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Current perspective

Trastuzumab in gastric cancer

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ABSTRACT

Trastuzumab is a fully humanised monoclonal antibody directed at the human epidermal growth factor receptor-2 (HER-2) which has been a component of standard therapy for advanced and resected HER-2-positive breast cancers for almost a decade.

HER-2 over-expression, defined as HER-2 protein over-expression using immunohistochemistry scored as 3+ and/or *erb*B-2 amplification detected by fluorescent in situ hybridisation, was detected in 22.1% of 3807 patients with advanced gastric and oesophagogastric junction (OGJ) adenocarcinoma screened for eligibility for the phase III ToGA study. The validated scoring system for HER-2 positivity in gastric cancers differs from that recommended for breast cancer due to an increased frequency of incomplete membranous immunoreactivity and heterogeneity of HER-2 expression in gastric cancers. The highest rates of HER-2 over-expression are observed in patients with OGJ rather than gastric tumours and intestinal-type rather than diffuse or mixed histology.

The international multicentre randomised phase III ToGA study assessed the addition of trastuzumab to a cisplatin plus fluoropyrimidine (FP) chemotherapy doublet for patients with HER-2-positive advanced gastric or OGJ adenocarcinoma. The investigators reported a clinically and statistically significant benefit in terms of response rate (47.3% versus 34.5%, $p = 0.0017$), median progression-free survival (6.7 versus 5.5 months, $p = 0.0002$) and median overall survival (13.8 versus 11.1 months, $p = 0.0046$). Trastuzumab plus FP chemotherapy is now the standard of care for patients with advanced gastric and OGJ cancers which over-express HER-2.

Further research to evaluate trastuzumab delivered beyond progression, in combination with alternative first-line chemotherapy regimens, and in the perioperative and adjuvant setting is urgently needed. Additionally, research into mechanisms of resistance and strategies to overcome primary or acquired resistance to trastuzumab must now be expedited, using lessons learnt over the past decade in HER-2-positive breast cancer to maximise the benefit from this agent.

1. Background

Gastric cancer was the fifth most commonly diagnosed cancer in Europe in 2006, yet only modest gains in survival have been achieved when compared to two of the most common cancers; breast and colorectal.[1] This is exemplified by the recent integration of trastuzumab into the first-line treatment of HER-2-positive advanced gastric cancer, almost a decade

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after a survival benefit was demonstrated from its addition to standard first-line chemotherapy for HER-2-positive advanced breast cancer.[2] Compounding the relative chemoresistance of the disease, the often late stage at presentation, the frequent co-morbidities and the resultant poor performance status of many patients, this delayed progress in gastric cancer treatment has contributed to the poor overall survival. Worldwide, gastric cancer remains the second most common cause of cancer-related death.[3]

Outcomes from operable gastric cancer have improved since the introduction of multimodality therapy for localised disease.[4–6] For example, perioperative chemotherapy with ECF, a triplet combination of epirubicin, cisplatin and infused 5-fluorouracil (5-FU), increased the 5-year overall survival from 23% with surgery alone to 36% with the combined modality therapy (hazard ratio (HR) 0.75, 95% confidence interval (CI) 0.60–0.93, $p = 0.009$).[4] Similarly, adjuvant chemoradiation[5] or oral fluoropyrimidine monotherapy[6] improves survival compared to surgery alone.

During the 1990s, two published studies demonstrated that chemotherapy improves survival compared to best supportive care for advanced, inoperable gastric cancer.[7,8] Combination chemotherapy is more effective than monotherapy[9] but only modest improvements in overall survival have been reported from refinements to combination chemotherapy regimens in the past decade,[10–13] reflecting the relative chemoresistance of the disease. Chemotherapy agents with activity in gastric cancer include intravenous and oral fluoropyrimidines,[14–18] cisplatin,[19,20] oxaliplatin,[12,21] epirubicin,[10–12] docetaxel,[13] paclitaxel[22] and irinotecan,[23,24] but the median survival for patients with advanced gastric cancer treated with triplet combination chemotherapy regimens is less than one year.[12,13] The survival for the sub-group of patients with locally advanced inoperable disease is more favourable than that for the patients with metastatic disease with a median survival of 14.0 compared with 9.3 months, respectively, in one study.[25] There is no established standard first-line regimen for advanced disease, but combination regimens based on a platinum/fluoropyrimidine backbone are most commonly utilised, frequently with the addition of epirubicin[12] or docetaxel.[13] The addition of targeted agents to combination regimens is hoped to improve survival for these patients and allow selection of patients who will benefit from different regimens. The positive results of the randomised phase III ToGA trial[26] and the subsequent introduction of trastuzumab into routine clinical practice are the first steps towards personalised medicine for patients with advanced gastric cancer.

2. The human epidermal growth factor receptor-2 (HER-2)

HER-2 was the second member of the epidermal growth factor (EGF) receptor family to be identified,[27,28] following the earlier landmark discoveries of EGF[29] and its receptor.[30] The discovery followed the observation that the *neu* oncogene, found in rat neuroglioblastomas,[31] was homologous to *erb*B, which encodes the EGF receptor (EGFR).[27] The same group reported that whilst homologous to *erb*B in the tyrosine kinase domain, the *neu* oncogene was a distinct novel gene located on q21 of chromosome 17,[28] rather than chromosome 7 where the *erb*B had previously been mapped to. HER-2 is a 185 kD glycoprotein[27,32], 15 kD larger than the EGFR[27] and the product of the c-*erb*B-2/*neu* oncogene.[28] Like EGFR, HER-2 is a tyrosine kinase receptor and the most marked homology between the two receptors has been observed in the amino acid sequences specifying the tyrosine kinase domain.[28,33] EGF is not a ligand for HER-2 and to date, no ligand for the receptor has been identified. Instead, the receptor must homodimerise (ligand-independent dimerisation) or heterodimerise with another, ligand-bound member of the EGFR family, either EGFR, HER-3 or HER-4 (ligand-dependent dimerisation), to undergo activation. Ligand-independent homodimerisation will occur where there is over-expression of HER-2.[34,35] Dimerisation will then stimulate autophosphorylation of the intracellular tyrosine kinase domain (plus trans-phosphorylation if combined with HER-3 which itself lacks a kinase domain) and activation of a down-stream signalling cascade. The down-stream effects will be determined by both the ligand and the composition of the dimer[36] and include cell proliferation, differentiation, adhesion, migration and apoptosis. The HER-2/HER-3 heterodimer is the most potent combination of receptors.[37] Binding of Heregulin, a ligand to HER-3[38] or HER-4[39] and subsequent heterodimerisation with HER-2 stimulate the mitogen-activated protein kinase (MAPK) and phosphatidylinositol-3-kinase (PI3K) pathways.[40,41] The down-stream effects of HER-2 activation are depicted in Fig. 1.

3. Pre-clinical rationale for targeting HER-2 in gastric cancer

Amplification of *erb*B-2/*neu* was described in a breast cancer cell line (MAC117) in 1985,[42] and subsequently in a gastric cancer cell line in 1986 (MKN-7).[43] These results were confirmed in breast and gastric cancer resection samples in the same year,[44] indicating a potential role in oncogenesis. Further investigation in 668 breast cancer and 120 ovarian cancer specimens with correlation to outcome quickly identified HER-2/*neu* amplification to be an independent predictor of prognosis in terms of relapse ($p = 0.006$) and overall survival ($p = 0.045$) in breast cancer and overall survival in ovarian cancer ($p < 0.0001$). The rate of HER-2/neu amplification reported in each primary tumour site was similar at 27% for breast and 26% for ovarian cancer.[45] This was followed by the publication of a Japanese study of 260 primary gastric tumours, where HER-2 protein expression detected by immunohistochemistry was reported in 11.9% of cases, with a significant negative effect on overall survival ($p < 0.05$).[46] However, these results have not been consistently reproduced and several contradictory studies have since been published, including a large combined German/UK study of 924 resected gastric cancer specimens which showed no overall prognostic effect of HER-2 expression measured by immunohistochemistry (IHC). Of note, the rates of HER-2 expression were relatively low, with <10% of cases described as positive,[47] which may in part be due to the age of the paraffin-embedded samples.[48] Additionally, conflicting results were observed in the German and UK cohorts with a non-significant negative prognostic effect observed in the HER-2-positive patients from Germany

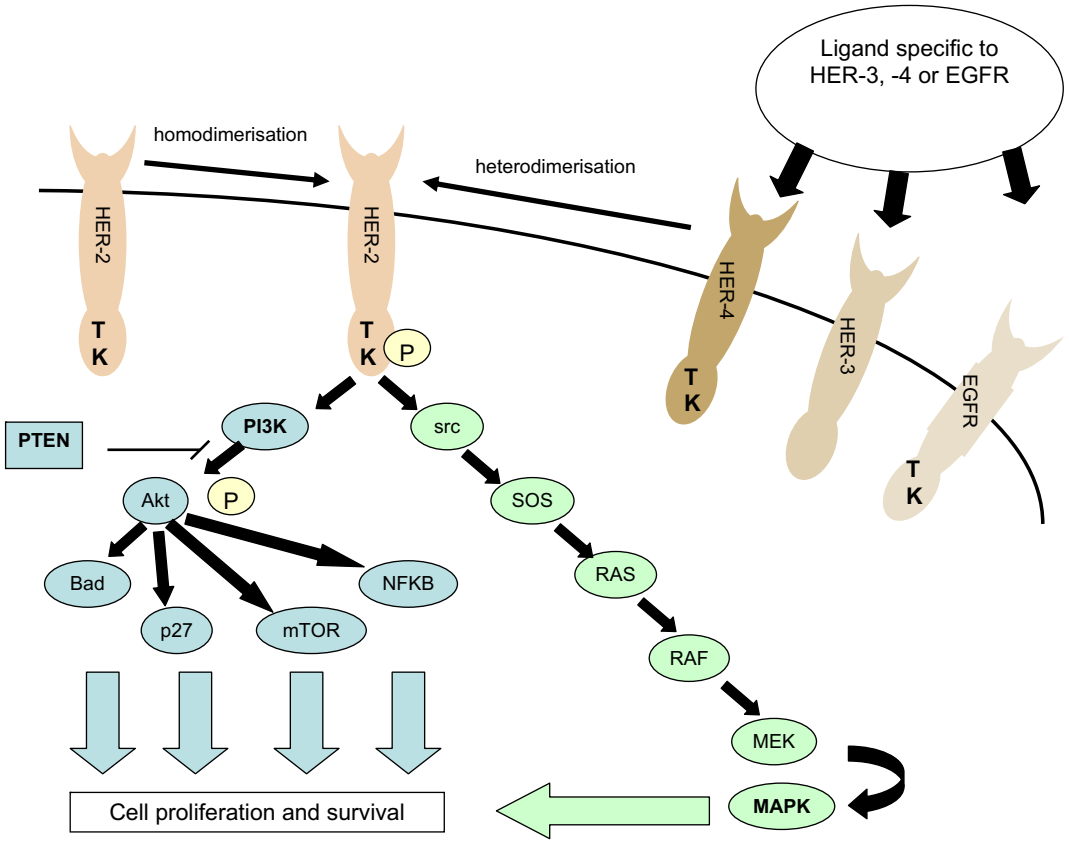

Fig. 1 – A simplified diagram of HER-2 signalling.

using full tissue sections ($p = 0.277$) and a non-significant positive prognostic effect was observed in the HER-2-positive UK group using tissue microarrays ($p = 0.167$).[47] The reasons for these conflicting results, summarised in Table 3, are unclear, but the lack of a standardised definition of HER-2 positivity in gastric cancer and subsequent differences in HER-2 scoring between studies may be a contributing factor.

A Japanese group published a proposed standard definition for HER-2 amplification in gastric cancer, measured by fluorescent in situ hybridisation (FISH) of mean gene copy number $\geqslant 7.0$ and/or a c-*erb*B-2/centromeric probe 17 (CEP17 ratio) ratio of $\geqslant 2$, which correlated to an IHC score of 2+ or 3+ in 83% of specimens.[49] An HER-2 scoring system was validated for the ToGA trial in 168 gastric cancer resection specimens using breast cancer scoring system for IHC and demonstrating 93.5% concordance with FISH, with FISH positivity again defined by c-*erb*B-2/CEP17 ratio of $\geqslant 2$. The authors noted that heterogeneity and incomplete membranous immunoreactivity was more common in gastric than in breast cancer, leading to changes in the recommended IHC scoring system for the phase III study. These comprised the recommendation to use identical scoring for samples with complete membranous reactivity and those with staining limited to the basolateral membrane and that pattern of reactivity should be scored as positive, irrespective of the relative number of positive cells; abandoning the breast cancer cut off of 10%, to allow for heterogeneity.[50]

HER-2 over-expression is more common in cancers of the OGJ than gastric tumours (33.2% versus 20.9%; $p < 0.001$) and intestinal than diffuse or mixed histology (32.2% versus 6.1% versus 20.4%; $p < 0.001$), confirmed in 3883 patients screened for HER-2 over-expression for the phase III ToGA trial.[51]

Murine monoclonal antibodies directed to the extracellular domain of the HER-2 receptor were developed[52] and evaluated in cell lines both *in vitro*[53,54] and as xenografts in animal models, with evidence of inhibition of cell growth and complete tumour regression using a combination of two antibodies.[54] Trastuzumab, a fully humanised monoclonal antibody, was subsequently developed to reduce the immunogenicity and enhance the antibody-dependent cellular cytotoxicity and the complement-dependent cytotoxicity.[55] Trastuzumab suppresses cell proliferation in the HER-2-positive gastric cancer cell line, NCI-N87,[56,57] and enhances the cytotoxicity of doxorubicin in NCI-N87 and YCC-2.[58] In xenograft models, trastuzumab monotherapy improved the survival of mice with peritoneal dissemination of the cell line, MKN-45P ($p < 0.01$), in one study.[56] In a second report, trastuzumab monotherapy was active in two HER-2-positive gastric cancer xenograft models (NCI-N87 and 4-1ST) and was most potent in combination with a combination of cisplatin and capecitabine,[59] providing a scientific basis for the ToGA study. The progression from bench to bedside is depicted in Fig. 2.

4. Clinical data: trastuzumab in gastric cancer

Prior to the presentation of results of the ToGA trial in 2009,[26] three phase II studies evaluating trastuzumab in patients with gastric cancer have been presented, although all three

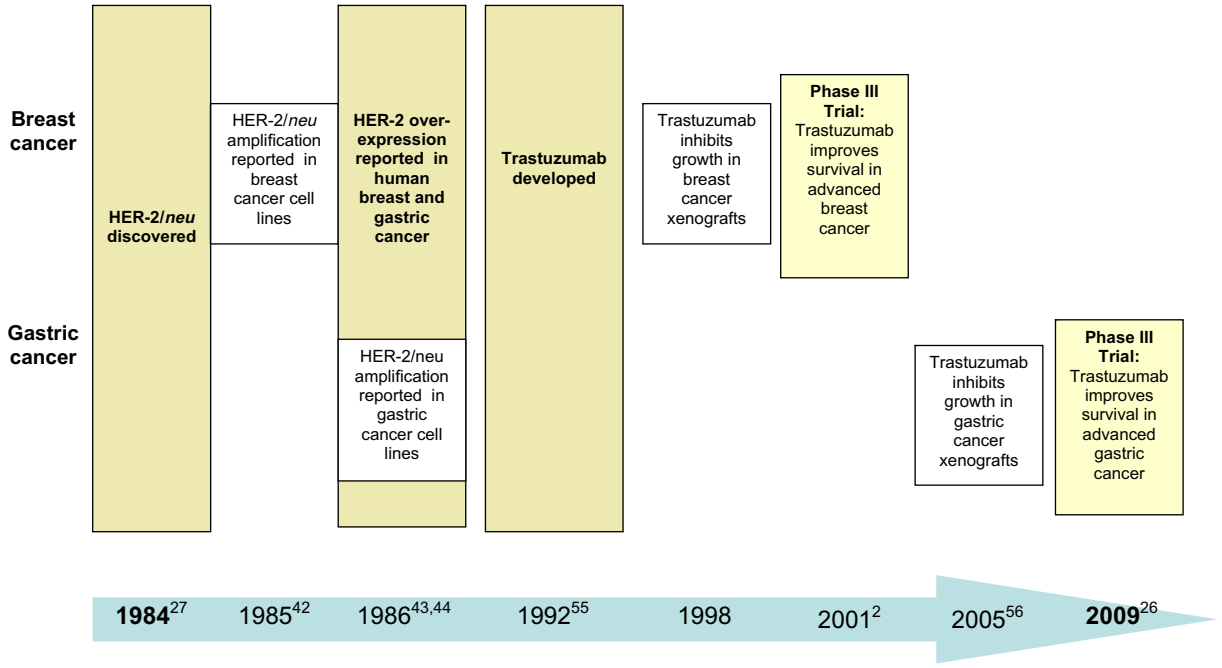

Fig. 2 – Key discoveries in HER-2 targeting in breast and gastric cancer.

remain unpublished.[60–62] Early data from a small phase II evaluation of trastuzumab combined with a cisplatin/docetaxel doublet were reported in 2006, with a radiological response observed in 4/5 patients with HER-2-positive (defined as IHC 3+ or FISH+) metastatic gastric or OGJ carcinoma treated.[60] In a second study in the first-line setting, 21 patients with HER-2-positive (defined as IHC 2+ and FISH+ or IHC 3+) advanced gastric or OGJ adenocarcinoma were treated with cisplatin 75 mg/m^2 plus trastuzumab (8 mg/kg loading dose then 6 mg/kg for future cycles) every 21 d until disease progression. The regimen was well tolerated with no grade 4–5 toxicities and investigators reported a 35% response rate in 17 evaluable patients who received a median of just two cycles of treatment (range 1–14). This radiological response rate would be considered relatively poor in the context of a phase II trial, but is likely to reflect the inadequate delivery of chemotherapy, due to use of cisplatin monotherapy rather than an established doublet or triplet regimen. The early results of a second-line study of trastuzumab monotherapy reported a 24-week sustained response in one of the three eligible HER-2-positive (defined as IHC 3+) patients out of 33 patients screened.[61] The results of the first-line phase II studies are summarised in Table 1.

Trastuzumab has been extensively evaluated in breast cancer with a wide range of chemotherapeutic agents and no significant overlapping toxicity, with one important exception. Trastuzumab is associated with an increased risk of cardiotoxicity,[63] as are anthracyclines, which are commonly used in the treatment of breast and gastric cancers. Trastuzumab-related cardiac dysfunction is largely reversible

Table 1 – Results of phase II studies of trastuzumab and lapatinib in the first-line treatment of advanced gastric cancer.

Trial	Patients (*n*)	Treatment	Response rate (%)	Median time to treatment failure	Median overall survival
Nicholas et al.[60]	HER-2-positive untreated advanced gastric or OGJ cancer[5]	Trastuzumab 8 mg/kg d1 loading dose then 6 mg/kg + cisplatin 75 mg/m^2 + docetaxel 75 mg/m^2 q21 d until progression	80	NR	NR
Cortés-Funes et al.[62]	HER-2-positive untreated advanced gastric cancer[21]	Trastuzumab 8 mg/kg d1 loading dose then 6 mg/kg + cisplatin 75 mg/m^2 d1 q21 d until progression	35	NR	NR
SWOG S0413 Iqbal et al.[80]	Unselected patients with untreated advanced gastric cancer[47]	Lapatinib 1500 mg daily until progression	12	2.0 months	5.0 months

NR = not reported.

on withdrawal of the antibody[64] and, as such, has been classified as type II chemotherapy-related cardiac dysfunction (CRCD).[65] The mechanism of cardiotoxicity from trastuzumab differs from that of anthracyclines, which cause well-described, dose-related pathological changes including vacuole formation, myocyte loss and necrosis.[66,67] Anthracycline cardiotoxicity is predominantly irreversible damage and classified as type I CRCD.[65] The concomitant administration of trastuzumab with the anthracycline, doxorubicin, was associated with unacceptably high rates of cardiac dysfunction (27%) in a combined analysis of seven breast cancer trials.[63] Cumulative doses of doxorubicin above 500–550 mg/m^2 delivered without trastuzumab cause an unacceptable rate of cardiotoxicity (>18%).[68] The anthracycline, epirubicin, is less cardiotoxic than doxorubicin, with a <5% incidence at a cumulative dose of 900 mg/m^2.[69] Epirubicin is widely used in oesophagogastric cancer as part of a triplet regimen in combination with a platinum agent and fluoropyrimidine in both the advanced and perioperative settings. The cumulative dose of epirubicin used in these regimens is relatively low (300–400 mg/m^2),[4,12] therefore, the risk of anthracycline-induced cardiotoxicity is small. Trastuzumab has been safely combined with epirubicin in advanced breast cancer in a randomised phase I/II study for which the primary endpoint was dose-limiting cardiotoxicity, defined as symptomatic cardiac failure or reduction of left ventricular ejection fraction by at least 10–<50%. Dose-limiting cardiotoxicity was reported in 1.7% of patients treated with trastuzumab, cyclophosphamide and epirubicin 60 mg/m^2 for six cycles and then with trastuzumab until disease progression. Of interest, the rate of cardiotoxicity was 5% in patients treated with epirubicin 90 mg/m^2 (cumulative dose 540 mg/m^2) in combination trastuzumab and cyclophosphamide, illustrating the dose-related effect. None of the HER-2-negative patients treated with the same regimen without trastuzumab developed dose-limiting cardiotoxicity,[70] consistent with previous data at this cumulative dose of epirubicin.[69] Based upon these results, the rate of expected cardiotoxicity should be relatively low for patients treated with trastuzumab in combination with 6–8 cycles of epirubicin-based triplet regimens for oesophagogastric cancer, but further prospective evaluation with careful cardiac monitoring is warranted.

In the ToGA study, patients underwent monitoring of left ventricular ejection fraction every 12 weeks during treatment. A 3-weekly regimen with a cisplatin (80 mg/m^2 day 1) and fluoropyrimidine backbone, with infused 5-FU (800 mg/m^2 days 1–5) or capecitabine (2000 mg/m^2/day days 1–14), was used at the Investigators' choice. This study was an impressive undertaking, as 3807 patients from 24 countries were screened for HER-2 over-expression, defined as IHC 3+ and/or FISH+ for the study.[51] A 22.1% HER-2 positivity rate was reported, with the highest proportion in OGJ tumours (33.2% compared to 20.9% in gastric tumours, $p < 0.001$) and intestinal-type cancers (32.2% compared to 6.1% of diffuse and 20.4% of mixed types, $p < 0.001$).[51] Five hundred and eighty-four patients with HER-2-positive gastric cancer were randomised to the chemotherapy doublet, with or without trastuzumab in this un-blinded comparison. The protocol allowed patients who completed six cycles of FP plus trastuzumab to continue trastuzumab monotherapy until disease progression. Patients received a median of eight cycles of trastuzumab (range 1–49), demonstrating that secondary resistance developed a median of two cycles after the chemotherapy was ceased. The regimen was well tolerated, with expected levels of haematological toxicity for the chemotherapy doublet and no additional toxicity other than a low rate of asymptomatic reduction in left ventricular ejection fraction to below the normal range (reported in 5.9%). Importantly, in this patient group with a relatively short life expectancy, the addition of trastuzumab did not compromise patients' quality of life.[71] The study met the primary endpoint of improved overall survival, as well as secondary endpoints of improved progression-free survival and response rate (Table 2). The actuarial gain in median survival was 2.7 months in the intent to treat population, which was disappointing compared to the 4.8 months gain in survival in advanced breast cancer in the pivotal trial by Slamon and colleagues.[2] However, the entry criteria for the ToGA study used a slightly permissive definition of HER-2 amplification, allowing patients with FISH positive (defined as HER-2 gene copy number (GCN):centromeric probe (CEP)17 ratio (2:2)) but IHC 0 or 1+ to be randomised. This scoring system had been previously validated in an independent study of 178 gastric cancer resection specimens.[50] However, this definition of HER-2 positivity is in contrast to the Slamon study in which IHC 2+ or 3+ was required,[2] or current ASCO recommendations for HER-2 testing for breast cancer of IHC 3+ or FISH+ (HER-2 GCN:CEP17 ratio 2:2).[72] In an exploratory sub-group analysis of the ToGA trial which excluded patients with IHC 0–1+ FISH+ disease, the gain in median survival was 4.2 months[26], comparable to that observed in breast cancer. There was no apparent benefit seen in the small sub-group of patients with IHC 0–1+ FISH+ disease, although these data must be interpreted with

Table 2 – Results from the ToGA trial in the overall study population and exploratory sub-group (IHC 2+/Fish+ or IHC 3+ only).

Population (*n*)	Definition of HER-2+	Response rate (%)		Median PFS/months		Median OS/months	
		FP	FP + T	FP	FP + T	FP	FP + T
Intent to treat (584)	IHC 3+ and/or FISH+	34.5%	47.2% ($p = 0.0017$)	5.5	6.7 HR 0.71, 95% CI 0.59–0.85, ($p = 0.0002$)	11.1	13.8 HR 0.74, 95% CI 0.60–0.91, ($p = 0.0046$)
Exploratory sub-group (446)	IHC 2+/FISH and/or IHC 3+	NR	NR	NR	NR	11.8	16.0 HR 0.65, 95% CI 0.51–0.83

NR = not reported.

Table 3 – Large ($n > 100$) studies examining HER-2 as a prognostic marker in gastric cancer.

Study	Number of samples	Method of HER-2 testing	HER-2 positive (%)	Effect of HER-2 on prognosis
Yonemura et al.[46]	260 Resected gastric cancers	IHC	11.9	*Positive*: Significant reduction in overall survival ($p < 0.05$)
Tateishi et al.[92]	179 Curatively resected gastric cancers	IHC	12	*Negative*: No effect on 5-year survival
Ohguri et al.[93]	136 Primary gastric tumours, 50 metastatic lymph-nodes	IHC	25.7 44	*Negative*: No significant correlation with 5-year survival
Mizutani et al.[94]	226 Resected gastric cancers	IHC	14.2	*Positive*: Correlation with poor survival when limited to patients with early-stage disease ($p < 0.001$)
Motojima et al.[95]	120 Resected gastric cancers	IHC	27.5	*Positive*: Independent predictor of recurrence, ($p = 0.0051$)
Lee et al.[96]	225 Resected locally advanced gastric cancers	IHC	27.4	*Negative*: Trend towards reduced survival, ($p = 0.08$)
Nakajima et al.[97]	128 Curatively resected gastric cancers	IHC Southern blot	16.4 11.7	*Positive*: Significant reduction in overall survival with HER-2 protein over-expression ($p = 0.039$) or gene amplification ($p = 0.0146$)
Allgyer et al.[98]	203 Resected gastric cancers	IHC	91	*Positive*: Independent predictor of poor survival ($p = 0028$; relative risk 1.33; 95% CI 1.28–1.38)
Pinto-de-Sousa et al.[99]	157 Resected gastric cancers	IHC	15.3	*Positive*: Significant reduction in 5-year survival ($p = 0.004$)
Tanner et al.[57]	131 Resected gastric cancers 100 OGJ tumours stage I-IV	CISH	12.2 24.0	Positive: reduced cancer-specific survival ($p = 0.0089$)
Grabsch et al.[47]	Total 924 resected gastric cancers German cohort (418) UK cohort (447)	IHC, DAKO score 2–3	4 5.7 2.5	*Negative*: No correlation with survival ($p = 0.903$) Trend towards reduced survival Trend towards improved survival

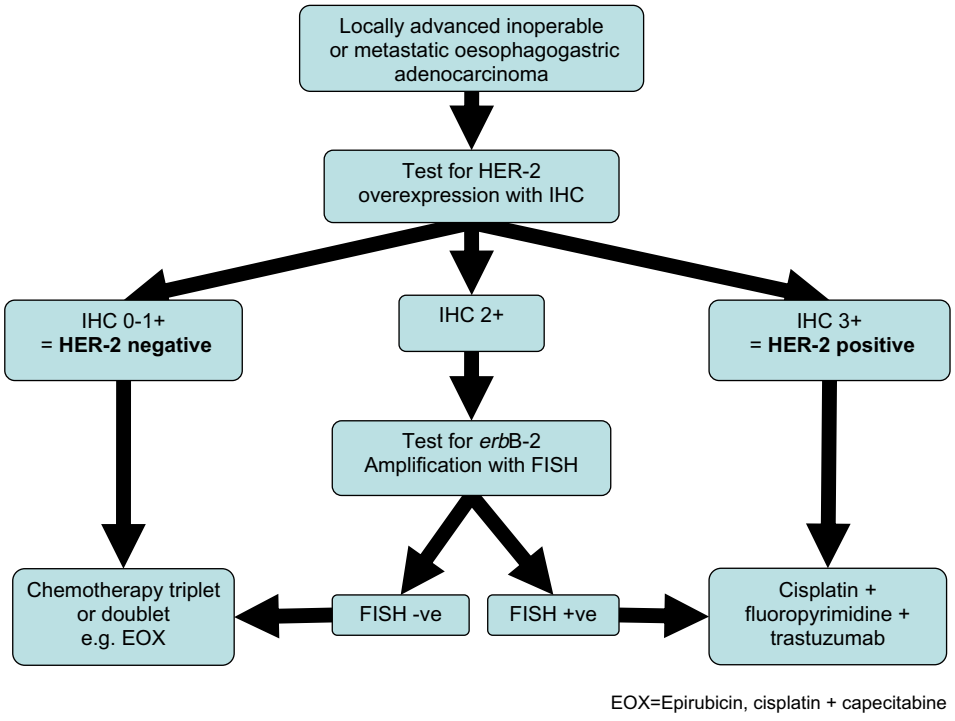

Fig. 3 – Treatment algorithm for advanced oesophagogastric cancer.

caution due to the exploratory nature of the analysis and the limited sample size. Of interest, despite these results having been generated by an exploratory analysis, the license granted by the EMEA earlier this year was limited to patients

with IHC 3+ or IHC 2+/FISH+ metastatic gastric cancer. Based upon this licensed indication, a suggested treatment algorithm is depicted in Fig. 3.

An interesting observation from the ToGA study is the relatively favourable survival in the standard arm of the study, despite the known poor prognostic effect of HER-2 overexpression (add ref.). The median survival in patients treated with the chemotherapy doublet was 11.1 months,[26] which is unprecedented in studies outside Japan, where the median survival was 13 months in one study of patients with advanced gastric cancer treated with the oral fluoropyrimidine, S-1, plus cisplatin.[19] In all other studies of a cisplatin plus fluoropyrimidine doublet in an unselected population, the median survival with the chemotherapy doublet has not exceeded 10.5 months.[13,20,73,74] Possible explanations for the encouraging median survival in this poor prognostic group include the high proportion of patients from Asia randomised (55%), where more patients will receive second and even third-line chemotherapy. Second-line chemotherapy was received by over 40% of patients in ToGA.[26]

5. Other agents targeting HER-2: lapatinib in gastric cancer

Lapatinib is an orally active, small molecule dual tyrosine kinase inhibitor of EGFR and HER-2 with known efficacy in trastuzumab-resistant advanced breast cancer.[75,76] Activity has been reported in the HER-2-amplified gastric cancer cell lines SNU-216 and NCI-N87 with unexpected additional activity in selected HER-2- and EGFR-negative cell lines such as SNU-484.[77] Additive or synergistic anti-tumour effect with 5-FU, cisplatin, oxaliplatin, paclitaxel,[77] irinotecan[78] and trastuzumab[79] has been demonstrated in gastric cancer cell line studies, providing rationale for evaluating lapatinib in combination regimens.

A phase II study of lapatinib monotherapy as first-line treatment for advanced gastric cancer has been presented although not yet published.[80] Forty-seven patients with previously untreated advanced gastric cancer were treated with lapatinib 1500 mg daily and the investigators reported evidence of limited single agent activity with a 12% response rate, median time to treatment failure of 2 months and overall survival of just 5 months in the 46 evaluable patients. However, this was an unselected population and the efficacy in the sub-group of patients with HER-2 and/or EGFR overexpression is not yet known. These data are summarised in Table 1.

A second phase II study of lapatinib monotherapy in patients with HER-2-positive (measured by IHC or FISH) previously treated adenocarcinoma of the OGJ ($n = 13$) or the oesophagus ($n = 12$) reported no objective responses but two patients had sustained disease stabilisation, for 5 and 9 months, respectively.[81]

6. Future directions

There are no current clinical trials of trastuzumab in gastric cancer in the advanced or operable disease settings at this time. A randomised placebo-controlled phase III study (LOGiC) will evaluate the addition of lapatinib to first-line capecitabine plus oxaliplatin in patients with HER-2-positive advanced gastro-oesophageal cancer, with a target accrual of 410 patients. Additionally, two phase II studies in advanced HER-2-positive gastric cancer are open to recruitment, evaluating lapatinib in combination with capecitabine and weekly paclitaxel in the first- and second-line settings, respectively.

It is our hope that HER-2 testing for advanced gastric and OGJ tumours and the administration of trastuzumab with a platinum/fluoropyrimidine doublet to patients with HER-2-positive disease will become an international standard of care and that health economics will not prohibit the use of this effective agent. Despite the initial efficacy demonstrated by the improved response rate, progression-free and overall survival in the phase III ToGA trial, some patients with HER-2-positive disease demonstrated primary resistance and the remainder developed secondary resistance. Mechanisms of resistance and potential strategies to overcome these have been extensively researched in breast cancer. Mechanisms in this setting include loss of phosphatase and tensin homologue protein (PTEN),[82] activating mutations in the gene encoding PIK-3 (*PI3KCA*)[83,84] and increased signalling through other receptors such as EGFR[85] and the insulin-like growth factor 1 receptor (IGF1R).[86] Lapatinib, the dual HER-2/EGFR small molecule inhibitor, prolongs time to progression in patients with trastuzumab-resistant HER-2-positive breast cancer[75,76] and warrants evaluation in trastuzumab-resistant HER-2-positive gastric cancer. Multiple novel therapeutic strategies to overcome resistance for HER-2-positive breast cancer are currently under evaluation, including combining anti-HER-2 therapies with agents targeting EGFR, IGF1R and c-met to overcome increased signalling through these receptors. However, whether these resistance mechanisms are also relevant to gastric cancer remains unknown and pre-clinical and clinical evaluation must be expedited.

Other questions that remain unanswered in HER-2-positive advanced gastric cancer include whether trastuzumab monotherapy is effective for patients unsuitable for chemotherapy, whether maintenance trastuzumab following a triplet regimen is as effective as trastuzumab delivered with a doublet regimen, whether trastuzumab could be safely added to a triplet regimen; especially anthracycline-based regimens where cardiotoxicity may be prohibitive. Equally, the use of trastuzumab beyond disease progression, an established practice in advanced breast cancer,[87] may be of interest if an effective second-line regimen can be established. Perhaps most importantly, trastuzumab must be evaluated in the adjuvant or perioperative setting, where meaningful gains in survival could be achieved if the oncology community's experience in breast cancer[88–90] once again translates to gastric cancer. Many clinicians will extrapolate the results of the ToGA trial to the operable disease setting without the supporting data from a randomised controlled trial. However, experience in other tumour types has taught us that the efficacy of targeted agents in the advanced disease setting does not always translate to the operable disease setting, evidenced by the recent negative trial of bevacizumab in the adjuvant treatment of colon cancer.[91] Instead, there is a genuine clinical requirement for a well-designed randomised study in this setting.

Conflict of interest statement

Dr. Okines previously received an honorarium from Roche for a presentation. Professor Cunningham has received research funding from Roche.

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