

Targeting HER-2 in gastric cancer – incorporation of trastuzumab into the treatment of operable disease

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Abstract: Gastric cancer is the fourth most common malignancy and second leading cause of cancer death world-wide, and is therefore a significant global health problem. Radical surgery with a D2 lymph node dissection is an accepted standard approach, and is a key component of multimodality therapy. Perioperative chemotherapy significantly improves 5-year overall survival compared with surgery alone. A significant improvement in overall survival has also been demonstrated with postoperative 5-fluorouracil-based chemoradiotherapy and adjuvant oral S-1 chemotherapy; approaches commonly used widely in North America and Japan, respectively. Approximately 10% to 20% of gastric cancers and 20% to 30% of esophago-gastric junction cancers are HER-2 positive. The effect of HER-2 overexpression and *HER-2* gene amplification on gastric cancer prognosis remains unresolved. The results of the first randomized phase III trial of trastuzumab, a monoclonal antibody directed at the HER-2 receptor, in patients with metastatic gastric cancer were reported recently. Response rate, median progression-free survival, and median overall survival were all significantly improved with the addition of trastuzumab to a cisplatin/fluoropyrimidine doublet. Evaluation of trastuzumab in HER-2 positive operable esophago-gastric cancer is now underway. Lapatinib, a small-molecule inhibitor targeting EGFR and HER-2 is well established in the treatment of trastuzumab-refractory HER-2 positive breast cancer and phase III trials in advanced esophago-gastric cancers are ongoing. Novel, small molecule pan-HER inhibitors have entered early phase evaluation and the antibody-drug conjugate, trastuzumab-DM1, and pertuzumab, a monoclonal antibody which prevents HER-2/HER-3 dimerization, are currently undergoing phase II/III evaluation in breast cancer. It is our hope that advances in the targeted treatment of HER-2 positive breast cancer will be replicated in HER-2 positive esophago-gastric cancers.

Keywords: gastric cancer, adjuvant, perioperative, chemotherapy, trastuzumab, HER-2

Introduction

Approximately 1 million new cases of gastric cancer were diagnosed in 2008, making gastric cancer the fourth most common malignancy in the world, after lung, breast and colorectal cancers.¹ The highest incidence is detected in Eastern Asia, Eastern Europe, and South Africa, the lowest in North America.² Regional differences have been attributed to environmental factors, such as high dietary intake of salt, and smoked or cured meats. In addition, there are significant differences in incidence across the socioeconomic groups. Although the incidence and mortality of gastric cancer have been steadily decreasing since 1975, advanced stage at presentation, frequent patient co-morbidities, and the relative chemoresistance of the disease, have all contributed to the poor overall survival (OS).

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The main identified risk factors for gastric cancer are male sex, *Helicobacter pylori* infection, high levels of dietary salt and nitrates, smoking, medical conditions such as atrophic gastritis and pernicious anemia, previous gastrectomy, and family history. Obesity has been identified as a probable risk factor for gastric cardia and junctional tumors, most likely through increased gastroesophageal reflux and subsequent Barrett's metaplasia.³

Sporadic gastric cancers arise through a multi-step process, accumulating mutations in genes regulating key biologic processes, such as those regulating cell cycle, apoptosis, and proliferation. The tumor suppressor gene, *p53*, plays an important role in cellular response to DNA damage, leading to cell cycle arrest and apoptosis. Mutations in *p53* or loss of this gene are found in more than a half of sporadic diffuse and intestinal types of gastric cancer.⁴ Other genes that are mutated or suppressed include *CDH1*, *SMAD4*, *FHIT*, and *CDKN2A*, a cyclin-dependent kinase inhibitor. Chromosomal aberrations do not differ between *H. pylori* positive or negative gastric cancers.

The human epidermal growth factor receptor 2 (HER-2) is a transmembrane receptor tyrosine kinase involved in signal transduction and cell growth, encoded by *ErbB2* gene. The timing of *HER-2* gene amplification in gastric carcinogenesis is uncertain. However, as HER-2 overexpression and amplification is detected in early⁵ as well as in metastatic gastric cancer⁶ and there is high concordance between primary tumors and paired metastatic sites,⁷ this would suggest that it is not a late event.

HER-2 overexpression was first detected in gastric cancer cells in 1986.⁸ In the early 1990s, the role of HER-2 as a potential therapeutic target in gastric cancer was recognized when antibodies blocking HER-2 were reported to inhibit the growth of human gastric tumor cells in vitro, and of established human HER-2 positive tumors in mice xenografts.⁹ However, it was not for another decade when trastuzumab, a humanized monoclonal antibody directed at HER-2, already licensed in breast cancer, was demonstrated to enhance the cytotoxic effects of doxorubicin in gastric cancer cells and to show direct anti-proliferative activity.^{10,11} These and other reports from the preclinical setting precipitated further evaluation of trastuzumab in clinical trials. HER-2 overexpression was found in approximately 20% of gastric and 33% of esophago-gastric junction (OGJ) cancers in the screening study for the pivotal ToGA trial.¹² However, more recent reports have suggested that the rate of HER-2 overexpression may be lower, especially in distal gastric cancers.⁵

This review will focus on trastuzumab and its incorporation into current adjuvant treatment strategies for resectable gastric cancer.

Current strategies for localized gastric cancer

Surgery

Surgery remains critical to the successful treatment of resectable gastric cancer. The optimal extent of lymph node dissection during curative resection for stomach cancer has been a matter of debate for several decades. Japanese surgeons advocate the "D2 resection" comprising en-bloc resection of perigastric nodes and nodes along the main branches of the celiac axis. However, outside Japan, despite radical lymph node dissection, survival remains poor, with 15-year survival of 33% for stage II and 19% for stage IIIA disease reported in a randomized Dutch trial comparing D1 versus D2 lymph node dissection. Although D2 lymphadenectomy was associated with lower loco-regional recurrences (13% versus 15% for D1 group) and lower local and distant recurrences (17% compared with 26% for D1 group, $P = 0.015$ for overall recurrence pattern), a significantly higher surgical mortality and complication rate was observed (10% and 43% compared with 4% and 25% for D2 and D1 groups, respectively) and no difference in overall survival was detected.^{13,14} Pancreatico-splenectomy was often performed as a part of the D2 lymphadenectomy in this trial, which is likely to have contributed towards the higher surgical mortality. Of note, in the subgroup of patients undergoing D2 resection without pancreatectomy or splenectomy, a significant survival benefit over D1 resection was reported. D2 dissection without resection of the pancreas and spleen is now a standard procedure in patients with resectable tumors. A more extensive lymphadenectomy with para-aortic nodal dissection did not improve overall and recurrence-free survival rates compared with D2 dissection alone.¹⁵

Several approaches incorporating chemotherapy and radiotherapy into multimodality strategies have been investigated to improve R0 resection and reduce the rate of local and distant recurrences.

Adjuvant chemoradiotherapy

Adjuvant chemoradiotherapy was investigated by the US Southwest Oncology Group (Intergroup-0116) trial which randomized 556 patients with resected adenocarcinoma of stomach or OGJ to adjuvant chemoradiotherapy or observation only. Patients in the chemoradiotherapy arm received 1 cycle of 5-fluorouracil (5-FU) and leucovorin (LV)

chemotherapy before, and 2 cycles after chemoradiotherapy with concomitant 5-FU/LV.¹⁶ The median survival was 36 months in the chemoradiotherapy arm compared with 27 months in the observation group (hazard ratio [HR] 1.35, 95% confidence intervals [CI]: 1.09–1.66, $P=0.005$) and this benefit was maintained after 10 years of follow-up.^{16,17} Only 10% of the patients in this study underwent recommended D2 dissection and 54% had less than D1 dissection, therefore it is unclear whether the radiotherapy is necessary after optimal surgery. Several small, probably underpowered studies have investigated the addition of radiotherapy to adjuvant 5-FU or cisplatin-based chemotherapy after D2 resection without demonstrating any significant benefit.^{18,19} The role of radiotherapy after optimal surgery will be established by the results of the Korean ARTIST study of adjuvant chemotherapy compared with adjuvant chemoradiation after D2 resection, which are expected shortly. Although postoperative chemoradiotherapy is commonly practiced in US, it has not gained wider acceptance in Europe or Asia.

Perioperative chemotherapy

Perioperative chemotherapy was investigated by the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial in which 503 patients with adenocarcinoma of stomach, lower esophagus, or OGJ were randomized to 3 cycles of chemotherapy with 5-FU, cisplatin and epirubicin (ECF) before and after radical surgery, or to surgery alone.²⁰ A significant improvement in 5-year OS (23% versus 36.3%, $P=0.009$ for control versus perioperative arms, respectively), higher likelihood of progression-free survival (PFS), higher rate of curative surgery, reduced tumor size, and less advanced nodal disease were reported in the perioperative chemotherapy group. The benefit of perioperative strategy was confirmed by the results of the FNCLCC/ACCORD07/FFCD 9703 trial, reporting a similar improvement in 5-year survival with perioperative 5-FU and cisplatin (CF).²¹

Adjuvant chemotherapy

Adjuvant chemotherapy has been investigated in over 30 trials using various agents, either alone or in combination, with the majority reporting no benefit. However, a meta-analysis of individual patient data from 3838 patients in 17 trials reported a benefit from adjuvant chemotherapy compared with surgery alone, with an estimated median OS of 7.8 years following adjuvant chemotherapy compared to 4.9 years following surgery, and absolute survival benefit with adjuvant chemotherapy of 5.8% at 5 years.²² A randomized phase III Japanese trial of adjuvant chemotherapy with

oral S-1 compared to D2 gastrectomy alone demonstrated significant improvement in OS (from 61% to 72% at 5 years) and established this treatment approach as a standard in Japan.^{23,24} Of note, the OS with surgery alone was much higher than reported in studies outside Japan, so that these results cannot currently be extrapolated to a non-Japanese population.

Targeting HER-2 in gastric cancer

Despite the important advances establishing multimodality treatment for operable gastric cancer, 5-year OS remains poor and new systemic treatment options are urgently needed. Refinement of established adjuvant and perioperative chemotherapy and chemoradiation regimens may confer additional survival benefits, but the magnitude of the gains are likely to be limited. As such, attention has shifted to targeted agents that have known efficacy in other solid tumors. One such target is the HER-2 transmembrane tyrosine kinase receptor, a member of the epidermal growth factor receptor (EGFR) family. The HER-2 receptor is the product of the *c-erbB-2/neu* oncogene located on the long arm of chromosome 17, which is involved in signal transduction, cell proliferation, migration, and survival. No ligand has been identified for the HER-2 receptor; instead, the receptor must homodimerize (ligand-independent dimerization) or heterodimerize with another member of the EGFR family, such as HER-3 or HER-4 (ligand-dependent dimerization) to undergo activation, autophosphorylation, and triggering of the downstream signalling cascade. Crystal structure studies of HER-2 receptor have revealed fixed conformation resembling ligand-activated state, capable of interacting with other EGFR family members in the absence of direct ligand binding.^{25,26}

HER-2 can enhance signalling by forming a heterodimer with HER-3, where this has been reported to be the most mitogenic dimer.²⁷ HER-2 can additionally increase the binding affinity of EGFR or HER-3/4 to their ligands.^{28,29} Binding of the ligand, neuregulin, to HER-3 allows for heterodimerization with HER-2 and subsequent transphosphorylation. Activated HER-3 is capable of activating downstream pathways, and in particular, is a potent activator of phosphatidylinositol-3-kinase (PI3K)/Akt pathways.³⁰

HER-2 overexpression or amplification was reported in approximately 20% of gastric and 33% of OGJ tumors in patients screened for the ToGA trial.¹² However, more recent reports suggest that it is a less common finding, especially in distal gastric cancers, where in one study, only 7% of tumors were reported to be HER-2 positive, compared with 24% of OGJ cancers.⁵ HER-2 overexpression is more common

in intestinal type (32%) than in diffuse (6%) or mixed type gastric cancers (20%).

Pharmacology of trastuzumab

Trastuzumab, a fully humanized monoclonal antibody directed to the extracellular domain of HER-2 receptor was developed in the 1990s after preclinical studies demonstrated an antitumor effect in HER-2 positive breast cancer cell lines.³¹ Trastuzumab binding to the extracellular domain of HER-2 initiates antibody-dependent cell-mediated cytotoxicity, as well as inhibition of downstream HER-2 receptor signalling, leading to cell cycle arrest, reduction of angiogenesis and cell death.³⁰

In vitro, trastuzumab inhibits the proliferation of HER-2 amplified gastric cell line NCI-N87 and demonstrates synergistic effect with cisplatin and additive effects with oxaliplatin and 5-FU on the SNU216 gastric cell line.^{10,32} The synergistic effect in combination with cisplatin and capecitabine provided rationale for the phase III ToGA trial. Treatment with trastuzumab produces a significant reduction of HER-2 phosphorylation and reduction in phosphorylated forms of downstream effector molecules such as p-STAT, p-Akt, and p-ERK in these cell lines. In addition, trastuzumab demonstrates antibody-dependent cellular cytotoxicity in the NCI-N87 cell lines.³³

Trastuzumab in gastric cancer

In an early report on gastric cancer, HER-2 protein expression, detected by immunohistochemistry (IHC), was positive

in 11.9% of gastric tumors with a negative correlation with survival reported.³⁴ However, several other studies have explored the prognostic impact of HER-2 overexpression or amplification, with conflicting results. The largest, a combined study from the UK and Germany of 924 resected gastric cancer specimens was unable to determine any prognostic value of HER-2, and less than 10% of cases were reported to be HER-2 positive.³⁵ These conflicting results most likely reflect the use of nonstandardized assays, intratumoral heterogeneity of the HER-2 staining pattern and variation in tissue processing with subsequent differences in the HER-2 scoring between these studies. A standardized scoring system for gastric cancer was developed and validated for the ToGA trial and has now been accepted into routine clinical practice.^{36,37} The recommended scoring for HER-2 in advanced gastric cancer is summarized in Table 1. The notable differences between gastric and breast cancer HER-2 scoring relate to an increased frequency of incomplete membranous staining and intratumoral heterogeneity of HER-2 expression in gastric cancer.³⁶

In the pivotal randomized phase III ToGA trial of trastuzumab in gastric cancer, HER-2 status was evaluated in 3807 patients by IHC and fluorescence in situ hybridization (FISH). HER-2 positivity was defined as either IHC 3+ or FISH positive (equal or more than 2 HER-2 gene signals to centromere 17 signals, $HER2/CEN17 \geq 2$) in patients with IHC 0, 1+ or 2+. Patients with IHC 0 and 1+ disease were eligible if the cancer was FISH+, which is in contrast to guidelines from American Society of Clinical Oncology (ASCO) for breast cancer (IHC 3, IHC 2+ with FISH +, $HER2/CEN17 \geq 2.2$).³⁸ Five

Table 1 The recommended scoring for HER-2 in advanced gastric cancer

Evaluation criterion			
Number of cells considered positive	5 cells in biopsy 10% in surgical specimen		
Pattern of membrane staining	Distinct and regular Often lateral or U-shaped reactivity		
Score assignment	Negative	0–1+	No/faint reactivity, only in part of membrane
	Equivocal	2+	Weak/moderate, complete/basolateral reactivity
	Positive	3+	Moderate/strong, complete/basolateral reactivity, visible at low magnification
Histologic tumor type/site	32% interstitial type 20% mixed type 6% diffuse type (signet-ring usually negative) 20% gastric origin 33% OGJ		
Heterogeneity	Frequent within the same tumor		
In situ hybridization	FISH – most widely used in reported studies CISH, SISH, BDISH – allow for morphologic evaluation in addition to gene amplification $HER2/CEN17$ ratio ≥ 2		

Abbreviations: OGJ, esophagogastric junction; FISH, fluorescence in situ hybridization; CISH, chromogenic in situ hybridization; SISH, silver in situ hybridization; BDISH, brightfield double in situ hybridization.

hundred and eighty-four eligible patients were randomized to receive cisplatin 80 mg/m² iv on day 1 with fluoropyrimidine (capecitabine 1000 mg/m² orally twice daily for 14 days or 5-FU 800 mg/m² on days 1–5) with or without trastuzumab on a 3-weekly schedule. Patients received up to 6 cycles of chemotherapy with or without trastuzumab, and those randomized to the investigational arm continued to receive the antibody until disease progression. Median OS was 13.8 months in the trastuzumab arm compared to 11.1 months in the chemotherapy only arm (HR 0.74, 95% CI 0.60–0.91, *P* = 0.0046). Response rate and median PFS were also increased (5.5 to 6.7 months, HR 0.71, 95% CI 0.59–0.85, *P* = 0.0002).⁶ In a preplanned analysis by HER-2 expression level, patients with IHC3+ disease attained the greatest benefit from the addition of trastuzumab, with a median survival of 17.9 vs 12.3 months (HR 0.58, 95% CI 0.41–0.81). Furthermore, in an exploratory subgroup analysis of the ToGA trial which excluded the IHC 0–1+ patients in line with breast cancer convention, the magnitude of benefit was again greater than for the intention to treat population, and median OS was increased from 11.8 months to 16.0 months with the addition of trastuzumab (HR 0.65, 95% CI 0.51–0.83). These results are summarized in Table 2. Despite these results being derived from a post-hoc exploratory analysis, the European Medicine Agency (EMA) has limited the approval of trastuzumab to patients with IHC 3+ or 2+/FISH+ metastatic gastric/OGJ adenocarcinoma. Moreover, the UK National Institute for Clinical Excellence has restricted its recommendation for trastuzumab to patients with IHC3+ disease only, based upon a cost-efficacy analysis. The FDA has approved trastuzumab for HER-2 overexpressing patients without further specification.

Trastuzumab is well tolerated both as monotherapy and in combination with several regimens in breast cancer studies.^{39–44} The only significant overlapping toxicity identified is cardiotoxicity, where trastuzumab cannot be safely delivered concurrently with standard cumulative doses of the anthracycline, doxorubicin: the incidence of cardiac dysfunction was reported in up to 27% of patients.⁴² Instead, sequential delivery is feasible, with more acceptable rates of cardiotoxicity reported.^{39–41,43,44} The combination of trastuzumab and anthracyclines has been investigated in neoadjuvant and metastatic setting in breast cancer. Trastuzumab in combination with neoadjuvant FEC regimen utilizing lower epirubicin dose of 75 mg/m² for 4 cycles was well tolerated in 23 operable patients. No cases of congestive heart failure (CHF) were observed and although an asymptomatic drop in left ventricular ejection fraction (LVEF) was noted in 7 patients, there was return to normal levels on follow-up evaluation.⁴⁵ Similarly, 4 cycles of epirubicin (90 mg/m²) with cyclophosphamide were safely delivered in combination with trastuzumab in neoadjuvant GeparQuattro study. Trastuzumab was given in 78% of 445 HER-2 positive patients, and each CHF, cardiac ischemia and persistent decrease in LVEF occurred only in 1 patient.⁴⁶ Six cycles of the same regimen were used in HERCULES trial which randomized 120 patients into 2 different doses of epirubicin (60 and 90 mg/m²) in combination with cyclophosphamide and trastuzumab. Asymptomatic LVEF declines and symptomatic CHF were more frequent with the higher dose of epirubicin, but all CHF occurred after the end of chemotherapy administration and resolved or improved with or without specific treatment.⁴⁷ Trastuzumab delivered concurrently with doxorubicin has

Table 2 Overall, preplanned, and post-hoc exploratory analyses of patients in the ToGA trial¹² stratified by HER-2 status

	n	Median OS		HR	95% CI
		Trastuzumab + chemotherapy	Chemotherapy only		
Overall population					
FISH+ or IHC 3+	584	13.8	11.1	0.74	0.6–0.91
Pre-planned exploratory analysis					
FISH+					
IHC 0	61	10.6	7.2	0.92	0.48–1.76
IHC 1+	70	8.7	10.2	1.24	0.7–2.2
IHC 2+	159	12.3	10.8	0.75	0.51–1.11
IHC 3+	256	17.9	12.3	0.58	0.41–0.81
FISH–					
IHC 3+	15	17.5	17.7	0.83	0.2–3.38
Post-hoc exploratory analysis					
FISH+					
IHC 0, 1+	131	10.0	8.7	1.07	0.7–1.62
FISH+					
IHC 2+	446	16.0	11.8	0.65	0.51–0.83
or IHC 3+					

Abbreviations: OS, overall survival; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; HR, hazard ratio; CI, confidence intervals.

also been re-evaluated in Neoadjuvant Herceptin (NOAH) trial. Doxorubicin was given at 60 mg/m² for 3 cycles in a combination regimen with or without trastuzumab. CHF was observed in 2 patients treated with trastuzumab (2%) compared with 0 in the chemotherapy only arm.⁴⁸

In the ToGA trial, the adverse event profile was similar between the 2 groups, with no difference in the overall rate of adverse events. The frequency of CHF was less than 1% in both arms; and asymptomatic drops in LVEF (defined as $\geq 10\%$ and to $< 50\%$) was 1% compared with 5% in the control and experimental arms, respectively. The frequency of CHF and ventricular dysfunction may have been confounded by relatively short follow-up in this study due to poor OS of metastatic gastric cancer, but importantly, the rate of symptomatic events which could affect quality of life (QoL) was low.

Impact of trastuzumab on quality of life

QoL is a perception of one's health, and includes physical, emotional and social function in addition to disease and treatment-related side-effects.⁴⁹ Assessment of quality of life by validated questionnaires (European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30) as well as gastric-cancer specific module STO22 were used in the ToGA trial. Global health status scores from the QLQ-C30 increased during the chemotherapy and showed further improvements after chemotherapy was ceased in both arms. Physical, emotional, and social functions improved after chemotherapy and cognitive functions remained same in both arms. Disease-specific scores from the QLQ-STO22 (evaluating dysphagia, anxiety, reflux, and eating restrictions) decreased after the first cycle of chemotherapy, indicating improvement in disease-specific symptoms.⁵⁰ Overall, the addition of trastuzumab did not negatively impact in the QoL of participants in the ToGA trial.

Trastuzumab in the adjuvant treatment of gastric cancer

The benefit of trastuzumab in the post-hoc analysis of the ToGA trial in the treatment of advanced gastric cancer approximates that reported in the treatment of advanced breast cancer. Absolute increases in overall survival of 4 and 5 months were reported in the ToGA trial and the first phase III advanced breast cancer trial, respectively.^{6,42} Trastuzumab also improves survival in the adjuvant treatment of HER-2 positive breast cancer.^{40,41,51} However, activity of targeted agents in metastatic disease should not automatically be

extrapolated into adjuvant setting, as several trials with active agents in metastatic colon cancer were negative in the treatment of early disease.⁵²⁻⁵⁴ Evaluation of trastuzumab in the perioperative treatment of gastric cancer is therefore critical to determine if a similar improvement in survival can be gained. As yet, only 2 trials recently open to recruitment are investigating HER-2 targeting in this setting. A small phase II study (ML25189) plans to accrue 45 patients with resectable, HER-2 positive adenocarcinoma of stomach or OGJ type I-III into a single treatment arm consisting of 3 cycles of neoadjuvant chemotherapy with oxaliplatin, capecitabine and trastuzumab. Patients achieving R0 or R1 resection will receive a further 3 cycles of the same chemotherapy regimen postoperatively with trastuzumab continuing for 12 months. The primary endpoint of this trial is DFS at 18 months.⁵⁵ A larger, phase III trial sponsored by US Radiation Therapy Oncology Group (RTOG)-1010 plans to enrol 480 patients with HER-2 positive adenocarcinoma of middle or lower esophagus or OGJ. The extent of the disease must be encompassed in one radiotherapy field and patients must be able to undergo curative resection after completion of chemoradiotherapy treatment. Eligible patients are randomized to chemotherapy with weekly paclitaxel and carboplatin for 6 weeks with concomitant radiotherapy. The experimental arm consists of the same chemotherapy schedule with the addition of weekly trastuzumab and an additional trastuzumab dose on day 57. Commencing 3 to 14 weeks post resection, all patients receive 13 cycles of 3-weekly trastuzumab. The primary endpoint is DFS and secondary outcomes are pathologic complete response (pCR), OS, toxicity, QoL, predictors of cardiotoxicity and molecular correlates of efficacy.⁵⁶ These studies are summarized in Table 3.

Other HER-2 targeting agents

Pertuzumab is a monoclonal antibody which inhibits HER-2 heterodimerization. Its binding site on HER-2 receptor is different from trastuzumab, therefore these compounds do not compete with one another. Pertuzumab delivered in combination with trastuzumab has been evaluated in a phase II study in patients with trastuzumab-resistant HER-2 positive metastatic breast cancer. The median PFS reported was 5.5 months and the objective response rate of 24% was encouraging in this pretreated patient population.⁵⁷ Pertuzumab has also been evaluated in a randomized comparison of gemcitabine plus pertuzumab or placebo in a HER-2-unselected population of patients with platinum-resistant ovarian cancer. A significant increase in response rate was reported, with greatest benefit noted in the subgroup of patients with low HER-3 mRNA expression.⁵⁸

Table 3 Active, recruiting phase II/III studies of neoadjuvant and adjuvant trastuzumab in gastric or esophageal cancer

Study and sponsor, Clinical trials.gov ID	n	Phase	Inclusion	Schedule	Primary endpoint	Country
ML25189 Hoffmann-La Roche, NCT01130337 ⁵⁵	45	II	Gastric adenocarcinoma	3 × CAPOX + H neoadjuvant 3 × CAPOX + H adjuvant 12 months adjuvant trastuzumab	DFS	Spain
RTOG-1010 NCI/RTOG, NCT01196390 ⁵⁶	480	III	Middle, lower esophageal and OGJ adenocarcinoma	Weekly carboplatin, paclitaxel and radiotherapy with or without H (6 weeks) + additional dose of H on day 57. Surgery within 5–6 weeks after completion of radiotherapy; adjuvant H for 39 weeks for all patients	DFS	USA

Abbreviations: CAPOX, capecitabine and oxaliplatin; H, trastuzumab; DFS, disease-free survival; NCI, National Cancer Institute; RTOG, Radiation Therapy Oncology Group; OGJ, esophagogastric junction.

Several phase III trials are currently investigating pertuzumab in trastuzumab-naïve as well as trastuzumab-refractory patients with breast cancer.

Trastuzumab emtansine (trastuzumab-DM1) is a conjugate of cytotoxic drug maytansine derivative DM1 and trastuzumab. DM1 binds microtubules, inhibits their assembly and blocks mitosis, similarly to vinca alkaloids. By conjugating DM1 to trastuzumab, the delivery of DM1 is more specific and reduces its systemic toxicity. A single arm phase II study demonstrated a response rate of 26% and median PFS of 4.6 months in the treatment of breast cancer patients who were refractory to prior HER-2 targeted therapies.⁵⁹ Two large phase III trials evaluating the addition of trastuzumab-DM1 to lapatinib and capecitabine in pretreated patients, and in combination with pertuzumab compared with trastuzumab plus a taxane in the first-line setting in advanced breast cancer, are currently open to recruitment.^{60,61} Trastuzumab-DM1 has antitumor activity in HER-2 positive gastric cell lines and xenografts, as well as in trastuzumab-resistant tumors.⁶² These encouraging preclinical data provide rationale for clinical trials of trastuzumab-DM1 in trastuzumab-resistant gastric cancer, and might represent a useful second-line treatment option, potentially free of the side-effects associated with systemic cytotoxic chemotherapy.

Lapatinib, a small molecule inhibitor targeted at the intracellular tyrosine-kinase domains of HER-2 and EGFR has been investigated extensively in trastuzumab-refractory breast cancer. In the pivotal phase III study, heavily pretreated HER-2 positive patients were randomized to oral capecitabine chemotherapy with or without lapatinib. Response rate and median time to progression were significantly increased with the addition of lapatinib and the combination was well tolerated. Diarrhea was the most common grade 3–4 toxicity, reported in 14% with the combination compared to 11% with capecitabine alone.⁶³ There were no symptomatic cardiac events reported

and LVEF values were comparable at scheduled assessments, with 4 asymptomatic cardiac events noted in the combination group, compared with 1 in the monotherapy arm.

Lapatinib has been investigated in a phase II, single arm study in the first-line treatment of advanced gastric cancer. Overall response rate was 9% and median OS 5 months.⁶⁴ Even though lapatinib has demonstrated modest single-agent activity, the response rates and survival were poor in this study compared with cytotoxic chemotherapy in first-line treatment of gastric cancer, therefore combination studies are underway. Two large randomized phase III studies in advanced gastric cancer are currently accruing patients; the LOGiC study will evaluate the combination of lapatinib with oxaliplatin and capecitabine as first-line treatment and the TYTAN study will evaluate lapatinib in combination with weekly paclitaxel in the second-line setting.^{65,66} No significant safety issues were reported on interim analyses of these studies.^{67,68} An amendment to the UK National Cancer Research Institute phase III study of neoadjuvant chemotherapy ECX with or without bevacizumab (ST03) is planned, to introduce baseline HER-2 testing and randomization of HER-2 positive patients to ECX with or without lapatinib.

Second-generation, irreversible pan-HER tyrosine kinase inhibitors are currently being intensely investigated in early phase clinical trials. PF-00299804 has demonstrated significant antitumor activity in human xenograft models, including xenografts with activating mutations in *EGFR* that are associated with resistance to the anti-EGFR tyrosine kinase inhibitors, gefitinib and erlotinib.⁶⁹ A phase II trial in advanced nonsmall cell lung cancer has reported efficacy in erlotinib-pretreated patients.⁷⁰ A phase II monotherapy study in advanced gastric cancer is underway.⁷¹ Neratinib, a further irreversible pan-HER inhibitor has demonstrated efficacy in combination with trastuzumab and as monotherapy in trastuzumab-refractory breast

Table 4 Active, recruiting trials of other HER-2 targeting agents open to patients with OG tumors

Study and sponsor, Clinical trials.gov ID	n	Phase	Inclusion	Schedule	Primary endpoint	Country
Lapatinib						
Gastrolap, National Center for Tumor Diseases, Heidelberg, Germany NCT01145404 ⁶⁵	76	II	HER-2 positive adenocarcinoma of esophagus, OGJ, stomach, 2nd line	Lapatinib vs lapatinib + capecitabine	ORR	Germany
GSK, NCT00526669 ⁶⁶	64	II	Adenocarcinoma of OGJ and stomach, 1st line	Lapatinib + capecitabine	Changes in gene expression markers	USA + others
LOGIC, GSK, NCT00680901 ⁶⁶	535	III	HER-2 positive adenocarcinoma of esophagus, OGJ, stomach, 2nd line	Lapatinib + capecitabine + oxaliplatin vs capecitabine + oxaliplatin	OS	USA + others
TYTAN, GSK, NCT00486954 ⁶⁵	314	III	HER-2 positive adenocarcinoma of stomach, 2nd line	Lapatinib + paclitaxel vs paclitaxel	OS	Asia
EORTC (400711), NCT01123473 ⁸⁷	192	II	HER-2 or EGFR positive adenocarcinoma of OGJ or stomach, 1st line	Lapatinib + epirubicin, cisplatin, 5-FU/ capecitabine (ECF/X) vs ECF/X	PFS	Switzerland
PF-00299804						
Seoul National Univ, NCT01152853 ⁷¹	28	II	HER-2 positive adenocarcinoma of OGJ or stomach, 2nd line	PF-00299804 monotherapy	PFS	Korea
Neratinib						
Wyeth/Pfizer, NCT00838539 ⁸⁸	65	I	Solid tumors	Neratinib + temsirolimus	MTD	USA + France
AZD8931						
AstraZeneca, NCT01003158 ⁸⁹	30	I	Solid tumors	AZD8931 monotherapy	Toxicity	Japan

Abbreviations: CAPOX, capecitabine and oxaliplatin; H, trastuzumab; PFS, progression-free survival; OS, overall survival; ORR, overall response rate; MTD, maximum tolerated dose; NCI, National Cancer Institute; RTOG, Radiation Therapy Oncology Group; OG, esophagogastric; OGJ, esophagogastric junction.

cancer patients.⁷² Anti-tumor activity of AZD8931, a reversible pan-HER inhibitor was confirmed in preclinical models, significantly affecting EGFR, erbB2, and erbB3 phosphorylation and downstream signalling pathways.⁷³ Early phase clinical trials are currently ongoing in breast cancer and other solid tumors. We remain hopeful that these new agents will be further investigated in patients with esophagogastric tumors in future clinical trials. Current ongoing clinical trials with these agents that are recruiting patients with gastro-intestinal and/or solid tumors are summarized in Table 4.

Future directions

In addition to the currently planned evaluation of trastuzumab in the perioperative and adjuvant settings and of lapatinib in the perioperative setting, further important questions on the role of HER-2 targeting in gastric cancer remain. The safety of trastuzumab in combination with the widely-used ECF or ECX regimens has not yet been established. Neo-adjuvant studies in breast cancer^{45,46,48,74} support the concurrent use of trastuzumab with anthracyclines, provided that less cardiotoxic anthracyclines, such as epirubicin, and low cumulative doses are used, with careful cardiac monitoring and early cessation of the cardiotoxic agents where indicated. The cumulative epirubicin dose in the MAGIC trial of 300 mg/m² is well below the maximum recommended cumulative dose of 900 mg/m².⁷⁵ Trastuzumab should therefore be evaluated with perioperative ECF or ECX for carefully selected patients according to pre-existing cardiac conditions and baseline LVEF, with careful monitoring for cardiotoxicity. However, to our knowledge, no such study is currently planned.

The optimal duration of trastuzumab in the adjuvant treatment of breast cancer has not yet been established, with benefits reported from as little as 9 weeks treatment.³⁹ One year's adjuvant therapy is the currently accepted standard, based upon the survival benefit reported in the NSABP B-31, BCIRG 006, and HERA studies.^{40,41,44} Whether continuation for longer than 1 year is beneficial is not currently known.

Delivery of trastuzumab beyond disease progression has been widely practiced in advanced breast cancer treatment and should be prospectively evaluated in advanced gastric cancer as soon as an effective second-line treatment is established. Response rates as well as median time to progression were improved in HER-2 positive metastatic breast cancer patients who experienced progression during trastuzumab treatment and were randomized to capecitabine with continuation of trastuzumab, compared with capecitabine alone.⁷⁶ Several phase II trials have investigated second-line chemotherapy in esophago-gastric cancers using irinotecan

and taxanes,^{77–79} but phase III data are currently lacking. Trials evaluating trastuzumab beyond progression, and other HER-2 targeting agents in trastuzumab pretreated patients with esophago-gastric cancers, are urgently needed.

The combination of trastuzumab and lapatinib is synergistic in breast cancer, therefore evaluation in advanced and, in the future, localized gastric cancer is warranted. Preclinical studies have demonstrated synergistic effect of lapatinib and trastuzumab in gastric cancer cell lines; synergy was also demonstrated in HER-2 amplified xenografts.⁸⁰ These preclinical data provide rationale for combination studies of these agents in gastric cancer.

The combination of trastuzumab with pertuzumab may also be worthy of investigation in early gastric cancer. Activity of pertuzumab and trastuzumab demonstrated in trastuzumab-resistant breast cancer has precipitated ongoing first-line and neoadjuvant studies in breast cancer. Extended HER-2 blockade with enhanced antitumor efficacy makes this combination an attractive investigational therapy in esophago-gastric cancers and should be evaluated without delay.

Compensatory signalling and cross-talk between HER-2 and other family members is likely to contribute to trastuzumab resistance. Blocking multiple HER homo- and heterodimers have demonstrated enhanced growth inhibition when compared with single agents.⁸¹ Highly-selective, small molecule pan-HER inhibitors have the potential to improve antitumor activity and overcome trastuzumab resistance. Encouraging results have already been reported in nonsmall cell lung cancer.⁸² The relative merit of the pan-HER inhibitors compared with more selective anti-HER-2 targeting will be of interest, and will determine the future role of these agents in breast and gastric cancers.

Strategies to overcome primary and acquired resistance to trastuzumab are an area of intense investigation in breast cancer oncology. Combination with PI3K inhibitors and mTOR inhibitors are currently undergoing evaluation. Rapid investigation into mechanisms of resistance in gastric cancer is needed to determine whether the same or different mechanisms predominate, to establish whether successful strategies in breast cancer can similarly be employed in trastuzumab-resistant gastric cancer. Irreversible pan-HER inhibitors could abrogate some of the mechanisms of trastuzumab resistance, and new dual PI3K and mTOR inhibitors are currently under investigation this setting.^{83,84}

Conclusion

Multimodality therapy with surgery, plus adjuvant fluoropyrimidine-based chemotherapy or chemoradiation or perioperative combination chemotherapy, are the current

standard treatment options for operable gastric cancer. However, survival remains poor and new strategies incorporating targeted agents are needed.

In advanced gastric and OGJ cancer, establishing the HER-2 status has become part of the routine diagnostic histopathological assessment and trastuzumab, added to a cisplatin/fluoropyrimidine chemotherapy doublet is now a standard treatment option for patients with HER-2 positive disease. Anti-HER-2 targeted agents are presently undergoing substantial clinical evaluation in advanced gastric cancer, with currently relatively limited evaluation in the perioperative and adjuvant settings. We are hopeful that further randomized studies will be undertaken to determine the value of anti-HER2 targeting in early disease and whether the survival benefits reported in early breast cancer can be replicated in operable gastric cancer. Further clinical evaluation of novel combinations of chemotherapy with trastuzumab, novel antibodies including pertuzumab, antibody–drug conjugates such as trastuzumab–DM1, and small molecule inhibitors of HER-2 must be expedited in molecularly selected patients with both advanced and operable disease to improve outcomes for patients with esophagogastric cancer.

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Disclosure

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