Newer HER2 Therapies for Gastric Adenocarcinomas

Subjects: Oncology

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Human epidermal growth factor receptor-2 (HER2) is a well-known target for approximately 15% of gastric adenocarcinomas (GACs). Although a plethora of HER2-targeted agents are marketed, currently only two agents are approved for GAC. These two agents are used only in the metastatic setting. Trastuzumab is utilized in combination with front-line chemotherapy, and trastuzumab deruxtecan is given following failure of trastuzumab therapy.

human epidermal growth factor receptor-2 | trastuzumab | trastuzumab deruxtecan | ZW25 | margetuximab | antibody drug conjugates (ADCs) | gastric adenocarcinomas

1. Introduction

Metastatic gastric adenocarcinomas (GACs) carry a poor prognosis with limited therapy options after first-line failure [1]. Some GACs (~15%) over-express human epidermal growth factor receptor-2 (HER2), making them candidates for HER2-targeted therapy. According to the guidelines, HER2 over-expressing GACs are classified by HER2 protein 3+ via immunohistochemistry (IHC), HER2 protein 2+ via IHC+ with an ERBB2/CEP17 ratio ≥ 2 using fluorescence in situ hybridization (FISH), or an average of *ERBB2* copy number ≥ 6 signals/cell. Newer HER2 therapies are challenging these designations by exploring effectiveness in those with lower expression (or assessments using other platforms such as liquid biopsy or Next Gen Sequencing). This research focuses on the current understanding of HER2 agents in HER2-positive advanced GAC management.

2. Antibody Drug Conjugates (ADCs)

ADCs are a novel drug design in which antibodies are chemically linked to cytotoxic therapy [2][3][4][5]. The antibody component exerts its anti-tumor effects by recognizing the antigen on the target cells, facilitating the formation of an antigen–antibody conjugate, which allows the cytotoxic payload to be rapidly internalized, leading to release of the cytotoxic component [5]. Ideally, this mechanism should reduce off-target toxicity; however, as mentioned previously, trastuzumab deruxtecan, an ADC that consists of trastuzumab with a topoisomerase inhibitor, carries substantial toxicity [6][7]. The hope is that newer generations of ADCs and continued development in this area will yield safer agents. Additional HER2 ADCs are being explored in HER2-positive GAC. RC48 is an ADC composed of hertuzumab, an anti-HER2 mAb conjugated to a microtubule inhibitor, monomethylauristatin E (MMAE) [8][9]. A

phase 2 trial in ICH 2+/3+ advanced GAC patients in the refractory setting showed an ORR of 24.8%, median PFS of 4.1 months, and median OS of 7.9 months [5][8][9]. Those with HER2 IHC 2+/FISH− showed an ORR of 16.7%. Of note, RC48 was approved in China for GAC. Phase 3 in this population is under investigation using NCT04714190 [10]. Other HER2 ADCs are being explored in solid tumors. Preliminary results of ZW49 (auristatin) in heavily pretreated HER2-positive solid tumor patients showed an ORR of 31% with disease control of 72% [11][12]. For the GAC patients (n = 11), the ORR was 37% with a disease control rate of 73%. ARX788 (amberstatin conjugate) showed encouraging phase 1 results in HER2 refractory GAC patients (n = 30) with an ORR of 37.9%, disease control of 55.2%, median PFS of 4.1 months, and median OS of 10.7 months [13]. ARX788 was granted orphan drug status with the FDA in 2021 [14]. Examples along with their cytotoxic payload include MRG002 (microtubule disrupting agent monomethyl auristatin E), SYD985 (duocarmyicin), PF-06804103 (Aur0101), FS-1502 (monomethyl auristatin F), GQ1001 (DM1), A166 (microtubule cytotoxic agent), XMT-1522 (auristatin), BDC-1001 (toll-like receptor), ALT-P7 (monomethyl auristatin E), and SBT6050 (toll-like receptor) [2][4][5]. Trial examples of these agents are described in **Table 1** [10][15][16][17][18][19][20][21][22][23].

Table 1. HER2-targeted antibody-drug conjugate examples currently under investigation [10][15][16][17][18][19][20][21][22][23].

Drug Name	HER2 bsAb	Trial Number	Phase	Population
RC48	Anti-HER2 + MMAE	NCT04714190 NCT05514158 NCT05982834	3 1 1/2	Locally advanced/metastatic HER2 GAC Locally advanced/metastatic HER2 GAC Metastatic HER2 GAC
ZW49	Anti-HER2 bsAb (ZW25) + Auristatin	NCT03821233	1	Advanced HER2-expressing cancers
MRG002	Anti-HER2 IgG1 + MMAE	NCT04492488 NCT05141747	1 2	Advanced HER2 solid tumors Locally advanced/metastatic HER2-positive/HER2 low GAC
FS-1502	Anti-HER2 + MMAF	NCT03944499	1	HER2-positive advanced breast or solid tumors
GQ1001	Anti-HER2 + DM1	NCT04450732	1	HER2-positive advanced solid tumors
ARX788	Modified Trastuzumab + MMAF	NCT03255070	1	HER2-positive advanced solid tumors
BDC-1001	Trastuzumab biosimilar + TLR7/8 agonist	NCT04278144	1/2	HER2-positive advanced solid tumors

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bsAb (bispecific antibody); HER2: human epidermal growth factor receptor-2.

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3. Antibodies

Zanidatamab (ZW25), a HER2-targeted bispecific antibody, has emerged as a promising therapy. It binds to two extracellular domains of HER2, extracellular domain IV and II. These are the same domains targeted by trastuzumab and pertuzumab, respectively. Meric-Bernstam et al. published phase 1 results in HER2 IHC 3+ or 2+ advanced refractory (median prior therapies = 2–3) GACs [24]. Parts 1 and 2 were given single-agent zanidatamab (n = 36), whereas part 3 (n = 26) utilized zanidatamab in combination with a fluoropyrimidine or a taxane. Most patients had prior HER2 therapies (>90%). The ORR was 38% for the single-agent parts and 60% for zanidatamab + chemotherapy, with a median duration of response of 6 months (95% CI 1.9–9.2 months) and 8.9 months (95% CI 3.5-NE months), respectively. Xu et al. reported preliminary results on phase 2 of zanidatamab in combination with front-line fluoropyrimidine plus platinum HER2 IHC 3+ or IHC 2+/FISH + advanced GAC [25]. For 28 patients, the outcomes showed a benefit (75% ORR, median duration of response of 16.4 months, and median PFS of 12 months). Further evaluations are underway with NCT03929666, a phase 2 trial with zanidatamab + chemotherapy, and HERIZON-GEA-01, a phase 3 trial with zanidatamab + chemotherapy +/− tislelizumab, an anti-PD-1 antibody [26][27]. Of note, preliminary results of NCT03929666 have shown remarkable outcomes thus far. Zanidatamab + chemotherapy (CapeOx, FOLFOX, 5-FU + cisplatin) (n = 38) achieved an ORR of 79%, and 13% had stable disease, showing a disease control rate of 92% with a median duration of response of 20.4 months [28]. The median PFS was 12.5 months and median OS was NE. The 12-month OS was 88% and 18-month OS was 84%. Results of phase 3 HERIZON-GEA-01 [27] are looked forward to.

Margetuximab, a HER2 mAb similar to trastuzumab, has been engineered to increase affinity for the stimulatory Fc receptor (CD16A) and decrease affinity for the inhibitory Fc receptor (CD32B) on natural killer cells to increase antibody-dependent cellular cytotoxic response [29][30]. In vitro, margetuximab enhances the PD-1/PD-L1 axis expression and LAG-3 on natural killer and NK T cells. Blocking PD-1 would, in theory, enhance margetuximab NK cell activation, proliferation, and cytotoxicity. CP-MGAH22-05, a multicenter phase 1b/2 trial, combined margetuximab with pembrolizumab in refractory (1–2 previous therapies) HER2 IHC 3+ or IHC 2+/FISH+ advanced GAC (n = 95) [29]. PD-L1 expression was not an inclusion criterion but was explored (expression considered CPS ≥ 1). Overall outcomes were 18% ORR, median PFS of 2.73 months, and median OS of 12.48 months. HER2 amplification by ctDNA was associated with better ORR (HER2 amplification 31% ORR vs. HER2 amplification negative 6% ORR). Those with both HER2 IHC 3+ and PD-L1 expression also showed an ORR of 44%, and those with HER2 amplification by ctDNA with PD-L1 expression showed an ORR of 50%. The role of ctDNA in outcomes poses a unique question, namely whether following ctDNA expression during HER2 therapy may hold keys to establishing patients who can truly benefit. Interim analysis (n = 43) of the MAHOGANY trial, a phase 2/3 trial, was reported on the combination of margetuximab + retifanlimab, anti-PD-1 mAb, given as a front-line treatment for HER2 IHC 3+ and PD-L1 positive patients [31]. The best ORR was 52.5% with a median PFS of 6.4 months. MAHOGANY is also exploring the combination of margetuximab +/− tebotelimab, anti-LAG-3, and anti-PD-1 mAb [30].

KN026, a bispecific HER2 mAb targeting extracellular domains IV and II, has shown activity. Xu et al. showed phase 2 activity in two cohorts (cohort 1 (n = 25): IHC 3+ or IHC 2+/FISH +; cohort 2 (n = 14): IHC 0/1 +; FISH +) of refractory GAC and GEJ adenocarcinoma patients (≥one prior therapy) [32]. Cohort 1 reported an ORR of 55.6%, median PFS of 8.3 months, and median OS of 16.3 months. Of note, activity was seen in those that received prior

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HER2 therapy. Cohort 2 (n = 14) showed a minimal response with 14% ORR, median PFS of 1.4 months, and median OS of 9.6 months, indicating the importance of patient identification for trials. Dong et al. reported results of KN026 with KN046, anti-CTLA4/PD-L1 mAb in phase 1b GAC patients (n = 47). Eligibility included HER2 alterations (low expression, overexpression, mutation, or amplification), in naïve or refractory treatment. The ORR was 71.4% in the treatment naïve group and 37.5% in the refractory group. No response was seen in those with low HER2 expression or mutations. Of note, activity was still present in those that had prior HER2 and PD-1 agents. NCT05427383 is a current phase 2/3 trial evaluating KN046 in combination with chemotherapy (taxane or irinotecan) in the second-line HER2-positive advanced GAC [33].

4. Other Strategies

Promising results reported by ASPEN-01, a phase 1 trial on ALX148, a CD47 inhibitor, show novel combination strategies [34]. ASPEN-01 studied the combination of ALX148 + trastuzumab (n = 20) or ALX148 + trastuzumab + ramucirumab + paclitaxel (n = 18) in the second-line setting for HER2-positive advanced GAC patients. Most patients had prior HER2-targeted agent exposure. The ORR was 72% in the arm with ramucirumab plus paclitaxel, and the ALX148 and trastuzumab arm ORR was 21%. ALX148 + trastuzumab + ramucirumab + paclitaxel is being evaluated in ASPEN-06, a phase 2/3 trial, in advanced HER2-positive GAC patients [35]. NCT05027139 is looking at ALX148 with ZW25 in HER2-positive solid tumor patients [36]. Triplet combinations with HER2 kinase inhibitors in combination with chemotherapy and PD-1 inhibition are also being explored, such as in NCT05111444 [37]. Additionally, studies of vaccine and chimeric antigen receptor T-cell (CAR-T) HER2 targets are underway. Oral HER2 tyrosine kinase combination studies are also underway, including MOUNTAINEER-02, which is studying tucatinib in combination with trastuzumab, ramucirumab, and paclitaxel compared to ramucirumab and paclitaxel alone in the refractory setting [38].

Chen et al. recently published five potential hub genes that contribute to GAC [39]. The researchers used gene expression profiles and an RNA-sequencing dataset of GAC acquired from the Gene Expression Omnibus dataset and The Cancer Genome Atlas dataset. Ten important genes associated with cancer were identified. Linking these discoveries with clinical practice is necessary for further success. More understanding in this area will lead to advancements in HER2 resistance.

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