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Antibody-Coupled Drugs in HER2-Positive Gastric Cancer

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Abstract

Antibody drug conjugates (ADCs) are a new class of drugs that combine chemosynthetic drugs with antibody drugs through a linker. Antibody drug conjugates combine the targeting characteristics of traditional antibody drugs with the cytotoxic characteristics of small molecule drugs, while reducing the side effects of both drugs, making them a kind of "biological missile" and representing a relatively new and evolving class of anti-cancer drugs. Antibody-coupled drugs are currently used in many solid tumors, and this article reviews the clinical application of antibody-coupled drugs in HER2-positive gastric cancer.

Keywords

Antibody-Coupled Drugs, HER2-Positive Gastric Cancer, Review

1. HER2-ADC Drug Targets

EGFR (epidermal growth factor receptor) is one of the anticancer drug targets for certain malignancies. HER2 (Human Epidermal Growth Factor Receptor 2, ErbB2, c-erB2, ERBB2), a member of the EGFR family, also known as Human Epidermal Growth Factor Receptor 2 (ERBB2), is a proto-oncogene encoding a transmembrane receptor-like HER2 protein that initiates a signaling pathway by aberrant tyrosine kinase expression, leading to deregulation of cell proliferation, differentiation, and vascular and lymphatic vasculature generation [1]. ERBB2 alterations, including mutations, amplification and overexpression [2], are also known. The oncogenic role of *ERBB2 amplification* is now well established in breast and gastric cancers [3] [4]. Activating mutations in the ERBB2 gene are increasingly reported in a variety of solid cancers and have been shown to have similar oncogenic effects to *ERBB2 amplification* [5] [6] [7]. Inhibition of HER2

by targeting can effectively prolong the life cycle of patients with HER2-positive gastric cancer, as demonstrated by the TOGA (Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer) trial. However, many patients eventually progressed after treatment due to resistance to HER2 targeted therapy [8], and the emergence of drug resistance led to a new wave of exploration of targeted therapy, and novel antibody-drug coupling technologies and new linker-payload systems were applied and born to address the drug resistance problem to some extent [9] [10]. Antibody drug conjugates consist of three main components: the monoclonal antibody responsible for selective recognition and targeting of the tumor + the linker connecting the antibody to the payload + the payload (payload, currently often a small molecule cytotoxic drug), respectively. It also brings benefits to patients with advanced solid tumors expressing HER2 mutations [11]. Currently, HER2 targets are the more established targets for ADC drugs in many solid tumors and are also the targets with the highest number of drugs currently under investigation.

2. Clinical Application of HER2-ADC in HER2-Positive Gastric Cancer

2.1. Clinically Approved ADCs

2.1.1. Trastuzumab Deruxtecan (T-DXd, DS-8201a)

Prior to the DESTINY-Gastric01 study of T-DXd, there were no other globally recognized HER2-targeted agents for gastric cancer (GC) that progressed after trastuzumab. T-DM1 (trastuzumab emtansine, kadcyla) was the first ADC drug to explore the efficacy of treatment for advanced gastric cancer, and phase II/III clinical studies GATSBY included 415 patients with HER2-positive advanced gastric cancer or adenocarcinoma of the gastroesophageal junction treated with T-DM1 or paclitaxel in second line. Median overall survival was 7.9 and 8.6 months (P = 0.86), median progression-free survival was 2.7 and 2.9 months (P = 0.31) in the T-DM1 and paclitaxel treatment groups, respectively. The GATSBY study showed that T-DM1 was not superior to paclitaxel in the second-line treatment of HER2-positive advanced gastric cancer [12]. The reason for its failure to succeed in the treatment of advanced gastric cancer is that the linker is not cleavable, resulting in the inability of the carrier drug to cross the cell membrane, which does not have a bystander effect and therefore cannot overcome tumor heterogeneity. T-DXd has received much attention in recent years and has been beneficial in several gastroesophageal adenocarcinoma (GEA) studies. The DESTINY-Gastric01 [13] results showed an ORR of 51.3% vs 14.3% for the T-DXd group and the physician's choice chemotherapy group, respectively. The DCR was 86% and 62% for the two groups, and the median DoR was 11.3 and 3.9 months, respectively. The median PFS was 5.6 and 3.5 months in both groups, and the PFS rates at 6 and 12 months were 43% vs. 21% and 30% vs. 0%, respectively. And, median OS was significantly longer in the T-DXd group compared to the physician's choice chemotherapy group, 12.5 and 8.4 months in

both groups, with 6- and 12-month OS rates of 80% vs 66% and 52% vs 29%, respectively. Of the 119 patients treated with T-DXd, 10 patients achieved complete remission (CR), while no patients in the physician's choice chemotherapy group achieved CR. more than 80% and approximately 50% of patients in the T-DXd and physician's choice chemotherapy groups, respectively, had tumor shrinkage. Similar benefits were shown in most subgroup analyses. t-DXd demonstrated antitumor activity in patients with HER2-positive advanced gastric cancer (AGC). Moreover, it can penetrate neighboring tumor cells that do not necessarily express HER2 or have low expression (bystander antitumor effect), allowing T-DXd to be a potential treatment for patients with low HER2 tumors, as explored in the DESTINY-Gastric02 anti-HER2-treated patients with HER1 low (IHC 2+/ISH- or IHC 01+) gastric/GEJ adenocarcinoma cohort has been demonstrated [14]. T-Dxd can also be applied in patients with advanced HER2 mutation expressing solid tumors [11], and it is expected that more evidence will be generated for T-Dxd against HER2 mutated gastric cancer as well, which will be a boon for patients with advanced solid tumor mutations. T-DXd is currently evaluated for the treatment of HER2-positive and low HER2-expressing breast cancer, HER2-overexpressing colorectal cancer, HER2-positive gastric cancer, and non-small cell lung cancer expressing HER2 or mutations, with a particular focus here on possible combination strategies of T-DXd with other agents (e.g., immunotherapy, chemotherapy, and targeted therapies) to increase T-DXd activity and ultimately overcome future impending drug resistance mechanisms [15]. The DESTINY-Gastric03 study evaluating T-DXd for first-line therapy, the DESTINY-Gastric04 study evaluating head-to-head the efficacy of T-DXd for second-line therapy, the DESTINY-Gastric06 study with a sample of our patients, and the use in neoadjuvant phase therapy (NCT05034887) are currently We are looking forward to the publication of the results.

2.1.2. Vedicitumomab (RC48)

RC48, which consists of Hertuzumab (humanized anti-HER2 monoclonal antibody) coupled to monomethyl auristatin E (MMAE) via a cleavable linker, is an ADC drug developed in China. With a DAR of approximately 4, the drug carrier is membrane-permeable and therefore also possesses bystander effects. The safety and tolerability of RC-48 in HER-2-positive solid tumors have been evaluated in clinical trials [16]. The phase II study C008 trial suggested that RC48 resulted in an ORR of 24.8% and a median OS of 7.9 months in patients with HER2-positive GEA who had previously received ≥ 2 lines of therapy [17], has been approved for the backline treatment of HER2 overexpressing gastric cancer and gastroesophageal junction cancer [18]. The results of the RC48 phase I study for the treatment of HER2 low-expressing GC showed that the antitumor response in HER2 IHC2+/FISH- patients was similar to that in IHC2+/FISH+ and IHC3+ patients, with significant cancer shrinkage achieved in 72.7%, 60.0% and 52.6% of patients, respectively [19]. For the present study, it can be concluded that RC48 has an anticancer effect in patients with HER2 low-expressing GC.

The antitumor activity of RC48 in her2 gastric cancer has been confirmed, and further exploration of its indication population, combination extension protocols is needed. The combination of RC48 with immune checkpoint inhibitors in a human homozygous breast cancer model expressing HER2 resulted in immune marker activation and massive T cell infiltration enhanced tumor suppression and anti-tumor immunity [20]. This combination therapy may exhibit better antitumor activity in HER2-positive gastric cancer, but more clinical trials are needed to validate it.

2.2. ADCs That Have Not Yet Been Approved

2.2.1. Dual Anti-ADC

ZW25 (Zanidatamab) is a novel bispecific antibody that binds to two unlinked epitopes of HER2. This antibody effectively inhibits HER2 activity and doubly blocks HER2 signaling within the cell, thus acting as an anti-cancer agent [21]. Earlier the FDA has granted ZW25 as fast-track therapy for first-line gastroesophageal adenocarcinoma and as an orphan drug for the treatment of gastric and ovarian cancers. In clinical phase I, 69 HER2+ solid tumors received ZW25 (20 mg/kg, Q2W or 10 mg/kg, Q1W) in a median of 3 lines of therapy, and the included cancer types included biliary tract cancer, gastric/gastroesophageal cancer, and CRC, 59% of patients had received HER2-targeted therapy (up to 93% in gastric/gastroesophageal cancer), with an overall patient ORR of 44% (25/69) and DCR 70%, safely tolerated, and major adverse effects were G1-2, manifested as nausea, diarrhea, and infusion reactions [19] (NCT02892123). (https://beta.clinicaltrials.gov/). In patients with gastric/gastroesophageal cancer who had received median 3 lines of therapy in clinical phase II (75% treated with trastuzumab), the single-agent ORR was 33% and mDOR 6 months; it further improved patient response after combination chemotherapy, with an ORR of 54% and mDOR 8.9 months. Phase II study of ZW25 in HER2 amplified biliary tract cancer is in enrollment trial and results are pending [22] (NCT04466891) (https://beta.clinicaltrials.gov/).

ZW49 (Zanidatamab Zovodotin) another novel bispecific antibody-drug coupling (ADC), composed by adding the toxin MMAE to Zanidatamab, uses the former's enhanced antibody internalization to deliver the toxin to tumor cells and induce tumor cell death. The first human dose escalation (DE) and dose extension (DX) studies for the treatment of patients with locally advanced or metastatic HER2-positive cancers are ongoing, with an ORR of 31% and a disease control rate (DCR) of 72% for multiple cancer types identified in 29 patients with assessable efficacy treated with ZW49 2.5 mg/kg Q3W [23]. The ZW49 1.75 mg/kg QW dose level in the DE cohort continues to be recruited and the 1.5 mg/kg QW dose in the DX cohort continues to be recruited [24].

Our self-developed bispecific antibody KN026 (anti-HER2 bispecific antibody) in combination with KN046 (PD-L1/CTLA-4 bispecific single-domain antibody) for HER2-positive solid tumors was announced at SITC with a disease

control rate of 92.9% (13/14) and an objective remission rate of 64.3% (9/14), based on which the US Food Drug Administration (FDA) granted it as an orphan drug for the treatment of HER2-positive or HER2-low-expressing gastric cancer and gastroesophageal junction cancer (GC/GEJ) [24]. Several clinical trials are currently underway in China and the United States in various stages for indications including breast cancer, gastric/gastroesophageal junction cancer, etc. Two registration clinical studies are underway for KN026 in combination with chemotherapy and KN026 in combination with KN046 without chemotherapy for gastric cancer.

Other innovative developments of HER2 dual antibodies such as MBS301, SCTB72, JSKN003, KM501, TQB2102, etc. have entered the development study. In addition, the development of CD3 and PD-1 and Her2 bispecific antibodies has become a hot spot. In China, CD3/Her2, PD-1/Her2 bispecific antibodies, such as MQ0127, M802, IBI-315, have been developed respectively.

2.2.2. ARX788

ARX788 is a novel antibody-coupled drug. ARX788 recognizes and enters HER2-positive tumor cells and releases the microtubule protein inhibitor pAF-AS269, which induces tumor cell growth arrest and death to achieve antitumor effects. The ACE-Gastric-01 study is a phase I dose extension trial in China of trastuzumab in patients with HER2-positive advanced gastric cancer. A phase I dose-expansion trial in patients was conducted in China to evaluate the safety, tolerability, PK profile and antitumor activity of ARX788. A total of 30 patients were enrolled in the study, nine treated with ARX788 at 1.3 mg/kg, 14 at 1.5 mg/kg, and seven at 1.7 mg/kg. Four patients (13.3%) experienced grade ≥ 3 drug-related adverse events (TRAE), including ocular adverse events, interstitial lung disease (ILD), anemia, and elevated glutamyl transferase levels. The duration of remission in the total population was 8.4 months, with an objective remission rate of 37.9%, progression-free survival of 4.1 months, and overall survival of 10.7 months [9].

2.2.3. Other Unapproved ADC Drugs

SYD985 is a novel HER2-targeted antibody-coupled drug, which is a combination of trastuzumab and a drug containing duocarmycin (betacamycin). Clinical trials for SYD985 for advanced breast, endometrial, gastric and other solid tumors are currently underway, and phase I results showed a remission rate of 6% for advanced gastric cancer [25]. On July 18, 2023, the European Medicines Agency (EMA) accepted trastuzumab duocarmazine (SYD985) marketing application for the treatment of patients with unresectable HER2-positive locally advanced or metastatic breast cancer. The indication of SYD985 in HER2-positive gastric cancer needs to be further explored. XMT1522 and MED14276, which are still in clinical phase in the article by Wang Na [26], have both been declared suspended from clinical trials by the FDA due to safety reasons.

2.2.4. Degradate-Antibody Coupled (DAC) Drugs

In recent years, researchers have successfully developed degradate-antibody coupling (DAC) in combination with target protein degradation (TPD) for more effective delivery of chemotherapeutic drugs, and this coupled drug not only allows selective delivery but also improves the therapeutic index of toxins [27] [28]. DAC is one of the most promising new paradigms in medicinal chemistry. DAC drugs targeting BRD4, STEAP1, Era, and BRM are in the development stage [29] [30]. In conclusion, this DAC drug paradigm greatly overcomes the various problems faced by PROTAC (protein degradation targeted chimeras) and promises to be a drug candidate for the treatment of many human diseases. We need to continue to optimize the existing degradation technology to challenge more difficult to target "hard to drug" targets, improve druggability and achieve clinical translation.

3. Summary and Prospect

This paper summarizes the HER2-ADC drugs marketed and in clinical trials and finds that they have antitumor activity in HER2-positive gastric cancer, but still need to be validated by a large amount of clinical evidence. However, as more and more therapeutic targets are tapped for ADC candidates, the prospects for ADC development are greatly increased, including the diversity of targets, indications, and combinations of different coupling and linker options. Undeniably, among all these ADC targets, HER2 has become a fertile ground for antibody-coupled drug hunters, and antibody-coupled drugs for HER2 targets may not yet reach saturation, and given the expanding clinical candidates and the continued development of trastuzumab biomimetics, as well as the potential for ADC biosimilars, research on antibody-coupled drugs for HER2 will continue to rise. It is believed that as technology advances, these antibody-coupled drug agents will significantly improve patient survival in the treatment of Her2-positive tumors.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Hayes, D.F. (2019) HER2 and Breast Cancer—A Phenomenal Success Story. *New England Journal of Medicine*, **381**, 1284-1286. https://doi.org/10.1056/NEJMcibr1909386

[2] Yan, M., Schwaederle, M., Arguello, D., Millis, S.Z., Gatalica, Z. and Kurzrock, R. (2015) HER2 Expression Status in Diverse Cancers: Review of Results from 37,992 Patients. *Cancer and Metastasis Reviews*, **34**, 157-164. https://doi.org/10.1007/s10555-015-9552-6

[3] Najjar, S. and Allison, K.H. (2022) Updates on Breast Biomarkers. *Virchows Archiv*, **480**, 163-176. https://doi.org/10.1007/s00428-022-03267-x

[4] Kanayama, K., Imai, H., Usugi, E., Shiraishi, T., Hirokawa, Y.S. and Watanabe, M.

(2018) Association of *HER*2 Gene Amplification and Tumor Progression in Early Gastric Cancer. *Virchows Archiv*, **473**, 559-565. https://doi.org/10.1007/s00428-018-2433-y

[5] Subramanian, J., Katta, A., Masood, A., Vudem, D.R. and Kancha, R.K. (2019) Emergence of *ERBB*2 Mutation as a Biomarker and an Actionable Target in Solid Cancers. *The Oncologist*, **24**, e1303-e1314. https://doi.org/10.1634/theoncologist.2018-0845

[6] Sato, H., Offin, M., Kubota, D., Yu, H.A., Wilhelm, C., SToyooka, S., Somwar, R., Kris, M.G. and Ladanyi, M. (2021) Allele-Specific Role of ERBB2 in the Oncogenic Function of *EGFR* L861Q in *EGFR*-Mutant Lung Cancers. *Journal of Thoracic Oncology*, **16**, 113-126. https://doi.org/10.1016/j.jtho.2020.09.019

[7] Van Bockstal, M.R., Agahozo, M.C., van Marion, R., Atmodimedjo, P.N., Sleddens, H.F.B.M., Dinjens, W.N.M., Visser, L.L., Lips, E.H., Wesseling, J. and van Deurzen, C.H.M. (2020) Somatic Mutations and Copy Number Variations in Breast Cancers with Heterogeneous *HER*2 Amplification. *Molecular Oncology*, **14**, 671-685. https://doi.org/10.1002/1878-0261.12650.

[8] Yonesaka, K. (2021) HER2-/HER3-Targeting Antibody-Drug Conjugates for Treating Lung and Colorectal Cancers Resistant to EGFR Inhibitors. *Cancers*, **13**, Article No. 1047. https://doi.org/10.3390/cancers13051047

[9] Skidmore, L., Sakamuri, S., Knudsen, N.A., Hewet, A.G., Milutinovic, S., Barkho, W., *et al.* (2020) ARX788, a Site-Specific Anti-HER2 Antibody-Drug Conjugate, Demonstrates Potent and Selective Activity in HER2-Low and T-DM1-Resistant Breast and Gastric Cancers. *Molecular Cancer Therapeutics*, **19**, 1833-1843. https://doi.org/10.1158/1535-7163.MCT-19-1004

[10] Gandullo-Sánchez, L., Capone, E., Ocaña, A., Iacobelli, S., Sala, G. and Pandiella, A. (2020) HER3 Targeting with an Antibody-Drug Conjugate Bypasses Resistance to Anti-HER2 Therapies. *EMBO Molecular Medicine*, **12**, e11498. https://doi.org/10.15252/emmm.201911498

[11] Tsurutani, J., Iwata, H., Krop, I., Jänne, P.A., Doi, T., Takahashi, S., Park, H., *et al.* (2020) Targeting HER2 with Trastuzumab Deruxtecan: A Dose-Expansion, Phase I Study in Multiple Advanced Solid Tumors. *Cancer Discovery*, **10**, 688-701. https://doi.org/10.1158/2159-8290.CD-19-1014

[12] Thuss-Patience, P.C., Shah, M.A., Ohtsu, A., Van Cutsem, E., Ajani, J.A., Castro, H., Mansoor, W., Chung, H.C., Bodoky, G., Shitara, K., Phillips, G.D.L., van der Horst, T., Harle-Yge, M.L., Althaus, B.L. and Kang, Y.-K. (2017) Trastuzumab Emtansine Versus Taxane Use for Previously Treated HER2-Positive Locally Advanced or Metastatic Gastric or Gastro-Oesophageal Junction Adenocarcinoma (GATSBY): An International Randomised, Open-Label, Adaptive, Phase 2/3 Study. *The Lancet Oncology*, **18**, 640-653. https://doi.org/10.1016/S1470-2045(17)30111-0

[13] Shitara, K., Bang, Y.J., Iwasa, S., Sugimoto, N., Ryu, M.H., Sakai, D., Chung, H.-C., Kawakami, H., Yabusaki, H., Lee, J., Saito, K., Kawaguchi, Y., Kamio, T., Kojima, A., Sugihara, M. and Yamaguchi, K. (2020) Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer. *New England Journal of Medicine*, **382**, 2419-2430. https://doi.org/10.1056/NEJMoa2004413

[14] Shitara, K., *et al.* (2019) Trastuzumab Deruxtecan (DS-8201a) in Patients with Advanced HER2-Positive Gastric Cancer: A Dose-Expansion, Phase 1 Study. *The Lancet Oncology*, **20**, 827-836. https://doi.org/10.1016/S1470-2045(19)30088-9

[15] von Arx, C., De Placido, P., Caltavituro, A., *et al.* (2023) The Evolving Therapeutic Landscape of Trastuzumab-Drug Conjugates: Future Perspectives beyond HER2-Positive Breast Cancer. *Cancer Treatment Reviews*, **113**, Article ID: 102500.

https://doi.org/10.1016/j.ctrv.2022.102500

[16] Shi, F., Liu, Y., Zhou, X., Shen, P., Xue, R. and Zhang, M. (2022) Disitamab Vedotin: A Novel Antibody-Drug Conjugates for Cancer Therapy. *Drug Delivery*, **29**, 1335-1344. https://doi.org/10.1080/10717544.2022.2069883

[17] Peng, Z., Liu, T., Wei, J., Wang, A., He, Y., Yang, L., Zhang, X., *et al.* (2021) Efficacy and Safety of a Novel Anti-HER2 Therapeutic Antibody RC48 in Patients with HER2-Overexpressing, Locally Advanced or Metastatic Gastric or Gastroesophageal Junction Cancer: A Single-Arm Phase II Study. *Cancer Communications*, **41**, 1173-1182. https://doi.org/10.1002/cac2.12214

[18] Deeks, E.D. (2021) Disitamab Vedotin: First Approval. *Drugs*, **81**, 1929-1935. https://doi.org/10.1007/s40265-021-01614-x

[19] Xu, Y., Wang, Y., Gong, J., Zhang, X., Peng, Z., Sheng, X., Mao, C., *et al.* (2021) Phase I Study of the Recombinant Humanized Anti-HER2 Monoclonal Antibody-MMAE Conjugate RC48-ADC in Patients with HER2-Positive Advanced Solid Tumors. *Gastric Cancer*, **24**, 913-925. https://doi.org/10.1007/s10120-021-01168-7

[20] Huang, L., Wang, R., Xie, K., Zhang, J., Tao, F., Pi, C., Feng, Y., Gu, H. and Fang, J. (2022) A HER2 Target Antibody Drug Conjugate Combined with Anti-PD-(L)1 Treatment Eliminates HHER2+ Tumors in HPD-1 Transgenic Mouse Model and Contributes Immune Memory Formation. *Breast Cancer Research and Treatment* **191**, 51-61. https://doi.org/10.1007/s10549-021-06384-4

[21] (2019) ZW25 Effective in HER2-Positive Cancers. *Cancer Discovery*, **9**, 8. https://doi.org/10.1158/2159-8290.CD-NB2018-162

[22] Meric-Bernstam, F., *et al.* (2022) Zanidatamab, a Novel Bispecific Antibody, for the Treatment of Locally Advanced or Metastatic HER2-Expressing or HER2-Amplified Cancers: A Phase 1, Dose-Escalation and Expansion Study. *The Lancet Oncology*, **23**, 1558-1570. https://doi.org/10.1016/S1470-2045(22)00621-0

[23] Jhaveri, K., *et al.* (2022) Preliminary Results from a Phase I Study Using the Bispecific, Human Epidermal Growth Factor 2 (HER2)-Targeting Antibody-Drug Conjugate (ADC) Zanidatamab Zovodotin (ZW49) in Solid Cancers. *Annals of Oncology*, **33**, S749-S750. https://doi.org/10.1016/j.annonc.2022.07.589

[24] Gong, J., Shen, L., Dong, Z., Liu, D., Xu, J., Yang, J., Yang, Y., *et al.* (2020) 810 Preliminary Safety, Tolerability and Efficacy Results of KN026 in Combination with KN046 in Patients with HER2 Aberrated Solid Tumors. *Journal for ImmunoTherapy of Cancer*, **8**, A485-A486. https://doi.org/10.1136/jitc-2020-SITC2020.0810

[25] Banerji, U., van Herpen, C.M.L., Saura, C., Thistlethwaite, F., Lord, S., Moreno, V., Macpherson, I.R., Boni, V., Rolfo, C., de Vries, E.G.E., Rottey, S., Geenen, J., Eskens, F., Gil-Martin, M., Mommers, E.C., Koper, N.P. and Aftimos, P. (2019) Trastuzumab Duocarmazine in Locally Advanced and Metastatic Solid Tumours and HER2-Expressing Breast Cancer: A Phase 1 Dose-Escalation and Dose-Expansion Study. *The Lancet Oncology*, **20**, 1124-1135. https://doi.org/10.1016/S1470-2045(19)30328-6

[26] Wang, N., Wang, Z.W., Mei, Q.Y., Zhao, L., Zhang, D. and Kong, F.M. (2022) Research Progress of Clinical Application of Antibody-Coupled Drugs in HER2-Positive Gastric Cancer. *Chinese Cancer Clinics*, No. 19, 1009-1014. (In Chinese)

[27] Dragovich, P.S. (2022) Degrader-Antibody Conjugates. *Chemical Society Reviews*, **51**, 3886-3897. https://doi.org/10.1039/D2CS00141A

[28] Hong, K.B. and An, H. (2023) Degrader-Antibody Conjugates: Emerging New Modality. *Journal of Medicinal Chemistry*, **66**, 140-148. https://doi.org/10.1021/acs.jmedchem.2c01791

[29] Dragovich, P.S., Pillow, T.H., Blake, R.A., Sadowsky, J.D., Adaligil, E., Adhikari, P., Chen, J., Corr, N., Dela Cruz-Chuh, J., Del Rosario, G., Fullerton, A., Hartman, S.J., Jiang, F., Kaufman, S., Kleinheinz, T., Kozak, K.R., Liu, L., Lu, Y., Mulvihill, M.M., Murray, J.M., O'Donohue, A., Rowntree, R.K., Sawyer, W.S., Staben, L.R., Wai, J., Wang, J., Wei, B., Wei, W., Xu, Z., Yao, H., Yu, S.F., Zhang, D., Zhang, H., Zhang, S., Zhao, Y., Zhou, H. and Zhu, X. (2021) Antibody-Mediated Delivery of Chimeric BRD4 Degraders. Part 2: Improvement of *in Vitro* Antiproliferation Activity and *in Vivo* Antitumor Efficacy. *Journal of Medicinal Chemistry*, **64**, 2576-2607. https://doi.org/10.1021/acs.jmedchem.0c01846

[30] Dragovich, P.S., Adhikari, P., Blake, R.A., Blaquiere, N., Chen, J., Cheng, Y.X., den Besten, W., Han, J., Hartman, S.J., He, J., He, M., Rei Ingalla, E., Kamath, A.V., Kleinheinz, T., Lai, T., Leipold, D.D., Li, C.S., Liu, Q., Lu, J., Lu, Y., Meng, F., Meng, L., Ng, C., Peng, K., Lewis Phillips, G., Pillow, T.H., Rowntree, R.K., Sadowsky, J.D., Sampath, D., Staben, L., Staben, S.T., Wai, J., Wan, K., Wang, X., Wei, B., Wertz, I.E., Xin, J., Xu, K., Yao, H., Zang, R., Zhang, D., Zhou, H. and Zhao, Y. (2020) Antibody-Mediated Delivery of Chimeric Protein Degraders Which Target Estrogen Receptor Alpha (ERα). *Bioorganic & Medicinal Chemistry Letters*, **30**, Article ID: 126907. https://doi.org/10.1016/j.bmcl.2019.126907