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Antibody-Mediated Therapy in Gastric Cancer: Past, Present, and Future

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Review

Antibody-Mediated Therapy in Gastric Cancer: Past, Present, and Future

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Abstract

Gastric cancer has historically relied on cytotoxic chemotherapy, yet its considerable mo lecular heterogeneity has limited therapeutic efficacy. The development of antibody-mediated therapies has marked a new era in precision oncology, enabling selective targeting of biomarkers such as HER2, VEGFR2, PD-1/PD-L1, and CLDN18.2. This review summarizes the evolution of antibody-based strategies in gastric cancer, beginning with trastuzumab, the first HER2-targeted treatment, followed by the decade-long stagnation after the failure of T-DM1, and the recent establishment of trastuzumab deruxtecan (T-DXd) as a new standard of care. We further examine advances in anti-angiogenic therapy with ramucirumab, the incorporation of immune checkpoint inhibitors such as nivolumab and pembrolizumab into first-line regimens, and the clinical validation of CLDN18.2, culminating in the approval of zolbetuximab. Emerging modalities—including next-generation antibody–drug conjugates (ADCs), bispecific antibodies, TROP2-directed agents, and CLDN18.2-targeted CAR-T cells—are also discussed. Finally, key challenges such as treatment resistance, real-time biomarker monitoring, and optimal sequencing in multi-biomarker–positive patients are explored. Collectively, antibody-mediated therapy continues to shift gastric cancer management toward increasingly personalized and durable treatment strategies.

Keywords: gastric cancer; antibody-mediated therapy; HER2; VEGFR2; PD-1/PD-L1; CLDN18.2; immune checkpoint inhibitors; antibody–drug conjugates (ADCs); bispecific antibodies

1. Introduction

Since the development of monoclonal antibody (mAb) mass-production technology by Köhler and Milstein in 1975, antibody-mediated therapy has been established as an effective treatment modality, offering high efficacy with minimal adverse events due to its specificity, which allows for selective targeting and destruction of cancer cells based on the presence of specific surface antigens [1,2].

Since the 2000s, the field of oncology has witnessed the advent of rituximab, which targets CD20 in non-Hodgkin's lymphoma, and trastuzumab, which targets HER2 in breast cancer. Targeted therapy, a form of second-generation cancer treatment, has been shown to improve survival rates across various cancers, including blood cancers and solid tumors. Cetuximab, which targets epidermal growth factor receptor (EGFR), and bevacizumab, which targets vascular endothelial growth factor (VEGF), have enhanced survival rates of cancer patients [3–6]. In particular, the primary therapeutic methods used in targeted therapy are classified into two distinct approaches: tyrosine kinase inhibitors (TKIs), which directly inhibit the intracellular tyrosine kinase (TK) domain to block signaling pathways but generally elicit weaker immune responses; and mAbs, which bind to specific antigen receptors on the cell surface to exert their effects; and mAbs, which bind to specific

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antigen receptors outside the cell to exert their effects. Among these, the anticancer effects of therapeutic mAbs—pioneers of antibody-mediated therapy and the focus of this study—can be explained along two major axes. These two mechanisms act in a complementary manner to induce potent anticancer effects [7–8].

The first mechanism entails a direct assault on tumor cells by means of the fragment, antigen-binding region (Fab region) of the antibody. This mechanism has been shown to block receptors, thereby inhibiting downstream signaling pathways that are essential for tumor cell survival and proliferation, resulting in cell death. For instance, trastuzumab exerts its anticancer effect by binding to the HER2 receptor and blocking key cell growth pathways such as PI3K-AKT and RAS–RAF–MEK–ERK [4–9].

The second mechanism involves Fc-mediated immune mobilization, in which antibodies recognize antigens and summon immune cells to the tumor site to induce an attack. Specifically, this mechanism involves antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and antibody-dependent cellular phagocytosis (ADCP), underscoring the conclusion that targeted antibody therapy exhibits immunotherapeutic properties that extend beyond the scope of mere signaling blockade mechanisms [10–12]. Monoclonal antibodies have demonstrated the capacity to expand treatment options for recalcitrant solid tumors by virtue of their multifaceted mechanisms of action. These mechanisms encompass the suppression of the tumor itself and the mobilization of the immune system, thereby establishing a foundation for future research and the advancement of immuno-oncology therapy [13]. Until the early 2000s, various combinations of cytotoxic anticancer drugs have been used for the treatment of gastric cancer. However, no study regimen has achieved a median survival period exceeding 12 months. The limitations of anticancer therapy in gastric cancer can be primarily attributed to drug resistance and the significant molecular biological heterogeneity of gastric tumors. Even though the stomach is a singular organ, the response rates to anticancer drugs vary significantly between individual tumors [14]. Recent advances in molecular biology through the Cancer Genome Atlas (TCGA) project have enabled the classification of gastric cancer into four distinct types: Epstein–Barr virus (EBV)-positive, microsatellite instability-high (MSI-high), genomically stable (GS), and chromosomal instability (CIN). Based on this classification, new antibody therapies have been developed for each type, and research continues to establish standards for them [15].

This review aims to examine the past, present, and future of antibody-mediated therapies for gastric cancer, in the order of HER2, VEGF, PD-L1, and CLDN18.2.

2. Past and Present: Targets that Established the Standard for Gastric Cancer Antibody Therapy

2.1. HER2

The human epidermal growth factor receptor 2 (HER2) is a key target that ushered in the era of antibody-mediated precision medicine in gastric cancer. HER2 was identified as a poor prognostic factor in breast cancer in the late 1980s, prompting research into its potential as a therapeutic target. In 1998, trastuzumab, a mAb targeting HER2, was approved by the FDA, signaling the beginning of targeted anticancer therapy for solid tumors [16,17]. The exploration of HER2's role in cancers other than breast cancer led to the discovery that HER2 overexpression or gene amplification was observed in approximately 15–20% of gastric cancer patients [18]. In 2010, the Trastuzumab for Gastric Cancer (ToGA) study identified HER2 as a key therapeutic target in gastric cancer, initiating the use of antibody-based anticancer therapy for this disease.

The ToGA study compared the effectiveness of combination therapy (standard chemotherapy with 5-fluorouracil and cisplatin plus trastuzumab) versus chemotherapy alone in patients with HER2-positive advanced or metastatic gastric or gastroesophageal junction adenocarcinoma. The trastuzumab combination therapy group demonstrated a statistically significant prolongation of median overall survival (mOS) of 13.8 months, compared to 11.1 months in the control group (HR =

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0.74, p = 0.0046). Notably, combination therapy had a remarkable effect on the HER2 IHC 3+ subgroup, extending mOS up to 16 months. This study was the first to demonstrate an mOS exceeding 12 months in gastric cancer, rendering it significant as the first instance in which molecularly targeted therapy improved survival rates in gastric cancer [19].

Notwithstanding the success of the ToGA study, HER2 antibody-targeted therapy for gastric cancer has encountered numerous limitations over the past decade, failing to demonstrate the same dramatic efficacy seen in breast cancer. The primary reasons for this phenomenon included intratumoral heterogeneity, wherein HER2 expression levels exhibited significant variations within a single tumor, depending on its location. This heterogeneity was observed even in cases where the tumor was initially diagnosed as HER2-positive. Furthermore, treatment resistance emerged from the loss of gene amplification during therapy or the activation of alternative bypass pathways, such as EGFR or MET, which are other growth signaling pathways [18–20]. Subsequent studies sought to address these limitations; however, in contrast to the notable advancements observed in breast cancer research, the majority of efforts in gastric cancer research proved unsuccessful. For instance, lapatinib, a TKI that simultaneously inhibits HER2 and EGFR, which had shown efficacy in breast cancer, failed to demonstrate improved overall survival when combined with chemotherapy in gastric cancer, as shown in the LOGIC study and the TyTAN study targeting Asian patients [21,22]. In the context of breast cancer, antibody-drug conjugates (ADCs) were explored as a novel form of antibody therapy. ADCs entail the targeted delivery of a cytotoxic anticancer drug connected to a monoclonal antibody via a linker to tumor cells, with the objective of eradicating cancerous cells [23,24]. In breast cancer, trastuzumab emtansine (T-DM1) has been established as a subsequent treatment modality following the success of the EMILIA study. However, in gastric cancer, the findings of the GATSBY study (mOS 7.9 months vs 8.6 months; HR= 1.15) similarly rendered HER2 therapy challenging [25]. The failure of T-DM1 in the treatment of gastric cancer underscored the inherent limitations of early-generation ADC technology, including a low drug-to-antibody ratio (DAR) and the absence of a bystander effect due to a non-cleavable linker. This failure provided the impetus for researching new therapeutic approaches [20, 25].

In 2017, early clinical data for trastuzumab deruxtecan (T-DXd), a completely novel ADC, was presented. T-DXd aimed to address the limitations of T-DM1. It combines a payload (topoisomerase I inhibitor) with a high DAR of up to 8, a linker cleavable selectively only within tumor cells, and potent cytotoxicity, while also possessing high cell membrane permeability to enable bystander killing effects capable of eliminating surrounding HER2-low or HER2-negative tumor cells [26]. T-DXd first demonstrated outstanding efficacy in breast cancer based on the 2019 DESTINY-breast results. Subsequently, in gastric cancer, the DESTINY-Gastric01 study involving patients in Japan and South Korea receiving third-line or later treatment showed significantly improved outcomes compared to standard chemotherapy in terms of objective response rate (ORR; 51% vs 14%) and mOS (12.5 months vs 8.4 months; HR=0.59, p<0.001). Consistent efficacy was subsequently replicated in the DESTINY-Gastric02 study involving Western patients [27, 28].

In the recently published DESTINY-Gastric04 Phase 3 study comparing T-DXd with the standard second-line therapy ramucirumab plus paclitaxel in patients with HER2-positive gastric cancer who failed first-line therapy, the T-DXd group significantly improved mOS (14.7 months vs. 11.4 months; HR=0.70, p=0.0044) and progression-free survival (PFS) (6.7 months vs. 5.6 months) in the T-DXd group, demonstrating significant improvement. This advancement has elevated T-DXd to the status of a second-line standard treatment for HER2-positive gastric cancer [29].

2.2. VEGF

Anti-angiogenesis has also emerged as a pivotal element within the field of oncology, with VEGF emerging as a particularly salient target. Antibody therapy targeting VEGF selectively binds to VEGF or its receptor (VEGFR), thereby blocking signaling that induces endothelial cell proliferation and migration, ultimately suppressing tumor angiogenesis at its source. This key mechanism has been demonstrated to impede the provision of nutrients and oxygen to tumors, thereby hindering the

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progression of cancer and the process of metastasis. Although bevacizumab, which has proven effective in the treatment of colorectal cancer, was studied in the context of gastric cancer, it did not demonstrate a survival benefit [30]. However, ramucirumab, a mAb targeting VEGFR-2, demonstrated efficacy in the RAINBOW and REGARD studies, confirming that the VEGF/VEGFR pathway is also a crucial therapeutic target in gastric cancer. It is currently employed as the prevailing second-line treatment for patients with gastric cancer [31-32].

2.3. PD-1/PD-L1: The Beginning of Immune Checkpoint Inhibitors

Immune checkpoint inhibitors (ICIs), frequently designated as third-generation cancer treatments, have been shown to reinvigorate the anti-tumor activity of suppressed T cells by obstructing immune checkpoint pathways such as PD-1/PD-L1. These pathways have been identified as a primary mechanism by which cancer cells evade the potent anti-tumor immune response of T cells, thereby demonstrating anticancer effects. This finding paved the way for the exploration of ICI therapy, which was subsequently validated in the treatment of melanoma and non-small cell lung cancer, thus spurring further research in the field of gastric cancer. The ATTRACTION-2 Phase 3 trial was the inaugural study to demonstrate the potential of ICIs in gastric cancer, as it demonstrated that nivolumab monotherapy significantly prolonged mOS compared to placebo in patients with stage III or higher advanced gastric cancer (5.26 months vs 4.14 months; HR=0.63, p <0.0001) [13,33]. The KEYNOTE-061 study compared the efficacy of pembrolizumab monotherapy with that of paclitaxel in patients who had previously received first-line therapy, and the mOS did not differ significantly in the overall patient population. In the PD-L1 CPS ≥10 patient group, however, the HR of 0.64 suggests the potential for survival extension, thereby emphasizing the critical role of biomarker selection in ensuring the efficacy of ICI treatment [34].

Based on research on other cancer types indicating that ICI may exhibit synergistic effects when combined with anticancer chemotherapy rather than as monotherapy, studies were also conducted on gastric cancer. The CheckMate 649 study was a Phase 3 trial that compared nivolumab plus chemotherapy (XELOX/FOLFOX) with chemotherapy alone as the first-line treatment in patients with HER2-negative advanced gastric cancer, gastroesophageal junction cancer, or esophageal adenocarcinoma. In the PD-L1 CPS ≥ 5 patient subgroup, nivolumab combination therapy demonstrated a significant improvement in mOS (14.4 months vs. 11.1 months: HR=0.71, p <0.0001) and produced a cohort of patients who exhibited long-term survival. Based on these findings, the combination of nivolumab and chemotherapy has been established as the standard first-line treatment for patients with HER2-negative, PD-L1 CPS ≥5 advanced gastric cancer [35].

In patients diagnosed with HER2-positive gastric cancer, a triple combination therapy involving targeted therapy, immunotherapy, and chemotherapy has been attempted. The present study compared the efficacy of adding pembrolizumab to trastuzumab plus chemotherapy as a first-line treatment for patients with gastric cancer with that of a placebo group. In the initial interim analysis, the pembrolizumab combination group demonstrated an overwhelming response rate of 74.4%, in comparison to 51.9% in the placebo group, resulting in accelerated approval by the US FDA in 2021. The final analysis presented at the 2024 ESMO Congress demonstrated that following a median follow-up period of 50.2 months, the pembrolizumab combination group attained a mOS of 20.0 months. This outcome was statistically significant when compared to the 16.8 months observed in the placebo group (HR=0.80, p=0.004). This survival benefit was particularly marked in the PD-L1 CPS ≥ 1 patient subgroup, as evidenced by a significant difference in mOS (20.1 months vs. 15.7 months; HR=0.79). These findings established triple combination therapy as the new standard of care for HER2-positive, PD-L1-positive gastric cancer [36].

2.4. CLDN18.2: Emergence of New Targets and Clinical Validation

Claudin proteins are pivotal membrane proteins that form tight junctions in normal epithelial cells. CLDN18.2 is expressed exclusively in gastric mucosal epithelial cells in normal tissue and remains hidden within the intercellular junction, thus avoiding exposure to the immune system.

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However, in the event of malignant transformation in gastric cancer, the loss of cellular polarity results in the exposure of CLDN18.2 on the surface of tumor cells. This characteristic, which is particularly evident in malignant tumors, has led to the proposal of a therapeutic target that can selectively attack cancer cells while minimizing damage to normal gastric tissue [37].

In early research, CLDN18.2 was found to be expressed in approximately 30–50% of all gastric cancer patients, with particularly high expression rates in the diffuse type and genetically stable (GS) subtypes. This finding indicated that it could serve as a new therapeutic target for patient groups that had previously experienced challenges from existing targeted therapies [38].

Zolbetuximab, a pioneering IgG1 monoclonal antibody, has been identified as the first antibody to target CLDN18.2. It exerts its anticancer effects by binding to tumor cells expressing CLDN18.2, leading to the induction of direct cell death through both ADCC and CDC mechanisms [39]. The efficacy of zolbetuximab was confirmed in two large Phase 3 trials, SPOTLIGHT and GLOW, which evaluated the effectiveness of adding zolbetuximab to standard treatments FOLFOX or XELOX. Both studies enrolled patients with HER2-negative, CLDN18.2-positive (moderate or strong membrane staining in ≥75% of tumor cells by IHC) advanced gastric cancer receiving first-line chemotherapy [40, 41].

First, the SPOTLIGHT study evaluated the combination effect of mFOLFOX6 chemotherapy, demonstrating that the zolbetuximab combination group significantly extended the median progression-free survival (PFS) compared to the placebo group: 10.61 months vs. 8.67 months (HR=0.75, p=0.0066). The mOS was also extended, from 18.23 months vs. 15.54 months (HR = 0.75, p =0.0053), indicating a substantial increase [40]. Second, the GLOW study also evaluated the combination effect with CAPOX chemotherapy. In this study, the zolbetuximab combination group also showed a consistent improvement in median PFS compared to the placebo group: 8.21 months versus 6.80 months (HR=0.687, p=0.0007), and mOS of 14.39 months versus 12.16 months (HR=0.771, p=0.0118) [41].

The findings of the two studies provided compelling evidence that CLDN18.2 is the third key biomarker in first-line gastric cancer treatment, following HER2 and PD-L1. Zolbetuximab received approval in September 2024 from the European EMA and in October 2024 from the US FDA as a first-line treatment for HER2-negative, CLDN18.2-positive advanced gastric cancer. However, since CLDN18.2 is also expressed in normal gastric mucosa, gastrointestinal adverse events such as nausea and vomiting frequently occur. Therefore, proactive use of prophylactic antiemetics and patient education are essential for managing such events.

3. Current Progress and Future Prospects in Antibody Therapy for Gastric Cancer

The HER2, VEGFR2, PD-L1, and CLDN18.2 targets reviewed thus far have been used in gastric cancer antibody therapy to increase anticancer response rates and significantly improve survival rates. However, resistance to these therapies invariably develops, thereby diminishing their effectiveness. Research is warranted to ascertain the most potent target and the optimal sequence for administering these treatments.

A review of current studies reveals several ongoing research projects, the first of which focuses on the evolution of ADCs. Next-generation ADCs, equipped with diverse targets and payloads, are being studied for the treatment of gastric cancer. For example, disitamab vedotin (RC48) targets HER2, but uses a different payload called monomethyl auristatin E (MMAE) attached to a different antibody site. This agent is of particular interest because it reportedly exhibits anticancer properties, even within the HER2 low-expression group. In early clinical studies, the drug achieved an objective response rate (ORR) of approximately 24% as a monotherapy. In a recently published first-line Chinese randomized controlled trial (RCT), triple combination therapy with an ICI (tislelizumab) and an oral anticancer drug (S-1) demonstrated a high ORR of 92.1% and a median PFS of 12.6 months in patients with HER2-positive gastric or gastroesophageal junction adenocarcinoma, raising expectations for further research [42,43].

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Trophoblast cell-surface antigen 2 (TROP2) is a target whose expression is elevated in various cancers, including breast and lung cancer, and is associated with a poor prognosis. Sacituzumab govitecan and datopotamab deruxtecan, which have already received approval for the treatment of breast cancer, are currently undergoing clinical trials for the treatment of gastric cancer [44, 45]. Datopotamab deruxtecan employs the same DXd payload as T-DXd, and the results from the gastric cancer patient cohort in the TROPION-PanTumor01 Basket study are expected [46]. The success of zolbetuximab has prompted research into the development of new ADCs targeting CLDN18.2. **CMG901 (AZD0901) ** and EO-3021 are illustrative examples, with each exhibiting an ORR of 42.8% in Phase 1 studies, exceeding the typical efficacy thresholds used in early-phase trials and warranting further evaluation in Phase 2 and 3 studies. The oncology community is eagerly awaiting the outcomes of these trials [47].

Second, bispecific antibody therapy involves a single antibody recognizing two different antigens simultaneously. This drug class can overcome tumor heterogeneity and maximize efficacy, and it has been extensively studied and applied in hematologic malignancies. Additionally, its use for solid tumors is being studied [48]. T-cell engagers, which simultaneously bind tumor cell surface antigens and immune cell activation receptors (primarily T cells), are being actively investigated in gastric cancer.

Givastomig is a representative drug that targets both CLDN18.2 and the T-cell co-stimulatory receptor 4-1BB, demonstrating anticancer effects by selectively amplifying T cells within the tumor microenvironment (TME). This drug demonstrated a very high ORR of 83% in a Phase 1 combination therapy study presented at ESMO GI 2025, proving its potential as a dual-specific antibody to become a significant future therapeutic mechanism in gastric cancer [49]. Chimeric antigen receptor T-cell (CAR-T) therapy is a personalized biological treatment that involves the collection of a patient's T-cells, the introduction of a CAR gene that recognizes cancer cell surface antigens, and the subsequent reinfusion of these modified cells back into the patient. In the context of hematologic malignancies, the efficacy of CAR-T therapy has been found to exceed initial expectations, and its utilization in clinical settings is currently underway. However, in the context of solid tumors, the immune system encounters several obstacles that hinder its effectiveness. These include inadequate trafficking and infiltration capabilities to the tumor site, antigen escape due to tumor heterogeneity, potent immunosuppression that inhibits T-cell function, an immunosuppressive TME, and T-cell exhaustion due to persistent antigen stimulation [50]. However, the initial phase of CAR-T cell therapy investigation targeting advanced CLDN18.2 exhibited an ORR of 33% and a DCR of 57% in patients who had previously undergone unsuccessful treatment regimens, thereby substantiating the therapeutic potential of CAR-T therapy for solid tumors [51].

The most significant challenge in antibody-based therapy is the emergence of treatment resistance. For gastric cancer, the predominant mechanisms that confer resistance to HER2-targeted therapy have been identified as the loss of HER2 amplification after treatment and the activation of alternative pathways, such as MET and EGFR [18, 20, 51]. Even potent ADCs like T-DXd exhibit resistance mechanisms such as reduced HER2 expression, activation of drug efflux pumps, and increased immunosuppressive cells within the TME [14]. For ICI, the primary causes of resistance include an immunosuppressive TME (Tregs, MDSCs), defects in the IFN-γ signaling pathway, and JAK/STAT mutations.

Despite ongoing research aimed at overcoming these challenges, the extensive array of resistance mechanisms poses significant obstacles to the development of the next generation of therapeutic agents. Concurrently, research endeavors are underway to develop real-time diagnostic methods capable of detecting HER2 amplification loss or the emergence of new resistance mutations in circulating tumor DNA (ctDNA) through frequent analysis. Once resistance is confirmed, the objective is to promptly transition to the subsequent treatment strategy (e.g., switching to T-DXd or multi-target combination therapy) to overcome resistance. As rapid progress is made, determining which drug to use first and the sequence of drug administration when multiple biomarkers for gastric cancer antibody therapy are simultaneously positive also remains a challenge to be addressed.

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Gastric cancer, for instance, has three independent biomarker-based therapies—HER2, PD-L1 (CPS), and CLDN18.2—that have been approved for first-line treatment. However, there is a paucity of research on which therapy should be prioritized when patients test positive for two or more biomarkers. The reason for this is that the clinical studies establishing each treatment targeted different patient populations, or there is a lack of head-to-head comparative studies.

Clinicians must select the optimal treatment through reasonable inference based on indirect evidence. A subsequent discussion will encompass several such cases. For patients with HER2-positive and PD-L1-positive (CPS ≥ 1) diagnoses, the combination therapy of chemotherapy, trastuzumab, and pembrolizumab, as demonstrated in the KEYNOTE-811 study, offers the strongest evidence supporting its use. This therapeutic approach has yielded a noteworthy mOS of 20 months, marking the most protracted survival period documented thus far in first-line treatment for gastric cancer. Therefore, regardless of CLDN18.2 expression status, it is reasonable to prioritize this triple therapy regimen. Subsequently, patients with HER2-negative and PD-L1-positive (CPS ≥ 5) and CLDN18.2-positive status should be subjected to analysis of nivolumab in combination with chemotherapy (based on CheckMate 649) and zolbetuximab in conjunction with chemotherapy (based on SPOTLIGHT/GLOW). While both demonstrated superior survival, benefits compared to placebo plus chemotherapy, there is an absence of direct comparison data. The selection of treatment should be individualized based on the patient's comorbidities, the anticipated toxicity profile, and the treatment goals. Those prioritizing the potential for long-term survival, a hallmark of ICIs, may opt for ICI-based therapy. On the other hand, those seeking to impede the onset of disease progression by virtue of zolbetuximab's documented efficacy in enhancing PFS may advocate for CLDN18.2-targeted therapy.

The necessity of a prospective randomized comparative clinical trial targeting patients positive for multiple biomarkers is hereby proposed.

4. Conclusions

Antibody-mediated therapy for gastric cancer has undergone significant advancements over the past two decades, marking the advent of a new era in precision medicine that utilizes molecular targets and the immune system, shifting from the reliance on cytotoxic chemotherapy. The advent of trastuzumab, a drug that targets HER2, has led to the prospect of utilizing biomarker-based therapy in the treatment of gastric cancer. Innovative ADCs, such as T-DXd, which surmounted its limitations, advanced the treatment paradigm to the next level. ICIs have fundamentally reshaped the landscape of first-line therapy through the PD-L1 biomarker, and the recent success of CLDN18.2-targeted therapy is raising expectations for new treatment modalities.

However, despite significant progress, the road to conquering stomach cancer remains arduous and lengthy. Intrinsic and acquired resistance originating from tumor heterogeneity persists as a foundational challenge for all antibody therapies. Severe toxicities, such as ILD (interstitial lung disease) and irAEs (immune-related adverse events), act as factors impeding treatment. Furthermore, the selection of optimal treatment for patients who are positive for multiple biomarkers, as well as the development of rational sequential treatment strategies following the failure of new standard therapies, represent unmet needs that require further research.

The pivotal element for the advancement of gastric cancer antibody therapy is a "personalized combination and sequencing" strategy that is meticulously designed to circumvent existing challenges. This will be realized by transitioning from single-target, single-drug methodologies to more comprehensive approaches, such as ▲ the introduction of next-generation platform technologies such as bispecific antibodies and CAR-T; ▲ real-time resistance monitoring via liquid biopsy; ▲ deep understanding of the tumor microenvironment using advanced technologies like spatial transcriptomics; ▲ and the discovery of novel regulatory factors such as the gut microbiome.

In conclusion, the field of gastric cancer antibody therapy has evolved in a manner that builds upon prior achievements, thereby establishing contemporary standards and overcoming future limitations through progressively more sophisticated and multifaceted approaches. The fundamental

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mission of oncologists is to translate these scientific advances into improved survival rates and enhanced quality of life for actual patients through close collaboration between clinical and translational research. This will be an important milestone on the path toward transforming gastric cancer from an incurable disease into a manageable chronic condition.

Table 1. Summary of HER2-targeted clinical trials in gastric cancer.

	Line/Setting	Regimen	ORR (%)	mPFS (mo)	mOS (mo)	Study
Trastuzumab	1L	FP (orXP)+Cisplatin+Trastuzumab vs FP (or XP) +Cisplatin	47 vs 35	6.7 vs 5.5 (HR 0.71)	13.8 vs 11.1 (HR= 0.74)	ToGA
Lapatinib	1L	Lapatinib + CapeOx vs Placebo + CapeOx	53 vs 39	6.0 vs 5.4 (HR= 0.82) *	12.2 vs 10.5 (NS)	LOGiC (TRIO-013)
Lapatinib	2L (Asian)	Lapatinib + Paclitaxel vs Paclitaxel	27 vs 9	5.4 vs 4.4	11.0 vs 8.9 (NS)	TyTAN
Trastuzumab emtansine (T-DM1)	2L	T-DM1 vs Taxane	20.6 vs 19.6	2.7 vs 2.9	7.9 vs 8.6 (HR= 1.15)	GATSBY
Trastuzumab deruxtecan (T-DXd)	3L+ (JP/KR)	Trastuzumab deruxtecan (T-DXd) vs Chemo (physician's choice)	51 vs 14	5.6 vs 3.5 (HR= 0.47)	12.5 vs 8.4 (HR= 0.59)	DESTINY-Gastric01
Trastuzumab deruxtecan (T-DXd)	2L (Western)	T-DXd (single-arm)	41.8	5.6	12.1	DESTINY-Gastric02
Trastuzumab deruxtecan (T-DXd)	2L	T-DXd vs Ramucirumab + Paclitaxel	44.3 vs 29.1		14.7 vs 11.4 (HR= 0.70)	DESTINY-Gastric04

Abbreviations: 1L, first line; 2L, second line; ORR, objective response rate; mPFS, median progression-free survival; mOS, median overall survival; HR, hazard ratio; NS, not significant; FP, 5-fluorouracil plus cisplatin; XP, capecitabine plus cisplatin; Chemo, chemotherapy; JP, Japan; KR, Korea.

Table 2. Key phase 3 trials of VEGF/VEGFR-targeted therapy in gastric cancer.

	Line/Setting	Regimen	ORR (%)	mPFS (mo)	mOS (mo)	Study
Bevacizumab	1L	Bevacizumab + Cape/Cis vs Placebo + Cape/Cis	46.0 vs 37.4	6.7 vs 5.3 (HR= 0.80, p=0.0037)	12.1 vs 10.1 (HR= 0.87, p=0.10)	AVAGAST
Ramucirumab	2L	Ramucirumab vs Placebo	3.4 vs 2.6 (NS)	2.1 vs 1.3 (HR= 0.48,	5.2 vs 3.8 (HR= 0.78,	REGARD

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				p<0.0001)	p=0.047)	
Ramucirumab	2L	Ramucirumab + Paclitaxel vs Placebo + Paclitaxel	28.0 vs 16.0	4.4 vs 2.9 (HR= 0.64, p<0.0001)	9.6 vs 7.4 (HR= 0.81, p=0.017)	RAINBOW

Abbreviations: 1L, first line; 2L, second line; ORR, objective response rate; mPFS, median progression-free survival; mOS, median overall survival; HR, hazard ratio; NS, not significant; Cape, capecitabine; Cis, cisplatin.

Table 3. Key clinical trials of PD-1/PD-L1 inhibitors in advanced gastric cancer.

	Line/Setting	Regimen	ORR (%)	mPFS (mo)	mOS (mo)	Study
Nivolumab	3L~Asia	Nivolumab vs Placebo All-comers (PD-L1 not required);	11.2 vs 0.0	1.61 vs 1.45 (HR= 0.60)	5.26 vs 4.14 (HR= 0.63; p<0.0001)	ATTRACTION-2
Pembrolizumab	2L	Pembrolizumab vs Paclitaxel	16.3 vs 13.6	1.5 vs 5.4 (HR= 0.82) *	9.1 vs 8.3 (HR= 0.82 p=0.042, NS)	KEYNOTE-061
Nivolumab	1L, HER2(-) G/GEJ/esophageal adenocarcinoma; CPS>5	Nivolumab + Chemo (FOLFOX/XELOX) vs Chemo	60 vs 45 (3-y update)	7.7 vs 6.0 (HR= 0.68)	14.4 vs 11.1 (HR= 0.71; p<0.0001)	CheckMate 649
Pembrolizumab	1L, HER2+ metastatic G/GEJ; global	Pembrolizumab + Trastuzumab + Chemo vs Placebo + Trastuzumab + Chemo	74.6 vs 60.1 (interim)	10.0 vs 8.1 (HR= 0.73) CPS ≥1: **10.9** (Exp) vs **7.3** (Ctrl) (HR ≈ 0.71	20.0 vs 16.8 (HR= 0.80; p=0.004); CPS ≥1: 20.1 vs 15.7 (HR= 0.79)	KEYNOTE-811

Abbreviations: 1L, first line; 2L, second line; 3L, third line; ORR, objective response rate; mPFS, median progression-free survival; mOS, median overall survival; HR, hazard ratio; NS, not significant; G/GEJ, gastric/gastroesophageal junction; CPS, combined positive score; Chemo, chemotherapy; Exp, experimental arm; Ctrl, control arm.

Table 4. Phase 3 trials of CLDN18.2-targeted therapy in advanced gastric cancer.

	Line/Setting	Regimen	ORR (%)	mPFS (mo)	mOS (mo)	Study
zolbetuximab	Phase 3 / 1L CLDN18.2+, HER2(-) (global)	Zolbetuximab + mFOLFOX6 vs Placebo + mFOLFOX6 (cldn18.2 ≥75)	No meaningful difference (48% both arms) *	10.61 vs 8.67 (HR= 0.751; p=0.0066)	18.23 vs 15.54 (HR= 0.75; p=0.0053)	SPOTLIGHT

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zolbetuximab	Phase 3 / 1L CLDN18.2+, HER2(-) (global)	Zolbetuximab + CAPOX vs Placebo + CAPOX (cldn18.2 ≥75)	No difference (42.5% vs 40.3) both arms) *	8.21 vs 6.80 (HR= 0.687; p=0.0007)	14.39 vs 12.16 (HR= 0.771; p=0.0118)	GLOW

Abbreviations: 1L, first line; ORR, objective response rate; mPFS, median progression-free survival; mOS, median overall survival; HR, hazard ratio; CLDN18.2+, claudin 18.2–positive; mFOLFOX6, modified FOLFOX6 (oxaliplatin, leucovorin, and fluorouracil); CAPOX, capecitabine plus oxaliplatin.

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References

1. Scott, A.M.; Wolchok, J.D.; Old, L.J. Antibody therapy of cancer. *Nat. Rev. Cancer* **2012**, *12*, 278–287.
2. Köhler, G.; Milstein, C. Continuous cultures of fused cells secreting antibody of predefined specificity. *Nature* **1975**, *256*, 495–497.
3. Maloney, D.G.; Grillo-López, A.J.; Bodkin, D.; White, C.A.; Liles, T.M.; Royston, I.; *et al.* IDEC-C2B8: Results of a phase I multiple-dose trial in patients with relapsed non-Hodgkin's lymphoma. *Blood* **1997**, *90*, 2188–2195.
4. Slamon, D.J.; Leyland-Jones, B.; Shak, S.; Fuchs, H.; Paton, V.; Bajamonde, A.; *et al.* Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N. Engl. J. Med.* **2001**, *344*, 783–792.
5. Hurwitz, H.; Fehrenbacher, L.; Novotny, W.; Cartwright, T.; Hainsworth, J.; Heim, W.; *et al.* Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N. Engl. J. Med.* **2004**, *350*, 2335–2342.
6. Cunningham, D.; Humblet, Y.; Siena, S.; Khayat, D.; Bleiberg, H.; Santoro, A.; *et al.* Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N. Engl. J. Med.* **2004**, *351*, 337–345.
7. Beck, A.; Wurch, T.; Bailly, C.; Corvaia, N. Strategies and challenges for the next generation of therapeutic antibodies. *Nat. Rev. Immunol.* **2010**, *10*, 345–352.
8. Weiner, L.M.; Surana, R.; Wang, S. Monoclonal antibodies: Versatile platforms for cancer immunotherapy. *Nat. Rev. Immunol.* **2010**, *10*, 317–327.
9. Baselga, J.; Cortés, J.; Kim, S.B.; Im, S.A.; Hegg, R.; Im, Y.H.; *et al.* Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N. Engl. J. Med.* **2012**, *366*, 109–119.
10. Cartron, G.; Dacheux, L.; Salles, G.; Solal-Céligny, P.; Bardos, P.; Colombat, P.; *et al.* Therapeutic activity of humanized anti-CD20 monoclonal antibody and polymorphism in IgG Fc receptor FcγRIIIa gene. *Blood* **2002**, *99*, 754–758.
11. Di Gaetano, N.; Cittera, E.; Nota, R.; Vecchi, A.; Sabatti, M.; Micciché, F.; *et al.* Complement activation determines the therapeutic activity of rituximab in vivo. *J. Immunol.* **2003**, *171*, 1581–1587.

 doi:10.20944/preprints202511.1385.v1

12. Clynes, R.A.; Towers, T.L.; Presta, L.G.; Ravetch, J.V. Inhibitory Fc receptors modulate in vivo cytotoxicity against tumor targets. *Nat. Med.* **2000**, *6*, 443–446.
13. Kang, Y.K.; Boku, N.; Satoh, T.; Ryu, M.H.; Chao, Y.; Kato, K.; *et al.* Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): A randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* **2017**, *390*, 2461–2471.
14. Li, J.; Qin, S.; Bai, Y.; Wu, C.; Liu, T.; Xiong, J.; *et al.* Targeted therapy and immunotherapy for gastric cancer: Rational strategies, novel advancements, challenges, and future perspectives. *Cancer Commun.* **2025**, *44*, 1075.
15. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature* **2014**, *513*, 202–209.
16. Slamon, D.J.; Clark, G.M.; Wong, S.G.; Levin, W.J.; Ullrich, A.; McGuire, W.L. Human breast cancer: Correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* **1987**, *235*, 177–182.
17. Ross, J.S.; Fletcher, J.A.; Linette, G.P.; Stec, J.; Clark, E.; Ayers, M.; *et al.* The HER-2/neu gene and protein in breast cancer: Biomarker and target of therapy. *Oncologist* **2003**, *8*, 307–325.
18. Gravalos, C.; Jimeno, A. HER2 in gastric cancer: A new prognostic factor and a novel therapeutic target. *Ann. Oncol.* **2008**, *19*, 1523–1529.
19. Bang, Y.J.; Van Cutsem, E.; Feyereislova, A.; Chung, H.C.; Shen, L.; Sawaki, A.; *et al.* Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): A phase 3, open-label, randomised controlled trial. *Lancet* **2010**, *376*, 687–697.
20. Yoon, H.H.; Shi, Q.; Sukov, W.R.; Wiktor, A.E.; Khan, M.; Sattler, C.A.; *et al.* Association of HER2-low status with clinicopathologic features and patient outcomes in gastric cancer. *J. Clin. Oncol.* **2020**, *38*, 2412–2421.
21. Hecht, J.R.; Bang, Y.J.; Qin, S.K.; Chung, H.C.; Xu, J.M.; Park, J.O.; *et al.* Lapatinib in combination with capecitabine plus oxaliplatin in human epidermal growth factor receptor 2–positive advanced or metastatic gastric, esophageal, or gastroesophageal junction cancer: TRIO-013/LOGiC—a randomized phase III trial. *J. Clin. Oncol.* **2016**, *34*, 443–451.
22. Satoh, T.; Xu, R.H.; Chung, H.C.; Sun, G.P.; Doi, T.; Xu, J.M.; *et al.* Lapatinib plus paclitaxel versus paclitaxel alone in the second-line treatment of HER2-amplified advanced gastric cancer in Asian populations: TyTAN—a randomized, phase III study. *J. Clin. Oncol.* **2014**, *32*, 2039–2049.
23. Beck, A.; Goetsch, L.; Dumontet, C.; Corvaïa, N. Strategies and challenges for the next generation of antibody-drug conjugates. *Nat. Rev. Drug Discov.* **2017**, *16*, 315–337.
24. Diamantis, N.; Banerji, U. Antibody-drug conjugates—An emerging class of cancer treatment. *Br. J. Cancer* **2016**, *114*, 362–367.
25. Thuss-Patience, P.C.; Shah, M.A.; Ohtsu, A.; Van Cutsem, E.; Ajani, J.A.; Castro, H.R.; *et al.* Trastuzumab emtansine versus taxane use for previously treated HER2-positive advanced gastric cancer (GATSBY): A randomised, open-label, multicentre, phase 2/3 study. *Lancet Oncol.* **2017**, *18*, 640–653.
26. Modi, S.; Saura, C.; Yamashita, T.; Park, Y.H.; Kim, S.B.; Kennecke, H.; *et al.* Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. *N. Engl. J. Med.* **2020**, *382*, 610–621.
27. Shitara, K.; Bang, Y.J.; Iwasa, S.; Sugimoto, N.; Ryu, M.H.; Sakai, D.; *et al.* Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. *N. Engl. J. Med.* **2020**, *382*, 2419–2430.
28. Van Cutsem, E.; Di Bartolomeo, M.; Smyth, E.; Chau, I.; Park, H.; Siena, S.; *et al.* Trastuzumab deruxtecan in patients in the USA and Europe with HER2-positive advanced gastric or gastroesophageal junction cancer with progression after a trastuzumab-containing regimen (DESTINY-Gastric02): A single-arm, phase 2 trial. *Lancet Oncol.* **2023**, *24*, 744–756.
29. Shitara, K.; Van Cutsem, E.; Gümüş, M.; Lonardi, S.; de la Fouchardière, C.; Coutzac, C.; *et al.* Trastuzumab deruxtecan or ramucirumab plus paclitaxel in gastric cancer. *N. Engl. J. Med.* **2025**, *393*, 336–348.
30. Ohtsu, A.; Shah, M.A.; Van Cutsem, E.; *et al.* Bevacizumab in combination with capecitabine and cisplatin in patients with advanced gastric cancer: A randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol.* **2011**, *12*, 1050–1058.

 doi:10.20944/preprints202511.1385.v1

31. Wilke, H.; Muro, K.; Van Cutsem, E.; *et al.* Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): A double-blind, randomised phase 3 trial. *Lancet Oncol.* **2014**, *15*, 1224–1235.
32. Fuchs, C.S.; Tomasek, J.; Yong, C.J.; *et al.* Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): An international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet* **2014**, *383*, 31–39.
33. Robert, C.; Schachter, J.; Long, G.V.; Arance, A.; Grob, J.J.; Mortier, L.; *et al.* Pembrolizumab versus ipilimumab in advanced melanoma. *N. Engl. J. Med.* **2015**, *372*, 2521–2532.
34. Shitara, K.; Ozguroglu, M.; Bang, Y.J.; Di Bartolomeo, M.; Mandala, M.; Ryu, M.H.; *et al.* Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): A randomised, open-label, controlled, phase 3 trial. *Lancet* **2018**, *392*, 123–133.
35. Janjigian, Y.Y.; Shitara, K.; Moehler, M.; Garrido, M.; Salman, P.; Shen, L.; *et al.* First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, or oesophageal adenocarcinoma (CheckMate 649): A randomised, open-label, phase 3 trial. *N. Engl. J. Med.* **2021**, *384*, 1191–1203.
36. Janjigian, Y.Y.; *et al.* Pembrolizumab plus trastuzumab and chemotherapy for HER2-positive advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-811): A randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* **2024**, *403*, 2549–2561.
37. Singh, A.B.; Sharma, A.; Dhawan, P. Claudin-1 and claudin-2: A versatile nexus in health and disease. *Cell Adhes. Migr.* **2010**, *4*, 248–258.
38. Sahin, U.; Koslowski, M.; Dhaene, K.; Usener, D.; Brandenburg, G.; Seitz, G.; *et al.* Claudin-18 splice variant 2 is a pan-cancer target suitable for therapeutic antibody development. *Cancer Res.* **2008**, *68*, 5748–5755.
39. Türeci, Ö.; Sahin, U.; Koslowski, M.; Seitz, G.; Braun, M.; Samatov, T.; *et al.* A multicentre, phase IIa study of zolbetuximab (IMAB362) in patients with metastatic gastric cancer. *Ann. Oncol.* **2013**, *24*, 564–571.
40. Shitara, K.; Lordick, F.; Janjigian, Y.Y.; Carmona-Bayonas, A.; Tjulandin, S.; Ilson, D.H.; *et al.* Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): A multicentre, randomised, double-blind, phase 3 trial. *Lancet* **2023**, *401*, 1655–1668.
41. Janjigian, Y.Y.; Kawazoe, A.; Yanez, P.E.; Lonardi, S.; Tokunaga, M.; Satake, H.; *et al.* Zolbetuximab plus capecitabine and oxaliplatin (CAPOX) in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (GLOW): A multicentre, randomised, double-blind, phase 3 trial. *Lancet* **2023**, *401*, 1669–1679.
42. Peng, Z.; Liu, T.; Wei, J.; Wang, T.; He, Y.; Yang, J.; *et al.* 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 Commun.* **2021**, *41*, 1173–1182.
43. Xu, J.; Wei, J.; Zhang, Y.; Lin, Y.; Liu, C.; Wang, T.; *et al.* Disitamab vedotin, tislelizumab, and S-1 as first-line therapy for HER2-positive advanced gastric or gastroesophageal junction adenocarcinoma: A single-arm, phase II trial. *J. Clin. Oncol.* **2025**, *43*, 4030.
44. Bardia, A.; Hurvitz, S.A.; Tolaney, S.M.; Loirat, D.; Punie, K.; Oliveira, M.; *et al.* Sacituzumab govitecan in metastatic triple-negative breast cancer. *N. Engl. J. Med.* **2021**, *384*, 1529–1541.
45. Bardia, A.; Krop, I.E.; Meric-Bernstam, F.; Sadelain, M.; Officer, A.; Shin, M.; *et al.* Datopotamab deruxtecan (Dato-DXd) in patients with advanced triple-negative breast cancer: Results from the phase 1 TROPION-PanTumor01 study. *J. Clin. Oncol.* **2021**, *39*, 3291–3301.
46. Goto, Y.; Su, W.C.; Levy, B.P.; Garon, E.B.; Heist, R.S.; Spira, A.I.; *et al.* Datopotamab deruxtecan (Dato-DXd) in patients with advanced non-small cell lung cancer: Results from the phase 1 TROPION-PanTumor01 study. *J. Clin. Oncol.* **2022**, *40*, 9015.
47. Li, J.; Qin, S.; Xu, J.; Xiong, J.; Wu, C.; Bai, Y.; *et al.* A phase I/II study of TST001 (a humanized anti-Claudin 18.2 monoclonal antibody) in combination with nivolumab ± capecitabine and oxaliplatin in patients with locally advanced or metastatic solid tumors. *J. Clin. Oncol.* **2023**, *41*, 309.
48. Labrijn, A.F.; Janmaat, M.L.; Reichert, J.M.; Parren, P.W. Bispecific antibodies: A mechanistic review of the pipeline. *Nat. Rev. Drug Discov.* **2019**, *18*, 585–608.

 doi:10.20944/preprints202511.1385.v1

49. Li, K.; He, L.; Zhang, Y; Wu, X.; Yao, W.; He, Y.; *et al.* CLDN18.2 and 4-1BB bispecific antibody givastomig exerts antitumor activity through CLDN18.2-expressing tumor-directed T-cell activation. *J. Immunother. Cancer* **2024**, *12*, e008129.
50. Majzner, R.G.; Rietberg, S.P.; Mackall, C.L. T-cell therapies for solid tumors. *Nat. Cancer* **2020**, *1*, 143–153.
51. Qi, C.; Li, B.; Sun, D.; Zhao, J.; Gao, F.; Wu, Q.; *et al.* A novel Claudin 18.2-targeted chimeric antigen receptor T-cell therapy for patients with advanced gastric cancer. *Nat. Med.* **2022**, *28*, 1188–1195.