From Anti-HER-2 to Anti-HER-2-CAR-T Cells: An Evolutionary Immunotherapy Approach for Gastric Cancer

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Abstract: Current Therapeutic modalities provide no survival advantage to gastric cancer (GC) patients. Targeting the human epidermal growth factor receptor-2 (HER-2) is a viable therapeutic strategy against advanced HER-2 positive GC. Antibody-drug conjugates, small-molecule tyrosine kinase inhibitors (TKIs), and bispecific antibodies are emerging as novel drug forms that may abrogate the resistance to HER-2-specific drugs and monoclonal antibodies. Chimeric antigen receptor-modified T cells (CAR-T) targeting HER-2 have shown considerable therapeutic potential in GC and other solid tumors. However, due to the high heterogeneity along with the complex tumor microenvironment (TME) of GC that often leads to immune escape, the immunological treatment of GC still faces many challenges. Here, we reviewed and discussed the current progress in the research of anti-HER-2-CAR-T cell immunotherapy against GC.

Keywords: CAR-T, HER-2, gastric cancer, immunotherapy, target

Introduction

Gastric cancer (GC) ranks fifth in incidence and fourth in mortality among all malignancies worldwide, which was equal to more than 1 million new cases and 769 thousand deaths in 2020. Given the considerable tumor heterogeneity, the five-year survival rate of advanced GC is reported to be less than 30%. At present, the treatment of GC mainly includes surgical resection, chemotherapy, traditional Chinese medicine (TCM) therapy, targeted therapy and immunotherapy (Figure 1).

Based on the results of CLASS01 and CLASS02 clinical trials, laparoscopic total gastrectomy is a potentially safe alternative to open total gastrectomy for both advanced and early stage (I) GC patients. Recent studies have also reported high efficacy and low toxicity of TCM-based treatment of GC, although the molecular mechanisms are still unclear. Furthermore, perioperative chemotherapy for GC has reached a consensus based on the results of CLASSIC, MAGIC, RESOLVE and other randomized controlled trials conducted over the past decade. Despite advances in the molecular typing of GC and the development of targeted and immunogenic drugs, their clinical applications remain limited, especially for the human epidermal growth factor receptor type 2 (HER-2) positive, microsatellite instability-high and Epstein–Barr virus-associated subtypes. Moreover, studies have increasingly shown that conventional chemotherapy is not the optimum choice for perioperative treatment, and the outcomes of the patients depend significantly on the specific tumor stage and mutation status.

HER-2 is a member of the epidermal growth factor receptor (EGFR) family, and is overexpressed in many solid tumors including breast cancer (BC), stomach cancer, colon cancer and ovarian cancer. The Phase 3 ToGA trial established trastuzumab as a first-line treatment for advanced HER-2 positive GC. However, lapatinib, trastuzumab...
emtansine (T-DM1) and pertuzumab have not shown encouraging results after first-line treatment progression.\textsuperscript{24} Immunotherapy and targeted therapy are now indispensable for GC treatment. The development of immune inhibitors against advanced GC cells has been one of the most significant improvements in recent years.\textsuperscript{25} Chimeric antigen receptor T cell therapy (CAR-T) is a promising treatment strategy against cancers.\textsuperscript{26} Two CAR-T cell-based therapies have been approved by the Food and Drug Administration (FDA) to treat refractory leukemia and lymphoma.\textsuperscript{27} However, the efficacy of CAR-T cells against sarcomas and other solid tumors is limited due to the immunosuppressive tumor microenvironment (TME).\textsuperscript{28,29} Compared to conventional therapies, CAR-T cells can directly recognize antigens on the surface of tumor cells and kill tumor cells, thereby reducing the rejection response.\textsuperscript{30} New-generation cellular immunotherapies, such as combined immune checkpoint inhibitors, cytokine-induced lymphocyte and T-cell targeted killing, are promising strategies against solid tumors\textsuperscript{31} but are still at the stage of clinical trials for GC.

Nevertheless, EGFR or CAR-T targeting alone cannot achieve ideal efficacy against GC due to the heterogeneity of tumor cells, immunosuppressive TME and antigen migration. Here, we reviewed and discussed the various immunotherapeutic strategies that have been developed so far to target HER-2 in GC.

**Targeted HER-2 Therapy**

**Structure and Function of HER-2**

The first EGFR was discovered in the 1970s, and since then four members of the family, namely EGFR/HER-1/ErbB1, HER-2/ErbB2, HER-3/ErbB3 and HER-4/ErbB4,\textsuperscript{32,33} have been characterized. The HER-2 and ErbB2 oncoproteins were initially identified in rodents and humans, respectively, but were later found to be homologous to each other.\textsuperscript{34–36} All the members of

\textbf{Figure 1} Treatment strategies for gastric cancer. Surgical resection, chemotherapy, traditional Chinese medicine, targeted therapy and immunotherapy.
HER family have the same extracellular domains, lipophilic transmembrane regions, intracellular domains containing tyrosine kinases, and carboxy-terminal regions. Binding of ligands to the extracellular domains of HER proteins leads to dimerization and transphosphorylation of their intracellular domains. However, ErbB2 has no direct ligand, and the crystal structure of its extracellular region indicates an extended configuration with four domains arranged in a manner similar to that seen in the EGFR dimer. Thus, ErbB2 has a ligand-independent active conformation. This is consistent with the fact that ErbB2 homodimers are spontaneously formed in cells overexpressing ErbB2, which is the preferred dimer partner of other ErbB receptors. Activation of HER-2 and EGFR leads to the phosphorylation of the ErbB dimer, which stimulates the downstream RAS/MEK, PI3K/AKT, Src kinases and STAT pathways. HER-2 initiates GC development in the form of EGFR, HER-2 dimers, and HER-2/HER-3 dimers.

**EGFR in GC**

The EGFR family is highly expressed in 40–60% of GC tumors. Anti-EGFR drugs block the downstream signal transduction pathway in cancer cells by targeting the extracellular, transmembrane and intracellular regions of EGFR. EGFR-specific ligands, such as EGF, bind to their extracellular region and mediate homo/heterodimerization, resulting in autophosphorylation of the receptor and activation of a series of downstream signal transduction pathways in GC cells, including VAV2-RhoA, STAT5, PI3K/AKT/mTOR, etc. (Figure 2). The pathways culminate in the activation of transcription factors, leading to tumor cells’ proliferation, infiltration, and metastasis, inhibiting tumor cells’ apoptosis, and enhancing tumor angiogenesis.

**Figure 2** Related molecular mechanisms of targeting HER-2 in gastric cancer. HER-2 is mainly involved in the occurrence and development of gastric cancer through EGFR, HER-2 dimer and HER-2/HER-3 dimer. The three receptors signal via the PI3K-AKT, RAS-MEK-MAPK, VAV2-RhoA and SRC-FAK pathways, thus affecting cell adhesion, migration, growth, proliferation and metastasis of gastric cancer cells.
HER-2/HER-2 Dimer in GC

The HER receptor exists as a monomer or as a homo/heterodimer, and HER-2 preferentially binds to the dimeric form. The HER-2 pathway is altered during GC development, either due to aberrant changes in HER-2 structure, dysregulation of downstream effectors of HER-2, or interaction of HER-2 with other membrane receptors. As shown in Figure 2, dimerization of HER-2/HER-2 activates the SRC-FAK, GRB2/SOS/JAK2, and RAS-MEK-MAPK signaling pathways in GC cells, and promotes cell adhesion, migration, growth, proliferation, and metastasis.

HER-2/HER-3 Dimer in GC

The HER-2/HER-3 heterodimer is the most mitogenic of all ErbB receptors, and is constitutively active in GC cells overexpressing the HER-2 gene. Recent studies have shown that the HER-2-HER-3 dimer is related to the occurrence, growth, metastasis and drug resistance of tumors. The HER-2/HER-3 dimer signals through the RAS-MEK-MAPK and PI3K-AKT pathways (Figure 2) upon EGF binding. Activation of the PI3K/AKT pathway can lead to tumor drug resistance, and preclinical trials of PI3K inhibitors have indicated that this pathway is a suitable target for tumor therapy. In addition, some studies have shown that inhibition of PI3K or MEK alone, or in combination with anti-HER-2 therapy, might be a reformatory treatment scheme for some patients with HER-2 positive GC. Approximately 34–59% of the patients with HER-2 positive GC also overexpress HER-3 and are resistant to trastuzumab, which can be attributed to the negative feedback regulation of HER-3 mediated by the HER-2-dependent P13K-AKT pathway, making trastuzumab unresponsive to ligand-dependent dimerization of HER-2/HER-3.

Drugs Targeting HER-2 in the Treatment of GC

Currently, drugs targeting HER-2 in the treatment of GC can be divided into four categories: first-generation HER-2 monoclonal antibody, second-generation HER-2 monoclonal antibody, small-molecule tyrosine kinase inhibitors (TKIs), antibody-drug conjugates (ADCs) and bispecific antibodies. The latest research progress on these drugs is detailed in Table 1.

First-Generation HER-2 Monoclonal Antibody

Trastuzumab was the first monoclonal antibody approved by FDA to treat HER-2 positive GC. The TOGA trial demonstrated for the first time that the combination of trastuzumab and fluorouracil was superior to chemotherapy for the treatment of HER-2 positive advanced GC, and significantly prolonged overall survival (OS) of patients. Since then, several studies have confirmed the efficacy and safety of trastuzumab against advanced HER-2 positive GC. However, acquired resistance to trastuzumab has been a major challenge and has a genetic basis in some patients, which eventually limits its therapeutic efficacy. Early clinical studies had also reported cardiac side effects of trastuzumab, such as left-heart insufficiency and congestive heart failure.

Second-Generation HER-2 Monoclonal Antibody

The second generation of HER-2 targeted drugs has been developed to counteract the emergence of trastuzumab resistance. Pertuzumab binds to the extracellular domain II of the HER-2, blocking ligand-induced heterodimerization of HER-2 and downstream signaling. It has been proved to significantly improve the outcomes in patients with advanced HER-2 positive BC compared to the combination of chemotherapy and trastuzumab. Another study found that pertuzumab extended the median progression-free survival (PFS) of patients with BC by 7.7 months compared to that of the placebo arm. However, the JACOB trial showed that the combination of pertuzumab, trastuzumab and chemotherapy did not significantly improve the survival of HER-2 positive patients with GC or gastroesophageal junction cancer (GEJC) compared to the placebo. Therefore, more studies are needed to further determine the efficacy of pertuzumab in stomach and other cancers.

Small-Molecule TKIs

Small-molecule TKIs can also be used to target HER-2. For instance, lapatinib is an oral TKI specific for both EGFR and HER-2. It blocks HER-1 and HER-2 by reversibly binding to the cytoplasmic ATP binding sites in the tyrosine kinase
| Category                          | Compound           | Mechanism of Action                                                                 | Clinical Trial Phase/ NCT No. | Category                  | Study Arms                                                                                     | Period            | Median OS (m/ 95% CI)                         | References |
|----------------------------------|--------------------|-----------------------------------------------------------------------------------|------------------------------|---------------------------|---------------------------------------------------------------------------------------------|------------------|---------------------------------------------|------------|
| HER-2 monoclonal antibody        | Trastuzumab        | HER2 (domain IV): prevents ligand-independent dimerization, induces HER-2 endocytotic destruction, ADCC and inhibits HER-2 cleavage | III/ 01041404                | Advanced GC and AEG       | Trastuzumab plus chemotherapy vs chemotherapy                                             | 2005.09–2008.12 | 13.8 (12–16) vs 11.1 (10–13)                  | [23]       |
|                                  |                    |                                                                                   |                              | II/ 01396707               | Advanced GC                                                                   | 2011.08–2013.02 | 21.0 (6.4–35.7) vs 9.8 (7.0–12.6)            | [67]       |
|                                  | Pertuzumab         | HER-2 (domain II): inhibits dimerization                                           | III/01774786                 | Metastatic GC and AEG       | Pertuzumab plus trastuzumab and chemotherapy vs placebo plus trastuzumab and chemotherapy | 2013.06–2016.01 | 17.5 (16.2–19.3) vs 14.2 (12.9–15.5)         | [68]       |
|                                  | Lapatinib          | HER-1, HER-2, TKI                                                                  | II/ 00103324                 | Metastatic GC              | Lapatinib                                                                     | 2005.02–2006.05 | 4.8 (3.2–7.4)                               | [69]       |
|                                  |                    |                                                                                   | II/ 00486954                 | Advanced GC                | Lapatinib plus paclitaxel vs paclitaxel                                                   | 2007.06–2009.01 | 11.0 (9.5–14.5) vs 8.9 (7.4–11.1)            | [70]       |
|                                  |                    |                                                                                   | III/ 00680901                | Advanced AEG               | Lapatinib plus capecitabine and oxaliplatin vs placebo plus capecitabine and oxaliplatin | 2008.06–2012.01 | 12.2 (10.6–14.2) vs 10.5 (9.0–11.3)          | [71]       |
|                                  | Afatinib           | NF                                                                                | NF                           | NF                         | NF                                                                           | NF               | NF                                          | [72]       |
|                                  | Neratinib          | NF                                                                                | NF                           | NF                         | NF                                                                           | NF               | NF                                          | [73]       |

(Continued)
| Category                      | Compound                        | Mechanism of Action                                           | Clinical Trial Phase/ NCT No. | Category | Study Arms | Period          | Median OS (m/ 95% CI) | References |
|-------------------------------|---------------------------------|----------------------------------------------------------------|----------------------------|----------|------------|----------------|----------------------|------------|
| Antibody-drug conjugate       | Trastuzumab emtansine (T-DM1)   | HER-2 (domain IV): all the referred for trastuzumab plus targeted delivery of an anti-microtubule agent | II and III/ 01641939         | Metastatic GC and AEG | Trastuzumab emtansine vs taxane | 2012.09–2013.10  | 7.9 (6.7–9.5) vs 8.6 (7.1–11.2) | [74]       |
|                               | Trastuzumab deruxtecan (DS-8201a) |                                                                      | I/ 02564900                  | GC and AEG | DS-8201a   | 2015.08–2018.08  | 12.8 (1.4–25.4)     | [75]       |
|                               | Trastuzumab duocarmazin (SYD985) |                                                                      | I/ 02277717                  | Metastatic GC | SYD985     | 2014.10–2018.04 | NF                   | [76]       |
|                               | ARX788                          |                                                                      |                            | NF         | NF         | NF             | NF                   | [77]       |
| Bispecific antibodies         | ZW25 (Azymetric)                | Bispecific antibody that simultaneously binds to two HER-2 epitopes | NF                        | NF         | NF         | NF             | NF                   | [78]       |
|                               | MCLA-128                        | ADCC and inhibits HER-2                                            | NF                        | NF         | NF         | NF             | NF                   | [79]       |
|                               | Mm-111                          | HER-2/ HER-3                                                        | NF                        | NF         | NF         | NF             | NF                   | [80]       |

**Abbreviations:** ADCC, antibody-dependent cell-mediated cytotoxicity; AEG, adenocarcinoma of esophagogastric junction; CI, confidence interval; GC, gastric cancer; HER, human epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; OS, overall survival; m, month; NCT, national clinical trial; NF, not found.
A Phase II trial using lapatinib as a first-line monotherapy for patients with HER2-positive GC failed to achieve the desired results, showing an overall response rate (ORR) of 11% and a median OS of 4.8 months.99 Besides, one study showed that lapatinib is not superior to trastuzumab as the first- and second-line treatment for advanced GC.70 However, evidence showed that the combination of lapatinib and capecitabine could effectively treat HER2-positive GC with bone and meningeal metastasis in patients who were unresponsive to trastuzumab and chemotherapy.92 This can be attributed to the fact that lapatinib can cross the blood–brain barrier unlike larger antibodies.93 Furthermore, lapatinib is also a more suitable option than trastuzumab for patients at risk of cardiac events.93 Nevertheless, it is still at the stage of clinical trials. Afatinib and neratinib are other potential TKIs,72,73 although there are no clinical studies related to GC.

Antibody-Drug Conjugates
The combination of anti-HER-2 antibodies with effective drugs or cellular immunotherapy can effectively ablate HER-2-overexpressing tumors. T-DM1 or T-DM1 is a HER-2-targeting ADC that consists of a stable thioether linker between trastuzumab and the cytotoxic agent maytansine, and is currently in phase III development for HER-2 positive cancer.94 The efficacy and toxicity of T-DM1 were established in patients with HER-2 mutant lung adenocarcinoma,95 and a subsequent study in patients with GC indicated stronger anti-cancer activity compared to trastuzumab.96 However, the randomized, open-label, adaptive Phase 2/3 GATSBY trial reported a similar efficacy of T-DM1 and taxane in previously treated patients with HER-2 positive advanced GC.74 Furthermore, most patients with HER2-positive BC or GC exhibited primary or acquired resistance to T-DM1.20,97 XMT-1522 is another HER-2 ADC that was found to be effective against T-DM1 resistant HER-2 positive BC and GC cell lines, as well as xenograft models.98

DS-8201a is an ADC specific to HER-2 that consists of a human monoclonal antibody connected to a topoisomerase I inhibitor through a cleavable peptide-based linker.99 The most recently developed HER-2-targeting ADCs include SUY9D985 and ARX788. SYD985 couples a duocarmycin payload with trastuzumab,99 and ARX788 is a proprietary version of the monomethyl auristatin F payload connected via a non-cleavable linker.77 SYD985 has not been studied in GC, while ARX788 has shown antitumor effects in preclinical models of T-DM1 resistant HER-2 positive GC.77,100 Currently, more anti-HER-2 ADCs have been developed that can potentially overcome drug resistance and improve therapeutic outcomes in patients with GC.

Bispecific Antibodies
The fusion of two recombinant antibodies into bispecific antibodies (BsAbs) can achieve dual-targeting function.101 ZW25 (azymetric) is a BsAb specific for two HER-2 epitopes, the trastuzumab-binding ECD4 and pertuzumab-binding ECD2, and is effective and well tolerated in patients with various HER-2 positive cancers.75 However, its role in GC needs to be further explored. MCLA-128 is a full-length humanized IgG1 BsAb with enhanced antibody-dependent cell-mediated cytotoxicity (ADCC), targeting HER-2 and HER-3.102 It has been shown to be effective against HER-2 positive GC and GEJC.79,103 The BsAb Mm-111 targets HER-2 and HER-3, and its binding to HER-3 blocks protein binding and inhibits modulin-activated HER-3 signaling.104 McDonagh et al showed that the combination of Mm-111 with trastuzumab or lapatinib improved antitumor activity, and may supplement existing HER-2 targeted therapies against drug-resistant or recurrent tumors.105 Triad or quadruple antibodies against tumor-specific antigens are also being developed to benefit more patients.

CAR-T Cell Immunotherapy for GC
CAR-T cell immunotherapy uses genetically engineered T cells to eliminate tumor cells expressing specific antigens.106 CAR-T cells were developed two decades ago and have since been divided into four generations based on the structure of intracellular signal transduction regions. Gross et al107 first proposed the concept of CAR-T therapy in 1989 and successfully constructed the first-generation CAR by combining the single-chain fragment variable (scFv) monoclonal antibody with immunoreceptor tyrosine-based activation motifs (ITAMs) like CD3ζ and FcεRIγ.108 The second-generation CAR was constructed by Finney et al and consists of a costimulatory domain that can overcome the poor T cell amplification and cytokine production of first-generation CARs.109 The third-generation CAR was generated by combining two tandem costimulatory molecules to further enhance the effector function and in vivo persistence of the T cells.110 Fourth-generation CAR-T cells were engineered to secrete a large number of cytokines into the tumor site to activate the innate immune response and enhance the antitumor effect.111 The current status of CAR-T cell therapy against GC has been summarized in Figure 3A.
Several clinical trials are ongoing worldwide on first-, second-, and third-generation CAR-T cells targeting CD19, B7-1/B7-2, CD155, CEA, CLDN 18.2, EGFR, EpCAM, FOLR1, HER-2, HVEM, ICAM-1, LSECtin, MSLN, MUC1, NKG2D, PD-L1, PSCA and so on. Details are summarized in Table 2. The GC-related targets for CAR-T cell therapy are highlighted in Figure 3.

**Figure 3** The CAR-T cell therapy and gastric cancer. (A) CAR-T cell treatment procedure for gastric cancer. Patients were assessed for suitability for CAR-T therapy, and mononuclear cells were isolated from patient blood using a peripheral blood cell separator, and T cells were further purified by magnetic beads. The T cells are genetically engineered by introducing a viral vector expressing the chimeric antigen receptor that recognizes tumor antigens, and the engineered CAR-T cells are expanded in vitro and injected back into the body. (B) Targets of CAR-T cells in gastric cancer.

**CAR-T Targets in GC**

Several clinical trials are ongoing worldwide on first-, second-, and third-generation CAR-T cells targeting CD19, B7-1/B7-2, CD155, CEA, CLDN 18.2, EGFR, EpCAM, FOLR1, HER-2, HVEM, ICAM-1, LSECtin, MSLN, MUC1, NKG2D, PD-L1, PSCA and so on. Details are summarized in Table 2. The GC-related targets for CAR-T cell therapy...
include CLDN 18.2, FOLR1, HER-2, ICAM-1, MSLN, NKG2D, PD-L1 and PSCA (Figure 3B), and have been discussed in greater detail in the following sections. However, most clinical trials on CAR-T cell therapy have been on lymphoid leukemia, a considerable number of which have reported that CD19-targeting CAR-T cells can alleviate or even cure refractory and relapsed B-cell malignancies with a complete response (CR) rate of >80%. In recent years, CAR-T cells against hematoma antigens such as CD22, CD30, CD36 and CD123 have also been studied in clinical trials. For other solid tumors, tumor-associated antigens (TAAs) rather than tumor-specific antigens are the preferred targets for CAR-T cell therapy. The clinical studies on CAR-T cell therapy against solid tumors are listed in Table 3.

### Table 2 Tumor-Associated Receptors of CAR-T Cell Target

| Receptor | Full Name | Related Diseases | References |
|----------|-----------|------------------|------------|
| B7-1/B7-2 | Cluster of differentiation (CD) 80/CD86 | B-Cell Malignancies | [117,118] |
| CA125 | Cancer antigen 125 (also known as MUC16) | Epithelial ovarian cancers | [119] |
| CAIX | Carbonic anhydrase IX | Renal cell carcinoma; glioblastoma. | [120,121] |
| CD19 | Cluster of differentiation 19 (also known as T-cell surface antigen leu-12) | B-cell acute lymphoblastic leukemia; acute lymphoblastic leukemia | [122,123] |
| CD23 | Cluster of differentiation 22 | B-cell acute lymphoblastic leukemia; acute lymphoblastic leukemia | [59,124] |
| CD133 | Cluster of differentiation 133 (also known as prominin-1) | Glioblastoma; leukemia; hepatocellular carcinoma; gastric cancer | [125–128] |
| CD155 | Cluster of differentiation 155 | Thymus | [129] |
| CEA | Carinoembryonic antigen | Colorectal cancers; pancreatic malignancy; liver metastases; solid tumors | [130–133] |
| CLDN 18.2 | Claudin 18.2 | Gastric Cancer; solid tumors; pancreatic cancer | [134–136] |
| CTAG1B | Cancer/testis antigen 1B (also known as NY-ESO-1) | Melanoma and ovarian cancer | [137] |
| EGFR | Epidermal growth factor receptor | Central nervous system; rhabdomyosarcoma; Breast cancer; gastric cancer; non-small-cell lung cancer; epithelial carcinoma | [138–141] |
| EGFRvIII | Variant III of the epidermal growth factor receptor | Glioblastoma | [142] |
| EpCAM | Epithelial cell adhesion molecule | Acute myeloid leukemia; hepatocellular carcinoma | [143,144] |
| FAP | Fibroblast activation protein | Pancreatic cancers; Malignant pleural mesothelioma | [145,146] |
| FOLR1 | Folate receptor 1 | Gastric cancer | [147] |
| FR-α | Folate receptor-α | Breast cancer; ovarian cancer | [148,149] |
| GD2 | Disialoganglioside 2 | Neuroblastoma, melanoma | [150,151] |
| GPC3 | Glypican-3 | Mesothelin; hepatocellular carcinoma | [152,153] |
| HER-2 | Human epidermal growth factor receptor 2 | Gastric cancer; ovarian cancer; breast cancer, glioblastoma, colon cancer, osteosarcoma, medulloblastoma | [139,154–159] |
| HVE M | Herpes Virus Entry Mediator | Lymphoma | [160] |
| ICAM-1 | Intercellular adhesion molecule 1 | Breast cancer; gastric cancer | [161,162] |
| IL13Ra2 | Interleukin-13Ra2 | Glioma | [163] |
| L1-CAM | L1 cell adhesion molecule | Neuroblastoma, melanoma, ovarian adenocarcinoma | [164,165] |
| LSECtin | Liver sinusoidal endothelial cell lectin | Liver inflammatory diseases | [166] |
| MSLN | Mesothelin | Mesothelioma; ovarian cancer, pancreatic adenocarcinoma | [167–169] |
| MUC1 | Mucin 1 | Cholangiocarcinoma; seminal vesicle cancer | [170,171] |
| NKG2D | Natural killer group 2D | Cervical cancer; breast cancer; prostate cancer | [172–174] |
| PD-L1 | Programmed death ligand 1 | Non-small-cell lung cancer; gastric cancer; breast cancer | [175–177] |
| PSCA | Prostate stem-cell antigen | Gastric cancer; prostate cancer | [178,179] |
| PSMA | Prostate-specific membrane antigen | Prostate cancer; solid tumors | [180,181] |
**Table 3** CAR-T Related Clinical Studies in Solid Tumors

| Receptor | Clinical Trial Phase | NCT No. | Tumor Types | Patients | Study Arms | Period | Median OS (m/95% CI) | References |
|----------|----------------------|---------|-------------|----------|------------|--------|----------------------|------------|
| CD133    | II                   | 02541370| HCC         | 21       | CD133-CAR-T | 2015.06–2017.09 | 12 (9.3–15.3) | [126]       |
| CEA      | I                    | 02349724| CRC         | 10       | CEA-CAR-T   | 2014.12–2018.12 | 7.2 (3.5–11)  | [132]       |
| CEA      | I                    | 01373047| Liver       | 8        | CEA-CAR-T   | 2011.06–2013.07 | 3.75 (2–25.5) | [182]       |
| c-Met    | 0                    | 01837602| BC          | 6        | c-Met-CAR-T | 2013.04–2018.08 | 7.2 (3.5–11)  | [183]       |
| EGFR     | I                    | 03182816| NSCLC       | 9        | EGFR-CAR-T  | 2013.07–2018.06 | 15.63 (8.82–22.03) | [184]       |
| EGFR     | I                    | 01869166| Metastatic PC | 16       | EGFR-CAR-T  | 2015.04–2019.05 | 4.9 (2.9–30)  | [185]       |
| FAP      | I                    | 01722149| Metastatic MPM | 16       | FAP-CAR-T   | 2015.02–2019.07 | 2NF          | [186]       |
| MUC1     | I                    | 02587689| Metastatic SVC | 20       | MUC1-CAR-T  | 2006–2015.02    | 2NF          | [171]       |
| PSMA     | I                    | NF      | Prostate cancer | 6        | PSMA-CAR-T  | 2008.09–2010.04 | 2NF          | [187]       |
| HER-2    | I                    | 01935843| BTCs/PC     | 11       | HER-2-CAR-T | 2015.07–2016.06 | 4.8 (1.5–8.3) | [188]       |
| HER-2    | I/II                 | 00902044| Sarcoma     | 19       | HER-2-CAR-T | 2010.06–2013.09 | 10.3 (5.1–29.1) | [154]       |

Abbreviations: BC, breast cancer; BTCs, biliary tract cancers; CAR-T, chimeric antigen receptor T; CD, cluster of differentiation; CEA, carcino-embryonic antigen; CI, confidence interval; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; FAP, fibroblast activation protein; GC, gastric cancer; HCC, hepatocellular carcinoma; HER, human epidermal growth factor receptor; MPM, malignant pleural mesothelioma; MUC1, mucin 1; NSCLC, non-small cell lung cancer; PC, pancreatic carcinoma; PSMA, prostate-specific membrane antigens; SVC, seminal vesicle cancer. OS, overall survival; m, month; NCT, national clinical trial; NF, not found.

**CLDN 18.2**

CLDN 18, a member of the CLAUDIN (CLDN) family, is encoded by the CLDN 18 gene and is expressed in the epithelium. CLDN 18.2, the second isotype of Claudine 18, is located in the extracellular membranes. It is usually expressed in primary GC tumors but may also be present in differentiated gastric mucosal epithelial cells. CLDN 18.2 is expressed in 70% of the primary and metastatic gastric adenocarcinomas, and therefore is considered as a potential therapeutic target in GC. Hua Jiang et al found that CLDN18.2-CAR-T cells are effective against CLDN18.2 positive tumors, including GC. Besides, Guoyun Zhu et al indicated that targeting CLDN 18.2 through ADCs or BsAbs may be effective against GC and pancreatic cancer.

**FOLR1**

FOLR1 (folic acid receptor 1), also known as folic acid receptor α and folate-binding protein, is a glycosylphosphatidylinositol junction protein that is closely related to tumor progression and cell proliferation. It is overexpressed in the tumors of ovarian, breast, colorectal, kidney, lung, and other solid tumors, and is present at low levels in normal cells. As reported, FOLR1 is highly expressed in about one-third of patients with GC, and FOLR1-CAR-T cells have exhibited high anti-cancer activity in preclinical studies.

**ICAM-1**

ICAM-1 (intercellular cell adhesion molecule-1) belongs to the immunoglobulin superfamily of glycoproteins and mediates cell–cell and cell-matrix adhesion. It is overexpressed in various cancers, including GC, and is associated with poor survival. Recently, Min IM et al reported encouraging results with anti-ICAM-1 CAR-T cells in thyroid tumor models. In addition, the strategy of anti-ICAM-1 CAR-T cells with or without chemotherapy has been found to be promising for the treatment of ICAM-1+ patients with advanced GC.
MSLN
Mesothelin (MSLN) is a membrane protein (40 kDa) that is expressed in normal epithelial tissues and highly upregulated in breast, lung, pancreas, ovary, mesothelioma, and gastric tumor cells.\textsuperscript{201,203} MSLN-specific CAR-T cells have been engineered for solid cancers, including mesothelioma, pancreatic cancer, BC, lung cancer and GC.\textsuperscript{202,204–206} Jiang LV et al found that a peritumoral delivery strategy improved the infiltration of anti-MSLN CAR-T cells into a subcutaneous GC xenograft, which significantly inhibited tumor growth.\textsuperscript{202} Besides, Zhang Q et al discovered that MSLN-CAR-T cells reduced the growth of MSLN-positive tumor cells by significantly increasing the levels of T cells and cytokines.\textsuperscript{207} In addition, the growth of GC cells can also be inhibited by anti-MSLN-CAR-T cells,\textsuperscript{208} indicating its potential as a therapeutic option against GC.

NKG2D Receptor
Natural killer group 2 member D (NKG2D) receptor is a lectin-like transmembrane glycoprotein that is expressed primarily in natural killer (NK) cells, CD8\textsuperscript{+} T cells and auto-immunosuppressed CD4\textsuperscript{+} T cells.\textsuperscript{209} NKG2D is expressed at low levels or entirely absent in normal tissues or cells, although its expression increases rapidly in response to pathogens, genotoxic drugs, or malignant transformation of cells.\textsuperscript{210} Therefore, NKG2D is a potentially suitable target for CAR-T cell therapy. In addition, Spear et al found that NKG2D-specific CAR-T cells not only killed the tumor cells directly but also activated the host immune system.\textsuperscript{211} At present, NKG2D-targeting CAR-T cells have been proved to be effective against multiple myeloma,\textsuperscript{212} glioblastoma,\textsuperscript{213} and hepatocellular carcinoma.\textsuperscript{214} Furthermore, the up-regulation of NKG2D levels in GC cells can sensitize them to NKG2D-CAR-T cells-mediated cytotoxicity.\textsuperscript{215} The currently ongoing clinical trials of CAR-T cells targeting NKG2D, including those in patients with GC, are expected to be completed in 2021 (NCT04107142).

PD-L1
Programmed death ligand 1 (PD-L1) is a member of the B7 family and the ligand of PD-1.\textsuperscript{216,217} It is composed of 290 amino acids\textsuperscript{218} and is expressed on the surface of several tumor cells, including lung cancer,\textsuperscript{219} BC,\textsuperscript{220} and GC.\textsuperscript{221} Chimeric switch receptor PD-L1 can enhance the function of CAR-T cells in solid tumors.\textsuperscript{222,223} CAR-T cells targeting PD-L1 effectively suppressed the growth of GC patient-derived xenograft (PDX) in animal models.\textsuperscript{224} Further research revealed the killing effect of PD-L1 on GC, therefore improving the killing effect of CAR-T cells in GC.\textsuperscript{177}

PSCA
Prostate stem cell antigen (PSCA) is a glycosyl-phosphatidylinositol cell immobilized by a face protein that belongs to the Thy-1/Ly-6 family.\textsuperscript{225} Existing evidence has indicated that PSCA-CAR-T cells are effective against metastatic prostate cancer and non-small cell lung cancer (NSCLC).\textsuperscript{178,226} In vivo experiments have shown that PSCA-CAR-T cells inhibited the growth of prostate cancer PDX and extended the survival of tumor-bearing mice.\textsuperscript{227} A Phase I clinical trial was initiated to evaluate PSCA-CAR-T cells in patients with relapsed and refractory metastatic prostate cancer.\textsuperscript{228} In addition, Di Wu et al have confirmed the feasibility of anti-PSCA-CAR-T cells against GC,\textsuperscript{179} suggesting a potential clinical application.

HER-2-Specific CAR-T Cells in the Treatment of GC
Construction of HER-2-Targeted CAR
The CAR targeting HER-2 consists of an extracellular antigen-binding region, a transmembrane region, and an intracellular signal transduction region.\textsuperscript{229,230} The extracellular antigen-binding region is composed of a single-chain variable fragment (scFv) and the hinge region of the anti-HER-2 monoclonal antibody.\textsuperscript{231} The variable weight chain and the variable weight chain constitute the scFv,\textsuperscript{232} which recognizes and binds to the TAAs on the surface of tumor cells.\textsuperscript{233} In addition, it determines the specificity of CAR antigens and can bind to multiple TAAs in an MHC-independent, non-restrictive manner.\textsuperscript{234,235} IL13Ra2 can also be combined with HER-2 on the surface of tumor cells by CAR-T cells, further enhancing their activation.\textsuperscript{236} The transmembrane region is involved in signal transduction, although it is unclear whether it also has an effect on the structure and biochemistry of CAR.\textsuperscript{237} Finally, CAR-T cells can also increase the immune response by releasing tumor cell killing factors. The details of the process are illustrated in Figure 4.
Advances in HER-2-Targeted CAR-T Cell Therapy for GC

Current immunotherapeutic strategies against GC include nonspecific immunoboosters, tumor vaccines, adoptive cell transfer, and monoclonal antibodies. The HER-2 signaling pathway is a key target of the adoptive immune cell therapy against solid tumors. Although several HER-2 targeted drugs have entered clinical trials for patients with GC, the FDA has approved only trastuzumab for first-line treatment of patients with advanced GC. In addition, HER-2-targeted CAR-T cell therapy for GC is increasingly gaining attention to avoid drug resistance and improve treatment outcomes.

Song et al produced genetically modified human T cells that express HER-2-specific CAR consisting of CD137 and CD3ζ, which not only recognized and killed HER-2+ GC cells in vitro but also showed effective and persistent antitumor activity against HER-2+ GC xenografts in vivo. This suggested that HER-2-targeted CAR-T cells might be suitable for the treatment of advanced HER-2+ GC, although their toxicity and immunogenicity will have to be verified in future trials. Furthermore, the focus of future studies would be to improve the antitumor activity of HER-2 targeted CAR-T cells by improving their proliferation capacity, function and persistence.

Ahmed et al constructed the second generation of HER-2-targeted CAR composed of FRP5-CD28-CD3ζ, and found that CAR-T cells had high affinity for HER-2 monoclonal antibody and specifically recognized and killed HER-2+ glioblastoma cells. HER-2-specific T cells have also been found to be effective against HER-2+ osteosarcoma cells. Sun et al successfully constructed a novel humanized chA21-28z CAR consisting of a chA21 single-chain variable region and an intracellular signal transduction region containing CD28 and CD3ζ. The CD4+ and CD8+...
CAR-T cells\textsuperscript{248} recognized and killed HER-2\textsuperscript{+} ovarian cancer cells in vitro and significantly inhibited the growth of xenografts in mice.\textsuperscript{248} Taken together, HER-2 targeted CAR-T cell immunotherapy for GC can be further improved.

Current Status of Clinical Research on HER-2-CAR-T Therapy

HER-2-targeted CAR-T cell therapy is currently in the preclinical stage for GC, while clinical trials are underway for other solid tumors (summarized in Table 4). Ahmed et al administered high-dose HER-2-CAR-T cells to 10 patients with recurrent or refractory HER-2 positive sarcomas (5 osteosarcomas, 3 rhabdomyosarcomas, and 1 synovial sarcomas) who had received myeloablative therapy (fludarabine or fludarabine plus cyclophosphamide) and found that the combination of HER-2-CAR-T cells with other immunomodulatory agents cleared the tumors.\textsuperscript{154} The efficacy of CAR-T-HER-2 immunotherapy has also been demonstrated against tumors of the central nervous system,\textsuperscript{139} rhabdomyosarcoma,\textsuperscript{138} biliary tract cancers and pancreatic cancer.\textsuperscript{188} In addition, results of a phase I clinical trial indicated that the EGFR-CAR-T cell therapy was feasible and safe for patients with EGFR positive advanced NSCLC.\textsuperscript{184} Similar results were observed in patients with pancreatic carcinoma.\textsuperscript{185} O’Rourke et al suggested that overcoming adaptive changes in the local TME and addressing antigenic heterogeneity might improve the efficacy of EGFR variant III (EGFRvIII)-targeted strategies against glioblastoma.\textsuperscript{249} At present, more than 20 clinical trials are being conducted for HER-2-CAR-T therapy (Table 5), of which 2 are related to GC.

The Safety of HER-2-CAR-T

There are several concerns about HER-2-targeted CAR-T cell therapy. Side effects of CAR-T cell therapy include systemic toxicity associated with T cell activation and cytokine release, as well as local toxicity caused by the specific interaction between target antigens expressed by non-malignant cells and CAR-T cells.\textsuperscript{250,251} To avoid systemic toxicity while maintaining clinical efficacy, CAR-T cells should be injected at a threshold that activates cytokine secretion but not above the level that induces a cytokine storm.\textsuperscript{252} The degree of CAR-T cell activation is influenced by tumor burden, tissue distribution and antigen expression, affinity of the scFv to the antigen and the costimulatory elements included in the CAR.\textsuperscript{250,253} Therefore, tumor burden and antigen expression/distribution should be considered when designing CARs to reduce the risk of systemic toxicity. For instance, HER-2 is not a tumor-specific antigen and is also expressed in normal tissues.\textsuperscript{254,255} One study reported that patients with metastatic colon cancer developed acute respiratory distress and pulmonary edema 15 minutes after receiving HER-2-specific CAR-T cells, followed by multiple organ failure and even death, suggesting off-tumor effects caused by CAR-T cells that recognize HER-2 expressed in normal lung tissues.\textsuperscript{256} Differences in binding sites between various scFv and HER-2 might...
| NCT No. | Tumor                          | Phase | Study Title                                                                 | Locations                                                                                     | EE | Period            | Status       |
|---------|--------------------------------|-------|-----------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|----|------------------|--------------|
| 04650451 | Gastric cancer, breast cancer, et al | I/II  | Safety and Activity Study of HER2-Targeted Dual Switch CAR-T Cells (BPX-603) in Subjects with HER2-Positive Solid Tumors | City of Hope National Medical Center Duarte, California, United States; Winship Cancer Institute at Emory University Atlanta, Georgia, United States, John Theurer Cancer Center, Hackensack University Medical Center Hackensack, New Jersey, United States, The University of Texas MD Anderson Cancer Center Houston, Texas, United States | 220 | 2020.12–2021.04  | Recruiting   |
| 04511871 | Gastric cancer, breast cancer, et al | I     | A Phase I Trial of CCT303-406 in Patients with Relapsed or Refractory HER2 Positive Solid Tumors | Zhongshan Hospital Affiliated to Fudan University Shanghai, Shanghai, China | 15 | 2020.07–2023.04  | Recruiting   |
| 03198052 | Lung cancer                     | I     | HER2/Mesothelin/Lewis-Y/PSCA/MUC1/GPC3/AXL/EGFR/B7-H3/Claudin 18.2-CAR-T Cells Immunotherapy Against Cancers | The First Affiliated Hospital of Sun Yat-sen University Guangzhou, Guangdong, China; the Second Affiliated Hospital of Guangzhou Medical University Guangzhou, Guangdong, China | 30 | 2017.07–2023.08  | Recruiting   |
| 02442297 | Brain tumor                     | I     | T Cells Expressing HER2-specific Chimeric Antigen Receptors (CAR) for Patients with HER2-Positive CNS Tumors | Houston Methodist Hospital Houston, Texas, United States; Texas Children's Hospital Houston, Texas, United States | 28 | 2016.02–2036.01  | Recruiting   |
| 03500991 | Pediatric glioma, et al         | I     | HER2-specific CAR T Cell Locoregional Immunotherapy for HER2-positive Recurrent/Refractory Pediatric CNS Tumors | Seattle Children's Hospital; Seattle, Washington, United States | 48 | 2018.04–2021.03  | Recruiting   |
| 03696030 | BC, et al                       | I     | HER2-CAR T Cells in Treating Patients with Recurrent Brain or Leptomeningeal Metastases | City of Hope Medical Center; Duarte, California, United States | 39 | 2018.08–2023.08  | Recruiting   |
| 04684459 | Peritoneal cancer Bladder Cancer, et al | I     | Dual-targeting HER2 and PD-L1 CAR-T for Cancers with Pleural or Peritoneal Metastasis | West China Hospital, Sichuan University Chengdu, Sichuan, China | 18 | 2021.03–2024.01  | Active       |
| 03740256 | Pediatric solid tumor, et al     | I     | Binary Oncolytic Adenovirus in Combination with HER2-Specific Autologous CAR VST, Advanced HER2 Positive Solid Tumors | Baylor St. Luke's Medical Center Houston, Texas, United States | 45 | 2020.12–2038.12  | Recruiting   |
| 03618381 | Pediatric solid tumor, et al     | I     | EGFR806 CAR T Cell Immunotherapy for Recurrent/ Refractory Solid Tumors in Children and Young Adults | Seattle Children's Hospital Seattle, Washington, United States | 36 | 2019.06–2038.06  | Recruiting   |
| 04430595 | Breast cancer                   | I/II  | Multi-4SCAR-T Therapy Targeting Breast Cancer | The Seventh Affiliated Hospital, Sun Yat-Sen University Shenzhen, Guangdong, China | 100 | 2020.06–2023.12  | Recruiting   |
| 04483778 | Pediatric solid tumor, et al     | I     | B73 CAR T Cell Immunotherapy for Recurrent/Refractory Solid Tumors in Children and Young Adults | Seattle Children's Hospital Seattle, Washington, United States | 68 | 2020.07–2040.12  | Recruiting   |
| Trial Number | Disease Type  | Phase | Intervention                                                                 | Location                                                                                                                                  | EE  | Start Date       | Status       |
|--------------|--------------|-------|------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|-----|-----------------|--------------|
| 04020575     | Breast cancer| I     | Autologous huMNC2-CAR44 T Cells for Breast Cancer Targeting Cleaved Form of MUC1 (MUC1*) | City of Hope Medical Center Duarte, California, United States                                                                           | 69  | 2020.01–2035.01 | Active       |
| 04660929     | Solid tumors | I     | CAR-macrophages for the Treatment of HER2 Overexpressing Solid Tumors         | City of Hope National Medical Center Duarte, California, United States; UNC Lineberger Comprehensive Cancer Center Chapel Hill, North Carolina, United States; Abramson Cancer Center Philadelphia, Pennsylvania, United States | 18  | 2021.02–2023.02 | Recruiting   |
| 02792114     | Breast cancer| I     | T-Cell Therapy for Advanced Breast Cancer                                    | Memorial Sloan Kettering Cancer Center Basking Ridge, New Jersey, United States; Memorial Sloan Kettering Monmouth Middletown, New Jersey, United States; Memorial Sloan Kettering Bergen Montvale, New Jersey, United States; Memorial Sloan Kettering Cancer Center at Commack Commack, New York, United States; Memorial Sloan Kettering Westchester Harrison, New York, United States; Memorial Sloan Kettering Cancer Center New York, New York, United States; Memorial Sloan Kettering Nassau Uniondale, New York, United States | 186 | 2016.06–2022.06 | Active       |
| 03423992     | Glioma       | I     | Personalized Chimeric Antigen Receptor T Cell Immunotherapy for Patients with Recurrent Malignant Gliomas | Xuanwu Hospital Beijing, China                                                                                                           | 100 | 2018.03–2023.01 | Recruiting   |
| 04995003     | Sarcoma      | I     | HER2 Chimeric Antigen Receptor (CAR) T Cells in Combination with Checkpoint Blockade in Patients with Advanced Sarcoma | Texas Children's Hospital Houston, Texas, United States                                                                                   | 25  | 2021.12–2040.02 | Not yet recruiting |
| 00902044     | Sarcoma      | I     | Her2 Chimeric Antigen Receptor Expressing T Cells in Advanced Sarcoma         | Houston Methodist Hospital Houston, Texas, United States; Texas Children's Hospital Houston, Texas, United States                           | 36  | 2010.02–2032.07 | Active       |
| 03330961     | Leukemia; lymphoma | I     | A Feasibility and Safety Study of Dual Specificity CD19 and CD22 CAR-T Cell Immunotherapy for CD19+CD22+ Leukemia | Children's Hospital Los Angeles Los Angeles, California, United States; Children's National Medical Center Washington, District of Columbia, United States; Riley Hospital for Children Indianapolis, Indiana, United States; Seattle Children's Hospital Seattle, Washington, United States; Children's and Women's Health Centre of British ColumbiaActive, Vancouver, British Columbia, Canada. | 60  | 2017.11–2034.11 | Recruiting   |
| 04903080     | Ependymoma   | I     | HER2-specific Chimeric Antigen Receptor (CAR) T Cells for Children with Ependymoma | Pediatric Brain Tumor Consortium Texas Children’s Cancer Center Baylor College of Medicine                                              | 50  | 2021.09–2040.07 | Recruiting   |
| 03684889     | Leukemia; lymphoma | I/ II | CD19-specific CAR T Cells with a Fully Human Binding Domain for CD19+ Leukemia or Lymphoma | Children's Hospital Los Angeles Los Angeles, California, United States; Seattle Children's Hospital Seattle, Washington, United States          | 16  | 2018.11–2036.12 | Active       |

Note: The table data were downloaded from NIH; US National Library of Medicine. ClinicalTrials.gov [homepage]; 2022. Available at: https://www.clinicaltrials.gov/; 2022. Accessed July 11, 2022.

Abbreviations: AXL, anexelekto; CAR-T, chimeric antigen receptor T; CD, cluster of differentiation; CNS, central nervous system; EE, estimated enrollment; GPC3, glypican 3; HER, human epidermal growth factor receptor; MUC1, mucin 1; NCT, national clinical trial; PD-L1, programmed death ligand-1; PSMA, prostate-specific membrane antigen.
influence the antitumor and off-tumor effects of HER-2 blockade by CAR-T cell cells. Luo et al selected HER-2 and CD3-targeted CAR-T cells to reduce the damage to normal tissues. The route to administer CAR-T cells is another factor that affects toxicity. Katz et al found that the intraperitoneal rather than the intravenous injection of CAR-T cells had a stronger effect on peritoneal metastasis and ascites, along with less toxicity. Thus, the improvement of the safety level is a prerequisite for the clinical translation of HER-2-CAR-T cell therapy.

CAR-T cell therapy has been widely used to treat hematologic malignancies, but its use is limited in solid tumors due to factors, such as low penetration. Incorporation of the tumor-penetrating signal peptide iRGD can improve the penetration of HER-2-CAR-T cells and therefore improve their efficacy. The novel CAR design is also a viable direction for HER-2-specific CAR-T cell therapy. The HER-2 binding domain of HER-2-CAR-T cells is not limited to scFv; the designed ankyrin repeat protein (DARPin) has also been used to bind HER-2 in other tumors. Several novel DARPin molecules with high affinity to HER-2 receptor have been developed, including MP0274, DARPin 9.26, DARPin 9.29, etc. In addition, CAR-modified NK cells, cytokine-induced killer (CIK) cells, and γδ T cells are other promising cell-based options. CAR-NK and CAR-CIK cells targeting HER-2 have achieved good efficacy against BC and glioblastoma multiforme, and are expected to be introduced into the treatment of HER-2 positive GC.

**Conclusion**

HER-2-targeted drugs were initially developed for BC and have since been extended to other HER-2-overexpressing tumors, such as stomach and gastroesophageal cancers. The first-generation HER-2 monoclonal antibody of trastuzumab is still the first-line treatment for GC, despite the high rate of drug resistance. The second generation of pertuzumab has not been extensively studied in GC patients. The conjugation of HER-2 antibodies to novel cytotoxic drugs such as T-DM1 was deemed promising for the treatment of HER-2 overexpressing tumors. However, studies showed that most patients with BC or GC exhibited primary or acquired resistance to T-DM1. Although the HER-2-targeting TKI lapatinib has achieved a good effect in BC, it has not been effective against GC. Bispecific antibodies with dual-targeting functions have also shown encouraging results, but further research is still needed. In short, these HER-2-targeted therapies may obviate the resistance to first-line drugs, reduce metastasis or prevent recurrence, and may also be used in combination with chemoradiotherapy and monoclonal antibodies to further improve first-line therapy in patients with GC.

CAR-T cells are a highly promising immunotherapeutic approach for ablating solid tumors. However, the efficacy of HER-2-targeted CAR-T therapy in GC needs to be supported by large-scale, multi-center and high-quality randomized clinical trials and evidence-based studies before full-scale clinical application. Given inherent heterogeneity, immunosuppressive TME and antigen migration, single target CAR-T cell immunotherapy cannot achieve ideal outcomes. Future researches on HER-2-CAR-T therapy in GC may focus on the following aspects: 1) upgrading the structural design of CARs to improve antitumor activity and migration capacity, as well as constructing CARs to target multiple antigens; 2) exploring more therapeutic subsets of T cells to reduce tumor immune escape; 3) reversing the immunosuppressive TME (for example, PD-L1/PD-L2 blockade) and enhancing CAR-T cell proliferation and cytokine production; 4) adjusting and optimizing treatment regimens to minimize CAR-T cell-induced adverse reactions. Therefore, with the continuous development of genetic engineering technology, HER-2-CAR-T cell therapy will become a safe and effective treatment for GC and other solid tumors in the future.

**Disclosure**

The authors report no conflicts of interest in this work.

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