 18 (21.4%), 3 (3.6%) and 43 (51.2%) patients in controlled group, respectively. An exploratory analysis demonstrated that patients with higher CLDN18.2 expression (≥2+ intensity in ≥70% tumor cells) embraced superior outcomes (PFS, 9.1 *vs*. 6.1 months; HR=0.46; OS, 16.6 *vs*. 9.3 months; HR=0.44) (12). The median time of first health-related quality-of-life (HRQoL) minimally clinically important difference deterioration was improved

significantly in EOX + zolbetuximab arm *vs.* EOX only (8.6 months *vs.* 6.0 months) (13). Vomiting was the most frequent toxicity reported in the EOX + zolbetuximab arm (grade 1/2 vomiting rates were 55.8% *vs*. 34.0%, while grade 3/4 vomiting rates were 10.4% *vs*. 3.0%). The incidence and severity of vomiting had a dose-dependent relation with zolbetuximab. Grade 3/4 events were not increased in EOX + zolbetuximab arm, as nausea, neutropenia and anemia also occurred in small possibilities (12).

Ten questions on anti-CLDN18.2 therapy

Our results indicated a significant efficacy and safety profile of zolbetuximab in gastric cancer (14). Despite splendid results kept pouring in, the variability of CLDN18.2 report in many studies likely reflects the limitations in testing populations, and differences in cutoff used. In the following part, we have been focusing on 10 questions arisen recently, anticipating finding future directions of CLDN18.2 treatments.

Is there a uniform detection means?

Highly specific agents should be employed to differentiate CLDN18.2 from spliced variant (claudin 18.1). CLAUDETECT™ 18.2 Kit [generated by Ganymed (now acquired by Astellas)], which is a semi-quantitative immunohistochemically test, was utilized in the first in-human study and the FAST study. The MONO trials reported assessing specimen by anti-CLDN18.2 rabbit antiserum (Zymed). This may partially account for distinct positivity threshold and efficacy in these trials. Unified detection means to identify CLDN18.2 were advocated (15).

What are population prevalence characteristics?

Considerable distribution of CLDN18.2 positive population lays the cornerstone for its widely application. The FAST trial and MONO trial revealed an optimistic distribution of 48% (12) and 45% (7) of the Caucasian population, respectively. Higher expression levels appeared in 36% and 24% of patients. Several investigations supplemented the prevalence of CLDN18.2 positive patients with confined sample size in other trials. Positivity (eligibility criterion in FAST) was observed in 52% (135/262) of primary tumors in a Japanese study, which supported the therapeutic assessment of zolbetuximab in Asians (16). A further study revealed that high CLDN18.2 reach to 34% in American samples and 24% in Asian samples. Whether Asian or Caucasian groups are more eligible remains to be explored. Total HER-2 positive occurred in 10% of the same cohort (17). It suggested that zolbetuximab may benefit more population, compared to the prevalence of HER-2 (16.6%). In FAST study, only 14% of CLDN18.2 positive patients co-expressed HER-2, clearly indicating that CLDN18.2 can be set as a non-overlapping target in a novel subpopulation of gastric cancers.

What is prognostic value of CLDN 18.2?

Similar to HER-2, it's not clear whether CLDN18.2 links with meaningful prognosis and further direct evidence may be pursued. Firstly, it is controversial whether the expression levels correlate with Lauren subtypes and molecular subtypes of The Cancer Genome Atlas (TCGA) and The Asian Cancer Research Group (ACRG). Whether CLDN18.2 prevalence was higher in diffuse types or in intestinal subtypes or no significant differences is disputable (17-20). Whereas there is no significant correlation discovered in CLDN18.2 expression level and Lauren subtypes in a Caucasian cohort (n=481), strong CLDN18.2 is correlated with Epstein-Barr virus (EBV) status, the TCGA molecular subtypes (19). This is proved by another tissue microarray (n=523) where CLDN18.2 positivity is associated with EBV-associated cancers and diffuse type (21). Secondly, gene alteration warrants our attention. Recently, CLDN18-ARHGAP26/6 fusions were found prevalent in diffuse-type gastric cancers accompanying lymphatic and distant metastases, indicating failing to respond to oxaliplatin/fluoropyrimidines-based chemotherapy. Therefore, fusion status may constitute a useful response predictor for efficacy (22). Histological samples revealed that claudin 18 at the invasive front is inversely correlated with proliferative potential (23). Further analyses are warranted to identify its prognostic value using omics.

Is a new cutoff value needed?

Notably, cutoff value for the CLDN18.2 levels varied in different trials. Firstly, there are gaps of PFS between MONO and FAST trials (14.5 weeks *vs.* 7.5 months), which may be attributed to patient status and different cutoff value (resulted from different testing agents). Secondly, subgroup analysis of high expression levels of CLDN18.2 (≥2+ intensity in ≥75% tumor cells), always achieved better efficacy (16.6 months *vs.* 9.3 months) than

moderate levels (12). However, patients with ≥2+ CLDN18.2 in ≥70% of tumor cells gained same ORR in the MONO study (7). A phase III trial (NCT03505320) was inspired to further confirm that, enriching patients with as high levels as FAST trial. Further studies that investigate the optimal cutoff value of the expression are warranted. Whether different testing agents and patient groups (ethnicity) need unique cutoff value also requires further exploration.

Is zolbetuximab qualified to be the second targeting candidate (compared with HER-2)?

There is no doubt that zolbetuximab takes the lead in targeting therapy in HER-2 positive advanced gastric cancer patients. EOX + zolbetuximab achieved the optimal outcome of mOS (13.2 months), which could be compared with that of ToGA (13.3 months) (3), indicating its greater potential playing the second promising target in gastric cancer. The mOS of subgroup of high expression levels of CLDN18.2 (16.6 months) presented even superior than that of ToGA (13.8 months). Similar to trastuzumab, nausea and vomiting were the most frequent and severe adverse effects. Up to now, no therapeutic resistance related to zolbetuximab has been observed. Despite CLDN18.2 and HER-2 co-expression in FAST study manifests effect to zolbetuximab, trials aiming at CLDN18.2 positive/HER-2 positive, as well as CLDN18.2 positive/HER-2 negative patients are expected.

Will combination therapy obtain better results?

The clinical hotspot mainly concentrated on the cooperative effects of target agents and chemotherapy regimens/immunotherapy. Although no results of immunotherapy combination have been reported, targeting CLDN18.2 theoretically promote T cells infiltration and antigen-presentation, which can enhance the efficacy of immune checkpoint inhibitors. Antiangiogenic agents like bevacizumab can initiate downstream effectors of IgGs that involve in ADCC, therefore assisting zolbetuximab in effects. Chemotherapy can not only enhance ADCC induced by zolbetuximab, but may also directly induce apoptosis of cancer cells (24). Moreover, chemotherapy sensitizes tumor cells to zolbetuximab by increasing CLDN18.2 expression, thereafter inducing pro-inflammatory cytokines (25,26). Preclinical and clinical data have both shown that chemotherapy regimens can assist zolbetuximab in achieving survival benefit in patients with CLDN18.2 positive advanced gastric cancer (22). Significance was attached to the combination of zolbetuximab with common chemotherapeutic regimens. In Caucasian groups, a phase II trial (NCT03505320) applying zolbetuximab + mFOLFOX to HER-2 negative/CLDN18.2 positive unresectable gastric/GEJ cancer, has been carrying out since 2018. Besides efficacy and safety, pharmacokinetics and immunogenicity of zolbetuximab will also be assessed. This will be followed by a phase III trial (NCT03504397) to investigate the combined efficacy of zolbetuximab + mFOLFOX in a larger population. An alternative first-line therapeutic option CAPOX will also cooperate with zolbetuximab in a phase III trial (NCT03653507) to validate its effects.

However, given that distinction between Eastern and Western population, three-drug-combination adds more toxicity than efficacy, which is hard to duplicate in Asian people. To avoid intolerance while maintaining the effect, cisplatin + fluorouracil (S-1) emerges as the first-line therapy and is anticipated to partner with zolbetuximab. CLDN18.2 positive patients in Asian population warrant more consideration (*Table 2*).

Are there alternative targeting agents that play a part?

Other molecules which possess high selectivity and affinity, such as GB7004-09hu15 (27) and IMAB362 VCME, elicited strong anti-tumor efficacy with mild toxicity (28). They exemplify the application of antibody-drug conjugate in CLDN18.2 positive target and have also guided novel perspectives for extended clinical exploration. Besides, immunization utilizing virus-like particle as antigen carriers with CLDN18.2 specific epitopes of a highly selective differentiation antigen may yield tumoricidal potential and inhibit the metastases (29).

Will CAR-T cells therapy be effective in gastric cancer?

Since the high specificity of CLDN18.2 can facilitate the T cells in recognizing tumors, it was exploited for chimeric antigen receptor T (CAR-T) target cell therapy. Although CAR-T cell therapy used to encounter setbacks in solid cancers, a breakthrough could be achieved as *in vivo* efficacy can be validated in PDX models compared with standard therapies, demonstrating that CLDN18.2-specific CAR-T cells could be utilized as a promising treatment strategy for other potential CLDN18.2 positive tumors, specifically, gastric cancer (30).

The ongoing phase I study (NCT03159819) explored

the clinical application of CLDN18.2-specific CAR-T cells including safety, tolerability and cytokinetics. Targeting 12 patients with CLDN18.2 positive solid tumors, among whom 7 were gastric cancer. Among the 11 evaluable subjects, 1 achieved a CR (gastric), 3 had PR (including 2 gastric cancer), 5 had SD and 2 had progression disease. The ORR in gastric cancer was 42.8% (3/7), and the total ORR reached 33.3%, with mPFS of 130 days (10).

Will CAR-T cells therapy be safe in gastric cancer?

Although CAR-T cell therapy is challenging for its toxicity like cytokine storm, the preclinical studies and ongoing trials alleviated the worry. Jiang *et al.* combined T cells with hu8E5–2I, the antigen-binding element, to construct CLDN18.2 CAR-T cells, and showed that it not only endowed CAR-T cells with potent capacity to eliminate murine CLDN18.2 positive cells, but also brought no obvious toxicities on normal tissues in PDX models. The phase I trial reported no severe gastro-toxicity or cytokine release syndromes (CRS), no grade 4 AEs except for decreased lymphocytes, neutrophils were observed (30). The mild on-target off-tumor effect may be associated with unique tumor microenvironment. Unravelling the underlying mechanisms may enlighten the arrangement of TRAEs (30).

How to improve CAR-T cell therapy?

Engineered to have two binding sites, bispecific T-cell engagers (BiTEs) both against CD3 and CLDN18.2 were effected in the PDX model. BiTEs thus can guide T cells via binding its CD3 to target CLDN18.2, therefore improving ADCC with little toxicity. Such therapeutics proved superior to that of traditional ones (31). A novel tetravalent bispecific (TetraBi) platform for CLDN18.2 showed impressive antitumor activity, which provided a potentially better therapeutic index than bispecific formats (32). In preclinical studies, despite triumph of BiTEs over PDX models, whether effects and safety on orthotopic model would stay optimistic remained uncertain. Whereas no remarkable AEs were reported, CAR-T cell therapy specific CRS of grade 1 or 2 happened, suggesting cytokine storms may challenge clinical application theoretically. With Zhan *et al*. proceeding, several ongoing phase I trials are exploring the therapeutic concentration and safety of CLDN18.2 CAR- T cell therapy in large populations, including dose-limiting toxicity and maximum tolerated dose (NCT03874897, NCT03890198). They will strengthen the evidence of efficacy.

Future outlook

Firstly, CLDN18.2 tends to be the second important target following HER-2 in gastric cancer. It even outperforms HER-2 as for high positivity. The OS in FAST trial was no inferior to that of HER-2 efficacy. Further studies are warranted to identify ideal cutoff values of CLDN18.2 levels to obtain optimal benefit.

Secondly, combining therapies are anticipated. With combination regimens of zolbetuximab with chemotherapy sprang up, conjoint therapy with other targeting agents may also be worth pursuing. As HER-2 positive/PD-L1 positive patients who received trastuzumab plus pembrolizumab achieved a response rate of 87% and mPFS of 11.4 months (33), it's noteworthy that combination of zolbetuximab with immunotherapy may stimulate T cell infiltration, which orchestrates with immune checkpoint inhibitors.

Last, but not least, more prognostic meanings warrant further investigations. The molecular subtype has greater potential in guiding precise medicine therapy, like CLDN18-ARHGAP26/6 fusions indicating a worse survival outcome and resistance to chemotherapy (22). More prognostic predictors of CLDN18.2 could be explored and validated, thereafter, benefiting the distinctive population.

Conclusions

CLDN18.2 is a promising target among HER-2 negative gastric cancer patients, not only on high selectivity, but also on population prevalence, acting as a perfect supplement for target therapy in gastric cancers. The novel antibody, zolbetuximab, has illustrated a significant superior efficacy and safety profile either as monotherapy or in combination with chemotherapy. CLDN18.2 CAR-T cells therapy explores another possibility with an excellent performance recently. The strategy will progress to phase III trials, leaving further result on its efficacy when combined with other therapies eagerly anticipated. With well-depicted molecular profiles and well-designed clinical trials presenting soon, anti-CLDN18.2 therapies will answer questions perfectly and bring more surprises in future.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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