Commentary

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Bispecific Antibodies in Gastric Cancer Therapeutics: New Hope for High Efficacy and Tolerability

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Bispecific antibodies represent a new weapon in the solid tumor oncology armamentarium. In gastric cancer, where available targeted therapies are restricted to a minority of patients, bispecific antibodies may provide much needed new targeted options. This commentary discusses the main constructs and targets of bispecific antibodies in development for gastric cancer.

Keywords: bispecific; biparatopic; cadonilimab; givastomig; zanidatamab

Bispecific Constructs and Concepts of Targeting

Progress in recombinant DNA technologies have allowed for the development of structurally complex molecular constructs as targeted drugs [1]. Antibody scaffolds paired with recombination strategies allow currently for the discovery and evaluation of antibody based structures that can target more than one epitope. Bispecific antibodies target two different epitopes either in the same or in different target proteins. Modifications in the structures, as well as introduction of point mutations, disulfide bonds and glycosylations, can affect the pharmacokinetics of the constructs and optimize therapeutic targeting [1]. Specificity for two antigens with single chain antibody-like constructs can also be achieved with single chain variable Fragments (scFv) and diabodies.

Biscpecific antibodies have progressed to clinical use in hematologic malignancies and, more recently, four bispecific antibodies have been approved for solid tumors by the FDA [2]. Amivantamab, a bispecific antibody blocking Epidermal Growth Factor Receptor (EGFR) and cellular Mesenchymal to Epithelial Transition (MET) receptor has been approved and has been used in Non-Small Cell Lung Cancer (NSCLC) with EGFR exon 20 insertions and other EGFR mutations [3]. A more recent approval concerns the bispecific T cell engager tarlatamab, with a specificity for receptor delta-like ligand 3 (DDL3) and for Cluster of Differentiation (CD3), for previously treated extensive stage Small Cell Lung Cancer (SCLC) [4]. The bispecific biparatopic anti-Human EGFR family Receptor 2 (HER2) antibody zanidatamab is the third approval in the group, with an indication in biliary cancer and tebemtafusp is approved for uveal melanoma [5]. Beyond these approvals in lung and biliary cancers and uveal melanoma, no other bispecific antibodies are used in the western countries but additional approvals, including for other gastrointestinal cancers, have been granted in China, where a lot of pre-clinical and clinical research has been in progress, as discussed next. A prominent concept in bispecific antibody development is engaging the immune system by serving as a bridge between immune effectors and target cells expressing specific proteins that are not immune receptors. Other bispecific antibodies engage two immune receptors with the goal to maximize beneficial effects in immune attack of tumor cells. A third concept involves non-immune targets in tumor cells with the goal to maximize tumor cell targeting specificity and anti-tumor efficacy by direct targeting or antibody-mediated cytotoxicity.

Immune Checkpoint Bispecific Antibodies

A prominent bispecific antibody category uses proteins that play roles in the immune system as targets of both specificities. Cadonilimab (formerly known as AK104) is a lead drug in this category. It is a tetravalent bispecific antibody targeting immune receptors Programmed Death 1 (PD-1) and Cytotoxic T Lymphocyte Antigen 4 (CTLA-4) and it is investigated in several solid tumors. Cadonilimab is approved in China for later line therapy of metastatic uterine cervix cancers and more recently for the first line treatment of metastatic gastric and gastroesophageal junction carcinomas [6]. The construct combines a classic monoclonal antibody with PD-1 specificity, linked through its heavy chains with 2 scFv with anti-CTLA-4 specificity [7]. In unresectable or metastatic gastric and gastroesophageal junction carcinomas, a phase 3 multicenter, randomized trial, performed in China compared chemotherapy with or without cadonilimab as a first line therapy [8]. The trial enrolled 610 patients, with about three fourths being male and suffering from gastric cancer, while one fourth had gastroesophageal junction carcinomas. About half of the pa-

tients in the trial had a Combined Positive Score (CPS) for Programmed Death Ligand 1 (PD-L1) below 5. The trial showed an improvement of Overall Survival (OS) in the entire population with the addition of cadonilimab (Hazard Ratio (HR): 0.66, 95% confidence interval (CI): 0.54–0.81). The benefit was more pronounced in the groups with CPS above 5 (HR: 0.58, 95% CI: 0.41–0.82), but an OS benefit was also observed in the group with CPS below 5 (HR: 0.75, 95% CI: 0.56–1.00). In another exploratory sub-group analysis, male patients appeared to benefit more by the addition of cadonilimab to chemotherapy (OS HR: 0.61, 95% CI: 0.48–0.77 versus HR: 0.90, 95% CI: 0.59–1.37 in females). The addition of cadonilimab was overall well tolerated but there was an increase in serious adverse events from 21.7% in the placebo/chemotherapy arm to 30.5% in the chemotherapy/cadonilimab arm [8]. These led to discontinuation of treatment in 5.3% receiving chemotherapy with placebo and in 15.4% of patients receiving chemotherapy and cadonilimab. Consistent with similar observations during treatment with classic immune checkpoint inhibitors, the positive anti-tumor effect of cadonilimab may persist despite discontinuation of the drug due to immune adverse effects [9]. Increased expression of Cluster of Differentiation 74 (CD74), a chaperone for Major Histocompatibility (MHC) II molecules and receptor for cytokine Macrophage Migration Inhibitory Factor (MIF), was correlated with increased immune cell infiltration and better outcomes from cadonilimab treatment [10]. Protocols for incorporating cadonilimab with nab-paclitaxel in the second line treatment of metastatic gastric cancer patients and in the neo-adjuvant setting are on-going [11,12]. A case report with cadonilimab in combination with the small molecule Vascular Endothelial Growth Factor Receptor 2 (VEGFR2) inhibitor apatinib showed a long-lasting partial response in a patient with refractory microsatellite instability (MSI) high gastric cancer [13]. Previous treatment with nivolumab had not been successful in the patient.

Cadonilimab has also been studied in the treatment of early stage gastric and gastroesophageal junction adenocarcinomas [14]. In a phase 2, multicenter study performed in China that included 38 patients with lymph node positive HER2 negative disease, cadonilimab was added to 5-FU, leucovorin, oxaliplatin, docetaxel (FLOT) chemotherapy as a neo-adjuvant treatment for 3 or 4 cycles. Most patients (36 of 38, 94.7%) had microsatellite stable tumors. Complete pathologic response, the primary trial endpoint, was observed in 8 patients (21.1%, 95% CI: 9.7%–32.4%) and 9 additional patients had major pathologic responses, for a major pathologic response rate of 44.7% (95% CI: 30.9%–58.5%). These encouraging results await confirmation in randomized trials in more diverse populations. Optimally, direct prospective comparison of PD-1 and CTLA-4 blockade with cadonilimab will be performed in trials against both PD-1 monotherapy and combinations of the respective monoclonal antibodies.

Bispecific Antibodies Combining Immune Checkpoint Targeting and Non-immune Targets

In this category, Ivonescimab (also known as AK112) is a bispecific antibody blocking PD-1 and Vascular Endothelial Growth Factor A (VEGF-A) which has been developed in China and has received approval in combination with chemotherapy for EGFR mutated NSCLC after failure of EGFR inhibitors [15]. In gastric cancer, a phase 1 trial performed in China examined monotherapy with ivonescimab in 59 pts with various cancers, including 10 patients with gastric and esophageal cancer [16]. Serious adverse effects were rare and efficacy results are awaited.

The bispecific antibody PT886 targeting claudin 18.2 (CLDN18.2) and the macrophage “don’t eat me” inhibitory receptor CD47 is tested in combination with chemotherapy and pembrolizumab in different cohorts of gastric/gastroesophageal and pancreatic cancers in the ongoing signal generating TWINPEAK study [17]. PT886 mediates antibody dependent cellular cytotoxicity and phagocytosis and may synergize with pembrolizumab in invigorating the immune response. CD47 is also one of the targets of the bispecific antibody NILK-2401, with the other target being CEACAM5 (Carcinoembryonic Antigen cell adhesion molecule 5, also called CEA) [18]. This bispecific antibody consists of a heavy chain and two different light chains, a κ light chain with low affinity specificity for CD47 and a λ light chain with specificity for CEACAM5. NILK-2401 showed good tolerability and efficacy against gastric, colorectal and lung cancer cell lines expressing CEACAM5, potentially warranting clinical evaluation [18].

Bispecific T Cell Engagers (BiTEs)

In this type of bispecific antibodies one of the targets is an immune receptor or co-receptor expressed in T lymphocytes and the other target is a non-immune system related protein. BiTEs are designed to bring targeted cells to close proximity with T cells in order to facilitate a cytotoxic interaction. AMG910 is a bispecific antibody binding to CD3 to engage T cells and to claudin 18.2. Preclinical studies in gastric and pancreatic cancer cell lines and mouse xenograft models, both expressing claudin 18.2, showed engagement of T cells with cancer cells and anti-tumor activity was observed [19]. Another BiTE targeting claudin 18.2, givastomig (also known as ABL111) engages T cells through receptor 4-1BB (also known as CD137 or TNFRSF9) instead of CD3 [20]. Development of monoclonal antibodies against 4-1BB was hampered by on target hepatotoxicity, mediated by the activation of the receptor in immune cells in the liver. Givastomig showed both activity and safety in pre-clinical mouse models, as the engagement of 4-1BB and activation of immune cells depends on expression of claudin 18.2 which is tumor cell specific. A dose escalation and expansion phase 1 trial of givastomig in

heavily pretreated (median of 3 previous lines of treatment) patients with metastatic gastroesophageal cancers expressing claudin 18.2 in at least 1%, with at least 1+ intensity, showed a partial response rate (PRR) in 13% and a Disease Control Rate (DCR) in 46.2% of patients [21]. All 5 responders had claudin 18.2 expression in at least 11% of tumor cells.

CC-3, a T cell engager targeting CD3 and the immune receptor B7-H3 (CD276) frequently expressed in gastric, pancreatic and liver cancers is in pre-clinical development, with data from cell lines confirming effectiveness in T cell engagement and activation [22].

NILK-2301 is a CD3 and CEACAM5 bispecific antibody T cell engager with a common heavy chain and two different light chains, a κ light chain with specificity for CEACAM5 and a λ light chain with lower affinity specificity for CD3 [23]. It also includes a mutation that abrogates binding to FcϒR. Preclinical evaluation has been completed *in vitro* and *in vivo*, confirming safety and activity and clinical trials are planned.

Bispecific Antibodies With Non-Immune Targets

In this category of bispecific antibodies, the immune system plays no direct role in the antigen engagement, as the two targets are not expressed in immune cells, but it can still have a role through antibody dependent cytotoxicity. Zanidatamab (previously known as ZW25) is a bispecific antibody targeting two different non-overlapping epitopes (biparatopic) of receptor HER2 and has recently obtained accelerated approval by the FDA for the treatment of HER2 positive metastatic biliary cancers [24]. The drug binds simultaneously to the two epitopes and interferes with HER2 activation. In addition, it induces antibody-dependent cellular cytotoxicity. Given that a sizable minority of gastric cancers display also HER2 positivity, zanidatamab is of interest for this patient population, potentially in combination with other effective therapies [25]. Another anti-HER2 biparatopic bispecific antibody, KN026, has been developed in China. In a phase 2 trial in patients with metastatic gastric and gastroesophageal junction adenocarcinomas, who had previously received 1 or more therapies, KN026 showed an objective response rate (ORR) of 56% (95% CI: 35%–76%) in patients with high level HER2 expression and an ORR of 14% (95% CI: 2%–43%) in patients with low level HER2 expression [26]. KN026 was well tolerated, with the most frequent severe (grade 3 or 4) toxicities being gastrointestinal in 11% of patients. The efficacy signal especially in patients with high HER2 expression warrantees further confirmatory studies.

A new bispecific antibody, HC-2G4S, targeting HER2 and CLDN18.2, both targets of monoclonal antibodies already in use in gastric cancer, is in preclinical development [27]. HC-2G4S compared favorably to monoclonal antibodies and their combination in a gastric cancer tumor spheroid model *in vitro*. Another bispecific antibody in development combined HER2 with the TNFR family receptor CD40 (TNFRSF5), which is implicated in the resistance of gastric cancer cells to HER2 blockade [28]. HER2 and HER3 are targets of a diabody combined with an Fc fragment, which is in preclinical development [29]. The construct was active in mice bearing gastric cell line xenografts.

Targeting of P cadherin (CDH3) together with apoptosis receptor TRAILR2 (also called Death Receptor 5- DR5) by a bispecific antibody was reported in a preclinical study in gastric, pancreatic, colorectal and triple negative breast cancer cell lines [30]. This bispecific antibody combines two identical heavy chains and two identical light chains with binding specificity for CDH3. The construct is linked through a flexible linker through the constant region of the heavy chains to the variable region of a single chain anti-TRAILR2 fragment. Moreover, the construct includes mutations that prevent binding of the FcϒR receptor and of the complement [30]. The antibody was efficient in activating the caspase cascade in cancer cells and xenograft models. The study further examined pancreatic cancer xenografts, which expressed extensively and uniformly the two targeted proteins and were treated with the bispecific antibody, chemotherapy or the combination. The combination of the bispecific antibody with chemotherapy was more effective in tumor reduction and produced longer effects than each component alone [30]. In gastric cancer, P cadherin over-expression may accompany E cadherin loss, an event that results in cancers with diffuse histology [31]. Expression of P cadherin alters the function of adherens junctions and increases cell migration [32]. At the same time, it provides an opportunity for targeted treatment as it endows specificity of action to the CDH3/TRAILR2 bispecific antibodies which require expression of both proteins for triggering the TRAILR2 apoptotic cascade. TRAILR2-induced apoptosis is p53 independent, which is an advantage in gastric carcinomas where p53 inactivating mutations are frequently present in about half of the cases [33,34]. Of note, monospecific TRAILR2 agonistic antibodies have been studied in clinical trials but have shown limited activity [35].

The anti-EGFR/anti-MET bispecific antibody amivantamab was investigated in a phase 2 trial in metastatic gastric and esophageal cancers in later line of therapy [36]. The trial, which was performed in Japan, enrolled patients not selected for either EGFR or MET alterations and was terminated after enrolling 62 patients. The ORR was 4.3% (95% CI: 0.1%–21.9%) in the gastric cancer cohort and 10.7% (95% CI: 2.3%–28.2%) in the esophageal cancer cohort. Median progression free survival (PFS) was 1.4 months in the gastric cancer cohort and 4.1 months in the esophageal cancer cohort. These results suggest that amivantamab has minimal activity as monotherapy in an unselected population of gastric cancer patients but does not ex-

clude the possibility of activity in patients with alterations of the targeted receptors. EGFR amplification is present in about 5% of gastric cancers in The Cancer Genome Atlas (TCGA) cohort and patients with amplification were suggested to derive benefit from the addition of anti-EGFR monoclonal antibodies targeting, in a retrospective analysis [34,37]. MET is amplified in a lower frequency in gastric cancer (2.7% of cases in the TCGA cohort). Whether amivantamab, either as monotherapy or combined with other targeted therapies or chemotherapy, has activity in gastroesophageal cancers selected for alterations in the target receptors remains to be confirmed.

Bispecific Antibody Drug Conjugates

A further development on the bispecific antibody concept combines bispecific antibodies with cytotoxics akin to monoclonal antibody drug conjugates that have been successfully used in the clinic for several years [38]. A drug in pre-clinical development based on this combined concept employs a bispecific antibody targeting two cadherins, P cadherin (CDH3) and LI cadherin (CDH17), which is linked to the cytotoxic agent monomethyl auristatin E (MMAE) [39]. This bispecific antibody drug conjugate (bi-ADC) showed *in vivo* activity in mice against xenografts expressing both cadherins but not against xenografts expressing only one of them. This suggests that the bi-ADC will provide specificity against tumors expressing both cadherins and will minimize adverse effects against normal epithelia not expressing the two targets.

Another adhesion molecule, claudin 18.2 is expressed in high proportion of gastric carcinomas and has been targeted successfully with the monoclonal antibody zolbetuximab [40]. Trials of ADCs targeting claudin 18.2 are in progress and development of bispecific T cell engagers is also pursued by the pharmaceutical industry [41,42].

In conclusion, dual targeting of gastric cancer with bispecific antibodies provides new hope for therapeutic improvement of outcomes in this difficult to treat type of cancer. An ever-growing number of targets and combinations, as well as elegant constructs are in development. Companion biomarkers will be, in this regard, instrumental for the successful drug development and to avoid failure of potentially useful drugs, due to testing in too broad populations, not selected for the targets, which may dilute positive signals. The immune system plays a critical role in the mechanism of action of bispecific antibodies with immune cells activated or brought into tumor cell proximity through bispecific antibody mediation. Even in the case of bispecific antibodies that have no immune receptor targets, immune cell mediated cytotoxicity could be a contributing factor to clinical efficacy. Therefore, developing combinations of bispecific antibodies with conventional cytotoxic chemotherapy presents a theoretical concern regarding immune suppression mediated by chemotherapy, which may interfere with the Immune mediated actions of bispecific antibodies. In this regard, the successful development of combinations of chemotherapy with immune targeting monoclonal antibodies is reassuring, and chemotherapy bispecific antibodies combinations could present incremental efficacy advantages. The bi-ADC concept is an alternative approach which also can benefit from lessons learned by classic monospecific ADCs that are already in clinical use for several years. Optimization of constructs, including linkers and payloads, has improved ADCs and could benefit similar optimization of bi-ADCs for improved targeting and efficacy.

Availability of Data and Materials

Not applicable.

Author Contributions

IAV is the sole contributor in this manuscript. The author confirms sole responsibility for the conception and design of the study, the preparation of the manuscript, and for being accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

The author declares no conflict of interest.

References

[1] Rathi C, Meibohm B. Clinical pharmacology of bispecific antibody constructs. Journal of Clinical Pharmacology. 2015; 55: S21–S28. https://doi.org/10.1002/jcph.445.

[2] Kassner J, Abdellatif B, Yamshon S, Monge J, Kaner J. Current landscape of CD3 bispecific antibodies in hematologic malignancies. Trends in Cancer. 2024; 10: 708–732. https://doi.org/10.1016/j.trecan.2024.06.001.

[3] Guidi L, Etessami J, Valenza C, Valdivia A, Meric-Bernstam F, Felip E, *et al*. Bispecific Antibodies in Hematologic and Solid Tumors: Current Landscape and Therapeutic Advances. American Society of Clinical Oncology Educational Book. 2025; 45: e473148. https://doi.org/10.1200/EDBK-25-473148.

[4] Dhillon S. Tarlatamab: First Approval. Drugs. 2024; 84: 995–1003. https://doi.org/10.1007/s40265-024-02070-z.

[5] Smolenschi C, Blanc JF, Lancry A, Klajer E, Debaillon-Vesque A, Vantelon JM, *et al*. Real-world efficacy of zanidatamab in patients with HER2 positive advanced biliary tract cancers. Eu-

ropean Journal of Cancer. 2025; 222: 115432. https://doi.org/10.1016/j.ejca.2025.115432.

[6] Keam SJ. Cadonilimab: First Approval. Drugs. 2022; 82: 1333–1339. https://doi.org/10.1007/s40265-022-01761-9.

[7] Surowka M, Klein C. A pivotal decade for bispecific antibodies? MAbs. 2024; 16: 2321635. https://doi.org/10.1080/19420862.2024.2321635.

[8] Shen L, Zhang Y, Li Z, Zhang X, Gao X, Liu B, *et al*. First-line cadonilimab plus chemotherapy in HER2-negative advanced gastric or gastroesophageal junction adenocarcinoma: a randomized, double-blind, phase 3 trial. Nature Medicine. 2025; 31: 1163–1170. https://doi.org/10.1038/s41591-024-03450-4.

[9] Lun J, Ma G, Wang X, Wang Q. Good response to cadonilimab as first-line treatment in superaged patient with advanced gastric cancer: a case report. Immunotherapy. 2024; 16: 1015–1019. https://doi.org/10.1080/1750743X.2024.2394405.

[10] Wang J, Li X, Xiao G, Desai J, Frentzas S, Wang ZM, *et al*. CD74 is associated with inflamed tumor immune microenvironment and predicts responsiveness to PD-1/CTLA-4 bispecific antibody in patients with solid tumors. Cancer Immunology, Immunotherapy: CII. 2024; 73: 36. https://doi.org/10.1007/s00262-023-03604-2.

[11] Wei J, Zhang P, Hu Q, Cheng X, Shen C, Chen Z, *et al*. Nab-paclitaxel combined with cadonilimab (AK104) as second-line treatment for advanced gastric cancer: protocol for a phase II prospective, multicenter, single-arm clinical trial. Frontiers in Immunology. 2025; 16: 1519545. https://doi.org/10.3389/fimmu.2025.1519545.

[12] Zhang PF, Zhang WH, Liu XJ, He D, Yang K, Gou HF, *et al*. Chemotherapy combined with cadonilimab (AK104) as neoadjuvant treatment for locally advanced gastric/gastro-oesophageal junction adenocarcinoma: study protocol for a single-arm, phase II clinical trial. BMJ Open. 2024; 14: e081529. https://doi.org/10.1136/bmjopen-2023-081529.

[13] Zhao J, Li X, Sun X, Xiao R, Xue J, Sui K, *et al*. Combination of cadonilimab (PD-1/CTLA-4 bispecific antibody) and apatinib as salvage therapy achieves partial response in MSI-H advanced gastric cancer: a case report. Frontiers in Immunology. 2025; 16: 1533700. https://doi.org/10.3389/fimmu.2025.1533700.

[14] Long B, Zhou H, Yu Z, Zhu J, Yang H, Huang Z, *et al*. Neoadjuvant cadonilimab plus FLOT chemotherapy in locally advanced gastric/gastroesophageal junction adenocarcinoma: A multicenter, phase 2 study. Med. 2025; 6: 100531. https://doi.org/10.1016/j.medj.2024.10.008.

[15] Dhillon S. Ivonescimab: First Approval. Drugs. 2024; 84: 1135–1142. https://doi.org/10.1007/s40265-024-02073-w.

[16] Wang F, Wei X, Zheng Y, Wang J, Ying J, Chen X, *et al*. Safety, Pharmacokinetics, and Pharmacodynamics Evaluation of Ivonescimab, a Novel Bispecific Antibody Targeting PD-1 and VEGF, in Chinese Patients With Advanced Solid Tumors. Cancer Medicine. 2025; 14: e70653. https://doi.org/10.1002/cam4.70653.

[17] Overman MJ, Laeufle R, Singh H, Henry J, Spira AI, Chisamore M, *et al*. TiP TWINPEAK phase I/II study, PT886 a bispecific antibody targeting claudin 18.2 and CD47 in combination with chemotherapy and/or pembrolizumab in gastric/GEJ-carcinomas or PDAC. Annals of Oncology. 2024; 35: S933–S934. https://doi.org/10.1016/j.annonc.2024.08.1594.

[18] Seckinger A, Buatois V, Moine V, Daubeuf B, Richard F, Chatel L, *et al*. Targeting CEACAM5-positive solid tumors using NILK-2401, a novel CEACAM5xCD47 κλ bispecific antibody. Frontiers in Immunology. 2024; 15: 1378813. https://doi.org/10.3389/fimmu.2024.1378813.

[19] Xu Y, Fu J, Henderson M, Lee F, Jurcak N, Henn A, *et al*. CLDN18.2 BiTE Engages Effector and Regulatory T Cells for Antitumor Immune Response in Preclinical Models of Pancreatic Cancer. Gastroenterology. 2023; 165: 1219–1232. https://doi.org/10.1053/j.gastro.2023.06.037.

[20] Gao J, Wang Z, Jiang W, Zhang Y, Meng Z, Niu Y, *et al*. CLDN18.2 and 4-1BB bispecific antibody givastomig exerts antitumor activity through CLDN18.2-expressing tumor-directed T-cell activation. Journal for Immunotherapy of Cancer. 2023; 11: e006704. https://doi.org/10.1136/jitc-2023-006704.

[21] Klempner SJ, Shen L, Liu D, Dayyani F, Kratz J, Pan H, *et al*. Updated safety and efficacy from the phase I study of givastomig, a novel claudin 18.2/4-1BB bispecific antibody, in claudin 18.2 positive advanced gastroesophageal carcinoma (GEC). Annals of Oncology. 2024; 35: S689.

[22] Lutz MS, Zekri L, Weßling L, Berchtold S, Heitmann JS, Lauer UM, *et al*. IgG-based B7-H3xCD3 bispecific antibody for treatment of pancreatic, hepatic and gastric cancer. Frontiers in Immunology. 2023; 14: 1163136. https://doi.org/10.3389/fimmu.2023.1163136.

[23] Seckinger A, Majocchi S, Moine V, Nouveau L, Ngoc H, Daubeuf B, *et al*. Development and characterization of NILK-2301, a novel CEACAM5xCD3 κλ bispecific antibody for immunotherapy of CEACAM5-expressing cancers. Journal of Hematology & Oncology. 2023; 16: 117. https://doi.org/10.1186/s13045-023-01516-3.

[24] Harding JJ, Fan J, Oh DY, Choi HJ, Kim JW, Chang HM, *et al*. Zanidatamab for HER2-amplified, unresectable, locally advanced or metastatic biliary tract cancer (HERIZON-BTC-01): a multicentre, single-arm, phase 2b study. The Lancet. Oncology. 2023; 24: 772–782. https://doi.org/10.1016/S1470-2045(23)00242-5.

[25] Tabernero J, Shen L, Elimova E, Ku G, Liu T, Shitara K, *et al*. HERIZON-GEA-01: Zanidatamab + chemo ± tislelizumab for 1L treatment of HER2-positive gastroesophageal adenocarcinoma. Future Oncology. 2022; 18: 3255–3266. https://doi.org/10.2217/fon-2022-0595.

[26] Xu J, Ying J, Liu R, Wu J, Ye F, Xu N, *et al*. KN026 (anti-HER2 bispecific antibody) in patients with previously treated, advanced HER2-expressing gastric or gastroesophageal junction cancer. European Journal of Cancer. 2023; 178: 1–12. https://doi.org/10.1016/j.ejca.2022.10.004.

[27] Yue J, Shao S, Zhou J, Luo W, Xu Y, Zhang Q, *et al*. A bispecific antibody targeting HER2 and CLDN18.2 eliminates gastric cancer cells expressing dual antigens by enhancing the immune effector function. Investigational New Drugs. 2024; 42: 106–115. https://doi.org/10.1007/s10637-024-01417-3.

[28] Sun W, Wang X, Wang D, Lu L, Lin H, Zhang Z, *et al*. CD40×HER2 bispecific antibody overcomes the CCL2-induced trastuzumab resistance in HER2-positive gastric cancer. Journal for Immunotherapy of Cancer. 2022; 10: e005063. https://doi.org/10.1136/jitc-2022-005063.

[29] Rau A, Kocher K, Rommel M, Kühl L, Albrecht M, Gotthard H, *et al*. A bivalent, bispecific Dab-Fc antibody molecule for dual targeting of HER2 and HER3. MAbs. 2021; 13: 1902034. https://doi.org/10.1080/19420862.2021.1902034.

[30] Jung P, Glaser SP, Han J, Popa A, Pisarsky L, Feng N, *et al*. A TRAILR2/CDH3 bispecific antibody demonstrates selective apoptosis and tumor regression in CDH3-positive pancreatic cancer. MAbs. 2024; 16: 2438173. https://doi.org/10.1080/19420862.2024.2438173.

[31] Barber M, Murrell A, Ito Y, Maia AT, Hyland S, Oliveira C, *et al*. Mechanisms and sequelae of E-cadherin silencing in hereditary diffuse gastric cancer. The Journal of Pathology. 2008; 216: 295–306. https://doi.org/10.1002/path.2426.

[32] São José C, Pereira C, Ferreira M, André A, Osório H, Gullo I, *et al*. 3D Chromatin Architecture Re-Wiring at the *CDH3/CDH1* Loci Contributes to E-Cadherin to P-Cadherin Expression Switch in Gastric Cancer. Biology. 2023; 12: 803.

https://doi.org/10.3390/biology12060803.

[33] Thapa B, Kc R, Uludağ H. TRAIL therapy and prospective developments for cancer treatment. Journal of Controlled Release: Official Journal of the Controlled Release Society. 2020; 326: 335–349. https://doi.org/10.1016/j.jconrel.2020.07.013.

[34] Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014; 513: 202–209. https://doi.org/10.1038/nature13480.

[35] Forero A, Bendell JC, Kumar P, Janisch L, Rosen M, Wang Q, *et al*. First-in-human study of the antibody DR5 agonist DS-8273a in patients with advanced solid tumors. Investigational New Drugs. 2017; 35: 298–306. https://doi.org/10.1007/s10637-016-0420-1.

[36] ClinicalTrials.gov. 2024. Available at: https://www.clinicaltrials.gov/ (Accessed: 29 April 2025).

[37] Maron SB, Moya S, Morano F, Emmett MJ, Chou JF, Sabwa S, *et al*. Epidermal Growth Factor Receptor Inhibition in Epidermal Growth Factor Receptor-Amplified Gastroesophageal Cancer: Retrospective Global Experience. Journal of Clinical Oncology. 2022; 40: 2458–2467. https://doi.org/10.1200/JCO.21.02453.

[38] Aoki Y, Nakayama I, Shitara K. Human Epidermal Growth Factor Receptor 2 Positive Advanced Gastric or Esophagogastric Adenocarcinoma: Reflecting on the Past to Gain a New Insights. Current Oncology Reports. 2025; 27: 15–29. https://doi.org/10.1007/s11912-024-01626-2.

[39] Synan A, Wu NC, Velazquez R, Gesner T, Logel C, Mueller K, *et al*. A bispecific antibody-drug conjugate targeting pCAD and CDH17 has antitumor activity and improved tumor-specificity. MAbs. 2025; 17: 2441411. https://doi.org/10.1080/19420862.2024.2441411.

[40] Voutsadakis IA. Molecular alterations in claudin 18 suppressed and non-suppressed gastric adenocarcinomas to guide targeted therapies. Tissue Barriers. 2025; 13: 2348852. https://doi.org/10.1080/21688370.2024.2348852.

[41] Ruan DY, Liu FR, Wei XL, Luo SX, Zhuang ZX, Wang ZN, *et al*. Claudin 18.2-targeting antibody-drug conjugate CMG901 in patients with advanced gastric or gastro-oesophageal junction cancer (KYM901): a multicentre, open-label, single-arm, phase 1 trial. The Lancet. Oncology. 2025; 26: 227–238. https://doi.org/10.1016/S1470-2045(24)00636-3.

[42] Zhu G, Foletti D, Liu X, Ding S, Melton Witt J, Hasa-Moreno A, *et al*. Targeting CLDN18.2 by CD3 Bispecific and ADC Modalities for the Treatments of Gastric and Pancreatic Cancer. Scientific Reports. 2019; 9: 8420. https://doi.org/10.1038/s41598-019-44874-0.