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Targeting Claudin-18.2 for cancer therapy: updates from 2024 ASCO annual meeting

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Abstract

Multiple classes of therapies targeting claudin-18 isoform 2 (CLDN18.2) are under development for the treatment of advanced gastroesophageal adenocarcinoma and other solid tumors. At the 2024 American Society of Clinical Oncology (ASCO) Annual Meeting, the final results of the phase 3 SPOTLIGHT trial were presented, demonstrating a significant survival benefit from the addition of the CLDN18.2-specific antibody zolbetuximab to chemotherapy in the first-line treatment of advanced gastroesophageal adenocarcinomas with ≥ 75% CLDN18.2 expression. Early-phase trial results presented at ASCO 2024 showed promising efficacy and safety of the afucosylated CLDN18.2-specific antibody FG-M108 in combination with chemotherapy in the first-line treatment of CLDN18.2-positive advanced gastroesophageal and pancreatic cancers. In addition, several early-phase trials presented at ASCO 2024 investigate other CLDN18.2-targeting approaches in CLDN18.2-positive refractory advanced solid tumors, including the CLDN18.2-targeting antibody–drug conjugates LM-302 and IBI343, the bispecific anti-CLDN18.2/CD3 antibody IBI38, and the chimeric antigen receptor T cell therapy satricabtagene autoleucel. These novel approaches could potentially expand the benefit of CLDN18.2-targeting therapies to a broader range of tumor types and to tumors expressing lower levels of CLDN18.2.

Keywords Claudin-18.2, Targeted therapies, Antibody therapies, Antibody–drug conjugates, Bispecific antibodies, Chimeric antigen receptor T cell therapy, Gastrointestinal cancers, Gastroesophageal adenocarcinoma

To the Editor:

Claudin-18 isoform 2 (CLDN18.2) is an emerging target in gastroesophageal adenocarcinoma and other solid tumors [1]. Here, we review some new developments in targeting claudin-18.2 from ASCO 2024.

Zolbetuximab for CLDN18.2-positive gastroesophageal adenocarcinoma

The phase 3 SPOTLIGHT and GLOW trials demonstrated the efficacy of the CLDN18.2-specific antibody zolbetuximab with chemotherapy for the first-line treatment of advanced gastric and gastroesophageal junction (GEJ) adenocarcinomas with ≥75% of tumor cells showing moderate-to-strong membranous CLDN18.2 expression [2, 3]. In the final analysis of SPOTLIGHT [4], PFS and OS remained significantly improved with

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the addition of zolbetuximab to mFOLFOX, with median PFS 11.0 versus 8.9 months (HR 0.73, 95% CI 0.59–0.91, $p=0.0024$) and median OS 18.2 versus 15.6 months (HR 0.78, 95% CI 0.64–0.95, $p=0.0075$). Objective response rate (ORR) was similar in both arms (48.1% versus 47.5%).

FG-M108 for CLDN18.2-positive gastroesophageal and pancreatic cancers

The afucosylated anti-CLDN18.2 antibody FG-M108 was designed to increase antibody-dependent cellular cytotoxicity. In a phase 1/2a study [5], patients with untreated advanced gastric or GEJ adenocarcinoma were treated with FG-M108 and CAPOX. The ORR was 77.8% and disease control rate (DCR) 97.2% among 36 patients with ≥40% of tumor cells showing CLDN18.2 expression of 2+/3+by immunohistochemistry (IHC), while the ORR was 46.7% and DCR 100% among 15 patients with ≥10% IHC 1+/2+/3+but <40% IHC 2+/3+CLDN18.2 expression. In 40 patients with untreated advanced pancreatic cancer with ≥10% IHC 1+/2+/3+CLDN18.2 expression [6], FG-M108 with gemcitabine and nab-paclitaxel led to an ORR of 32.5% and DCR of 100%. The authors concluded that the combination was well tolerated. This study is ongoing.

Novel therapeutic strategies for CLDN18.2-positive advanced solid tumors

In addition to CLDN18.2-specific antibodies, novel therapeutic approaches include antibody–drug conjugates (ADCs), bispecific antibodies, and chimeric antigen receptor T cell (CAR-T) therapies. The ADC LM-302 comprises a humanized anti-CLDN18.2 antibody conjugated to the microtubule-disrupting agent monomethyl auristatin E. In a phase 1/2 study [7], LM-302 yielded an ORR of 30.6% and DCR of 75.0% among 36 patients with refractory advanced gastric or GEJ cancer with ≥50% IHC 2+/3+CLDN18.2 expression. Median PFS was 7.2 months. Another ADC, IBI343, comprises a monoclonal anti-CLDN18.2 antibody conjugated to a topoisomerase I inhibitor. In a phase 1 trial [8], IBI343 generated an ORR of 28.0% and DCR of 80.0% among 25 patients with refractory advanced pancreatic or biliary tract cancer with ≥40% IHC 1+/2+/3+CLDN18.2 expression.

A phase 1 study is investigating the bispecific anti-CLDN18.2/CD3 antibody IBI389 in refractory advanced solid tumors [9, 10]. Among 26 patients with advanced gastric or GEJ adenocarcinoma with ≥10% IHC 2+/3+CLDN18.2 expression, the ORR was 30.8%, DCR 73.1%, and median PFS 3.5 months [9]. Among 27 patients with advanced pancreatic ductal adenocarcinoma with ≥10% IHC 2+/3+CLDN18.2 expression, the ORR was 29.6% and DCR 70.4% [10]. Among 120 enrolled patients, there was one treatment-related death from cerebrovascular accident after gastrointestinal hemorrhage [9]. Although cytokine release syndrome (CRS) occurred in 60% of patients, most were grade 1–2 [9].

CAR-T therapy provides yet another innovative approach to targeting CLDN18.2. The phase 1 CT041-CG4006 trial evaluated satricabtagene autoleucel (satri-cel), an autologous CAR-T product targeting CLDN18.2, in 98 patients with gastrointestinal cancers, of whom 75%

Table 1 Summary of clinical trials testing CLDN18.2-targeting agents from ASCO 2024

Treatment	Mechanism	Tumor type	Biomarker	ORR	DCR	PFS	Ref
zolbetuximab + mFOLFOX	Anti-CLDN18.2 antibody	1 L HER2-negative advanced gastric/GEJ adenocarcinoma	≥75% moderate-to-strong membranous CLDN18.2	48.1%	63.6%	11.0 months	[4]
FG-M108 + CAPOX	Afucosylated anti-CLDN18.2 antibody	1 L HER2-negative advanced gastric/GEJ adenocarcinoma	≥10% CLDN18.2 IHC 1+/2+/3 + and < 40% IHC 2+/3+	46.7%	100%	5.0 months	[5]
			≥40% CLDN18.2 IHC 2+/3+	77.8%	97.2%	9.6 months	
FG-M108 + nab-paclitaxel + gemcitabine		1 L advanced pancreatic cancer	≥10% CLDN18.2 IHC 1+/2+/3+	32.5%	100%	Not mature	[6]
LM-302	ADC with MMAE payload	Refractory advanced gastric/GEJ cancer	≥50% CLDN18.2 IHC 2+/3+	30.6%	75.0%	7.2 months	[7]
IBI343	ADC with exatecan payload	Refractory advanced pancreatic ductal adenocarcinoma or biliary tract cancer	≥40% CLDN18.2 IHC 1+/2+/3+	28.0%	80.0%	Not mature	[8]
IBI389	Anti-CLDN18.2/CD3 bispecific antibody	Refractory advanced gastric/GEJ adenocarcinoma	≥10% membranous CLDN18.2 IHC 2+/3+	30.8%	73.1%	3.5 months	[9]
		Refractory advanced pancreatic ductal adenocarcinoma	≥10% membranous CLDN18.2 IHC 2+/3+	29.6%	70.4%	Not mature	[10]
Satri-cel ± anti-PD-1	Autologous CAR-T	Advanced gastrointestinal cancers, mostly refractory but some after 1 L therapy	≥40% CLDN18.2 IHC 2+/3+ in 95% of patients	38.8%	91.8%	4.4 months	[11]

CLDN18.2: claudin-18 isoform 2; HER2: human epidermal growth factor receptor 2; GEJ: gastroesophageal junction; 1 L: first-line; mFOLFOX: modified 5FU, leucovorin, and oxaliplatin; CAPOX: capecitabine and oxaliplatin; MMAE: monomethyl auristatin E; ADC: antibody–drug conjugate; CD3: cluster of differentiation 3; satri-cel: satricabtagene autoleucel; PD-1: programmed cell death protein 1; CAR-T: chimeric antigen receptor T cell; ORR: objective response rate; DCR: disease control rate; PFS: progression-free survival; IHC: immunohistochemistry; Ref: reference.

had gastric or GEJ cancer [11, 12]. The dose-expansion stage included 61 patients with refractory gastrointestinal cancers who received satri-cel monotherapy, 15 who received satri-cel with anti-PD-1 therapy, 5 who received satri-cel as sequential treatment after first-line therapy, and 2 who received satri-cel after previous treatment with anti-CLDN18.2 antibody. The CRS rate was 97% (all grade 1–2) and gastric mucosal injury rate was 8.2%. No immune effector cell-associated neurotoxicity syndrome or treatment-related deaths were observed. The ORR was 38.8% and DCR 91.8% overall, with ORR 54.9% for gastric or GEJ cancer, 20% for pancreatic cancer, 50% for biliary tract cancer, and 50% in patients who received prior anti-CLDN18.2 antibody. However, median PFS was only 4.4 months, median OS 8.8 months, and median persistence of CAR-T cells was only 28 days.

Conclusions

All clinical trials are summarized in Table 1. These studies demonstrate the potential of CLDN18.2 as a target not only in gastric and GEJ adenocarcinoma, but also in other advanced solid tumors. Novel CLDN18.2-targeting therapies may have efficacy in tumors with lower CLDN18.2 expression or in tumors that are resistant to anti-CLDN18.2 antibodies. Further research is needed to determine the appropriate thresholds for CLDN18.2 expression, the potential synergy of combination therapies, and the optimal sequencing of CLDN18.2-targeting therapies.

Abbreviations

ADC	antibody-drug conjugate
ASCO	American Society of Clinical Oncology
CAPOX	capecitabine and oxaliplatin
CAR-T	chimeric antigen receptor T cell
CD3	cluster of differentiation 3
CLDN18.2	claudin-18 isoform 2
DCR	disease control rate
GEJ	gastroesophageal junction
HER2	human epidermal growth factor receptor 2
IHC	immunohistochemistry
mFOLFOX	modified 5FU, leucovorin, and oxaliplatin
MMAE	monomethyl auristatin E
ORR	objective response rate
PD-1	programmed cell death protein 1
PFS	progression-free survival
satri-cel	satricabtagene autoleucel

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Author contributions

Hui Chen and John Strickler designed the study. Katherine Zhou prepared the tables. All authors participated in the process of drafting and revising the manuscript. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This is not applicable for this summary.

Consent for publication

This is not applicable for this summary.

Competing interests

John Strickler is currently, or has recently been a consultant or advisor for Abbvie, Astellas, AstraZeneca, Bayer, Beigene, Daiichi-Sankyo, Eli Lilly, GE Healthcare, GSK, Johnson and Johnson, Jazz Pharmaceuticals, Merck, Natera, Pfizer, Roche/Genentech, Regeneron, Sanofi, Taiho, Takeda, Xilio Therapeutics. He has stock options in Triumvira Immunologics. He has also received recent research funding from or conducted contracted research with Abbvie, Amgen, AStar D3, Bayer, Beigene, Curegenix, Daiichi-Sankyo, Eli Lilly, Erasca, GSK, Leap Therapeutics, Novartis, Pfizer, Quanta Therapeutics, Revolution Medicines, Roche/ Genentech.

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