Molecular Therapy
Oncology
Review

Unveiling promising targets in gastric cancer therapy: A comprehensive review

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Gastric cancer (GC) poses a significant global health challenge, ranking fifth in incidence and third in mortality among all malignancies worldwide. Its insidious onset, aggressive growth, proclivity for metastasis, and limited treatment options have contributed to its high fatality rate. Traditional approaches for GC treatment primarily involve surgery and chemotherapy. However, there is growing interest in targeted therapies and immunotherapies. This comprehensive review highlights recent advancements in GC targeted therapy and immunotherapy. It delves into the mechanisms of various strategies, underscoring their potential in GC treatment. Additionally, the review evaluates the efficacy and safety of relevant clinical trials. Despite the benefits observed in numerous advanced GC patients with targeted therapies and immunotherapies, challenges persist. We discuss pertinent strategies to overcome these challenges, thereby providing a solid foundation for enhancing the clinical effectiveness of targeted therapies and immunotherapies.

INTRODUCTION

Gastric cancer (GC) is one of the most prevalent cancers worldwide, with a significant portion of GC cases occurring in developing countries, particularly in China.[1] The incidence of GC is frequently linked to factors such as *Helicobacter pylori* infection, excessive salt consumption, and tobacco use. Moreover, a hereditary predisposition plays a role in certain instances of GC. GC typically presents insidiously, leading to advanced diagnosis, and the available treatments have demonstrated limited efficacy, resulting in poor prognoses for the majority of GC patients.[2]

Surgical intervention remains the primary treatment for early-stage GC. However, for patients facing metastatic or advanced stages, sequential chemotherapy regimens become necessary. Current research indicates that median overall survival (mOS) for advanced GC patients is less than 1 year.[3] In recent years, targeted therapy and immunotherapy have emerged as novel treatment options, showing promise in enhancing the survival rates of GC patients.[4–6] Nevertheless, despite these advancements, the overall prognosis for GC patients remains unfavorable.

As our understanding of GC at the molecular levels continues to evolve, it has become evident that GC is a highly heterogeneous disease characterized by distinct pathogenic mechanisms.[7] However, our understanding of GC remains somewhat constrained, and consequently, there is ample room for improvement in targeted therapy and immunotherapy for GC.

This review article comprehensively explores the latest advances in GC targeted therapy, focusing on key signaling pathways, epigenetic alterations, the tumor microenvironment (TME), and cancer stem cells. It underscores the clinical relevance of these pathways and discusses potential strategies to address current challenges. The aim of this review is to offer further guidance to enhance the effectiveness of targeted therapies and immunotherapies for GC treatment. Table 1 provides a summary of clinical trials for essential medications.

TARGETING KEY SIGNALING PATHWAYS

Multiple signaling pathways play pivotal roles in the onset and progression of GC. Targeting these key pathways constitutes a primary approach in GC targeted therapy. Figure 1 depicts the significant signaling pathways associated with GC.

Targeting HER2 pathway

Human epidermal growth factor receptor 2 (HER-2) can activate various downstream pathways such as rat sarcoma (RAS)/mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) through heterodimerization and tyrosine kinase autophosphorylation, thus regulating multiple biological processes.[35,36] For HER2-positive metastatic GC patients, the current standard of care is trastuzumab combined with platinum/fluoropyrimidine agents as a first-line therapy.[37]

Trastuzumab

Trastuzumab, a monoclonal antibody designed to target HER2, garnered significant attention following the ToGA trial in 2010. This trial showcased that integrating trastuzumab into first-line capecitabine and cisplatin/5-fluorouracil and cisplatin (XP/FP) chemotherapy for HER2-positive advanced gastric cancer/gastroesophageal junction cancer (GC/GEJC) patients led to notable improvements in mOS and objective response rate (ORR) compared to chemotherapy alone.[4] Consequently, in the same year, the US Food and Drug

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Table 1. Key clinical trials in GC/GEJC targeted therapies and immunotherapies

Year	Drugs	Co-drugs	Phase	Patient number	Experimental vs. controlling	Clinical validity (month)	Grade 3/4 TRAE incidence	Lines of therapy	Guideline recommendations	Reference
2010	trastuzumab	XP/FP	III	594	trastuzumab + XP/FP (298) vs. XP/FP (296)	ORR: 47% vs. 35% mOS: 13.8 vs. 11.1	68% vs. 68%	1	CSCO ESMO NCCN	Bang et al.[4]
2018	trastuzumab	mDCF	II	26	trastuzumab + mDCF (26)	ORR: 65% mPFS: 13.0 mOS: 24.9	–	1	–	Mondaca et al.[8]
2021	disitamab vedotin	–	II	125	disitamab vedotin (125)	ORR: 24.8% mPFS: 4.1 mOS: 7.9	56.8%	3	CSCO	Peng et al.[9]
2020	trastuzumab-deruxtecan	–	II	187	trastuzumab-deruxtecan (125) vs. irinotecan/ paclitaxel (62)	ORR: 51% vs. 14% mOS: 12.5 vs. 8.4	–	3	ASCO ESMO NCCN	Shitara et al.[10]
2023	trastuzumab-deruxtecan	–	II	79	trastuzumab-deruxtecan (79)	ORR: 42%	–	2	–	Van Cutsem et al.[11]
2023	zanidatamab	CAPOX	Ib/II	33	zanidatamab 30 mg/kg + CAPOX (19) zanidatamab 1.8g/2.4g + CAPOX (14)	ORR: 75.8% mPFS: 16.7	66.7%	1	–	Lee et al.[12]
2014	ramucirumab	–	III	355	ramucirumab (238) vs. placebo (117)	mPFS: 5.2 vs. 3.8	–	2	NCCN	Fuchs et al.[13]
2014	ramucirumab	paclitaxel	III	665	ramucirumab + paclitaxel (330) vs. placebo + paclitaxel (335)	mOS: 9.6 vs. 7.4	69% vs. 47%	2	CSCO ASCO ESMO NCCN	Wilke et al.[14]
2019	ramucirumab	FP	III	645	ramucirumab + FP (326) vs. placebo + FP (319)	mPFS: 5.7 vs. 5.4 mOS[a]: 11.2 vs. 10.7	–	1	–	Fuchs et al.[15]
2021	ramucirumab	paclitaxel	III	440	ramucirumab + paclitaxel (294) vs. placebo + paclitaxel (146)	mPFS: 4.14 vs. 3.15 mOS[a]: 8.71 vs. 7.92	–	2	CSCO ASCO ESMO NCCN	Xu et al.[16]
2023	ramucirumab	trastuzumab + paclitaxel	II	50	ramucirumab + trastuzumab + paclitaxel (50)	ORR: 54% DCR: 96% mPFS: 7.1 mOS: 13.6	–	2	–	Kim et al.[5]
2024	apatinib	camrelizumab + SOX	I	34	apatinib + SOX (34)	ORR: 76.5% mPFS: 8.4 mEFS: 22.3	52.9%	1	–	Chen et al.[17]
2016	apatinib	–	III	267	apatinib (176) vs. placebo (91)	mPFS: 2.6 vs. 1.8 mOS: 6.5 vs. 4.7	–	2	–	Li et al.[18]
2023	apatinib	–	IV	1999	apatinib (1999)	ORR: 4.4% DCR: 35.8% mPFS: 2.7 mOS: 5.8	–	>1	CSCO	Li et al.[19]
2020	lenvatinib	pembrolizumab	II	29	lenvatinib + pembrolizumab (29)	ORR: 69%	–	1/2	–	Kawazoe et al.[20]
2022	anlotinib	toripalimab	II	62	anlotinib + toripalimab (62)	ORR: 32.3% DCR: 91.9% mPFS: 8.4%	11.3%	2	–	Jiang et al.[21]

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Table 1. *Continued*

Year	Drugs	Co-drugs	Phase	Patient number	Experimental vs. controlling	Clinical validity (month)	Grade 3/4 TRAE incidence	Lines of therapy	Guideline recommendations	Reference
2022	bemarituzumab	FOLFOX	II	155	bemarituzumab + mFOLFOX6 (77) vs. placebo + mFOLFOX6 (78)	mPFS[a]: 9.5 vs. 7.4	32% vs. 36%	1	–	Wainberg et al.[22]
2023	zolbetuximab	FOLFOX	III	565	zolbetuximab + mFOLFOX6 (283) vs. placebo + mFOLFOX6 (282)	mPFS: 10.61 vs. 8.67 mOS: 18.23 vs. 15.54	87% vs. 78%	1	CSCO ESMO	Shitara et al.[23]
2021	zolbetuximab	EOX	II	246	zolbetuximab + EOX (77) vs. EOX (84)	mPFS: 7.5 vs. 5.3 mOS: 13.0 vs. 8.3	70.1% vs. 64.3%	1	–	Sahin et al.[24]
2017	nivolumab	–	III	493	nivolumab (330) vs. placebo (163)	mOS: 5.26 vs. 4.14	10% vs. 4%	>2	CSCO	Kang et al.[25]
2022	nivolumab	trastuzumab + ipilimumab/FOLFOX	II	88	nivolumab + trastuzumab + ipilimumab (44) vs. nivolumab + trastuzumab + FOLFOX (44)	12-mo OS: 57% vs. 70%	82% vs. 88%	1	–	Stein et al.[26]
2022	nivolumab	SOX/CAPOX	III	724	nivolumab + SOX/CAPOX (362) vs. placebo + SOX/CAPOX (362)	mPFS: 10.45 vs. 8.34 mOS[a]: 17.45 vs. 17.15	58% vs. 50%	1	CSCO ASCO NCCN	Kang et al.[6]
2021	nivolumab	ipilimumab/CAPOX/ FOLFOX	III	2031	nivolumab + CAPOX/FOLFOX (789) vs. CAPOX/FOLFOX (792) nivolumab + ipilimumab (409) vs. CAPOX/FOLFOX (404)	mOS: 13.8 vs. 11.6 11.7 vs. 11.8	59% vs. 44% 38% vs. 46%	1	CSCO ASCO NCCN	Janjigian et al.[27]
2018	pembrolizumab	–	III	592	pembrolizumab (294) vs. paclitaxel (276)	mOS[a]: 9.1 vs. 8.3	14% vs. 35%	2	CSCO ESMO NCCN	Shitara et al.[28]
2023	pertuzumab	trastuzumab + FP	III	780	pertuzumab + trastuzumab + FP (388) vs. placebo + trastuzumab + FP (392)	ORR: 57.0% vs. 48.6% mPFS: 8.5 vs. 7.2 mOS: 18.1 vs. 14.2 mDOR: 10.2 vs. 8.4	80.5% vs. 74.2	1	CSCO ASCO NCCN	Tabernero et al.[29]
2023	pembrolizumab	FP/CAPOX	III	1579	pembrolizumab + FP/CAPOX (790) vs. placebo + FP/CAPOX (789)	mOS: 12.9 vs. 11.5	60% vs. 51%	1	CSCO ASCO ESMO NCCN	Rha et al.[30]
2023	pembrolizumab	trastuzumab + FP/CAPOX	III	698	pertuzumab + trastuzumab + FP/CAPOX (350) vs. placebo + trastuzumab + FP/CAPOX (348)	mPFS: 10.0 vs. 8.1 mOS[a]: 20.0 vs. 16.8	58% vs. 51%	1	CSCO ASCO NCCN	Janjigian et al.[31]
2021	sintilimab	CAPOX	III	650	sintilimab + CAPOX (327) vs. placebo + CAPOX (323)	ORR: 65.1% vs. 58.7% mOS: 15.2 vs. 12.3	59.8% vs. 52.5%	1	CSCO	Xu et al.[32]
2023	tislelizumab	FP/CAPOX	III	546	tislelizumab + FP/CAPOX (274) vs. placebo + FP/CAPOX (272)	ORR: 50.4% vs. 43.0% mPFS: 7.2 vs. 5.9 mOS: 17.2 vs. 12.6	64.7% vs. 62.9%	1	CSCO	Moehler et al.[33]
2023	sugemalimab	CAPOX	III	479	sugemalimab + CAPOX (241) vs. placebo + CAPOX (238)	ORR: 68.6% vs. 52.7% mPFS: 7.62 vs. 6.08 mOS: 15.64 vs. 12.65	31.1% vs. 28.7%	1	–	Zhang et al.[34]

[a]No statistical difference.

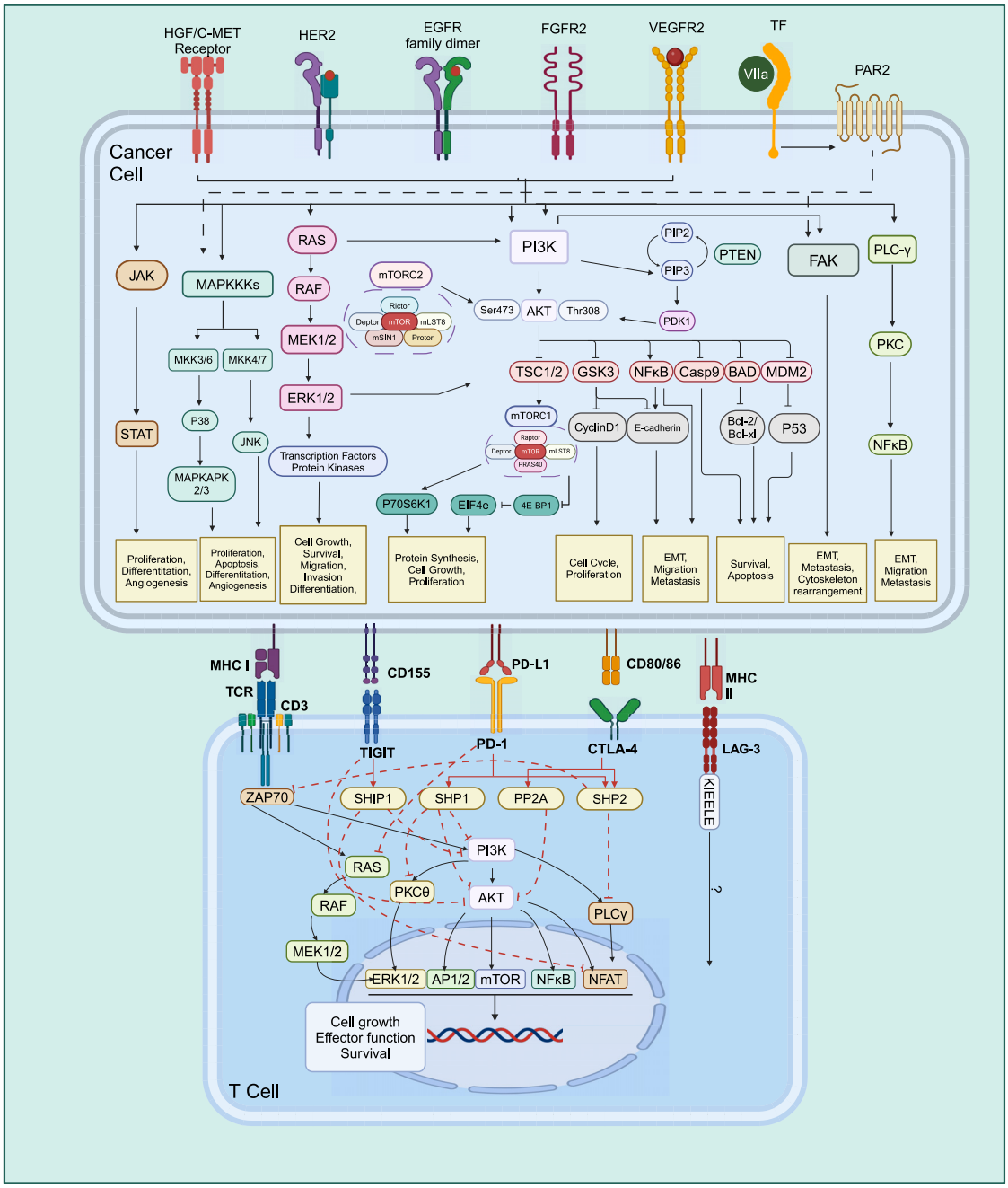

Figure 1. Main signaling pathways and fundamental factors in GC

The major signaling pathways and crosstalk of EGFR, HER2, FGFR2, HGF/c-Met, PI3K/AKT/mTOR, PD-1, CTLA4, and TIGIT pathways are illustrated. The specific mechanism of the LAG-3 signaling pathway has not been fully elucidated. This figure was created with Biorender.com.

Administration (FDA) granted approval for trastuzumab in combination with chemotherapy as a first-line treatment option for HER2-positive GC/GEJC patients. Pertuzumab, another monoclonal antibody targeting HER2, operates through a mechanism distinct from that of trastuzumab. Its combination with trastuzumab, forming a dual HER2-targeted therapeutic approach, has shown considerable efficacy in breast cancer treatment.[38] However, the JACOB trial explored this dual HER2-targeted therapy as a first-line treatment for advanced GC/GEJC, but the results did not meet expectations as anticipated.[29]

Studies indicate that more than two-thirds of patients with initially HER2-positive cancer experience treatment failure with trastuzumab-based therapy, possibly due to the loss of HER2 expression. Consequently, reassessing HER2 expression following trastuzumab treatment holds significance in treatment planning.[39] Additionally, findings also suggest that resistance to traditional HER2-targeted therapies may stem from the co-overexpression of HER3 and HER2, along with their collaborative signaling. Thus, targeting HER3 could be a potential strategy to prevent anti-HER2 resistance.[40–42]

Trastuzumab-deruxtecan, disitamab vedotin

Targeted HER-2 antibody-drug conjugates (ADCs) such as trastuzumab-deruxtecan (T-DXd) and disitamab vedotin have shown excellent efficacy in the multi-line treatment of advanced/unresectable GC patients.[9–11] However, the T-DXd exhibited a significantly higher rate of adverse reactions, including myelosuppression and interstitial lung disease.[10] A related phase III clinical trial is currently ongoing to further evaluate its efficacy and safety profile. Based on data from a phase II clinical study, disitamab vedotin received its initial approval in China on June 8, 2021 for the treatment of locally advanced or metastatic GC patients with HER2 overexpression who had undergone at least two prior systemic chemotherapy regimens.[43] A real-world study revealed that disitamab vedotin combined with immune checkpoint inhibitors (ICIs) had significant superior efficacy as a third-line treatment in patients with advanced or metastatic GC (ORR 36.0% vs. 10.0%).[44] A clinical study is currently underway (NCT05980481) to evaluate the combination of disitamab vedotin with toripalimab, along with either chemotherapy or herceptin, as a first-line treatment for HER2-positive advanced GC.

KN026

KN026, a novel bispecific antibody targeting HER2, possesses the ability to bind simultaneously to two distinct HER2 epitopes.[45] An exciting phase II clinical trial demonstrated its potential as a second-line treatment for patients with high HER2 expression in GC/GEJC. In the HER2-high cohort, KN026 achieved the ORR of 56%, with the median duration of response (mDOR) of 9.7 months. Importantly, KN026 exhibited significant anti-tumor efficacy in patients with HER2-positive disease progression following trastuzumab treatment, suggesting its potential for overcoming resistance to trastuzumab.[46] This underscores the promise of KN026 in addressing trastuzumab resistance. An associated phase III clinical trial (NCT05427383) and a clinical trial investigating the combination of ZW25, a bispecific antibody targeting HER2, with trastuzumab as a first-line treatment for patients with advanced HER2-positive GC/GEJC are currently ongoing. Data presented at the 2023 European Society for Medical Oncology (ESMO) conference indicated that the median progression-free survival (mPFS) reached 16.7 months, further highlighting the potential of these approaches in HER2-positive GC treatment.[12]

Targeting VEGF/VEGFR pathway

Vascular endothelial growth factor (VEGF) acts as a key regulator of angiogenesis.[47] The VEGF family acts through VEGF receptors (VEGFRs).[48] Specifically, VEGFA binds to VEGFR2, triggering endothelial cell proliferation and initiating cell migration via the RAS-RAF-MAPK-ERK signaling pathway.[49] In tumor tissues, VEGF stimulates endothelial cells, promoting new blood vessel formation.[50] Studies have consistently linked higher VEGF expression with poorer patient prognosis.[51] Thus, targeting VEGF/VEGFR to impede tumor angiogenesis emerges as a promising strategy in GC treatment.

Ramucirumab

Ramucirumab, a humanized monoclonal antibody targeting VEGFR2, was evaluated in the REGARD trial in 2014 as a monotherapy for patients with advanced GC/GEJ adenocarcinoma whose disease progressed after first-line chemotherapy. The results showed a significant improvement in mOS in the ramucirumab group compared to the placebo group.[13] In the same year, another phase III clinical study, RAINBOW, revealed that, in patients with GC, the combination of ramucirumab and paclitaxel yielded superior outcomes compared to a placebo combined with paclitaxel (mOS 9.6 vs. 7.4 months and mPFS 4.4 vs. 2.9 months).[14] The REGARD and RAINBOW trials demonstrated significant efficacy and manageable safety profiles of ramucirumab, leading to FDA approval for its use either as monotherapy or in combination with paclitaxel as a second-line treatment for GC. In 2023, a trial revealed highly satisfactory outcomes with the combination of trastuzumab, ramucirumab, and paclitaxel in patients with HER2-positive advanced GC/GEJ adenocarcinoma who had previously undergone first-line treatment (response rate 54%, mPFS 7.1 months, mOS 13.6 months).[5] The combination of ramucirumab with chemotherapy has demonstrated significant efficacy as a second-line treatment.[52] In 2023, the China Society of Clinical Oncology (CSCO) guidelines recommended the combination of ramucirumab with paclitaxel as the preferred second-line treatment for advanced metastatic GC.

Apatinib

Apatinib, a selective tyrosine kinase inhibitor (TKI) developed in China,[53] has demonstrated efficacy as a monotherapy in the treatment of advanced refractory GC in which previous chemotherapy had failed. Compared to patients in the placebo group, those treated with apatinib exhibited significantly improved mPFS and mOS.[18,19,54] These findings led to the approval of apatinib by the National Medical Products Administration (NMPA) in 2014 for the treatment of GC/GEJ adenocarcinoma that has progressed after second-line chemotherapy. In 2023, a phase II clinical study reported promising findings regarding the combination of sintilimab, apatinib, and chemotherapy in patients with advanced GC/GEJ adenocarcinoma. The regimen demonstrated notable anti-tumor activity and manageable safety, indicating potential as a treatment option for this patient population.[55] In 2024, a phase I clinical trial demonstrated the efficacy of combining apatinib with camrelizumab and chemotherapy as a first-line treatment for advanced GC/GEJC. Among the 34 enrolled patients, 10 underwent surgery, while those who did not undergo surgery achieved an impressive overall survival (OS) of 19.6 months.[17] Numerous ongoing clinical trials are exploring the combination of apatinib with various chemotherapy regimens for the treatment of

GC. These trials aim to further evaluate the efficacy and safety of this combination therapy and may provide valuable insights into its potential role in the management of GC.

Anlotinib, lenvatinib, regorafenib

Clinical research has demonstrated that TKIs such as anlotinib, lenvatinib, and regorafenib, which target VEGFR, exhibit enhanced efficacy when combined with immunotherapy. These agents can synergize with immunotherapy through various mechanisms, potentially enhancing the anti-tumor immune response and improving treatment outcomes.[56–58] The safety and efficacy of these TKIs, in conjunction with immunotherapy, have been extensively documented in numerous clinical trials, underscoring their potential as groundbreaking treatment approaches.[20,21,59] These findings suggest that such combination therapies hold promise for improving outcomes in GC, paving the way for more effective and personalized treatment strategies. A phase III clinical trial (NCT04879368) is further exploring this promising avenue of cancer therapy.

Targeting the HGF/c-Met pathway

C-Met, encoded by the proto-oncogene MET, functions as a tyrosine kinase receptor for hepatocyte growth factor (HGF). The interaction between HGF and c-Met plays a crucial role in regulating various aspects of tumor biology, including cell growth, invasion, metastasis, and angiogenesis.[60] Research indicates that overactivation of the HGF/c-Met pathway is implicated in the development and metastasis of advanced GC and is associated with poor prognosis in GC patients.[61,62] Consequently, targeting the HGF/c-Met pathway holds promise as a potential therapeutic strategy for MET-dependent GC.

Rilotumumab

Rilotumumab is a monoclonal designed to target HGF and its receptor MET. In a phase II clinical trial, the efficacy and safety of rilotumumab were evaluated in combination with the ECX chemotherapy (epirubicin, cisplatin and capecitabine) regimen in patients with advanced GC/GEJC. The results showed an improvement in mPFS in the rilotumumab group compared to the placebo group (5.7 vs. 4.2 months), with better outcomes observed in patients with MET-positive tumors.[63] Despite promising results in earlier phases, a subsequent phase III clinical trial of rilotumumab was halted by an independent data monitoring committee.[64] This decision suggests that further investigation is needed to fully understand the role of MET in tumor development and to optimize therapeutic strategies targeting this pathway. Several clinical trials exploring MET-targeted therapies in GC have not yielded satisfactory results, highlighting the complexities and challenges associated with targeting this pathway in clinical practice.

Volitinib

Volitinib, a TKI targeting c-MET, has shown promising anti-tumor efficacy in preclinical studies, particularly in GC patient-derived xenograft (PDX) models with c-MET dysregulation.[65] However, its effectiveness has yet to be validated in clinical trials. Currently, a phase II clinical trial investigating the treatment of MET-amplified gastric/GEJ cancer patients with volitinib is underway (NCT04923932). This trial aims to evaluate the safety and efficacy of volitinib in this patient population and may provide valuable insights into its potential as a therapeutic agent for GC.

Indeed, neither monotherapy nor combination therapies targeting HGF/c-Met have demonstrated significant efficacy in treating GC. Research has uncovered that c-MET exhibits nonkinase functions as well. Thus, directly blocking c-MET phosphorylation with antibodies or TKIs can trigger kinase reactivation, reassembly, and the emergence of resistance mechanisms.[62,66,67] However, strategies involving mRNA interference of MET transcription have demonstrated inhibitory effects on tumor cells and are currently under investigation in research studies. These approaches hold promise for suppressing c-MET signaling and overcoming resistance mechanisms in cancer therapy.[68,69] Moreover, studies have highlighted MET amplification as a significant mechanism for acquired resistance to various TKIs, including epidermal growth factor receptor (EGFR) inhibitors.[70–72] Therefore, targeted MET therapy holds promise as a second-line treatment for patients who have developed acquired resistance to EGFR-TKIs. Thus, combining MET-targeted treatment with EGFR inhibitors may represent a more effective approach to overcome resistance and improve treatment outcomes in GC. MCLA-129 is a bispecific antibody designed to target both EGFR and c-MET simultaneously. Clinical trials investigating its use in various solid tumors, including GC, are currently underway (NCT04868877).

These trials aim to evaluate the safety and efficacy of MCLA-129 and may provide valuable insights into its potential as a therapeutic option for patients with GC, particularly those with acquired resistance to EGFR-TKIs.

Targeting the mTOR-related pathway

The mammalian target of rapamycin (mTOR) belongs to the PI3K-related kinase family.[73,74] Disruption of mTOR signaling plays a pivotal role in tumorigenesis, angiogenesis, cell growth, and metastasis. mTORC1, one of the mTOR complexes, acts as an effector downstream of many frequently mutated oncogenic pathways that are overactivated in various cancers, including GC.[75] Therefore, the mTOR-related pathway represents a potential target for GC treatment.

Everolimus

Everolimus, an oral mTOR inhibitor, has shown promise in the treatment of advanced GC patients who have received prior treatment, with a disease control rate (DCR) of 56%.[76] However, clinical trials investigating the combination of everolimus with chemotherapy did not achieve satisfactory results.[77,78] Hence, identifying biomarkers associated with the efficacy of everolimus in GC patients may hold the key to improving survival outcomes. Several studies suggest that phosphorylated S6 (pS6) Ser240/4 could serve as a potential biomarker, but further research is necessary to validate this hypothesis.[79]

Targeting the FGF/FGFR2 pathway

Fibroblast growth factor receptor 2 (FGFR2) is a transmembrane tyrosine kinase receptor that plays a crucial role in regulating cell proliferation, survival, migration, and angiogenesis.[80] Dysregulation of the FGF/FGFR2 signaling pathway can impact the development and progression of various cancers by activating the downstream PI3K-AKT and MAPK-ERK pathways.[81,82] Research has shown that FGFR2 amplification occurs in 2%–11% of GCs.[83] In GC, FGFR2 amplification is frequently associated with more aggressive subtypes, leading to poorer prognosis.[84] Consequently, FGFR2 represents a promising target for the treatment of GC, and therapies aimed at inhibiting FGFR2 signaling may hold potential for improving outcomes in patients with GC, particularly those with FGFR2-amplified tumors.

Bemarituzumab

Bemarituzumab, also known as FPA144, represents the world's first humanized monoclonal antibody targeting FGFR2b.[22] It has demonstrated single-agent efficacy and good tolerability in advanced gastroesophageal adenocarcinoma (GEA) patients, with no significant overlapping toxicities observed with standard chemotherapy drugs such as platinum-based agents or fluoropyrimidines.[85] In 2022, the FIGHT trial revealed that, compared with the placebo group, the mPFS in the bemarituzumab group did not significantly differ (9.5 vs. 7.4 months). However, the mOS in the bemarituzumab group was extended by 5.7 months.[22] Currently, phase III clinical trials are underway to investigate the combination of bemarituzumab and nivolumab for the treatment of GC (NCT05052801, NCT05111626).

Pemigatinib

Pemigatinib is a selective inhibitor targeting the FGFR family, capable of inhibiting the tyrosine kinase activity of FGFR. In 2020, it received FDA approval, marking it as the first targeted therapy for cholangiocarcinoma (CC).[86] Studies have suggested that the FGFR3/AKT axis represents one of the mechanisms contributing to the escape pathway leading to resistance to trastuzumab in GC.[87] The FiGhTeR trial, a phase II clinical trial (EudraCT 2017-004522-14), is currently assessing the safety and activity of pemigatinib in patients with HER2 trastuzumab-resistant GC.[88] This trial aims to provide insights into the potential role of pemigatinib as a treatment option for GC patients who have developed resistance to trastuzumab therapy.

Targeting the TF pathway

Tissue factor (TF) is a transmembrane glycoprotein that serves as a major initiator of both endogenous and exogenous coagulation under normal physiological conditions.[89–91] However, in recent years, research has shown that TF is frequently overexpressed in malignant tumor tissues, including GC, and is often associated with poor histological differentiation.[92] TF can form a complex with factor VIIa, termed the TF-VIIa complex, which activates protease-activated receptor 2 (PAR2) signaling, thereby playing a critical role in tumor growth, invasion, metastasis, and angiogenesis. Additionally, TF-mediated cancer-related coagulopathies are closely linked to the formation of the TME and tumor progression. Given its pivotal role in both coagulation and tumor biology, TF has emerged as an attractive therapeutic target. However, targeting TF alone may pose challenges due to its essential role in hemostasis, potentially leading to severe coagulation abnormalities.

Tisotumab vedotin

Tisotumab vedotin, an ADC, has demonstrated the ability to impact TF FVIIa-dependent intracellular signaling, thereby exerting anti-tumor activity, while not affecting procoagulant activity. This unique mechanism of action allows tisotumab vedotin to target tumor cells specifically without disrupting normal hemostasis. Notably, tisotumab vedotin has shown promising efficacy in the treatment of cervical cancer,[93] leading to its FDA approval for cervical cancer treatment in 2021.[94] This success of tisotumab vedotin in treating cervical cancer has indeed demonstrated the feasibility of targeting TF in solid tumors. However, there is a lack of clinical evidence regarding its use specifically in GC treatment.

TARGETING KEY MOLECULES

Targeting CLDN18.2

Claudin18.2 (CLDN18.2) is a member of the claudin protein family and plays a crucial role in regulating tissue permeability, transcellular transport, and signal transduction processes.[95] In normal tissues, CLDN18.2 is exclusively expressed in the tight junctions of differentiated gastric mucosal epithelial cells and is concealed within tight junction supramolecular complexes. However, in GC, disruption of polarity in GC cells exposes the CLDN18.2 epitope, making it a tumor-specific antigen.[96,97] Research has indicated that CLDN18.2 expression is higher in diffuse-type GC patients compared to intestinal-type GC patients. This suggests that strategies targeting CLDN18.2 may achieve better efficacy in diffuse-type GC.[98] Thus, CLDN18.2 represents a promising therapeutic target in the context of GC, and further research into CLDN18.2-targeted therapies may lead to the development of more effective treatment strategies for GC patients.

Zolbetuximab

Zolbetuximab is a monoclonal antibody targets CLDN18.2.[99] The results of the MONO trial have indicated that zolbetuximab monotherapy demonstrates favorable anti-tumor activity in patients with advanced GC/GEJ adenocarcinoma who are positive for CLDN18.2. Additionally, there appears to be a potential correlation between CLDN18.2 expression levels and treatment efficacy. Preclinical studies have suggested that chemotherapy drugs have the potential to enhance antibody-dependent cellular cytotoxicity (ADCC) mediated by zolbetuximab. This finding indicates that the combination of zolbetuximab with chemotherapy may represent a promising treatment approach for GC/GEJ adenocarcinoma.[100,101] The SPOTLIGHT trial and GLOW trial, phase III clinical trials, evaluated the efficacy of zolbetuximab in combination with chemotherapy as a first-line treatment for HER2-negative advanced GC/GEJ adenocarcinoma. The trial results demonstrated a significant extension in mPFS and mOS compared to the placebo group.[23,102] These results from trials such as SPOTLIGHT and GLOW indeed suggest that

zolbetuximab in combination with chemotherapy offers favorable efficacy as a first-line treatment for advanced GC. These findings have led to the inclusion of zolbetuximab plus chemotherapy in the 2023 CSCO guidelines as a recommended first-line treatment for GC. Moreover, the combination of zolbetuximab with immunotherapy represents another promising treatment approach for GC. The ongoing ILUSTRO trial (NCT03505320) is investigating the efficacy and safety of zolbetuximab in combination with nivolumab in the first-line treatment of GC. This trial aims to assess the potential synergistic effects of combining zolbetuximab with immune checkpoint inhibition, which could provide additional benefits to patients with advanced GC. The results of this trial will be crucial in determining the role of zolbetuximab-based combination therapies in the evolving landscape of GC treatment.

Osemitamab

Osemitamab is a second monoclonal antibody that targets CLDN18.2, similar to zolbetuximab. However, osemitamab features an optimized Fc segment design, which enhances the affinity of the antibody for tumor cells. This modification leads to stronger ADCC and complement-dependent cytotoxicity (CDC) effects. Notably, this approach has shown particular effectiveness in GC cells with low to moderate CLDN18.2 expression levels. Current clinical studies are underway to investigate the efficacy and safety of combining osemitamab with capecitabine and oxaliplatin (CAPOX) chemotherapy as a first-line treatment for solid tumors, including GC/GEJ cancers. As of January 2023, in the GC/GEJC patient cohort, ORR was 66.7%, and DCR reached 97.6%, demonstrating promising therapeutic potential.[103] Additionally, preclinical studies have demonstrated that treatment with osemitamab in a mouse model of CLDN18.2-positive but PD-L1-negative GC PDXs led to an upregulation of PD-L1 expression. This finding provides a theoretical basis for combining osemitamab with immunotherapy in the treatment of GC.[104] To further evaluate this combination strategy, a phase III clinical trial is currently underway (NCT06093425). This trial aims to investigate the efficacy and safety of osemitamab in combination with chemotherapy and immunotherapy as a first-line treatment for GC. The results of this trial will provide valuable insights into the potential benefits of combining osemitamab with multiple treatment modalities for GC patients.

Givastomig

Givastomig (also known as ABL111, TJ-CD4B) is a bispecific antibody designed to target CLDN18.2 and 4-1BB. In the TME of GC patients, 4-1BB-positive (4-1BB+) T cells are naturally present. By utilizing a 4-1BB agonist such as urelumab, givastomig aims to effectively boost the proliferation, differentiation, and cytotoxicity of CD8+ T cells, thereby enhancing their ability to combat tumor cells. However, this systemic immune activation can result in severe adverse reactions.[105] In contrast, givastomig operates by facilitating 4-1BB costimulation in a CLDN18.2-dependent manner. This unique mechanism confines the immune response to the TME. By doing so, givastomig aims to limit immune activation and associated adverse effects to the TME, thereby reducing the risks of hepatotoxicity and systemic immune reactions linked to the drug. This localized immune reaction not only demonstrates outstanding anti-tumor effectiveness but also instills a long-lasting memory response against the tumor.[106] Currently, phase I clinical trials of givastomig in advanced solid tumors, including GC, are underway (NCT04900818). These trials aim to assess the safety, tolerability, pharmacokinetics, and preliminary efficacy of givastomig in patients with advanced solid tumors.

CT041

Chimeric antigen receptor T cell (CAR-T) therapy, initially successful in treating hematological malignancies, is now being explored as a novel approach for solid tumor therapy. CT041 represents a significant advancement in this field, as it is a genetically engineered autologous T cell expressing a CAR specifically targeting CLDN18.2. An analysis of mid-term results from a phase I clinical trial has shown promising outcomes for CT041 in CLDN18.2-positive GC patients who have undergone multiple prior treatments. These results indicate good efficacy and acceptable safety profiles, highlighting the potential of CAR-T therapy targeting CLDN18.2 in GC treatment.[107] Furthermore, numerous CAR-T cell therapies focused on CLDN18.2 are currently progressing through clinical trials across different phases.

Targeting CLDN18.2 has emerged as a promising approach in GC therapy. Various therapeutic modalities aimed at CLDN18.2, such as monoclonal antibodies, bispecific antibodies, and CAR-T cells, are demonstrating significant promise in the treatment of advanced GC. These innovative therapies are paving the way for more effective management of this challenging disease.

PARP inhibitors

DNA repair deficiencies are common hallmarks of cancer, and poly(-ADP-ribose) polymerase (PARP) plays a pivotal role in the DNA repair process. Among various forms of DNA damage, DNA double-strand breaks (DSBs) are particularly lethal.[108] After treatment with PARP inhibitors (PARPis), normal cells can still repair DSBs through homologous recombination repair (HRR). However, in cancer cells with homologous recombination deficiency (HRD), such as those with BRCA mutations, DSBs can only be repaired through alternative, error-prone mechanisms such as non-homologous end joining (NHEJ). This limited DNA repair capacity can ultimately cause the death of cancer cells.[109,110]

Olaparib

Olaparib, an oral PARPi, has garnered attention for its role in treating cancers with DNA repair deficiencies. Studies suggest that the ataxia telangiectasia mutated (ATM) protein serves as a crucial activator in the double-strand DNA damage response. Approximately 22% of metastatic GC patients exhibit low-level ATM expression.[111,112] However, the phase III GOLD study did not yield statistically significant improvements in survival with the addition of olaparib to paclitaxel, neither in the overall population nor in the ATM-negative metastatic setting.[113] Additionally, studies indicate that individuals highly sensitive to platinum-based chemotherapy may respond more favorably to PARPis.[114] In addition, research highlights that

tumor hypoxia can lead to HRD.[115] A phase I trial combining ramucirumab-induced tumor hypoxia with olaparib in treated metastatic GC/GEJC improved ORR, progression-free survival (PFS), and OS over historical ramucirumab alone, although outcomes did not meet expectations.[116]

IMMUNOTHERAPY

Immune checkpoints act as regulators in the cellular immune response, exerting a "braking" role to prevent excessive activation of immune cells. However, some tumors exploit these checkpoints to evade immune surveillance and attack, leading to immune escape. ICIs target specific molecules on immune cells or tumor cells, disrupting the inhibitory signals of immune checkpoints. This interference helps to reverse the immunosuppressive environment within tumors, enabling the immune system to recognize and eliminate cancer cells. FDA-approved immunotherapies, including inhibitors of programmed cell death 1 (PD-1) and its ligand (PD-L1), as well as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitors, have demonstrated promising results in cancer treatment by unleashing the ability of immune system to fight cancer.

PD-1/PD-L1-targeted therapies

PD-1, primarily expressed on various immune cells, plays a critical role in immune regulation by providing a signal to terminate immune activity upon binding with its ligand.[117] Targeting PD-1 has emerged as a promising approach for cancer treatment.

Nivolumab

Nivolumab is a human anti-PD-1 monoclonal antibody. The results from the CheckMate 649 trial demonstrated that combining nivolumab with chemotherapy as a first-line treatment for advanced GC/GEJ adenocarcinoma led to improved mOS at 14.4 months compared to 11.1 months with chemotherapy alone. Additionally, the combination therapy showed enhanced mPFS at 7.7 months compared to 6 months with chemotherapy alone, while maintaining manageable safety profiles.[118] In 2021, based on the positive results from the CheckMate 649 trial, nivolumab gained FDA approval for its use in combination with fluoropyrimidine and platinum-based chemotherapy as a first-line treatment option for patients with advanced or metastatic GC.[37]

Clinical trials investigating nivolumab in combination with targeted therapy are also ongoing. A phase II trial has revealed that adding nivolumab to the combination of trastuzumab and chemotherapy as the initial treatment for HER2-positive esophagogastric adenocarcinoma (EGA) patients can significantly enhance both PFS and OS.[26] This combination therapy approach has the potential to further improve outcomes for patients with HER2-positive GC. In 2023, a phase II clinical trial assessed the efficacy and safety of regorafenib in combination with nivolumab and FOLFOX (5-fluorouracil, oxaliplatin, and leucovorin) chemotherapy as a first-line treatment for advanced esophagogastric adenocarcinoma, demonstrating good anti-tumor activity (mPFS of 13.0 months) and manageable safety, regardless of PD-L1 combined positive score (CPS) status.[119] These findings underscore the importance of exploring novel combinations of targeted therapy and immunotherapy to improve outcomes for patients with advanced GC.

The combination therapy of nivolumab with ipilimumab has also demonstrated promising activity in advanced GC/GEJC. Despite being comparable to chemotherapy alone in terms of mOS, the combination therapy resulted in significantly reduced adverse reactions.[27]

Currently, for patients with HER2, PD-L1, or CLDN18.2-negative tumors, finding effective treatment options remains a critical challenge. However, there is hope on the horizon with ongoing research into combination therapies. One such promising approach involves combining nivolumab with lenvatinib and chemotherapy. This combination therapy is currently being investigated in phase III clinical trials (NCT04662710), offering a potential avenue for improving outcomes for patients with advanced GC/GEJ cancer who do not respond to traditional targeted therapies.

Pembrolizumab

Pembrolizumab is a humanized PD-1 monoclonal antibody that is distinct from nivolumab. Its efficacy is particularly notable in tumors that exhibit PD-L1 positivity. Additionally, studies have highlighted the potential benefits of pembrolizumab treatment for patients with microsatellite instability-high (MSI-H) GC. MSI-H status has emerged as a promising biomarker for identifying patients who may derive greater benefit from pembrolizumab therapy in the context of advanced GC/GEJ adenocarcinoma. The toxicity profile of pembrolizumab does not significantly overlap with the standard GC chemotherapy regimens, thus suggesting a potential for good tolerability when combined with chemotherapy.[28,120,121] In 2023, the phase III KEYNOTE-859 trial examined the effectiveness of pembrolizumab combined with chemotherapy as a first-line treatment for GC/GEJ adenocarcinoma. The results indicated a significant improvement in mOS for the pembrolizumab group compared to chemotherapy alone (12.9 vs. 11.9 months), with manageable safety profiles.[30] This underscores the potential of pembrolizumab to enhance treatment outcomes when used in combination therapy for GC, while also maintaining manageable safety profiles. Following the positive outcomes observed in the KEYNOTE-859 trial, the FDA granted approval to pembrolizumab in November 2023. This approval allows for the use of pembrolizumab in combination with chemotherapy as a first-line treatment option for patients diagnosed with advanced GC/GEJ adenocarcinoma.

The combination of pembrolizumab with targeted therapy is also being explored. According to the third interim analysis of the phase III KEYNOTE-811 trial, the addition of pembrolizumab to the trastuzumab and chemotherapy regimen resulted in a notable improvement in mOS (20.0 vs. 16.8 months). This enhancement was particularly significant among patients with positive PD-L1 expression.[31] In summary, the combination of pembrolizumab with targeted therapy and chemotherapy presents promising prospects.

Tislelizumab, sintilimab, sugemalimab

Other PD-1 monoclonal antibodies, including tislelizumab and sintilimab, have achieved promising efficacy in the treatment of GC. The RATIONALE 305 and ORIENT-16 trials evaluated the efficacy of tislelizumab or sintilimab in combination with chemotherapy as a first-line treatment for advanced GC, with satisfactory results.[33,32] Based on data from these studies, tislelizumab and sintilimab have both been CSCO approved in combination with chemotherapy as one of the first-line treatment options for advanced GC, particularly beneficial for HER2-negative patients. Sugemalimab is a PD-L1 monoclonal antibody. The GEMSTONE-303 trial demonstrated that combining sugemalimab with the CAPOX chemotherapy regimen significantly increased the ORR to 68.6%, highlighting the potential of PD-L1 monoclonal antibodies in the treatment of GC.[34]

AK104

AK104 (also known as cadonilimab) is a bispecific antibody that targets both PD-1 and CTLA-4. Ongoing clinical trials aim to assess the effectiveness and safety of AK104 when combined with mXELOX/XELOX chemotherapy regimens (capecitabine and oxaliplatin) as a first-line treatment for advanced GC/GEJ adenocarcinoma (NCT03852251). Although results from these trials are pending, there is anecdotal evidence of a patient with HER-2-positive advanced GEJ cancer achieving complete remission following treatment with PD-1/CTLA-4 bispecific immunotherapy in combination with chemotherapy.[122] This case underscores the potential clinical advantages of this strategy, indicating its viability as a first-line treatment option for HER-2-positive patients. However, substantial clinical trials are necessary to corroborate these observations. Currently, a phase III clinical trial investigating AK104 as a first-line treatment for advanced GC/GEJ adenocarcinoma is in progress (NCT05008783). In addition, there are limited treatment options for second-line therapy in GC/GEJC patients who have progressed following immunotherapy combined with chemotherapy. A phase III study (NCT06341335) is evaluating the efficacy of AK104 in combination with pulocimab (a VEGFR2 monoclonal antibody) and paclitaxel in treating GC/GEJC adenocarcinoma patients who have failed immunotherapy and chemotherapy. According to data presented at the American Society of Clinical Oncology (ASCO) 2024 conference, the ORR and DCR showed improvement compared to the placebo group (pulocimab and paclitaxel), suggesting that AK104 may be a potential treatment option to overcome resistance to immunotherapy.[123]

CTLA4-targeted therapies

CTLA-4 plays a crucial role in regulating T cell activation by binding to its ligands. It operates in conjunction with CD28, a costimulatory molecule involved in T cell activation, to maintain immune homeostasis. When CTLA-4 is upregulated, it suppresses the expression of interleukin-2 (IL-2) and IL-2 receptors, causing T cell arrest in the G1 phase of the cell cycle. Inhibitors of CTLA-4 block its interaction with ligands, thereby diminishing its inhibitory function on T cells. Moreover, since both CTLA-4 and CD28 share ligands CD80 and CD86, inhibiting CTLA-4 not only reduces its suppressive effects but also increases the availability of CD28 ligands. This dual action activates autoreactive T cells and alters the homeostasis of regulatory T cells (Tregs).[124]

Ipilimumab

Ipilimumab is a fully human anti-CTLA-4 monoclonal antibody. A phase II clinical trial (CheckMate-032) evaluated the efficacy and safety of the combination of ipilimumab and nivolumab in the treatment of metastatic esophagogastric cancer (EGC). The results revealed that the combination of ipilimumab and nivolumab achieved an mOS of 6.9 months with an ORR of up to 24%. These findings suggest that the ipilimumab and nivolumab combination exhibits significant anti-tumor activity and manageable safety in refractory EGC cases.[125] A phase III clinical trial is currently in progress for the treatment of HER2-negative advanced GC using a combination of nivolumab, ipilimumab, and chemotherapy (NCT05144854).

LAG-3-targeted therapies

Lymphocyte activation gene-3 (LAG-3), also referred to as CD223, is an immune checkpoint molecule primarily found on T lymphocytes. It exerts a negative regulatory effect on T cell activity by interacting with its ligand, and its expression is linked to tumor progression.[126] The expression of LAG-3 extends to a variety of solid tumors, including GC, making it a potential target for cancer therapy.

Relatlimab

Relatlimab, a monoclonal antibody targeting LAG-3, has demonstrated efficacy and safety in the treatment of melanoma.[127] However, its efficacy in GC is yet to be established, prompting the launch of a phase II clinical trial. This trial aims to evaluate the potential advantages of relatlimab in combination with nivolumab as a frontline therapy for patients with GC/GEJ cancer and is currently ongoing (NCT03662659).

TIGIT-targeted therapies

T cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains (TIGIT) is an immune checkpoint expressed on lymphocytes.[128] Its interaction with ligands triggers signaling pathways that affect immune cell function. Additionally, TIGIT suppresses T cell costimulatory signals mediated by CD226 or CD96, exerting an immunosuppressive effect.[129] Studies indicate that TIGIT is upregulated in various solid tumors, including GC, and its elevated expression is linked to poorer prognosis in patients with advanced GC.[130,131]

Tiragolumab

Monoclonal antibodies aimed at TIGIT have proved effective in reinstating T cell function and exhibiting anticancer properties. Tiragolumab, in particular, emerges as a potent TIGIT inhibitor, as shown by the CITYSCAPE trial, which demonstrated its favorable therapeutic outcomes when paired with the PD-L1 antibody atezolizumab in non-small cell lung cancer. Furthermore, tiragolumab has shown the ability to bolster the efficacy of atezolizumab.[132] The combination of tiragolumab and atezolizumab (a PD-L1 monoclonal antibody) holds promise as a potentially effective treatment approach.

Currently, a phase II clinical trial is in progress to explore the efficacy of tiragolumab in combination with atezolizumab and chemotherapy for advanced GC (NCT04933227).

Neoadjuvant treatment

Immunotherapy is revolutionizing the approach to neoadjuvant treatment for locally advanced GC, introducing a novel strategy to improve outcomes. While the chemotherapy-focused CROSS trial observed a pathologic complete response (pCR) rate of 23%, recent years have seen a significant increase in clinical research exploring the combined use of immunotherapy and chemoradiation for treating locally advanced GC in the neoadjuvant setting. These studies have produced promising results, summarized succinctly in Table 3. Clinical investigations demonstrate that combining immunotherapy with chemotherapy offers substantial benefits in treating GC/GEJC, notably enhancing rates of pCR and major pathological response (MPR). However, standalone immunotherapy as a neoadjuvant treatment appears to be less effective. Although this combination may result in higher rates of adverse reactions, the use of biomarkers to select patients can optimize benefits. Notably, pembrolizumab shows promising outcomes in MSI-H patients, with higher PD-L1 CPS and plasma PD-L1-expressing extracellular vesicles correlating with improved pCR outcomes[133–136] Table 2 provides a comprehensive summary of clinical trials pertaining to neoadjuvant immunotherapy in the context of GC/GEJC.

TME-TARGETED THERAPY

The TME is a complex and integrated system consisting predominantly of diverse immune cells, cancer-associated fibroblasts (CAFs), endothelial cells, stromal cells, and the extracellular matrix (ECM). In the past, the TME was mainly considered as a bystander in tumor development, but an increasing body of research has revealed the pivotal role of the TME in tumor initiation, progression, and metastasis.[140]

Targeting CAFs

CAFs constitute a crucial component of the TME, exerting significant influence on tumor growth, invasion, and metastasis.[141] Glypican-3 (GPC3), a member of the heparan sulfate proteoglycan family, is anchored to the cell membrane through phosphatidylinositol. Interestingly, studies have revealed high expression of GPC3 in both CAFs and hepatoid adenocarcinoma of the stomach (HAS). High GPC3 expression in CAFs is associated with GC progression and poor prognosis. Moreover, GC with high GPC3-expressing CAFs display insensitivity to *in vivo* PD-1 blockade therapy.[142,143] Downregulating GPC3 expression in GC has shown promise in inhibiting tumor metastasis, altering the tumor immune microenvironment, and improving the efficacy of PD-1 blockade therapy. Thus, GPC3 emerges as a promising target in the treatment of GC.

Targeting TAMs

Tumor-associated macrophages (TAMs) are pivotal immune cells present within the TME, playing a central role in cancer-related inflammatory responses.[144] Current strategies primarily focus on depleting TAMs or shifting their phenotype from M2 to M1. The colony-stimulating factor 1 (CSF-1)/CSF-1 receptor (CSF-1R) pathway plays a significant role in the transformation of TAMs from the M1 phenotype to the M2 phenotype.[145] Inhibiting TAMs directly by blocking CSF-1/CSF-1R signaling is a promising therapeutic method. Several clinical trials are underway, evaluating monoclonal antibodies and tyrosine kinase inhibitors targeting CSF-1/CSF-1R at various stages. Additionally, tumor cells can recruit monocytes expressing the CCR2 receptor to the tumor site by releasing CCL2. Elevated CCL2 levels are linked with unfavorable outcomes in different cancers. Targeting the CCL2-CCR2 axis presents another innovative strategy for inhibiting TAMs.

Targeting the ECM

The ECM is composed of various proteins and interacts with cells to transmit extracellular signals that can alter cellular phenotypes.[146,147] The remodeling of the ECM can induce alterations in the microenvironment, thereby fostering cancer progression and metastasis.[148] The E26 transformation-specific (ETS) transcription factor ELK3 plays a pivotal role in regulating the expression of genes related to ECM remodeling, facilitating the dissemination of cancer cells.[149] Furthermore, ELK3 is highly expressed in GC patients and is associated with poor prognosis.[149] Thus, ELK3 represents a potential target for GC therapy.

EPIGENETIC-TARGETED THERAPY

Cancer is characterized by widespread changes in epigenetic modifications, which play a crucial role in the transformation of normal cells into malignant ones. These alterations involve various epigenetic processes, notably DNA methylation, histone modifications, and RNA regulation. Dysregulation in these processes contributes significantly to the development and progression of cancer.[150]

DNA methyltransferase inhibitors

The methylation status of the genome is primarily regulated by DNA methyltransferase (DNMT) and DNA demethylases.[151] Moreover, prior studies have highlighted that aberrations in DNMT status are linked with tumorigenesis.[152] Excessive and abnormal activation of DNMTs can result in the silencing or inactivation of tumor-suppressor genes (TSGs), ultimately promoting the development of GC. Therefore, DNMT represents a potential target for GC treatment.

5-Azacitidine (Vidaza) is a cytidine analog that can reduce DNMT1 levels within cells, thereby inhibiting DNA methylation. In a phase I clinical study, preliminary evidence indicated that incorporating 5-azacitidine into neoadjuvant epirubicin, oxaliplatin, and capecitabine (EOX) therapy for locally advanced resectable esophageal/gastric adenocarcinoma (GAC) could potentially augment the efficacy of chemotherapy. Moreover, this treatment regimen demonstrated good tolerability among patients.[153]

Histone modification inhibitors

LSD1 inhibitors

Histone lysine specific demethylase 1 (LSD1), also referred to as KDM1A, plays a pivotal role in regulating gene expression by catalyzing the demethylation of H3K4me1/2 and H3K9me1/2.[154,155]

Table 2. Clinical trials of neoadjuvant therapy for GC/GEJC

Year	Drugs	Co-drugs	NCT number (phase)	Patient number	Experimental vs. controlling	Clinical validity (month)	Grade 3/4 TRAE incidence	Reference
2024	pembrolizumab	cisplatin-based chemotherapy	NCT03221426 (III)	804	pembrolizumab + chemotherapy (402) vs. placebo + chemotherapy (402)	mPFS[a]: 44.4 vs. 25.3 mOS[a]: 60.7 vs. 58.0 R0[a]: 80% vs. 75%	78% vs. 74%	Shitara et al.[134]
2022	pembrolizumab	chemoradiotherapy	NCT02730546 (Ib/II)	31	pembrolizumab + chemoradiotherapy (31)	pCR: 22.6% R0: 90.3%	54.8%	Zhu et al.[133]
2024	camrelizumab	apatinib + SOX	NCT03878472 (II)	25	camrelizumab + apatinib + SOX (25)	pCR: 15.8% MPR: 26.3% R0: 82.6%	8%	Li et al.[136]
2023	camrelizumab	ramucirumab + SOX	NCT04208347 (III)	360	SOXRC (180) vs. SOX (180)	pCR: 18.3% vs. 5.0% MPR:51.1% vs. 37.8% R0: 98.7% vs. 94.2%	36.3% vs. 16.3%	Li et al.[137]
2022	camrelizumab	chemoradiotherapy	NCT03631615 (II)	36	camrelizumab + chemoradiotherapy (31)	pCR: 33.3% MPR: 44.4% R0: 91.7%	77.8%	Tang et al.[138]
2022	nivolumab	–	JapicCTI-183895 (I)	31	nivolumab (31)	pCR: 3.2% MPR: 16.7% R0: 90%	29%	Janjigian et al.[27]
2023	sintilimab	radiotherapy + S-1 and nab-paclitaxel	ChiCTR1900024428 (II)	34	sintilimab + radiotherapy + S-1 and nab-paclitaxel (34)	pCR: 18.3% mDFS: 17.0% mEFS: 21.1%	50%	Wei et al.[139]
2024	toripalimab	SOX/XELOX	NCT04250948 (II)	108	toripalimab + SOX/XELOX (54) vs. SOX/XELOX (54)	pCR: 22.2% vs. 7.4% MPR:44.4% vs. 20.4% R0: 92.6% vs. 94.4%	35.2% vs. 29.6%	Yuan et al.[135]

[a]No statistical difference.

Additionally, it demethylates non-histone proteins, such as p53 and DNA methyltransferase 1 (DNMT1).[156,157] LSD1 is overexpressed in various cancer types, including GC, and promotes tumor growth and immune evasion through multiple mechanisms.[158–160] Interestingly, LSD1 can suppress the immunogenicity of tumor cells, facilitating immune escape immune escape.[161,162] LSD1 can also impede the migration, infiltration, and cytotoxicity of CD8+ T cells as well as the polarization of M1 macrophages.[163–166] Studies have demonstrated that LSD1 inhibitors not only inhibit the tumor growth but also activate and enhance the immune response. This suggests their potential as adjunct therapies to PD-1 ICIs.[162,167] Therefore, LSD1 can emerge as a highly promising target for GC treatment.

HDAC inhibitors

Histone deacetylases (HDACs) constitute a class of enzymes capable of removing acetyl groups from lysine residues, thereby regulating the structure and function of histones and chromatin, ultimately controlling DNA expression.[168] Research indicates that HDAC overexpression is common across various cancer types. HDACs can induce deacetylation of both histone and non-histone proteins, leading to functional impairment and playing a pivotal role in cancer progression.[169] HDAC inhibitors (HDACis) have the potential to restore the acetylation equilibrium within cells, thereby reinstating the normal expression and function of various proteins. This ability impedes tumor development and progression. Vorinostat, an orally administered HDACi, was subject to evaluation in a phase II clinical trial assessing its efficacy when combined with the XP chemotherapy regimen in advanced GC patients. The trial outcomes indicated that, in comparison to historical data from patients solely treated with the XP chemotherapy regimen, the addition of vorinostat did not significantly enhance patient prognosis. Moreover, the combination therapy was associated with increased toxicity levels.[170]

Tucidinostat, also known as chidamide, is a selective inhibitor of HDACs that specifically target HDAC1, HDAC2, HDAC3, and HDAC10. Despite lacking clinical evidence supporting its application in GC treatment, ongoing clinical trials are investigating its efficacy. Specifically, a clinical trial (NCT05163483) is currently underway to explore the potential of tucidinostat when administered in combination with a PD-1 inhibitor and bevacizumab for the treatment of advanced GC/GEJ cancer.

ncRNA inhibitors

Numerous studies have indicated that high expression of oncogenic non-coding RNAs (ncRNAs) plays a crucial role in the development of many cancers, including GC.[171,172] Targeting these oncogenic ncRNAs to suppress their expression emerges as a potential therapeutic strategy in GC treatment. Small interfering RNA (siRNA) stands out as a promising method for downregulating ncRNA expression. By precisely binding to the corresponding mRNA through base pairing, siRNA achieves specific inhibition of oncogenic ncRNAs. Additionally, antisense oligonucleotides (ASOs) and miRNA sponges

represent alternative approaches for inhibiting ncRNAs.[173] Despite these promising avenues, methods for targeting ncRNAs in GC treatment have not yet undergone clinical validation.

CSC TARGETED THERAPY

An increasing body of research indicates that cancer stem cells (CSCs) are associated with tumor initiation, recurrence, and metastasis. CSCs typically arise from non-malignant stem or progenitor cells. Several signaling pathways, including Notch, WNT, Hedgehog, and Hippo cascades, are intimately linked to stem cell homeostasis and function.[174] The involvement of these pathways in CSC regulation offers novel opportunities for cancer treatment strategies.

Targeting the Notch signaling pathway

The Notch signaling pathway is one of the pathways associated with cancer initiation most frequently disrupted. It plays a role in various biological features of cancers, including CSC phenotypes, angiogenesis, metastasis, and tumor immune evasion.[175] Dysregulation of Notch is also linked to resistance to multiple drugs. Approaches to modulate Notch pathway activity encompass both chemical and immune targeting of NOTCH receptors, Delta ligands, and γ-secretase.[176–178] Despite its significant role in cancer, research regarding the involvement of the Notch pathway in GC treatment remains limited.

Targeting the Wnt/β-catenin signaling pathway

The Wnt-β-catenin pathway plays a crucial role in regulating cell proliferation, differentiation, maintenance of gastric epithelial homeostasis, and maintaining the pluripotency of adult stem cells.[179] Aberrant activation of the Wnt/β-catenin pathway contributes to the maintenance of CSC properties, thus contributing to tumor development and progression.[180] Given that over half of GC patients show dysregulated Wnt/β-catenin signaling,[181–183] targeting this pathway holds promise for the treatment of GC.

ETC-159

ETC-159, an oral inhibitor of porcupine homolog (PORCN), can effectively suppress *β-catenin* gene activity, thereby inhibiting Wnt/β-catenin signaling. Ongoing clinical trials are assessing the safety and tolerability of ETC-159 as a monotherapy and in combination with pembrolizumab for the treatment of advanced solid tumors (NCT02521844).

DKN-01

DKN-01, a humanized IgG4 monoclonal antibody, functions by targeting the secreted protein Dickkopf-1 (DKK1) to block the Wnt/β-catenin signaling pathway. Studies have shown that treatment with DKN-01 results in an increase in PD-L1 expression in myeloid-derived suppressor cells (MDSCs).[184] As a result, a phase IB clinical study was conducted to evaluate the efficacy and safety of combining DKN-01 with pembrolizumab in the context of GC/GEJ cancer. The results were highly promising, particularly within the subset of patients exhibiting high DKK1 expression.[185] The treatment demonstrated notable anti-tumor effects and maintained manageable safety profiles, highlighting the promise of combining DKK1 and PD-1 monoclonal antibodies. Additionally, a phase II clinical trial (NCT04363801) is currently underway, exploring the potential of DKN-01 in combination with tislelizumab and chemotherapy as a treatment option for advanced GC/GEJ cancer, whether in the first- or second-line setting.

Targeting the Hedgehog signaling pathway

The Hedgehog signaling pathway plays a critical role in tissue regeneration, immune regulation, and organ development.[186] Dysregulation of the Hedgehog pathway can lead to excessive tissue growth, contributing to tumor development. There is evidence suggesting a connection between disruptions in the Hedgehog pathway and the onset and progression of GC.[187] Vismodegib (GDC-0449), a Smoothened (SMO) inhibitor, has been approved by the FDA for the treatment of advanced basal cell carcinoma and acts by inhibiting Hedgehog signaling.[188] However, clinical trials exploring its efficacy in GC (NCT00982592) have not yielded satisfactory results. Taladegib (ENV-101), another SMO inhibitor, is currently undergoing phase II clinical research to evaluate its safety and effectiveness in advanced solid tumor patients harboring PTCH1 loss-of-function mutations (NCT05199584).

Targeting the Hippo signaling pathway

The Hippo signaling pathway is crucial for tissue regeneration, immune responses, and organ development. When this pathway becomes dysregulated, it can result in uncontrolled tissue growth and the development of tumors. The key mediators of Hippo pathway effects include the transcriptional effectors yes-associated protein (YAP1) and TAZ, which regulate gene expression by modulating the activity of the transcriptional enhancer factor TEF-1 (TEAD) transcription factor family.[189] Elevated expression of YAP1 has been reported in both esophageal cancer (EC) and GC tissues, where it contributes to tumor development and resistance to chemotherapy.[190–194] The overexpression of YAP1 is an adverse prognostic indicator in GC.[195] Approximately 45% of advanced GAC patients experience peritoneal carcinomatosis (PC), which is associated with poor prognosis. Recent studies have revealed high levels of YAP1 expression in PC tumor cells, imparting them with characteristics of CSCs. YAP1 appears to play a pivotal role in the peritoneal dissemination of GC.[196] This evidence suggests that YAP1 is a promising target for GC treatment. Verteporfin, typically used as a photosensitizer in photodynamic therapy, also functions as a YAP inhibitor. It works by disrupting YAP activity, thereby interfering with the interaction between YAP and TEAD and consequently blocking the inhibition of Hippo pathway signaling. Interestingly, preclinical studies have demonstrated that verteporfin can reduce the tumorigenic properties of gastric CSCs and inhibit tumor growth in patient-derived xenograft models.[197] These findings highlight targeting YAP1 as a potential strategy for treating GC. However, further clinical trials are necessary to validate its efficacy in GC patients.

Conclusions

This article provides an overview of drugs used for GC targeted therapies and immunotherapies, as depicted in Figure 2. We have also compiled a summary of ongoing key clinical trials for targeted and immunotherapies, along with the current application status of various targeted therapy strategies for GC/GEJC, as delineated in Tables 3 and 4.

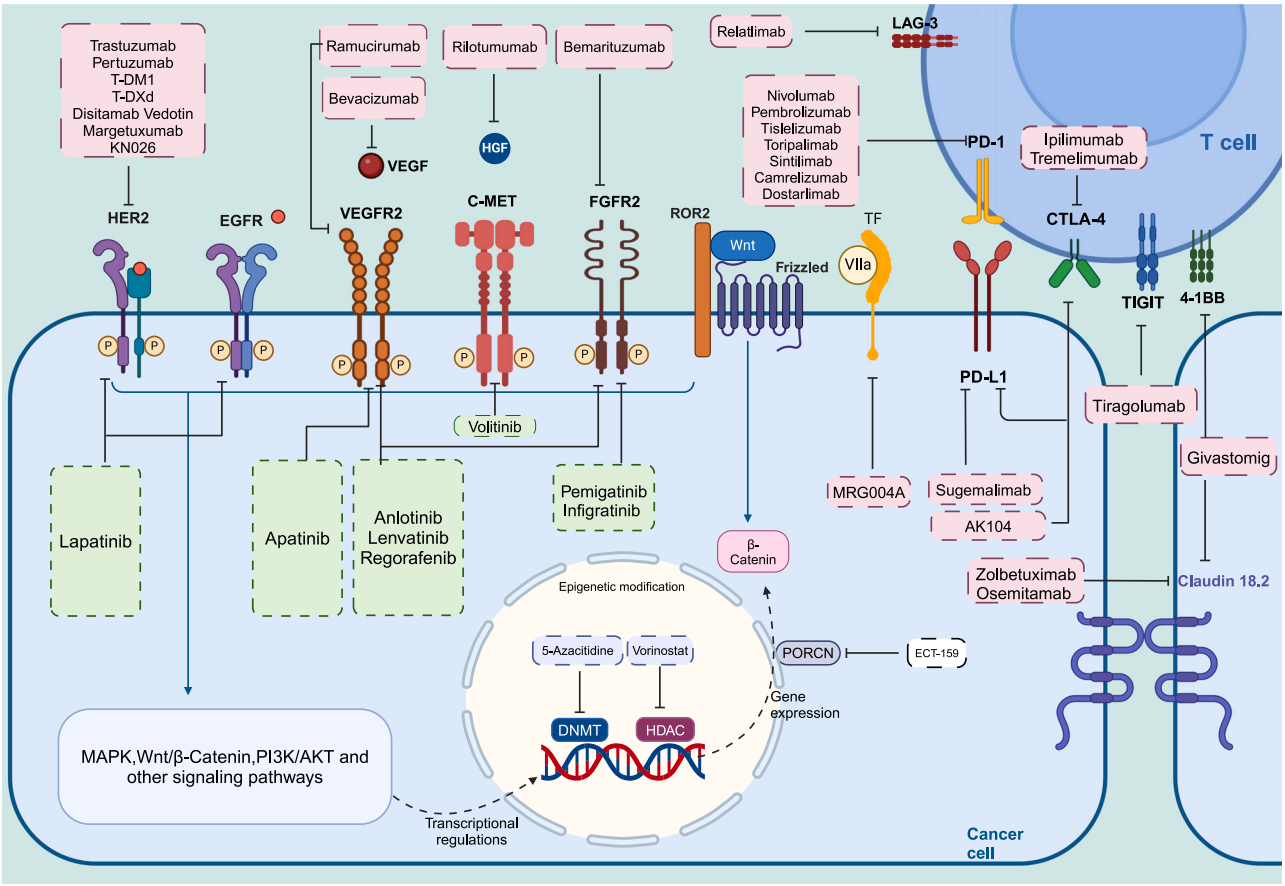

Figure 2. Overview of GC/GEJC targeted therapies and immunotherapy drugs

This paper describes representative therapeutic targets in GC and targeted or immunotherapy drugs that have entered clinical application or clinical research. This figure was created with Biorender.com.

At present, targeted and immune therapies represent the forefront of GC treatment, offering promising prospects for patient survival in clinical settings. However, GC, marked by its heterogeneity and intricate mechanisms, involves multiple pathways influencing its progression. Unfortunately, the existing repertoire of targets and drugs falls short in meeting the therapeutic needs for GC comprehensively. There is an urgent need for the development of additional therapeutic targets to enhance specificity and ensure a wider range of GC patients can benefit. Overcoming resistance to targeted and immune therapies requires in-depth research into the underlying resistance mechanisms, enabling proactive counteraction or prevention. Moreover, the significant challenge of adverse reactions associated with targeted and immune therapies looms large. Many of these adverse reactions stem from off-target effects. Consequently, there is a dual imperative: investment in drug development to produce medications with minimal side effects and maximal efficacy, and intensified fundamental research into tumor-specific antigens (TSAs).

Additionally, the combination of targeted therapy with chemotherapy or targeted and immune therapies has displayed promising anti-tumor effects in GC treatment. Evaluating the efficacy and safety of diverse treatment combinations holds paramount importance in the current landscape of GC treatment. Simultaneous targeting of multiple pathways emerges as a promising approach for GC treatment. Given the complexities of tumor development, multi-targeted treatments often yield superior outcomes, as shown by commercially available multi-kinase inhibitors such as sorafenib and regorafenib. Moreover, bispecific antibodies such as KN026 and givastomig have shown significant efficacy in GC treatment. The success of CAR-T cell therapy in hematological malignancies has provided valuable insights for GC treatment. With ongoing research into CAR-T cell therapy for solid tumors, a new era of cancer treatment has dawned. We are confident that the continuous discovery of novel treatment targets will lead to a growing array of highly effective targeted therapies for GC, ultimately triumphing over this deadly disease.

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Table 3. Current significant clinical trials for GC/GEJC

NCT number	Study title	Related drugs	Primary outcome measures	Phases	Enrollment	Study design (allocation, intervention model, masking, primary purpose)	Start date
NCT04704934	Trastuzumab Deruxtecan for Subjects With HER2-Positive Gastric Cancer or Gastro-Esophageal Junction Adenocarcinoma After Progression on or After a Trastuzumab-Containing Regimen (DESTINY-Gastric04)	trastuzumab-deruxtecan	OS	3	490	randomized parallel none treatment	2021/5/21
NCT05980481	A Study of RC48-ADC Combination Therapies as First-line Treatment in Advanced Metastatic Gastric Cancer	RC48-ADC	safety (adverse event)	2, 3	60	randomized parallel none treatment	2023/8/30
NCT04714190	A Study of RC48-ADC in Local Advanced or Metastatic Gastric Cancer With the HER2-Overexpression	RC48-ADC	OS	2, 3	351	randomized parallel none treatment	202one-third/24
NCT05427383	KN026 in Combination With Chemotherapy in the Second Line Treatment of HER-2 Positive Advanced or Metastatic Gastric Cancer	KN026	PFS,OS	2, 3	286	randomized parallel single treatment	2022/4/7
NCT03889626	The Maintenance Treatment of Apatinib/ Capecitabine Versus Observation in Advanced Gastric Cancer	apatinib	PFS	3	242	randomized parallel none treatment	2019/3/22
NCT04385550	A Study of Anlotinib Hydrochloride Capsule Combined With AK105 Injection in Subject With Advanced Gastric and Gastro-oesophageal Junction Adenocarcinoma	anlotinib	OS	3	528	randomized parallel none treatment	2020/5/20
NCT04879368	RegoNivo vs. Standard of Care Chemotherapy in AGOC	regorafenib	OS	3	450	randomized parallel none treatment	2021/6/1
NCT05620628	Ph2 Study of Savolitinib and Durvalumab (MEDI4736) Combination in Advanced MET Amplified Gastric Cancer (VIKTORY-2)	savolitinib (volitinib)	PFS, OS	2	25	randomized single group none treatment	2023/1/5
NCT04923932	Savolitinib for Treating Gastric Cancer and Esophagogastric Junction Adenocarcinoma Patients	savolitinib (volitinib)	ORR, PFS, AE	2	75	randomized single group none treatment	2021/7/27
NCT05322577	A Study Evaluating Bemarituzumab in Combination With Other Anti-cancer Therapies in Subjects With Previously Untreated Advanced Gastric or Gastroesophageal Junction Cancer	bemarituzumab	DLT, TEAE, OR	1	80	NA sequential assignment none basic science	2022/5/17
NCT05052801	Bemarituzumab or Placebo Plus Chemotherapy in Gastric Cancers With Fibroblast Growth Factor Receptor 2b (FGFR2b) Overexpression	bemarituzumab	OS	3	516	randomized parallel double treatment	2022/3/7

(*Continued on next page*)

Table 3. *Continued*

NCT number	Study title	Related drugs	Primary outcome measures	Phases	Enrollment	Study design (allocation, intervention model, masking, primary purpose)	Start date
NCT05111626	Bemarituzumab Plus Chemotherapy and Nivolumab Versus Chemotherapy and Nivolumab for FGFR2b Overexpressed Untreated Advanced Gastric and Gastroesophageal Junction Cancer	bemarituzumab	OS	3	528	randomized parallel double treatment	2022/3/14
EudraCT 2017-004522-14	A phase II trial of the FGFR inhibitor INCB054828 in patients with advanced esophageal-gastric junction (EGJ)/Gastric cancer trastuzumab Resistant: the FiGhTeR trial	pemigatinib	PFS-12w	2	–	NA single group none treatment	2019/01/30
NCT05997459	A Single Arm, Phase II Exploratory Clinical Study of Pemitinib in Advanced Gastric Cancer With Previous Standard Therapy Failure the FGFR Variant	pemigatinib	PFS	2	23	randomized single group none treatment	2023/8/25
NCT05019794	A Phase IIa of Infigratinib in Subjects With Locally Advanced or Metastatic Gastric Cancer or Gastroesophageal Junction Adenocarcinoma With FGFR2 Amplification or Other Advanced Solid Tumors With Other FGFR Alterations	infigratinib	ORR	2	80	NA parallel none treatment	2020/05/13
NCT04581473	Study to Evaluate the Efficacy, Safety and Pharmacokinetics of CT041 Autologous CAR T-cell Injection	CT041	incidence of TEAEs, MTD, PFS	1, 2	192	randomized parallel none treatment	2020/10/23
NCT04900818	Study of TJ033721 in Subjects With Advanced or Metastatic Solid Tumors	TJ033721 (givastomig)	DLTs, severity of AEs, MTD, MAD	1	102	NA sequential none treatment	2021/6/29
NCT06093425	A Phase 3, Randomized, Double-blind, Placebo-controlled Study Evaluating Combination of TST001, Nivolumab and Chemotherapy as First-Line Treatment in Subjects With Claudin18.2 Positive Locally Advanced or Metastatic Gastric or Gastroesophageal Junction (Gastric/GEJ) Adenocarcinoma	TST001 (osemitamab)	PFS	3	950	randomized parallel single treatment	2023/10/31
NCT04495296	A Phase I/IIa Clinical Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of TST001 - Claudin18.2 Monoclonal Antibody in the Treatment of Locally Advanced or Metastatic Solid Tumors	TST001 (osemitamab)	DLTs, severity of AEs, MTD, RP2D, MAD	1/2a	320	NA parallel none treatment	2020/08/13
NCT04868877	A Phase 1/2 Study Evaluating MCLA-129, a Human Anti-EGFR and Anti-c-MET Bispecific Antibody, in Patients With Advanced NSCLC and Other Solid Tumors	MCLA-129	MTD, RP2D, ORR	1, 2	380	NA parallel none treatment	2021/4/28
NCT05144854	A Study to Evaluate the Efficacy and Safety of ONO-4538 in Combination With Ipilimumab and Chemotherapy in Chemotherapy-naïve Participants With HER2-negative Unresectable	nivolumab	OS	3	626	randomized parallel none treatment	2021/11/5

(*Continued on next page*)

Table 3. *Continued*

NCT number	Study title	Related drugs	Primary outcome measures	Phases	Enrollment	Study design (allocation, intervention model, masking, primary purpose)	Start date
	Advanced or Recurrent Gastric Cancer (Including Esophagogastric Junction Cancer)						
NCT04662710	Efficacy and Safety of Lenvatinib (E7080/MK-7902) Plus Pembrolizumab (MK-3475) Plus Chemotherapy in Participants With Advanced/ Metastatic Gastroesophageal Adenocarcinoma (MK-7902-015/E7080-G000-321/LEAP-015)	pembrolizumab	PFS, OS	3	890	randomized parallel none treatment	2020/12/30
NCT05008783	A Study of AK104 in the First-line Treatment of Locally Advanced Unresectable or Metastatic G/GEJ Adenocarcinoma	AK104	OS	3	588	randomized parallel quadruple treatment	2021/9/17
NCT06341335	A Study of AK104/Placebo Plus AK109/Placebo And Paclitaxel in Gastric or Gastroesophageal Junction Adenocarcinoma	AK104	PFS, OS	3	506	randomized parallel quadruple treatment	2024/06/19
NCT04923932	Savolitinib for Treating Gastric Cancer and Esophagogastric Junction Adenocarcinoma Patients	savolitinib	ORR	2	75	NA single group none treatment	2021/7/27
NCT05640609	Capeox Regimen Combined With Sintilimab and Bevacizumab for Gastric Cancer	sintilimab	appropriate dose, ORR	1, 2	57	NA single group none treatment	2023/3/10
NCT05152147	A Study of Zanidatamab in Combination With Chemotherapy Plus or Minus Tislelizumab in Patients With HER2-positive Advanced or Metastatic Gastric and Esophageal Cancers	tislelizumab	PFS, OS	3	714	randomized parallel none treatment.	2021/12/2
NCT04843709	A Study of MRG004A in Patients With Tissue Factor Positive Advanced or Metastatic Solid Tumors	MRG004A	MTD, RP2D, AEs, ORR	1, 2	181	NA single group none treatment	2021/7/26
NCT05163483	Tucidinostat Plus PD-1 Inhibitor and Bevacizumab for Advanced Esophagus Cancer, AEG, Gastric Cancer	tucidinostat	ORR	2	87	NA single group none treatment	2022/7/1
NCT05007106	MK-7684A With or Without Other Anticancer Therapies in Participants With Selected Solid Tumors (MK-7684A-005) (KEYVIBE-005)	vibostolimab	ORR, PFS	2	610	randomized parallel none treatment	2021/9/16

Table 4. Current status of different targeted therapy strategies for GC/GEJC

Targets	Drug	Status	Approved for GC/GEJC
HER2	trastuzumab	clinically applied	FDA, EMA, NMPA
	trastuzumab-deruxtecan	clinically applied	FDA, EMA
	disitamab vedotin	clinically applied	NMPA
	trastuzumab-emtansine	clinical trial phase 3	–
	KN026	clinical trial phase 3	–
VEGF/VEGFR	ramucirumab	clinically applied	FDA, EMA, NMPA
	apatinib	clinically applied	NMPA
	anlotinib	clinical trial phase 3	–
	lenvatinib	clinical trial phase 2	–
	regorafenib	clinical trial phase 3	–
HGF/c-Met	rilotumumab	no Active Trials	–
	volitinib	clinical trial phase 2	–
	MCLA-129	clinical trial phase 2	–
mTOR	everolimus	no Active Trials	–
FGF/FGFR2	bemarituzumab	clinical trial phase 3	–
	pemigatinib	clinical trial phase 2	–
TF	tisotumab vedotin	preclinical	–
CLDN18.2	zolbetuximab	clinical trial phase 3	–
	osemitamab	clinical trial phase 3	–
	givastomig	clinical trial phase 1	–
	CT041	clinical trial phase 2	–
PARP	olaparib	clinical trial phase 2	–
PD-1/PD-L1	nivolumab	clinically applied	FDA, EMA, NMPA
	pembrolizumab	clinically applied	FDA, EMA, NMPA
	sintilimab	clinically applied	NMPA
	tislelizumab	clinically applied	NMPA
	dostarlimab	clinically applied	FDA
	camrelizumab	clinical trial phase 3	–
	toripalimab	clinical trial phase 2	–
	sugemalimab	clinical trial phase 3	–
	AK104	clinical trial phase 3	–
CTLA4	ipilimumab	clinical trial phase 3	–
LAG-3	relatlimab	clinical trial phase 1	–
TIGIT	tiragolumab	clinical trial phase 2	–
Epigenetics	5-azacitidine (Vidaza)	no active trials	–
	vorinostat	no active trials	–
	tucidinostat (chidamide)	clinical trial phase 2	–
CSC	ETC-159	clinical trial phase 1	–
	DKN-01	clinical trial phase 2	–
	taladegib	clinical trial phase 2	–
TME	–	laboratory	–

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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