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REVIEW ARTICLE

Current status and future perspectives in HER2 positive advanced gastric cancer

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Abstract

Gastric cancer is one of the most common malignancy worldwide with a prognosis less than 1 year in unresectable or metastatic disease. HER2 expression is the main biomarker to lead the addition of trastuzumab to first line systemic chemotherapy improving the overall survival in advanced HER2-positivegastric adenocarcinoma. The inevitable development of resistance to trastuzumab remains a great problem inasmuch several treatment strategies that have proven effective in breast cancer failed to show clinical benefit in advanced gastric cancer. In this review, we summarize the available data on the mechanisms underlying primary and secondary resistance toHER2-targeted therapy and current challenges in the treatment of HER2-positive advanced gastric cancer refractory to trastuzumab. Further, we describe the prognostic value of new non-invasive screening techniques, the current development of novel agents such us HER2 antibody–drug conjugates and bispecific antibodies, and the strategies with antitumor activity on going.

Keywords Advanced gastric cancer · HER2 · Trastuzumab · HER2 resistance

Introduction

Gastric cancer (GC) is the fifth most common cancer and the third cause of cancer death worldwide [1]. Most of patients present advanced or metastatic disease at diagnosis with a median overall survival (OS) of 10–12 months; palliative chemotherapy is the mainstay of treatment [2–7]. Several treatment and diagnostic improvements have been achieved in the last decades although prognosis remains still poor in advanced GC [8–10]. Four molecular subtypes of GC have been identified, with the subgroup overexpressing human epidermal growth factor 2 (HER2) that allowed major improvement in therapies [2, 11]. Herein, we reported the current status of HER2-positive advanced GC treatment, underlining the potential mechanisms involved in anti-HER2 drugs resistance.

Epidermal growth factor 2 signaling pathway

The human epidermal growth factor receptor (HER) family [HER-1 (ErbB1), HER-2 (ErbB2), HER-3 (ErbB3) and HER-4 (ErbB4)] plays a pivotal role in the development of different tumours [12]. All four HER receptors comprise

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a cysteine-rich extracellular ligand binding site, a transmembrane lipophilic segment, and an intracellular domain with tyrosine kinase catalytic activity (Fig. 1) [13]. They play a crucial role in the network of cell-signaling processes controlling normal growth and development(Fig. 1) [14]. HER receptors exist as monomers becoming dimers after binding of the ligand, thus leading to transphosphorylation of intracellular domains [14]. HER2 receptor is a 185 kD (1255 amino acid) transmembrane glycoprotein, firstly discovered by a group of scientist from Harvard University and Massachusetts Institute of Technology in 1985 [15, 16]. HER2 has no specific single activating ligand. The heterodimerization with other family members (HER1 and/or HER3)seems to able to constitutively activateHER2 [17], leading the activation of different signalling pathways, [such as protein kinase C (PKC), phosphatidylinositol-4,5 bisphosphate 3-kinase (PI3K) and the mitogen-activated protein kinase (MAPK)]through the autophosphorylation of tyrosine residues present in the cytoplasmic domains [14, 18]. The MAPK pathway results in cell survival, angiogenesis, and metastasis while the PI3K/Akt downstream pathway, activated by HER2-HER3 heterodimer is considered the leader regulator of cell growth [17, 19]. A higher binding affinity with the ligand and a more robust signal activation is observed with HER2-containing heterodimers compared to homodimers and heterodimers between different HER family members [17, 19]. However, other membrane receptors such as the insulin growth factor 1 (IGF1) can lead HER2 dimerization and its activation [20]. As aforementioned, HER2 overexpression due to *HER2* gene amplification and other secondary genetic mechanisms involves its inappropriate activation that correlates with the development of different malignancies such as gastric, breast, pancreatic, ovarian,

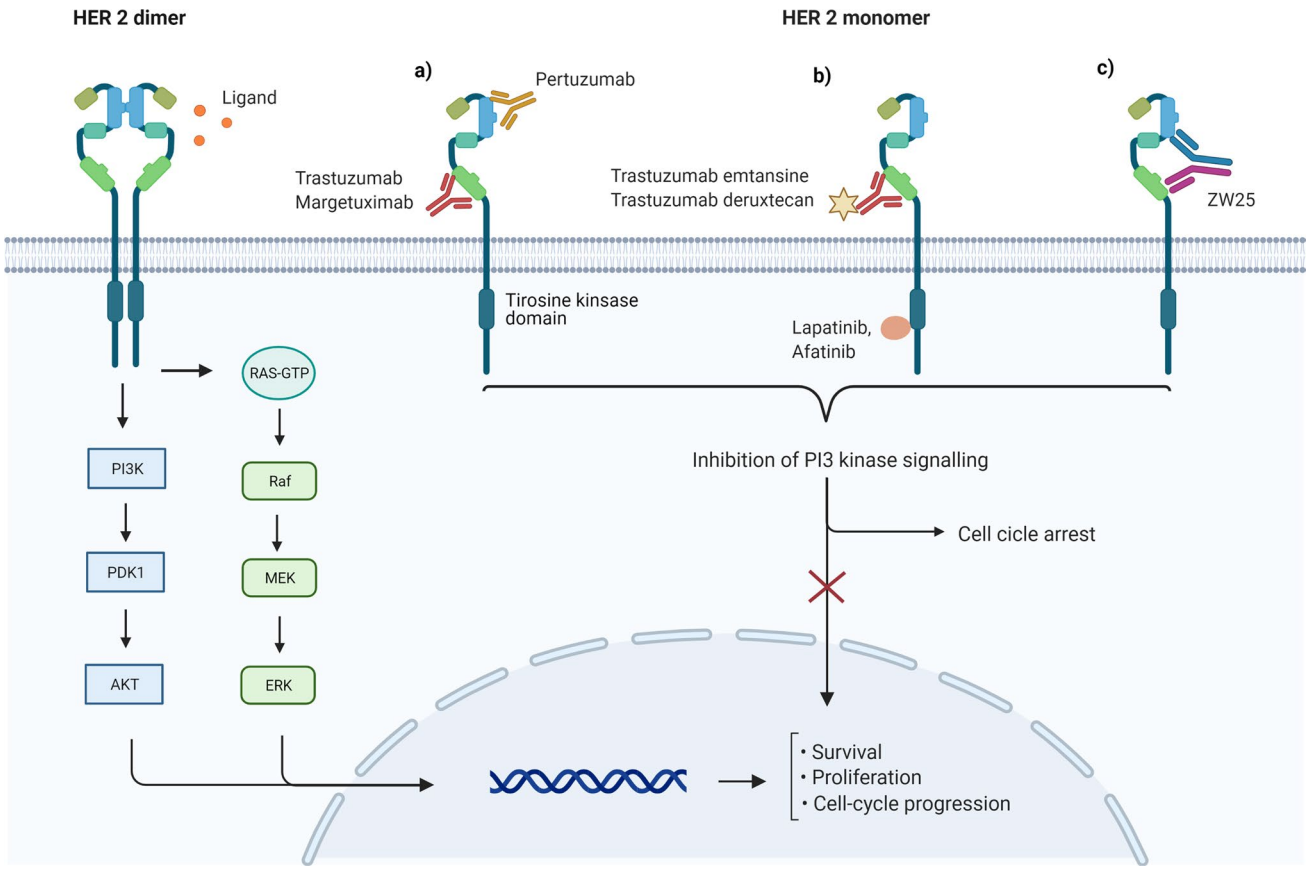

Fig. 1 Mechanism of action of agents targetingHER2. **a** Single-epitope monoclonal antibodies (trastuzumab, pertuzumab, margetuximab) bind to HER2 at a single extracellular domain. They induce antitumor effects through different mechanisms: inhibition of downstream signaling pathways, engagement of antibody dependent cellular cytotoxicity, or, only for pertuzumab, inhibition receptor dimerization. **b** Antibody–drug conjugates targeting HER2 (trastuzumabemtansine and trastuzumabderuxtecan) induce antitumor effects both through these pathways, and targeted cytotoxicity by releasing a highly cytotoxic agent close to HER2-positive tumor cells. Alternatively, small-molecule inhibitors (lapatinib, afatinib), bind to the intracellular tyrosine-kinase domain of HER2 and directly inhibit activation of the PI3K pathway. **c** Bispecific antibody (ZW25), target more than one extracellular region of HER2. ZW25 should provide a higher level of HER2 inactivation than single agents (*e.g.*, trastuzumab, pertuzumab), although clinical data are currently limited to early phase trials. *Figure created with Biorender.com*

colorectal and endometrial cancer [21, 22]; in gastric cancer, the HER2 overexpression ranges from 6 to 30% [2, 14, 18, 23–27].

HER2 status testing is performed on a biopsy tissue sample and immunohistochemistry and fluorescence in situ hybridization (FISH) are used to test HER2 status. Immunohistochemistry (IHC) measures the amount of HER2 protein in the cancer cells and the results are reported on a scale from 0 to 3 + : (negative 0–1 +, equivocal 2 + or positive 3 +). Fluorescence in situ hybridization investigate the number of HER2 gene copies and results are reported as either negative or positive: FISH negative means that the levels of the HER2 gene in the cells are normal, and the tumor is HER2 negative; FISH positive means that there are at least four copies of the HER2 gene in the cells, and the tumor is HER2 positive. In the case of equivocal HER2 score FISH can be diriment. Although the correlation between IHC and FISH is quite high, some factors (i.e., intra tumoral heterogeneity, technical errors) can lead to inconsistent results [28, 29]. The higher tumor grade found in HER2-positive tumors leads to faster growth and propagation of cancers with a normal amount of HER2. Although HER2 over-expression role remains still uncertain, it seems correlated with poor prognosis in GC [30–33].

First setting in her2 positive advanced gastric cancer

Trastuzumab

Trastuzumab is a monoclonal antibody targeting HER2, inducing an immune-mediated response that causes internalization and downregulation of HER2 resulting in inhibition of the proliferation of HER2 overexpressing tumor cell [34, 35]. It was approved for the treatment of HER2-positive advanced gastric cancer based on the result of the ToGA trial [36, 37]. This study, enrolled patients with advanced GC or gastroesophageal junction (GEJ) adenocarcinoma and HER2 overexpression (ICH3 + or FISH +) to receive first line trastuzumab in combination with chemotherapy (cisplatin and fluoropyrimidine) or chemotherapy alone. Trastuzumab was administered at a dose of 8 mg/kg on the first day of first cycle, followed by 6 mg/kg every 3 weeks. Overall survival represented the primary end point; secondary end point including progression free survival (PFS), overall response rate (ORR), time to progression and duration of response. Median OS was statistically better in patients treated with trastuzumab and chemotherapy than in patients treated with chemotherapy alone (13.8 months *vs* 11.1 months; $p = 0.0046$). The median PFS was 6.7 months and 5.5 months for trastuzumab plus chemotherapy and chemotherapy alone respectively ($p = 0.0017$); ORR was also significantly greater for trastuzumab plus chemotherapy group (47%) than for chemotherapy alone (35%) ($p = 0.0017$). Similar safety profile was recorded in the two groups. Post hoc exploratory analysis shown a different benefit related to the level of HER2 expression. Indeed, patient with IHC score 0 or 1 + and FISH +, obtained a lower or no benefit from adding trastuzumab to chemotherapy compared to patients with ICH 2 or 3 + and FISH +. Based on these results, trastuzumab was approved for patients with advanced GC and high HER2 expression level, who accounted for 7 to 17% of all individuals with GC, and the combination with platinum compounds and fluoropyrimidine is the standard first line treatment [2, 37, 38].

Several studies assessed the benefit of combining trastuzumab with chemotherapy. In a non-randomized phase II trial, Kurokawa et al. confirmed the advantage of trastuzumab in combination with S-1 plus cisplatin in OS (16 months) and PFS (7.8 months), with an ORR of 68% in HER2-positive advanced GC patients [39]. The combination of trastuzumab with capecitabine plus oxaliplatin was confirmed, achieving better median OS, PFS and ORR in patients treated with trastuzumab than chemotherapy alone [40, 41]. Another phase II study that combined trastuzumab with S-1 plus oxaliplatin, showed a median OS, a median PFS and an ORR of 18.1 months, 8.8 months and 70.7%, respectively [42]. Finally, Shah et al. in a phase III randomized trial, assessed the efficacy of high dose regimen of trastuzumab with cisplatin and capecitabine for patients with metastatic HER 2-positive GC, without evidence of benefit in OS and PFS [43].

Therefore, as a meta-analysis has highlighted, capecitabine or 5-FU can be replaced with S-1, and cisplatin with oxaliplatin maintaining the same efficacy in association with trastuzumab [44]. Moreover, as trastuzumab also seems to stimulate T cell response, it has been tested in association with antibodies to PD-1 [45]. In a phase II study on HER2 positive advanced GC patients, the combination of capecitabine, oxaliplatin, trastuzumab and pembrolizumab, was recorded an ORR of 83%, a median PFS of 11.4 months and a median OS not reached [46]. Results are being analyzed in a placebo-controlled, randomized phase III study.

Other anti HER 2 agents

After achieving successes for the treatment of breast cancer, other anti HER2 agents were evaluated in phase III trials as first line setting for patients with advanced HER2-positive GC.

Lapatinib is a dual tyrosine kinase inhibitor which interrupts the HER2/neu and epidermal growth factor receptor pathways [47]. It is used in combination therapy for HER2-positive breast cancer and was evaluated in the randomized phase III study for HER2-positive GC [48]. This trial

designed to assess lapatinib in combination with capecitabine and oxaliplatin for advanced HER2-positive gastric cancer failed to meet the primary endpoint of improved OS against chemotherapy alone, recording a median OS of 12.2 months and 10.5 months, respectively. Median PFS was 6 *vs* 5.4 months, response rate was 53% *vs* 39% and the duration of response was 7.3 *vs* 5.6 months in the combined treatment group compared to chemotherapy alone group [48]. In addition, in a subgroup analysis in younger and Asian origin patients, lapatinib was associated with significantly increased OS, whereas in patients undergoing to the prior gastrectomy removing pylorus, lapatinib may have had a negative impact due to lower absorption.

Pertuzumab is a recombinant humanized monoclonal antibody that blocks and inhibits the extracellular dimerization of HER2 with other HER family members. This inhibits ligand-initiated intracellular signaling, resulting in cell growth arrest and apoptosis [49]. It is used for the treatment in HER2-positive breast cancer, both in early and the metastatic stage [50, 51]. It was evaluated *versus* placebo, in addition to trastuzumab and chemotherapy in a randomized phase III study for patients with advanced GC HER2-positive [52]. The median OS reached with pertuzumab was 3.3 months higher than in the placebo group, but not statistically significant (14.2 *vs* 17.5, $p = 0.056$). Compared to breast cancer, these contrasting results could be due to heterogeneous pattern of HER 2-expression observed in GC.

Second line setting in her2-positive advanced gastric cancer

In a phase III trial, lapatinib was evaluated in association with paclitaxel in the second line setting for patients with advanced HER2-positive GC [53]. Lapatinib failed its primary endpoints in intention to treat population, although a significant improvement in OS was achieved in a subgroup of patients with baseline IHC3 + HER2 + cancer, with the combination therapy (14 *vs* 7.6 months, $p = 0.02$). Trastuzumab emtansine (T-DM1) is an antibody drug conjugate of trastuzumab linked to the tubulin inhibitor emtansine. A phase II/III trial compared T-DM1 with the physician's choice based on taxane regimen for HER2-positive GC in the second line setting [54]. The79% of patients in the taxane group and the 76% in the T-DM1 group had received trastuzumab in first line therapy. No improvement of the primary endpoint (OS) or of the secondary endpoint (PFS) was recorded. The evaluation of T-DM 1 plus capecitabine in first line treatment of HER2 + AGC is ongoing in a phase I/II trial (NCT01702558).

However, the results are discordant with breast cancer, suggesting the possibility of biological changes during first-line treatment which could be the basis of acquired resistance mechanisms to GC. Indeed, the success of such therapy achieved in HER2-positive breast cancer has not been reproduced in patients with advanced GC, highlighting the importance of understanding the mechanism of resistance to HER2 target therapy for selection patients who would benefit from these therapies in second line setting.

Trastuzumab is currently the only HER2 targeting agent that shown efficacy in a randomized phase III study. In patients with breast cancer HER2 positive, refractory to trastuzumab-based therapy, the continuation of trastuzumab in second line setting showed to prolong survival, and the use of trastuzumab beyond progression is an established strategy for this cancer [55]. Recently, this strategy was evaluated in HER2-positive advanced GC by several studies, but the results were contradictory.

In an observational study in patients with HER2-positive advanced GC, trastuzumab used beyond progression combined with chemotherapy has shown no significant improvement in OS and ORR compared to chemotherapy alone [56]. In a retrospective study, trastuzumab was evaluated as maintenance therapy in second line treatment in patients who had progressed on first line therapy with 5-fluorouracil(5-FU), platinum salt and trastuzumab [57]. A longer median PFS (4.4 months *vs* 2.3 months) and OS (12.6months *vs* 6.1 months), were recorded in patients treated with trastuzumab beyond progression than patients who had been treated with chemotherapy alone. In a multicenter retrospective study was confirmed that continuation of trastuzumab beyond progression, is significantly associated with the increase of PFS in selected subgroups of patients with HER2 IHC expression score of 3 + , intestinal type histology and a first line PFS > 6 months [58].

These results have been not confirmed in another study in which no difference in ORR, PFS and OR in patients treated with trastuzumab plus paclitaxel compared to paclitaxel alone in second line setting was observed [59]. The use of trastuzumab beyond progression was also evaluated in a randomized phase II trial where patients with advanced HER2-positive GC were randomized, after first line chemotherapy with fluoropyrimidine, cisplatin and trastuzumab, to receive weekly paclitaxel combined with trastuzumab or paclitaxel alone [60]. PFS (primary endpoint)not shown significantly increase in patients treated with trastuzumab or paclitaxel alone (3.19 *vs* 3.68 months), although patients that had not taken the anti HER2 agent for a period longer than 30 days, shown an increase in PFS with combination therapy compared to paclitaxel alone (4.68 *vs* 2.98 months).

Based on these results, albeit considering that HER2 expression can change after trastuzumab use in patients with advanced HER2-positive GC, phenomenon of resensitization of trastuzumab after a treatment free interval, should be considered [61].

Mechanism of resistance to anti-her2 agents

HER2 heterogenous expression

Highly heterogeneity and a complex genomic landscape of molecular alterations (15% HER2 positive) are typical features of gastric cancer [62]. HER2 expression and/or amplification is highly heterogeneous in GC biopsies and may negatively influence the response to anti-HER2 therapies [38, 63]. The mechanisms underlying HER2 expression heterogeneity are still widely unknown; the development of neoplastic clones with HER2 amplified/overexpressed in a primary HER2 negative tumor or silencing of HER2 expression in an area of a tumor with homogeneous HER2 amplification seem to be possible causes. Nevertheless, it is unclear if a higher rate of heterogeneous HER2 expression in endoscopic biopsies or surgical specimen associates with worse prognosis in patients treated with first-line chemotherapy combined to trastuzumab and guidelines assessing the type and grade of heterogeneity are lacking. The overall outcome of HER2 positive GC patients has been enormously influenced by the inhibition of HER2. However, the development of primary or secondary resistance during anti-HER2 causes disease progression within 12 months in about 75% these patients. Besides HER2 heterogeneous overexpression and/or amplification, many other different mechanisms may be involved in primary resistance such as specific point mutations or amplification that, leading to activation of different downstream mechanisms and hamper the inhibitory effect of HER2-directed agents (Fig. 2a) [64].

PI3KCA pathway

Loss of PTEN and/orgenomic aberrations of PI3KCA (*e.g.,* activating mutations of PIK3R1 and PIK3CA, encoding genes for PI3K p85α and p110α) can result in ineffective inhibition of HER2 due to aberrant activation of AKT-mTOR and the waterfall downstream. Actually, these alterations are linked to primary resistance to trastuzumab both in HER2 amplified cell lines and in HER2 amplified GC patients, suggesting to test other and more effective pharmacological strategies in these subjects [65–67]. No responses in patients to PTEN loss treated with trastuzumab were reported in these studies (Fig. 2b, c).

MET amplification/HGF hyperactivation

Amplification of MET or hyperactivation of the HGF(increases gene copy number and/or high serum HGF) may also be involved in the primary resistance in GC, as it

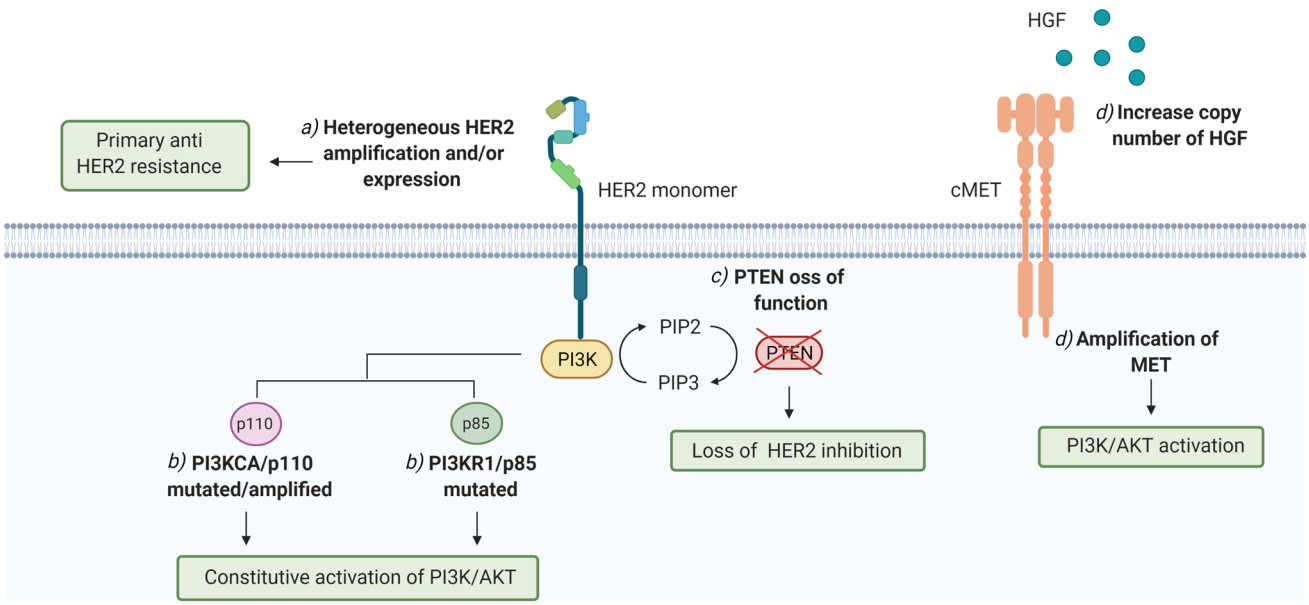

Fig. 2 Mechanisms of resistance to trastuzumab. **a** HER2 expression and/or amplification is highly heterogeneous in GC and this heterogeneity may negatively affect the response to HER2 blockage strategies leading to primary resistance. **b** Genomic aberrations in the PI3K pathway—activating mutations of PIK3R1 and PIK3CA, encoding genes for PI3K p85α and p110α—produce constitutive activation of the pathway, which will signal downstream to the nucleus regardless of trastuzumab binding to HER2. **c** PTEN is a tumor suppressor. Trastuzumab binding stabilizes and activates PTEN and consequently down-regulates the PI3K/Akt signaling pathway. If PTEN function is lost, PI3K remains constitutively active regardless of binding of trastuzumab to HER2 causing unresponsiveness to trastuzumab treatment. **d** c-Met is frequently co-expressed with HER2 in cell lines and its amplification or an increase of its ligand (HGF), contribute to trastuzumab resistance through sustained Akt activation. *Figure created with Biorender.com*

was suggested by the same resistance mechanism reported in HER2 amplified breast cancers (Fig. 2d) [68–70]. Interestingly, co-amplification of HER2 and HER1 is present in approximately 7% of GC and preclinical data have shown increased resistance to upfront trastuzumab in these cases.

Since the study of trastuzumab primary resistance has been limited by small and uncontrolled retrospective series, the confounding effects of the combined chemotherapy and the heterogeneity and multiplicity of its putative genomic mechanisms, to prospectively validate a multigene panel able to identify HER2 positive GC patients that may have primary resistance to trastuzumab remains of great importance (AMNESIA) included *EGFR/MET/KRAS/PI3K/PTEN* mutations and *EGFR/MET/KRAS* amplifications was tested in a multicenter, prospective, case–control study including 37 HER2-positive GC patients[71]. In this study, AMNESIA panel alterations were absent in sensitive patients and present in the 55% of the resistant patients ($p < 0.001$). Also, a significantly longer median progression-free (5.2 months *vs* 2.6 months, HR: 0.34 [95% CI 0.07–0.48]; $p = 0.001$) and overall survival (16.1 *vs*7.6 months, HR: 0.38 [95% CI 0.09–0.75], $p = 0.015$) were recorded in GC patients without panel alterations compared to the GC patients with positive panel. The predictive accuracy of the combined evaluation of AMNESIA panel and HER2 IHC was 84% versus 76% and 65%of AMNESIA panel and HER2 IHC separately. However, this study presents several limitation (such us retrospective nature, cost of the molecular screening, failure to detection rare mutations) that restrict the application of the panel in the clinical practice but which could be overcome by the ongoing prospective study (AMNESIA Global).

The increasing insights gained on the development of secondary resistance to HER2 inhibitors are even more intriguing. A comprehensive review of this topic has been recently reviewed [72]. Briefly, HER2 expression is not always consistent between primary tumors and metastases [73, 74]. Evidence suggests that a complete decline in HER2 expression can be observed in a substantial percentage of patients after exposure to trastuzumab [74], particularly in HER2 + classified as IHC2 + within FISH + . However, the need for HER2 reassessment at disease recurrence or disease progression is not considered mandatory in routine practice by any guidelines. Several gene alterations, such as acquired HER2 mutations, FGFR amplification, HER3 overexpression, and the activation of the MAP/ERK downstream pathways, as well as the upregulation of different micro RNAs, may contribute to the development of acquired resistance to HER2-targeted therapies [75–81].

Finally, preclinical evidence suggest that epithelial-to-mesenchymal transition may be involved in HER2-inhibition secondary resistance [82, 83]. Given the benefit given from trastuzumab and other HER2-inhibitors, such as trastuzumab deruxtecan to GC patients, future efforts in developing novel experimental strategies are urgently needed to overcome primary and secondary resistances.

New screening techniques

Despite numerous progresses, the clinical outcome of GC patients still remains poor and development of better diagnostic, prognostic and disease monitoring tools are crucial for its improvement [4]. Tissue simple were the main sources for evaluating tumor-associated genetic alterations in these patients albeit severely limited by the invasive nature and inability to reflect tumor heterogeneity [37]. Recently, other methods as circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), extracellular domain (ECD) of HER2 and new imaging agents, showed prognostic value several cancer types and/or to be used as non-invasive device to monitor disease progression during therapy [84–87].

Molecular method

Circulating tumor DNA is found in the bloodstream and refers to DNA that comes from cancerous cells and tumors [88]. ctDNA can originate from primary tumor cells, CTCs and/or distant metastases and provides various information relating to genetic alterations (such as mutations, amplifications, rearrangements), methylation status of genes, change in copy number (CNV) [89]. CtDNA represents a fraction of free circulating DNA (cfDNA) and unlike the latter, which is highly represented in advanced disease, ctDNA has also been detected in the plasma of early-stage cancer patients [90–92].

Circulating tumor DNA analysis allowed to identify tumor molecular traces circulating in the body fluids through liquid biopsy guaranteeing a deeper insight on the cancer heterogeneity, early biomarker detection, therapeutic target detection, real-time evaluation of treatment response and possible resistance and prognosis. With the use of modern techniques, such as digital droplet PCR, next generation sequencing, the concordance rate of HER2 expression between ctDNA and tumor tissue has increased from around 60 to 90% [93–95]. This discrepancy could be explained in part by the high heterogeneity of HER2 expression in GC cells; confirmation of the ctDNA validity could allow to use it as alternative method HER2 screening. Furthermore, as shown in recent studies, ctDNA could represent a complementary tool to predict the response to anti HER2 treatment and evaluate its effectiveness through evaluation over time. Reliable data and future confirmations are needed [95, 96].

Circulating tumor cells are cells that shed into the vasculature or lymphatics from a primary tumor and is carried around the body in the blood circulation. The enumeration of CTCs represents an effective prognostic and predictive

biomarker in numerous types of cancers, including GC [97–99]. Moreover, it has been shown that CTCs may represent the genetic compositions of both primary and metastatic tumors, and the real-time assessment of prognostic and therapeutic biomarkers on CTCs may be useful to improve the clinical outcome of these patients and also to have a significant effect on targeted cancer therapy [84, 85]. A strongly concordance of HER2 amplification between CTCs and tissue has been reported, making it considered a potential alternative to tumor biopsy although a subsequent study did not confirm this accordance [100, 101]. Another valid alternative to tissue biopsy seems to be represented by extracellular domain of HER2 whose serum concentration appears to significantly correlate with tissue levels of HER2 protein [102]. Moreover, as several studies suggested, HER2 ECD level could become a predictive marker of response to anti HER2 therapies [103, 104].

Imaging methods

HER2 can exhibit discordant expression within the same cancer site or between different sites, leading to sampling errors and confusion in therapeutic choice. Positron emission tomography PET-based measurement of HER2 expression using the radiolabeled mAb, [89Zr] trastuzumab, has shown firstly in breast cancer and then in GC, several advantages over biopsy-based methods. [89Zr] trastuzumab PET directly assesses the availability of HER2 to be bound to trastuzumab; thus, it is potentially a more reliable predictor of response to trastuzumab therapy. Furthermore, [89Zr] trastuzumab PET appears to be able to detect intra-tumor (within the same lesion) and inter-tumor (among multiple lesions) heterogeneity of HER2 expression (within the resolution limits of PET). As a non-invasive technique, it can be easily repeated to assess the response to treatment [105, 106].

Emerging therapeutic agents

Trastuzumab deruxtecan

Trastuzumab deruxtecan (DS-8201a) is an antibody–drug conjugate composed of an anti-HER2 antibody, a cleavable tetrapeptide-based linker, and a cytotoxic topoisomerase I inhibitor [107]. In a first phase I study, trastuzumab deruxtecan was administered every 3 weeks (at dose of 0.8 to 8.0 mg/kg intravenously) in patients with breast cancer and GC [108]. Grade ≥ 3 myelosuppression has been recorded most, while febrile neutropenia, intestinal perforation and cholangitis occurred in one patient each. In patients pretreated with multiple lines of chemotherapy, ORR and disease control rate were 43% and 91%, respectively. In another phase I study in patients with advanced GC, trastuzumab deruxtecan was administered at least one dose of 5.4 or 6.4 mg/kg every 3 weeks [109]. Serious treatment adverse events were recorded in 25% of patients, in line with the results of a previously phase I study, except four cases of pneumonitis [110]. Response to treatment was also confirmed with ORR of 43.2%.

Efficacy and safety of trastuzumab deruxtecan was compared to physician's choice (irinotecan 150 mg/m^2 bi-weekly or paclitaxel 80 mg/m^2 weekly) in a randomized phase II trial on advanced HER2-positive CG patients previously treated with two or more regimens including trastuzumab [111]. Primary endpoint was ORR resulted of 40.5% in trastuzumab deruxtecan group *vs*11.3% in control arm. Median OS and PFS were 12.5 and 5.6 months in the fam-trastuzumab deruxtecan arm compared with 8.4 and 3.5 months for those receiving irinotecan or paclitaxel. A manageable safety profile was recorded with predominant hematologic or gastrointestinal adverse events (AEs). Based on these results, fam-trastuzumab deruxtecan recently received the FDA approval for patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal (GEJ) adenocarcinoma previously treated with a trastuzumab-based regimen.

Several studies have shown that trastuzumab deruxtecan is effective not only against tumor cells positive for HER2 protein, but also in the presence of HER2-positive cells, against those negative for such expression [112]. This effect seems due to the internalization of trastuzumab deruxtecan by HER2 positive cells, the release of deruxtecan (DXd) into the cytoplasm of these cells and the subsequent transfer of the released of DXd into adjacent HER2 negative cells [113]. Indeed, as has been demonstrated in previous studies, the efficacy of trastuzumab deruxtecan has been proved against tumors that express HER2 withoutHER2 amplifications [112]. This could be significant when there is not homogeneity between HER2 amplification and HER2 expression.

Furthermore, the independence of trastuzumab deruxtecan from the presence of other gene alterations that by activating alternative pathways inducing resistance to trastuzumab suggests the possibility of this agent to overcome this resistance. A trial evaluating safety and efficacy of trastuzumab deruxtecan alone or in combination with chemotherapy and/or immunotherapy in HER2-positive advanced or metastatic gastric/gastroesophageal junction adenocarcinoma patients is currently ongoing (NCT004379596).

Margetuximab

Margetuximab is a chimeric, Fc-engineered, immune-activating anti-HER2 mAb created for increased binding to activating Fcγ receptor IIIA (CD16A) and decreased binding to

inhibitory Fcγ receptor IIB (CD32B) relative to trastuzumab with the aim of improving response rates. The toxicity profile, maximum tolerated dose, pharmacokinetics, and antitumor activity of margetuximab has been evaluated in a phase I trial in patients with HER2-overexpressing carcinomas over half of which received at least one prior anti-HER2 therapy in the metastatic setting [64]. Grade 2 toxicities were the most common while The AEs included increased lipase, blood amylase, blood alkaline phosphatase lymphocyte decreased, and infusion-related reaction, rarely of grade 3/4. No cardiotoxicity was observed.

Margetuximab demonstrated evidence of clinical activity despite the heavily pre-treated population (a median of three prior therapies): seven patients including one with gastroesophageal cancer, showed a confirmed partial response with ORR of 12%. These results have therefore proved that margetuximab as a single agent have a good potential for antitumor activity after progression to other anti-HER2 regimens. Subsequently, margetuximab has been tested in combination to pembrolizumab in HER2-positive advanced GC patients, as second line therapy showed after a median follow-up of 20 months, a manageable safety profile with grade > 3 AEs in about 9% of patients [114]. The response rate was approximately 20% in the 92 evaluable patients with HER2 3 + and more frequent if accompanied by the expression of PD-L1. It should be noted that all the responses have been reported in patients to the immunohistochemical evaluation and that the responses were more. Very preliminary data reported a median PFS and OS of 3 and 13 months, respectively [115]. Another phase II/III randomized trial is ongoing to determine the efficacy of margetuximab combined with an anti-PD-1 monoclonal antibody, target drugs and/or chemotherapy in patients with HER2-positive GC [116].

ZW25

ZW25 is an antibody that simultaneously and bi-specifically binds two HER2 epitopes: ECD4 and ECD2, transtuzumab and pertuzumab binding domains, respectively [117]. Preclinical studies suggested that ZW25 might effectively silence HER2 signaling more than trastuzumab or pertuzumab as well as stimulating the immune system. In a phase I trial in pretreated patients with HER2-positive gastroesophageal cancer ZW25 has been tested showing encouraging results: 44% of ORR and 56% of disease control rate [118]. The most common treatment-emergent AEs in the entire cohort were infusion reaction (55%), fatigue (38%), diarrhea (52%), and nausea (26%). AEs were all grade 1–2 except for in one patient who had reversible grade 3 hypophosphatemia, arthralgia, and fatigue. There were no serious AEs or discontinuations related to treatment. Therefore, ZW25 can be used for patients with HER2-overexpressing gastroesophageal adenocarcinoma in combination with chemotherapy. A trial is ongoing (NCT04276493) to evaluate the safety, tolerability and exploratory antitumor effect of ZW25, tislelizumab (antibody againstPD-1) and chemotherapy combination in patients with HER2-positive gastric/gastroesophageal junction adenocarcinoma.

The results of these studies re-open an interest that seemed to have greatly diminished in the strategy of blocking HER2 in gastric pathology. Indeed, 10 years after the publication of the TOGA randomized trial that demonstrated the superiority of the combination of chemotherapy and trastuzumab in the first line in HER2-positive gastric pathology, no other study had confirmed the validity of the strategy either in the first (HELOISE, LOGIC, JACOB) nor in the second line (TYTAN, GATSBY, T-ACT). These innovative molecules appear promising in the GC treatment, with the possibility of synergistic effect on immune system.

Tyrosine kinase inhibitors (TKIs)

Recent trials have focused on pan-HER inhibitors, considering that studies have suggested that the antitumor efficacy of pan-HER blockade is more promising than that of HER2 blockade alone [119].

Afatinib (oral protein kinase inhibitor acting on, HER2, HER3, HER4and EGFR) was assessed in a phase II trial enrolling patients with esophagogastric cancer (prior treated with trastuzumab), providing a mild therapeutic advantage (ORR 10%) [120] Because of its additional activity against HER2, it is being investigated for breast cancer as well as other EGFR and HER2 driven cancers including HER2-positive gastrointestinal tumors that are resistant to trastuzumab [121]. Currently, afatinib and paclitaxel in combination are being tested in patients HER2 GC progress to trastuzumab and chemotherapy (NCT02501603; NCT01522768).

An irreversibly target of TKI, Poziotinib, was evaluated in a phase I/II trial co-administrated with transtuzumab and paclitaxel enrolling patient with advanced HER-2 positive GC not-naïve to treatment (*i.e.,* prior one line of chemotherapy, regardless to trastuzumab). A median PFS and OS of 13 and 29.5 weeks, respectively, was recorded [122]. It worth noting that Poziotinib blocks signal transduction of HER2 as well as EGFR and HER4.

The use in monotherapy of Dacomitinib, an irreversible pan-HER inhibitor, was recently assessed in a multicenter phase II trial demonstrating efficacy in HER2-positiveGC. A median PFS of 2.1 months and OS of 7.1 months has been reached in patients that had received from one to more than three prior chemotherapy regimens [123].

HER2-directed immunotherapy

Immune checkpoint inhibitors (ICIs) against programmed cell death-1 (PD-1) and its ligand (PDL1 or B7-H1),

Table 1 Current and emerging therapeutic agents in HER2-positive gastric cancer patients

Drug	Type	Target	Therapeutic indication	Studies in gastric or gastroesophageal junction cancer		
				Positive	Negative	Ongoing
Trastuzumab (HERCEPTIN)	Humanized antibody	HER2/neu	- HER2-positive breast cancer - HER2-positive metastatic G/GEJ cancer	TOGA (2010) Kurokawa et al. (2014) Sha et al. (2017) Palle et al. (2017) Narita et al. (2017)	Li et al. (2016) Horita et al. (2019)	NCT04464967 INTEGA/NCT03409848
Lapatinib (TYKERB)	Tyrosine kinase inhibitor	HER2/neu, EGFR	In combination with: - Capecitabine in advanced or metastatic HER-2 positive breast cancer - Letrozole in HER-2 positive metastatic breast cancer		TRIO-013/LOGiC (2016) TyTAN (2014)	
Pertuzumab (PERJETA)	Humanized antibody-	HER 2/neu	In combination with trastuzumab and docetaxel in HER2-positive metastatic breast cancer		JACOB (2017)	
Trastuzumab emtansine (KADCYLA)	Humanized monoclonal antibody -microtubule inhibitor	HER 2/neu	Unresectable or metastatic HER2-positive metastatic breast cancer		GASBY (2017)	
Trastuzumab deruxtecan	Humanized monoclonal antibody -topoisomerase inhibitor	HER 2/neu	Unresectable or metastatic HER2-positive metastatic breast cancer and G/GEJ cancer	DESTINY-Gastric01/ NCT03329690		DESTINY-Gastic03/ NCT04379596
Margetuximab	Chimeric IgG monoclonal antibody	HER 2/neu				NCT02689284 MAHOGANY/ NCT04082364
ZW25	Bispecific antibody	HER 2/neu	Unresectable or metastatic HER2-positive breast cancer			NCT04276493
Afatinib (GILOTRIF)	Tyrosine kinase inhibitor	HER2/neu, EGFR	Unresectable or metastatic NSCLC			NCT01522768
Poziotinib	Tyrosine kinase inhibitor	HER2/neu, EGFR and Her 4				Kim et al. (2019)
Dacomitinib (VIZIMPRO)	Tyrosine kinase inhibitor	EGFR	Unresectable or metastatic NSCLC	Oh et al. (2016)		

Table 1 (continued)

Drug	Type	Target	Therapeutic indication	Studies in gastric or gastroesophageal junction cancer		
				Positive	Negative	Ongoing
Pembrolizumab (KEYTRUDA)	Humanized antibody	Programmed cell death protein 1 (PD-1)	- Adjuvant or metastatic melanoma - Unresectable or metastatic NSCLC - Unresectable or metastatic HNSCC - Unresectable or metastatic UC - Unresectable or metastatic RCC - Unresectable or metastatic CRC			NCT02689284 KEYNOTE-811/ NCT03615326

EGFR Epidermal growth factor receptor, *G/GEJ* gastric/gastroesophageal cancer, *RCC* renal cell carcinoma, *NSCLC* non-small cell lung cancer; *UC* urothelial cancer

has proven efficacy in several solid cancers, and seems to become a potential option in gastric cancer treatment [124]. Although, several studies have tested the efficacy of immunotherapy in GC, data concerning specifically patients with HER2-positive GC are limited. In the phase III KEYNOTE-061 trial, pembrolizumab did not demonstrate significant improvement in overall survival compared to paclitaxel as second-line therapy for advanced gastric/gastroesophageal junction(G/GEJ)cancer with PD-L1 combined positive score (CPS) ≥ 1 [125]. However, pembrolizumab had a better safety profile than paclitaxel. In the phase III KEYNOTE-062 trial pembrolizumab used as a first-line therapy, in patients with advanced G/GEJ cancer PD-L1positive HER2-negative, resulted noninferior in overall survival compared with standard chemotherapy [126]. Additionally, pembrolizumab showed significant improvement in OS among patients that had tumors with PD-L1 CPS ≥ 10.

Likewise, completed trial JAVELIN Gastric 300, showed that treatment of patients with G/GEJ PFS compared with standard chemotherapy [127].

Contrariwise, based on the results of the phase III ATTRACTION-2 trial, nivolumab was approved to treat advanced GC as a third-line therapy in Japan [128, 129]. In this study, patients with advanced G/GEJ cancer refractory to at least two previous chemotherapies, received nivolumab alone or placebo recording an OS of 5.26 months and 4.14 months, respectively. An exploratory subgroup analysis later assessed the efficacy of nivolumab in patients previously treated with trastuzumab assuming to be HER2-positive. In this subgroup, the median OS was significant longer in patients receiving nivolumab *vs* placebo (8.3 months *vs* 3.1 months). Whereas, in presumed HER2-negative patients, OS was 4.8 months and 4.2 months with nivolumab or placebo, respectively [130].

As a consequence, interim results of the phase II ATT RACTION-4 trial showed that nivolumab combined with standard chemotherapy could represent promising efficacy as a first-line therapy for unresectable advanced or recurrent HER2-negative GEJ cancer [131]. Indeed, ORR was 57.1% with nivolumab plus SOX and 76.5% with nivolumab plus CAPOX. Median OS was not reached in both groups and median PFS was 9.7 months and 10.6 months, respectively. Based on these results, the ATTRACTION-4 trial has proceeded to phase III to compare nivolumab plus standard chemotherapy versus placebo plus standard chemotherapy. Another phase III trial is ongoing to evaluate the efficacy and safety of nivolumab combined with standard chemotherapy or ipilimumab (anti-CTLA-4) as a first-line therapy in patients with advanced GEJ cancer [132].

In a phase II trial, patients with HER2-positive advanced GC treated in first line chemotherapy by CAPOX and trastuzumab in combination with pembrolizumab has been reported an ORR and 6-month PFS of 88.6% and 74%, respectively [46].

An ongoing phase III trial (KEYNOTE 811 study) is comparing chemotherapy plus trastuzumab with or without pembrolizumab (NCT03615326), while another phase II trial is assessing the efficacy of trastuzumab, nivolumab and ipilimumab or nivolumab combined to the standard regimen (FOLFOX chemotherapy and trastuzumab) (NCT03409848) as first line treatment strategies in advanced or metastatic esophagogastric adenocarcinoma.

Many other clinical trials to evaluate the safety and efficacy of a variety of immune checkpoint inhibitors in patients with advanced G/GEJ cancer such as tremelimumab (anti-CTLA-4), avelumab (anti-PD-L1) durvalumab (anti-PD-L1), and relatlimab (anti-LAG3) are ongoing [127, 133–136]. Current and emerging therapeutic agents are resumed in Table 1.

Conclusion

A large portion of patients with gastric cancers are initially diagnosed with unresectable or metastatic disease. Over the past decades, systemic treatments have led to modest improvement in overall survival when compared to best supportive care alone. Trastuzumab, remains the only molecular-targeted treatment that prolong OS and PFS in HER2-positive gastric cancer, but the development of drug resistance represents a major limitation. Tumoral heterogeneity seems to be the main underlying trastuzumab resistance mechanism and composite testing strategies are needed to properly identify and overcome it. New screening methods, such as, circulating tumor cells circulating tumor DNA, extracellular domain of HER2 and new imaging agents, could profoundly improve the therapeutic impact in gastric cancer allowing to select in a less invasive way patients who could benefit from anti HER2 therapy even beyond progression. Moreover, newly investigated therapeutic agents such as novel drug-antibody conjugates and anti-HER2 mAb combination therapies with immunotherapy could represent interesting future perspectives.

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Declarations

Conflict of interest No author declares any conflict of interest.

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