

Correlation between human epidermal growth factor receptor 2 expression level and efficacy of trastuzumab beyond progression in metastatic gastric cancer

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Abstract. There is currently no clinical data regarding the efficacy of trastuzumab treatment for the progression of human epidermal growth factor receptor 2 (HER2)-positive advanced gastric cancer (AGC) occurring during trastuzumab-based chemotherapy. The aim of this study was to retrospectively examine the clinical benefits of trastuzumab for HER2-positive AGC patients who progressed during first-line trastuzumab-based chemotherapy. Among the 108 patients treated with trastuzumab combined with fluoropyrimidine and cisplatin as first-line therapy, 46 HER2-positive AGC patients who received cytotoxic agents with or without trastuzumab subsequent to disease progression were included. Of these,

the efficacy and safety outcomes of 26 patients who continued trastuzumab were compared with those of the 20 patients who discontinued trastuzumab. No difference in response rate (18.2 vs. 15.8%, $P=1.00$) was observed between the two groups. Progression-free survival (PFS) time was numerically longer in the chemotherapy combination with trastuzumab group than in the chemotherapy combination without trastuzumab group (median, 4.0 vs. 2.3 months), with no significance [hazard ratio (HR), 0.63; $P=0.14$]. In the subset analysis, continuation of trastuzumab significantly improved PFS time in selected subgroups of patients with tumors exhibiting HER2 expression scores of 3+ (HR, 0.41; $P=0.04$), intestinal-type histology (HR, 0.32; $P<0.01$), and a first PFS time of >6 months (HR, 0.44; $P=0.04$). The survival times for the trastuzumab beyond progression (TBP) and non-TBP groups were similar (HR, 1.06; $P=0.88$), with equivalent overall survival times in the subgroups with immunohistochemistry scores of 3+ (HR, 0.97; $P=0.94$), intestinal-type histology (HR, 0.53; $P=0.19$), and a first PFS time of >6 months (HR, 0.62; $P=0.31$). There were no differences in the incidence rates of toxicity, including cardiac dysfunction, between the two groups. The study results suggest that selected HER2-positive AGC patients may benefit from trastuzumab continuation during first progression, and further prospective studies are warranted.

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Abbreviations: AGC, advanced gastric cancer; CI, confidence intervals; CR, complete response; DCR, disease control rate; FISH, fluorescent in situ hybridization; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IHC, immunohistochemistry; non-TBP, discontinued trastuzumab beyond progression; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease; TBP, trastuzumab beyond progression; ToGA trial, Trastuzumab for Gastric Cancer trial; TyTAN trial, Tykerb with Taxol in Asian ErbB2+ Gastric Cancer trial

Key words: gastric cancer, human epidermal growth factor receptor 2, metastatic gastric cancer, trastuzumab, trastuzumab beyond progression

Introduction

Gastric cancer is the third leading cause of cancer-associated mortality, with an estimated 723,027 mortalities worldwide in 2012 (1). Compared with the best supportive care, first-line chemotherapy for advanced gastric cancer (AGC) improves survival time and quality of life (2-4); however, the median overall survival (OS) time is short (9-13 months) (5-7). Several previous studies have demonstrated that second-line chemotherapy confers a significant survival benefit over best supportive care in AGC, with median OS time ranging from 4 to 9.5 months (8-11).

Among patients with AGC, the rate of human epidermal growth factor receptor 2 (HER2) positivity reportedly ranges from 8.2 to 23.0% as assessed by immunohistochemistry (IHC), and from 7.1 to 27.1% when assessed by fluorescence *in situ* hybridization (FISH) (12-15). On the basis of the Trastuzumab for Gastric Cancer (ToGA) trial results, addition of trastuzumab to platinum-based chemotherapy has become the standard first-line therapy for HER2-positive AGC (16). However, in the second-line setting, the Tykerb with Taxol in Asian ErbB2+ Gastric Cancer (TyTAN) trial did not demonstrate a survival benefit from the addition of lapatinib, a small-molecule tyrosine kinase inhibitor targeting HER2, to paclitaxel for the treatment of HER2-positive AGC (17). Preliminary evidence from a small phase II study demonstrated that a trastuzumab plus docetaxel-containing regimen was well tolerated and effective for HER2-positive AGC previously treated with fluorouracil-based chemotherapy; however, in this study, the patients had received no previous therapy with trastuzumab (18). On the other hand, several studies have reported that continued therapy with trastuzumab beyond progression (TBP) improves the survival outcome of patients with metastatic HER2-positive breast cancer (19,20), and represents a practical therapeutic option. However, there is currently no clinical data regarding the efficacy of trastuzumab for HER2-positive AGC progressing during trastuzumab-based chemotherapy. The aim of the present, retrospective study was to assess the clinical benefit of the continuation of trastuzumab for HER2-positive AGC patients who progressed during trastuzumab-based chemotherapy.

Patients and methods

Patients. The study population comprised patients with HER2-positive AGC who were treated at three Japanese institutions (Aichi Cancer Center Hospital, Nagoya, Japan; Tsuchiura Kyodo General Hospital, Tsuchiura, Japan; and Saitama Cancer Center Hospital, Saitama, Japan) between January 2006 and March 2014. The principal inclusion criteria were as follows: Histologically proven inoperable gastric cancer; an Eastern Cooperative Oncology Group performance status of 0-2 (21); sufficient bone marrow, liver and renal function; progressive disease diagnosed by computed tomography scans during first-line chemotherapy of trastuzumab combined with fluoropyrimidine plus platinum; and treatment with cytotoxic agents (docetaxel, 60 mg/m² every 3 weeks; paclitaxel 80 mg/m² on days 1, 8 and 15, every 4 weeks; irinotecan 150 mg/m² every 2 weeks; or irinotecan 60 mg/m² plus cisplatin 30 mg/m² every 2 weeks) with or without trastuzumab (8 mg/kg on day 1 of the first cycle, followed by 6 mg/kg every 3 weeks) as second-line chemotherapy. The second-line treatment regimens were selected by the treating physicians at each institution. HER2-positivity was defined as an IHC score of 3+, or an IHC score of 2+ and an *in situ* hybridization (ISH)-positive result determined by FISH or dual-color ISH (16,22), which are considered to be indications for using trastuzumab on the basis of subset analysis of the ToGA trial results (16,22). The HER2 status examination was performed prior to the start of the first-line chemotherapy. Written informed consent for treatment was obtained from each patient prior to treatment initiation. The Institutional Review Board of each participating center approved the study.

Data analysis. The main purpose of this study was to compare the efficacy and safety of trastuzumab treatment for patients who subsequently continued trastuzumab (TBP group) vs. those who discontinued trastuzumab beyond progression (non-TBP group). Treatment responses were evaluated in accordance with the Response Evaluation Criteria in Solid Tumors (version 1.1) (23) and the best overall response was recorded as the antitumor effect for each patient. The objective response rate (ORR) was defined as the proportion of patients with a complete response (CR) or a partial response (PR), and the disease control rate (DCR) was defined as the proportion of patients with a CR, a PR or stable disease (SD).

Progression-free survival (PFS) time was measured from the date of second-line therapy initiation to the date of progressive disease or mortality due to any cause. OS time was calculated from the date of second-line therapy initiation to the date of mortality or the last follow-up visit. The PFS and OS curves were constructed by using the Kaplan-Meier method. Survival status was updated in October 2014.

The P-values for the comparison of differences between the baseline patient characteristics of each group were calculated using χ^2 tests for homogeneity or trend, or by using Fisher's exact test. Univariate Cox proportional hazards models were used to assess the effects of TBP in terms of PFS and OS, which were indicated by hazard ratios (HR) and 95% confidence intervals (CI). The incidence and severity of adverse events were graded using the National Cancer Institute Common Toxicity Criteria version 4.0 (24). Statistical analyses were performed with R software version 2.13.2 (R Project for Statistical Computing, Vienna, Austria). All tests were two-tailed and P<0.05 was considered to indicate statistical significance.

Results

Patient characteristics. The characteristics of the patients are summarized in Table I. During the study period, 108 consecutive patients with HER2-positive AGC received trastuzumab combined with fluoropyrimidine plus platinum as first-line treatment, of which 34 patients enrolled in clinical trials, 28 patients did not receive second-line chemotherapy, and 46 patients met the inclusion criteria. A total of 26 patients (57%) continued and 20 (43%) did not continue trastuzumab. For all patients, HER2 status could not be tested at the time of disease progression during trastuzumab treatment. Between the TBP and non-TBP groups, no statistically significant differences were identified in histological subtypes (intestinal-type, 61.5 vs. 65.0%, respectively; P=0.81), IHC score (3+, 80.8 vs. 60.0%, respectively; P=0.19), presence of one or more measurable lesions (84.6 vs. 95.0%, respectively; P=0.34), time-to-first disease progression (first PFS time, 6.4 vs. 6.2 months respectively; log-rank P=0.59), or >6-month first PFS rate (57.7 vs. 60.0%, respectively; P=0.87). In the TBP group, for second-line chemotherapy, 22 patients (84.6%) received trastuzumab plus taxanes, 3 patients (11.6%) received trastuzumab plus irinotecan, and 1 (3.8%) received cisplatin plus irinotecan combined with trastuzumab. For third-line chemotherapy, 7 patients (26.9%) received taxanes/irinotecan and 8 (30.8%) received taxanes/irinotecan combined with trastuzumab. In the non-TBP group, 13 patients (65.0%) received taxanes, and the remaining patients (35.0%) received

Table I. Patient characteristics.

Characteristic	Non-TBP group (n=20)	TBP group (n=26)	P-value
Age, years [median (range)]	64 (33-74)	62 (29-86)	0.97 ^b
Gender, n (%)			0.40 ^c
Male	14 (70.0)	21 (80.8)	
Female	6 (30.0)	5 (19.2)	
ECOG PS, n (%)			0.26 ^c
0	9 (45.0)	6 (23.1)	
1	9 (45.0)	18 (69.2)	
2	2 (10.0)	2 (7.7)	
Disease status, n (%)			0.71 ^c
Unresectable	17 (85.0)	20 (76.9)	
Recurrent	3 (15.0)	6 (23.1)	
Number of metastatic sites, n (%)			0.73 ^c
1	4 (20.0)	7 (26.9)	
≥2	16 (80.0)	19 (73.1)	
Metastatic sites, n (%)			
Liver	12 (60.0)	11 (42.3)	0.23 ^b
Lung	3 (15.0)	9 (34.6)	0.18 ^c
Lymph node	15 (75.0)	22 (84.6)	0.47 ^c
Peritoneum	12 (60.0)	10 (38.5)	0.14 ^b
Prior gastrectomy, n (%)			0.34 ^c
Yes	4 (20.0)	9 (34.6)	
Histological subtypes, n (%)			0.81 ^b
Diffuse	7 (35.0)	10 (38.5)	
Intestinal	13 (65.0)	16 (61.5)	
HER2 status, n (%)			0.19 ^c
IHC 2+/FISH positive	8 (40.0)	5 (19.2)	
IHC 3+	12 (60.0)	21 (80.8)	
≥1 measurable target lesion, n (%)			0.34 ^c
Yes	19 (95.0)	22 (84.6)	
Adjuvant chemotherapy, n (%)			1.00 ^c
Yes	2 (10.0)	3 (11.5)	
Prior chemotherapy, n (%)			0.01 ^c
XP with trastuzumab	19 (95.0)	19 (73.1)	
SP with trastuzumab	0 (0)	7 (26.9)	
FP with trastuzumab	1 (5.0)	0 (0)	
Second-line chemotherapy, n (%)			0.16 ^{d,c}
Taxanes ^a	13 (65.0)	22 (84.6)	
Irinotecan	7 (35.0)	4 (15.4)	
Cisplatin	0 (0)	1 (3.8)	
Trastuzumab	0 (0)	26 (100)	
PFS of first-line chemotherapy, months [median (range)]	6.2 (2.118.1)	6.4 (1.621.6)	0.59 ^e

^aPaclitaxel or docetaxel; ^b χ^2 tests; ^cFisher's exact test; ^dcomparison of taxanes, irinotecan and cisplatin, excluding trastuzumab; ^elog-rank test. TBP, trastuzumab beyond progression; ECOG, Eastern Cooperative Oncology Group; PS, performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; FISH, fluorescence *in situ* hybridization; PFS, progression-free survival; XP, capecitabine plus cisplatin; SP, S-1 plus cisplatin; FP, 5-FU plus cisplatin.

irinotecan as second-line therapy. For third-line chemotherapy, 12 patients (60.0%) received taxanes/irinotecan and

3 (15.0%) received taxanes/irinotecan combined with trastuzumab.

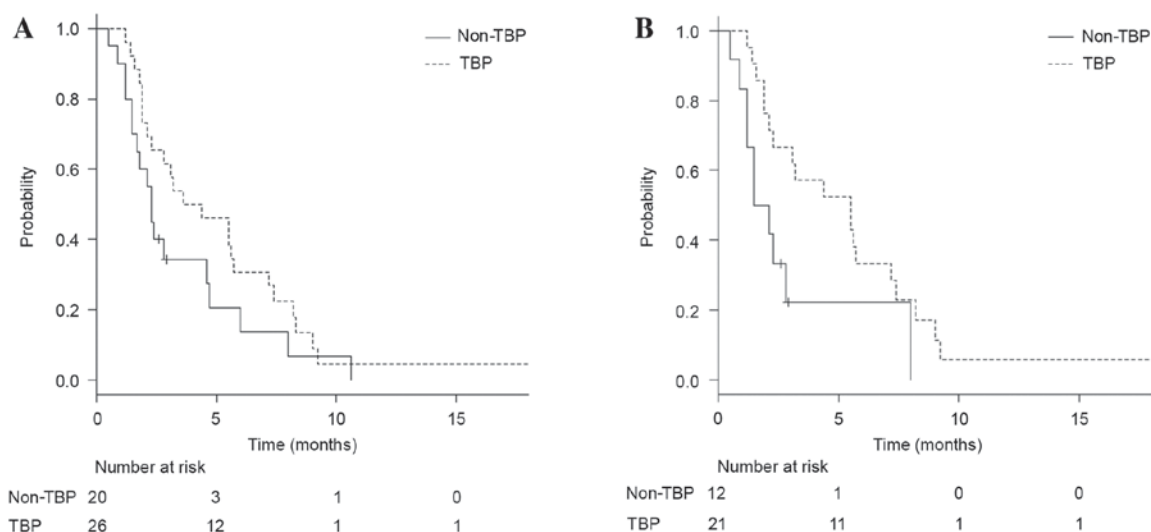


Figure 1. Kaplan-Meier survival curves of progression-free survival time for (A) all patients and (B) patients with an immunohistochemistry score of 3+ for epidermal growth factor receptor 2. TBP, trastuzumab beyond progression.

Treatment and efficacy. At a median follow-up time of 8.7 months, 43 (87.8%) patients had experienced disease progression and 32 (70%) patients had succumbed to the disease at the time of analysis. In the TBP group, among the 22 assessable patients, no patients achieved CR, 3 achieved PR, and 9 achieved SD, with an ORR of 13.6% and a DCR of 54.5%. In the non-TBP group, among the 19 assessable patients, 3 achieved PR, and 4 achieved SD, with an ORR of 15.8% and a DCR of 36.8%. The differences between the two groups were not significant, with P-values of 1.00 and 0.21 for ORR and DCR, respectively. No significant differences in response rates for any subgroups (age, gender, ECOG PS, disease status, number of metastatic sites, metastatic sites, prior gastrectomy, histological subtypes, HER2 status, adjuvant chemotherapy) between the TBP group and non-TBP group were identified.

Only 3 patients had not experienced disease progression at the time of analysis. Addition of trastuzumab (vs. no addition) numerically improved PFS time, with no significance (median, 4.0 vs. 2.3 months, respectively; HR, 0.63; 95% CI, 0.34-1.17; $P=0.14$; Fig. 1A). In the exploratory subset analysis of PFS time, three subgroups that could potentially benefit from continuing TBP vs. not continuing TBP were identified: Patients with a HER2 IHC score of 3+ (median, 5.5 vs. 1.8 months, respectively; HR, 0.41; 95% CI, 0.18-0.94; $P=0.04$; Fig. 1B), patients with histology of intestinal type (median, 5.7 vs. 2.3 months, respectively; HR, 0.32; 95% CI, 0.14-0.75; $P<0.01$), and patients with a first PFS of >6 months (median, 5.7 vs. 2.2 months respectively; HR, 0.44; 95% CI, 0.20-0.96; $P=0.04$).

The analysis of OS times revealed that the TBP group had a survival time similar to that of the non-TBP group (median, 10.8 vs. 9.5 months, respectively; HR, 1.06; 95% CI, 0.52-2.16; $P=0.88$). The OS time of the TBP group was also equivalent to that of the non-TBP group in the subgroups with HER2 IHC 3+ (median, 11.3 vs. 8.8 months respectively; HR, 0.97; 95% CI, 0.39-2.43; $P=0.94$), histology of intestinal type (median, 16.4 vs. 8.8 months, respectively; HR, 0.53; 95% CI, 0.21-1.36, $P=0.19$), and first PFS of >6 months (median, 16.3 vs. 11.5 months respectively; HR, 0.62; 95% CI, 0.25-1.57; $P=0.31$).

No statistically significant differences in the percentages of patients who received third-line chemotherapy (69.2 vs. 80.0%, respectively; $P=0.51$), and subsequent trastuzumab-containing therapy (30.7 vs. 15.0%, respectively; $P=0.15$), were identified between the TBP and non-TBP groups. Fourth-line chemotherapy or beyond was administered to 7 (26.9%) patients in the TBP group and 8 (40.0%) in the non-TBP group.

Toxicity. The majority of adverse events associated with chemotherapy (Table II) were grade 1 or 2. The frequency of any hematological toxicity of grades 3-4 was 62% in the TBP group and 50% in the non-TBP group, with no significant difference observed ($P=0.43$). The most common grade 3-4 hematological toxicity was neutropenia in the two groups: 42% in the TBP group and 40% in the non-TBP group. The frequencies of any non-hematological toxicity of grade 3-4 were also not different between the TBP and non-TBP groups (23 vs. 25%, respectively; $P=0.88$). No cardiac dysfunction occurred in either group.

Discussion

To the best of our knowledge, the present study is the first to evaluate a TBP strategy in second-line chemotherapy for HER2-positive AGC. There were two major findings. Firstly, the trastuzumab-combined therapy was numerically superior to chemotherapy alone for PFS, particularly in the subgroups with HER2 IHC 3+ tumors, histology of intestinal type, or a longer first PFS time (>6 months). Secondly, there was no significant difference in toxicity identified between the two groups, including cardiac dysfunction. These results suggest that the TBP strategy may be a second-line treatment option for patients with HER2-positive AGC.

Compared with the results from a prospective large observational study and a randomized phase III study involving metastatic breast cancer, which showed that the continued therapy with TBP improves the survival outcome of patients with metastatic HER2-positive breast cancer (19,20), the results of the present study did not demonstrate a clear

Table II. Adverse events of all grades and grades 3-4 occurring in the non-TBP and TBP groups.

Adverse events	Non-TBP (n=20)		TBP (n=26)		P-value ^a
	All grades, n (%)	Grades 3-4, n (%)	All grades, n (%)	Grades 3-4, n (%)	
Hematological toxicities					
Any	16 (80)	10 (50)	23 (88)	16 (62)	0.43 ^b
Leukopenia	12 (60)	5 (25)	18 (69)	7 (27)	0.88 ^c
Neutropenia	11 (55)	8 (40)	19 (73)	11 (42)	0.87 ^b
Anemia	14 (70)	6 (30)	18 (69)	7 (27)	0.82 ^b
Thrombocytopenia	4 (20)	1 (5)	1 (4)	0 (0)	0.43 ^c
Non-hematological toxicities					
Any	18 (90)	5 (25)	21 (81)	6 (23)	0.88 ^c
Nausea	11 (55)	2 (10)	7 (27)	2 (8)	1.00 ^c
Anorexia	7 (35)	1 (5)	5 (19)	1 (4)	1.00 ^c
Fatigue	8 (40)	2 (10)	12 (46)	1 (4)	0.57 ^c
Diarrhea	6 (30)	2 (10)	3 (12)	0 (0)	0.18 ^c
Stomatitis	2 (10)	0 (0)	3 (12)	0 (0)	1.00 ^d
Peripheral neuropathy	7 (35)	0 (0)	11 (42)	1 (4)	1.00 ^c
Infusion reaction	0 (0)	0 (0)	0 (0)	0 (0)	1.00 ^d
Cardiac dysfunction	0 (0)	0 (0)	0 (0)	0 (0)	1.00 ^d
Febrile neutropenia	1 (5)	1 (5)	2 (8)	2 (8)	1.00 ^c

^aComparison of adverse events of grade 3 or more; ^b χ^2 tests; ^cFisher's exact test; ^dcomparison of adverse events of all grades. TBP, trastuzumab beyond progression.

survival time benefit associated with trastuzumab therapy following first disease progression. However, the magnitude of unadjusted HR (0.63) for PFS in the present study was of the same order as that (0.69) in a German phase III trial comparing trastuzumab plus capecitabine vs. capecitabine alone in HER2-positive breast cancer patients whose disease had progressed during trastuzumab therapy (20), a finding which justified further investigation of HER2-positive AGC. The phenomenon of clinically relevant improvement of PFS time in the subgroup of patients with HER2 IHC 3+ tumors is congruent with the exploratory findings from the ToGA and TyTAN trials (16,17). The preplanned analyses of the ToGA trial revealed the greatest survival time gain in the subgroup of patients with HER2 IHC 3+ tumors, and in the TyTAN trial, the subgroup analysis based on HER2 IHC status identified significant survival time improvement only in the IHC 3+ subgroup.

Furthermore, the present study identified that patients with histology of intestinal-type demonstrated increased PFS time with trastuzumab treatment, which supported the subgroup result from the ToGA study in which patients with intestinal-type tumors had increased survival rates on trastuzumab-based chemotherapy (HR, 0.69; 95% CI, 0.54-0.88). The differences in efficacy according to HER2 IHC status and histological type may be partly explained by HER2 heterogeneity, which is more frequent in gastric cancer than in breast cancer (25). Previously, Lee *et al* (25) reported that only 8 (32.0%) of the patients studied exhibited heterogeneous HER2 overexpression in the IHC 3+ subgroup

whereas, in the IHC 2+ subgroup, it was identified in 46 (95.8%) of the 48 cases. Furthermore, only 3 (14.3%) of 21 patients with diffuse or mixed types exhibited homogeneous HER2 overexpression vs. 16 (30.8%) of the 52 cases with histology of intestinal type (25). Presumably, selection of subclones lacking HER2 overexpression is likely to confer resistance to anti-HER2 therapy in tumors with HER2 heterogeneity, and verification of this hypothesis is required in the future. In the present study, patients who had a longer first PFS (>6 months) benefited from continuing TBP, and this result is in accord with that of a previous study on metastatic breast cancer, in which patients with a longer first time-to-progression (≥ 8.6 months) had significantly improved survival times following first progression compared with those who had a shorter first time-to-progression (median, 24.3 vs. 15.4 months, respectively; $P=0.024$) (26). The dose of trastuzumab was 8 mg/kg on day 1 of the first cycle, followed by 6 mg/kg every 3 weeks, and this dose was representative of doses used by other studies (26). In the current study, it is unclear why OS time was not statistically different between the two groups, but it may be due to a high percentage of third-line or later treatment and trastuzumab use following second progression in the non-TBP group.

The limitations of this study are its retrospective nature and small sample size. In addition, the TBP strategy involves the additional cost of trastuzumab, and the current standard care in second-line treatment for gastric cancer is paclitaxel plus ramucirumab regardless of HER2 status (27); consequently, a certain degree of prudence is required when adapting this

strategy to patients. Therefore, these findings require confirmation in a well-designed prospective study.

There was no significant difference in toxicity identified between the two groups, a finding that is consistent with the results of the ToGA trial, in which the addition of trastuzumab did not increase the toxic effects associated with standard chemotherapy (16). In addition, no cardiac dysfunction was observed in either group, in contrast to the findings from a previous study of breast cancer (28) and the ToGA trial. In the study of breast cancer, the incidence rates of cardiotoxicity were 27% for patients who received trastuzumab combined with anthracyclines and 13% for those who received paclitaxel (28). In the ToGA trial, the incidence rate of cardiac events was as low as 6% for AGC patients (16). The lack of previous treatment with anthracyclines, the short duration of exposure to trastuzumab, and underestimation of cardiac dysfunction due to less-frequent evaluation may lead to a lack of detection of cardiac events.

To summarize, although the retrospective nature of this study and the small number of patients analyzed are major limitations, these findings indicate that trastuzumab-combined therapy provided a possible benefit of improved PFS time for subgroups of AGC patients with HER2 IHC 3+ tumors, histology of intestinal type, or a longer first PFS time (>6 months). An ongoing randomized phase II study (UMIN000009297; target sample size, n=90) comparing trastuzumab plus paclitaxel vs. paclitaxel-only following disease progression in patients treated with trastuzumab as first-line chemotherapy for HER2-positive AGC is likely to provide further insights into this strategy.

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