Multicenter phase II study of trastuzumab with S-1 plus oxaliplatin for chemotherapy-naïve, HER2-positive advanced gastric cancer

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Abstract

Background Trastuzumab with cisplatin and fluoropyrimidines improves overall survival (OS) in patients with HER2-positive advanced gastric cancer (AGC). S-1 plus oxaliplatin (SOX) is one of the standard regimens for HER2-negative AGC in Japan. However, few studies have evaluated trastuzumab combined with SOX in patients with HER2-positive AGC.

Methods This was a multicenter, phase II study conducted at 10 institutions in Japan. Patients with HER2-positive AGC received S-1 twice a day on days 1–14 and oxaliplatin and trastuzumab on day 1 of a 21-day cycle. The primary endpoint was the confirmed overall response rate (ORR), and the secondary endpoints were OS, progression-free survival (PFS), and safety. The sample size was 75 to have 90% power with an alpha error of 0.1 (one-sided), expecting an ORR of 65% and threshold of 50%.

Results From June 2015 to January 2018, 75 patients were enrolled. The ORR was 70.7% [95% confidence interval (CI) 59.0–80.6]. The median OS and PFS were estimated as 18.1 months (95% CI 15.6–26.5) and 8.8 months (95% CI 7.4–12.2), respectively. The major grade 3 or 4 adverse events were sensory neuropathy (16.0%) and neutropenia (10.7%).

Conclusions Trastuzumab with SOX had promising activity with well-tolerated toxicities for patients with HER2-positive AGC.

Clinical trial registration UMIN000017602.

Keywords Advanced gastric cancer · HER2-positive · Trastuzumab · S-1 · Oxaliplatin

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Introduction

Gastric cancer is the third leading cause of cancer-related death worldwide [1]. The mainstay of the treatment for advanced gastric cancer (AGC) is systemic chemotherapy. In AGC, human epidermal growth factor receptor 2 (HER2) amplification or protein over-expression is observed in up to 20% of cases. The ToGA trial demonstrated that trastuzumab with cisplatin and capecitabine or 5-FU (XP/FP) was associated with improved overall survival (OS) [2]. After this trial, different treatment strategies have been selected based on HER2 status in AGC.

In HER2-negative AGC, cisplatin plus fluoropyrimidines are the standard of care for first-line chemotherapy [3, 4]. The REAL-2 study, a randomized phase III study comparing triplet therapy of epirubicin, 5-FU or capecitabine, and cisplatin or oxaliplatin showed the non-inferiority of oxaliplatin to cisplatin in terms of survival with a two-by-two design [5]. In Japan, the G-SOX study, which compared S-1 plus oxaliplatin to S-1 plus cisplatin [6], also showed non-inferiority of oxaliplatin to cisplatin in terms of progression-free survival (PFS), and OS was comparable between the treatments. Since the toxicities of oxaliplatin are more manageable than those of cisplatin, especially in terms of hematological, gastrointestinal and renal toxicities [6], capecitabine or S-1 plus oxaliplatin (CapeOX, SOX) have been widely used as the standard regimens for HER2-negative AGC in Japan.

For HER2-positive AGC, several phase II studies [7, 8] investigated the efficacy and safety using trastuzumab with cisplatin plus S-1 (SP) instead of XP. However, few studies have evaluated the efficacy and safety of trastuzumab combined with oxaliplatin [9]. While some studies evaluated the efficacy and safety of oxaliplatin at a dose of 130 mg/m² in the SOX regimen (SOX₁₃₀) for HER2-negative AGC [10, 11], there are no clinical data about trastuzumab in combination with SOX₁₃₀. Here, we conducted a phase II study to investigate the efficacy and safety of combination chemotherapy of trastuzumab plus SOX₁₃₀ for patients with HER2-positive AGC.

Methods

Study design and patients

This is a multicenter, prospective, single-arm phase II study of trastuzumab with S-1 plus oxaliplatin for HER2-positive advanced gastric cancer (Herceptin® with SOX for Gastric Cancer; HIGHSOX study), which was conducted in accordance with the Declaration of Helsinki and Ethical

Guidelines for Clinical Studies in Japan. The protocol was approved by the ethics committees of all participating centers before patient enrollment was initiated. A Data and Safety Monitoring Committee (DSMC) reviewed all efficacy and safety data. The trial was registered with the University hospital Medical Information Network registry, number UMIN000017602.

The key inclusion criteria were as follows: histologically confirmed gastric or esophagogastric junction adenocarcinoma with measurable lesions according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and HER2-positive status determined by immunohistochemistry (IHC) and in situ hybridization (ISH) (IHC 3+, or IHC2+ and ISH positive). Patients were also required to fulfill all of the following conditions: age of 20–75 years at the time of registration; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; adequate organ function (leukocyte count $\geq 3000/\mu\text{l}$, neutrophil count $\geq 1500/\mu\text{l}$, platelet count $\geq 100,000/\mu\text{l}$, serum total bilirubin level ≥ 1.5 mg/dl, serum aspartate aminotransferase and alanine aminotransferase levels ≤ 100 U/l, and serum creatinine level ≤ 1.2 mg/dl and creatinine clearance ≥ 60 ml/min); a left ventricular ejection fraction (LVEF) of $\geq 50\%$ as measured on echocardiography or multiple-gated acquisition scanning within 28 days before registration; no prior chemotherapy or radiotherapy for gastric cancer therapy except for adjuvant chemotherapy with S-1 finished more than 6 months before relapse; sufficient oral intake of food; and expected survival of at least 3 months. Written informed consent was obtained from all patients.

The key exclusion criteria were as follows: active bleeding from gastric cancer/ulcer; severe diarrhea; sensory neuropathy; or history or current symptoms of heart failure, uncontrollable arrhythmia, angina pectoris, valvular disease, uncontrollable hypertension, interstitial pneumonia, pulmonary fibrosis, renal failure, hepatic failure, uncontrollable diabetes mellitus, or active double cancers within the 5 years preceding the beginning of the study period excluding carcinoma in situ and/or prior cured cancer.

Treatment

Patients received the treatment every 3 weeks according to the criteria in Supplementary Tables S-1 and S-2, until disease progression or unacceptable toxicity, patient's refusal, or physician's decision to discontinue. The treatment consisted of an intravenous infusion of trastuzumab (8 mg/kg at the first cycle and 6 mg/kg for the remainder of the cycles) and an intravenous infusion of oxaliplatin (130 mg/m²) on day 1 and oral administration of S-1 at a dose based on body surface area (BSA < 1.25 m², 40 mg; 1.25–1.5 m², 50 mg; > 1.5 m², 60 mg) twice daily on days 1–14 of each 21-day cycle. Trastuzumab monotherapy was not allowed.

If administration was delayed by more than 21 days, the treatment was terminated. Before oxaliplatin infusion, prophylactic antiemetics (e.g., neurokinin-1 receptor antagonist, a 5-hydroxytryptamine three receptor antagonist and dexamethasone) were recommended to prevent nausea and vomiting. S-1 and oxaliplatin were reduced according to adverse events. The S-1 doses at levels 1 and 2 were 60 and 50 mg/day for BSA < 1.25 m², 80 and 60 mg/day for BSA from 1.25 to < 1.5 m², and 100 and 80 mg/day for BSA ≥ 1.5 m², respectively. The oxaliplatin doses at levels 1 and 2 were 100 and 75 mg/m², respectively. The doses of S-1 and oxaliplatin were reduced by one level if the neutrophil count was less than 500/mm³ at any time, if the neutrophil count was less than 1500/mm³ on day 22, if grade 3 or higher febrile neutropenia occurred, or if the platelet count was less than 50,000/mm³. In the event of grade 3 or higher diarrhea, the S-1 dose was reduced by one level. If the platelet count was between 50,000/mm³ and 75,000/mm³ at any time or between 75,000 and 100,000/mm³ on day 22, then the oxaliplatin dose was reduced by one level. Oxaliplatin could be skipped when patients had received a total oxaliplatin dose of > 600 mg/m² or experienced grade 3 peripheral sensory neuropathy (PSN). Dose reduction of trastuzumab was not allowed. However, if the patient developed a grade 3 or higher infusion reaction or New York Heart Association III or IV heart failure, or an LVEF less than 40% or between 40 and 50% and more than ten points lower than the baseline, trastuzumab was discontinued.

Endpoints and assessment

The primary endpoint was the confirmed overall response rate (ORR) evaluated by each attending physician according to the RECIST v1.1 guideline. The secondary endpoints were OS, PFS, and safety. Tumors were measured by computed tomography every 6 weeks until disease progression occurred. Complete response (CR) and partial response (PR) were assessed 4 weeks after the initial assessment. Physical examinations and blood tests were mandatory before initiation of each treatment course, and also on days 8 and 15 in the first cycle. Electrocardiograms were performed and LVEF was assessed every 3 months during the protocol treatment. Adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Statistical analysis

Based on the results of the ToGA trial [2] and a phase II trial of trastuzumab with S-1 plus cisplatin [7, 8], we set a null hypothesis of ORR = 50% and an alternative hypothesis of ORR = 65%. To have 90% power with an alpha error of 0.1 (one-sided) using the binomial test, at least 71 patients

were required. After considering ineligible patients, the sample size was determined to be 75 patients. Efficacy was evaluated in all patients who met the inclusion criteria and received the study treatment (full analysis set: FAS). Given that this was the first study of this combination (trastuzumab with SOX), the tolerability within two cycles of the initial six cases was assessed by the DSMC. The safety analysis set included all patients who received at least one study treatment. OS and PFS were analyzed using the Kaplan–Meier method, and Greenwood's formula was used to calculate the 95% confidence intervals (CI). In the analysis of the subgroups defined by relative dose intensity (RDI) of oxaliplatin during eight cycles, the Cochran–Mantel–Haenszel test was used to compare ORR between groups and a log-rank test was used to compare PFS and OS between groups. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

Patients were enrolled from June 2015 to January 2018. 78 patients were screened in ten institutes in Japan. Due to not meeting the eligibility criteria, three patients were excluded from the FAS: one patient had inadequate organ function, one patient was aged older than 75 years and one patient had a history of myocardial infarction. The characteristics of the 75 patients are shown in Table 1.

Treatment exposure

The median number of treatment cycles was eight (range 1 to 36+), and the median RDI during eight cycles was 75.0% [interquartile range (IQR), 46.9–97.9] for S-1, 59.6% for oxaliplatin (IQR 42.3–83.5), and 96.0% for trastuzumab (IQR 52.0–100.0). At the time of analysis after the last follow-up on 31 August 2018, 11 patients (15%) were still receiving treatment, and all other patients had discontinued treatment. The main reasons for discontinuation of treatment were disease progression [39 patients (61%)], followed by more than 21 days delay of administration [nine patients (14%): neutropenia, four; thrombocytopenia, one; elevation of AST/ALT, one; elevation of creatinine, one; and pneumonitis, one]. Only four patients discontinued treatment due to adverse events (liver dysfunction, diarrhea, thrombocytopenia and sensory neuropathy). Eight patients with oligometastasis (lymph nodes, 3; peritoneum, 3; liver, 2) after at least three cycles of treatment underwent surgery. 44 patients (58.7%) received second or later-line chemotherapy, and 39 of those patients received either taxanes or irinotecan-containing regimens.

Table 1 Patient demographics and clinical characteristics

Characteristics	Total (n = 75) No. of patients (%)
Age at enrollment, years	
Median (range)	64 (21–75)
Gender	
Male	59 (78.7)
Female	16 (21.3)
ECOG PS	
0	57 (76.0)
1	18 (24.0)
Disease status	
Unresectable	66 (88.0)
Recurrent	9 (12.0)
Primary site	
Gastric	64 (85.3)
EGJ	11 (14.7)
Histology	
Differentiated	46 (61.3)
Undifferentiated	29 (38.6)
Previous gastrectomy	
Yes	10 (13.3)
No	65 (86.7)
Number of metastatic sites	
Median (range)	1 (1–5)
Metastatic site	
Lymph nodes	40 (53.3)
Liver	35 (46.7)
Peritoneum	20 (26.7)
Lung	9 (12.0)
Bone	3 (4.0)
Other (adrenal, pleural, ovary)	8 (10.7)
HER2 status	
IHC3+	55 (73.3)
IHC2+ and ISH positive	20 (26.7)

ECOG Eastern Cooperative Oncology Group, HER2 human epidermal growth factor receptor type 2, IHC immunohistochemistry, ISH in situ hybridization

Efficacy

The confirmed ORR (CR 1 patient; PR 52 patients) was 70.7% (95% CI 59.0–80.6); therefore, the null hypothesis for the primary endpoint (ORR = 50%) was rejected (Table 2). The disease control rate (CR + PR + SD) was 93.3% (95% CI 85.1–97.8). Waterfall plots for the patients are shown in Fig. 1. Except for four patients whose response was PD, all patients showed some tumor shrinkage. With a median follow-up time of survivors of 15.6 months, the median OS time was 18.1 months (95% CI 15.6–26.5), associated with a 1-year OS rate of 77.2% (95% CI 65.4–85.4) and a 2-year OS rate of 43.0% (95% CI 29.9–55.4; Fig. 2). The

Table 2 Objective tumor response with confirmation based on RECIST

Total	n = 75	(%)
Complete response	1	1.3
Partial response	52	69.3
Stable disease	17	22.7
Progressive disease	4	5.3
Not evaluable	1	1.3
Overall response rate (95% CI)	70.7	(59.0–80.6)
Disease control rate (95% CI)	93.3	(85.1–97.8)

RECIST Response Evaluation Criteria in Solid Tumor, CI confidence interval

median PFS time was 8.8 months (95% CI 7.4–12.2), with a 6-month PFS of 68.5% (95% CI 56.4–77.8) and a 1-year PFS of 39.5% (95% CI 27.5–51.2; Fig. 3). The estimated hazard ratio between IHC3+ (n = 55) and IHC2+/ISH-positive (n = 20) status was 0.734 (95% CI 0.366–1.475), the median survival times were 20.5 months and 16.9 months, respectively, and the ORRs were 70.9% and 70.0%, respectively. In the analysis of subgroups defined by the RDI of oxaliplatin during eight cycles (high RDI group, > 75%; middle RDI group, 50–75%; low RDI group, < 50%), the higher RDI groups (high RDI group and middle RDI group) showed better ORR than the low RDI group: 91.7% in the high group, 72.7% in the middle group, and 51.7% in the low group (general association $P = 0.0062$, trend $P = 0.0015$), but there were no statistically significant differences in PFS (9.8 months, 8.8 months, 8.7 months, respectively; $P = 0.54$) and OS (17.7 months, 18.1 months, 20.5 months, respectively; $P = 0.89$) among the groups (Supplementary Table 3).

Fig. 1 Waterfall plot of the confirmed maximum overall response for each patient

Fig. 2 Kaplan–Meier plot of overall survival. *OS* overall survival

Fig. 3 Kaplan–Meier plot of progression-free survival. *PFS* progression-free survival

Safety

As a result of the evaluation at up to the second cycle of treatment in the first six cases, the DSMC judged that the treatment was tolerable at the initial doses and gave their approval for the study to continue. Table 3 summarizes the treatment-related adverse events (TRAEs). Among the hematological adverse events, 10.7, 6.7 and 1.3% of the patients experienced grade 3 or higher neutropenia, anemia and thrombocytopenia, respectively. No febrile neutropenia was observed. The most common non-hematological toxicity

was PSN (any grade, 84%; grade 3 or higher, 16%). Among the gastrointestinal toxicities, 6.7, 5.3, and 4.0% of the patients experienced grade 3 or higher diarrhea, anorexia, and nausea and vomiting, respectively. Among the patients, 2.7% and 4.0% experienced grade 3 or higher AST and ALT elevation, respectively, and no grade 3 or higher elevation of creatinine was observed. Grade 3 or higher infusion-related reactions and heart failure were not observed in any patient. No treatment-related deaths occurred. Dose reductions of S-1, oxaliplatin, and trastuzumab due to adverse events were observed in 41 (54.6%), 38 (50.6%), and 8 (10.6%) patients;

Table 3 Treatment-related adverse events ($n = 75$)

	Any grade (%)	Grade 3 or 4 (%)
Any event	74 (98.6)	34 (45.3)
Hematological adverse events		
Leukopenia	25 (33.3)	1 (1.3)
Neutropenia	59 (78.7)	8 (10.7)
Febrile neutropenia	0 (0)	0 (0)
Anemia	72 (96.0)	5 (6.7)
Thrombocytopenia	59 (78.7)	1 (1.3)
Non-hematological adverse events		
Bilirubin increased	14 (18.7)	1 (1.3)
AST increased	69 (92.0)	2 (2.7)
ALT increased	45 (60.0)	3 (4.0)
Creatinine increased	6 (8.0)	0 (0)
LVEF decreased	8 (10.7)	2 (2.7)
Peripheral sensory neuropathy	63 (84.0)	12 (16.0)
Diarrhea	39 (52.0)	5 (6.7)
Anorexia	58 (77.3)	4 (5.3)
Nausea	49 (65.3)	3 (4.0)
Vomiting	15 (20.0)	3 (4.0)
Fatigue	43 (57.3)	2 (2.7)
Malaise	5 (6.7)	2 (2.7)
Constipation	17 (22.7)	1 (1.3)
Oral mucositis	19 (25.3)	1 (1.3)
Edema	6 (8.0)	1 (1.3)
Thromboembolic event	3 (4.0)	1 (1.3)
Injection site reaction	8 (10.7)	1 (1.3)
Fever	6 (8.0)	1 (1.3)
Hypoalbuminemia	14 (18.7)	0 (0)
Dysgeusia	11 (14.3)	0 (0)
Skin and subcutaneous tissue disorders	10 (11.3)	0 (0)

AST aspartate aminotransferase, ALT alanine aminotransferase

interruption in 38 (50.6%), 35 (46.6%), and 30 (40.0%); and discontinuation in 14 (18.6%), 22 (29.3%), and 0 (0%) patients, respectively.

Discussion

This is the first study to evaluate the efficacy and safety of trastuzumab in combination with S-1 plus oxaliplatin for chemotherapy-naïve, HER2-positive AGC. The actual ORR of 70.7% shows that this study met the primary endpoint. In addition, the disease control rate was rather high (93.3%), and eight patients achieved conversion to surgery. The median PFS and OS were 8.8 and 18.1 months, respectively. Furthermore, the toxicities were manageable and most patients were able to continue the treatments until disease progression. These results suggest that trastuzumab in combination with SOX₁₃₀ is effective and well tolerated in Japanese patients with HER2-positive AGC.

Table 4 summarizes the results of treatment with trastuzumab in combination with platinum and fluoropyrimidines in patients with HER2-positive AGC. From these results, the efficacy of trastuzumab with SOX in our study seems comparable to that of the other studies of patients with HER2-positive AGC, although comparisons with other studies should be interpreted with caution.

With respect to TRAEs, the safety profile of this combination therapy was considered acceptable. No new TRAE occurred with trastuzumab in combination with SOX₁₃₀. The most common grade 3 or higher TRAE was PSN (16.0%), followed by neutropenia (10.7%), and there were no other grade 3 or higher TRAEs > 10% including decreased LVEF (2.7%). Notably, the incidence rates of neutropenia (10.7%), anorexia (6.7%) and increased creatinine (0%) were lower than those of the cisplatin-containing regimens. These results suggest that trastuzumab with SOX₁₃₀ is a more tolerable regimen compared with trastuzumab with SP in patients with AGC. Furthermore, the proportion of patients

Table 4 Results of 1st line trastuzumab-based chemotherapy in HER2-positive advanced gastric cancer

	ToGA [#]	ToGA on Japanese pts [#]	HERBIS-1	WJOG7212	Ryu et al.	Current study
Regimen	XP/FP	XP/FP	SP	SP	XELOX	SOX
<i>n</i>	294	51	53	44	64	75
ORR (%)	47	64	68	61	68	71
PFS (months)	6.7	6.2	7.8	5.9	9.8	8.8
OS (months)	13.8	17.7	16.0	16.5	21.0	18.1
References	[2]	[12]	[7]	[8]	[9]	–

pts patients, *n* numbers, *XP* capecitabine + cisplatin, *FP* fluorouracil + cisplatin, *SP* S-1 + cisplatin, *XELOX* capecitabine + oxaliplatin, *SOX* S-1 + oxaliplatin, *ORR* overall response rate, *PFS* progression-free survival, *OS* overall survival

[#]Trastuzumab arm only

with grade 3 or higher thrombocytopenia in this study was lower (all grades, 78.7%; grade 3 or higher, 1.3%) than those in previous studies that evaluated the lower dose of oxaliplatin (100 mg/m²) in the SOX (SOX₁₀₀) [6], SOX₁₃₀ for HER2-negative [10] [11] or XELOX regimens [9] (grade 3 or higher, 10.1%, 15.4%, 16%, 4%, respectively) in AGC. The dose of oxaliplatin was reduced if the platelet count was 75,000–100,000/μL on the day of its administration in accordance with the criteria of the SOFT study, which evaluated SOX₁₃₀ plus bevacizumab in patients with advanced colorectal cancer [13]. In summary, the oxaliplatin dose reduction protocol appeared to have an improved safety profile especially thrombocytopenia compared with previous studies.

On the other hand, the proportion of patients with grade 3 or higher PSN in our study (16%) was higher than those in the studies of the SOX₁₀₀ [6] or SOX₁₃₀ [10, 11] regimens for HER-2 negative AGC (4.7%, 3.1%, 0%, respectively) and almost identical to that of the XELOX regimen [9] for HER-2 positive AGC (11%). These differences are probably due to the accumulated dose and long-term continuance of oxaliplatin in this study, which may have affected the severity of the neurotoxicity. PSN is a common dose-limiting toxicity observed with oxaliplatin. Even now, we have no effective therapies for preventing PSN outright; therefore, discontinuation of oxaliplatin before severe PSN develops may be a reasonable option. In patients with colorectal cancer, omitting oxaliplatin after 6 cycles of FOLFOX for 12 cycles (5-FU + leucovorin only) and then re-introduction of oxaliplatin achieved similar efficacy results to continuing oxaliplatin until progression, and greatly reduced the risk of severe PSN [14]. Similarly, Perk et al. [15] reported in their randomized phase II study for patients with HER-2 negative AGC that a stop-and-go strategy with a chemotherapy-free interval after six cycles of SOX did not show impaired OS and did reduce severe PSN compared with the chemotherapy continuation group (grade 3 or higher, 9.7% vs. 25.4%). In terms of efficacy without oxaliplatin, Kimura et al.

[16] reported encouraging results with an RR of 40.8%, an OS of 15.8 months, and a PFS of 5.1 months among elderly patients receiving trastuzumab with S-1 for HER-2-positive AGC. In addition, according to the subgroup analysis in our report, while the higher RDI of oxaliplatin did not appear to improve the PFS and OS, it was associated with improved ORR. These results indicate that when the patients achieve disease control after several cycles of trastuzumab with SOX₁₃₀, a stop-and-go strategy using S-1 plus trastuzumab as maintenance therapy still maintains a therapeutic effect while helping to reduce severe PSN, although this warrants further evaluation.

Several possible biomarkers such as serum HER2 level [17] and HER2 heterogeneity [18, 19] have been proposed for assessing trastuzumab efficacy in HER2-positive AGC. Therefore, in this study, additional analyses are ongoing using blood and tumor samples obtained from patients to examine these biomarkers.

Our study has some limitations. First of all, this was a single-arm phase II study. Therefore, it is not possible to make a direct comparison with other regimens or show whether 100 mg/m² or 130 mg/m² of oxaliplatin is a more suitable dose in this regimen. Second, the study only enrolled Japanese patients, so generalization to patients of other populations is limited. Third, an extramural response review was not performed. Therefore, an assessment bias cannot be excluded. However, 75 patients were enrolled in this phase II study, which was sufficient to achieve 90% statistical power, which in turn supports the consistency of the results in this study.

In conclusion, this study revealed that trastuzumab with SOX showed efficacy and well-tolerated toxicity in patients with HER2-positive AGC, suggesting that this regimen can be one option among the standard chemotherapy regimens with trastuzumab combined with fluoropyrimidines and platinum for patients with HER2-positive AGC. Further confirmative trials, and investigations of molecular correlates, are warranted.

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Compliance with ethical standards

Conflict of interest Dr. Takahari reports grants and personal fees from Taiho Pharmaceutical Co. and Ono Pharmaceutical Co., and personal fees from Eli Lilly Japan, Bristol-Myers Squibb, Yakult Honsha Co., Ltd., and Chugai Pharmaceutical Co., Ltd. Naoki Ishizuka reports personal fees from Bristol-Myers Squibb, Novartis, and Merck Sharp and Dohme. Dr. Takashima reports grants and personal fees from Taiho Pharmaceutical Co. and Takeda Pharmaceutical Company Ltd, personal fees from Eli Lilly Japan, Ono Pharmaceutical Co., Yakult Honsha Co., Ltd., and Chugai Pharmaceutical Co., Ltd., and grants from Sumitomo Dainippon Pharma and LSK BioPartners. Dr. Minashi reports grants from Merck Sharp and Dohme and Ono Pharmaceutical Co. Dr. Kadowaki reports grants and personal fees from Taiho Pharmaceutical Co. and Eli Lilly, grants from Ono Pharmaceutical Co. and Bristol-Myers Squibb, and personal fees from Yakult Honsha Co., Ltd., Chugai Pharmaceutical Co., Ltd., Bayer, and Merck. Dr. Nishina reports grants and personal fees from Taiho Pharmaceutical Co., grants and personal fees from Eli Lilly Japan, Ono Pharmaceutical Co., Bristol-Myers Squibb, Yakult Honsha Co., Ltd., and Chugai Pharmaceutical Co., Ltd., and grants from Daiichi Sankyo, Dainippon Sumitomo Pharma, Boehringer Ingelheim, and Merck Sharp and Dohme. Dr. Nakajima reports grants and personal fees from Taiho Pharmaceutical Co., Ono Pharmaceutical Co., Chugai Pharmaceutical Co., Ltd., Merck, Merck Sharp and Dohme, and Takeda Pharmaceutical Company Ltd, and personal fees from Eli Lilly Japan, Bristol-Myers Squibb, Yakult Honsha Co., Ltd., Bayer, Sanofi, Sawai Pharmaceutical Company, Limited, Mochida Pharmaceutical Company, Ltd, Kyowa Hakko-Kirin, Dainippon Sumitomo Pharma, Maruho Co. Ltd., Daiichi Sankyo, Eisai Co., Ltd, and AstraZeneca. Dr. Amagai reports grants and personal fees from Taiho Pharmaceutical Co., grants from Merck Sharp and Dohme, and personal fees from Eli Lilly Japan, Bristol-Myers Squibb, Yakult Honsha Co., Ltd., Chugai Pharmaceutical Co., Ltd., Daiichi-Sankyo, and Hisamitsu Pharmaceutical Co., Inc. Dr. Machida reports grants and personal fees from Taiho Pharmaceutical Co., personal fees from Eli Lilly Japan, Ono Pharmaceutical Co., Bristol-Myers Squibb, Yakult Honsha Co., Ltd., Chugai Pharmaceutical Co., Nippon Kayaku, Daiichi Sankyo, Merck Sharp and Dohme. Dr. Goto reports grants, personal fees and non-financial support from Taiho Pharmaceutical Co., Yakult, Chugai Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Takeda Pharmaceutical Company Ltd, Kyowa Hakko Kirin, Novartis, Bayer, and Mochida Pharmaceutical Company, Ltd. Dr. Wakatsuki reports personal fees from Taiho Pharmaceutical Co., Eli Lilly Japan, Bayer, and Chugai Pharmaceutical Co., Ltd. Dr. Hironaka reports personal fees from Taiho Pharmaceutical Co., Eli Lilly Japan, Ono Pharmaceutical Co., Bristol-Myers Squibb, Yakult Honsha Co., Ltd., Chugai Pharmaceutical Co., Ltd., and Daiichi-Sankyo. Dr. Boku reports grants from Taiho Pharmaceutical Co., Ono Pharmaceutical Co. and Bristol-Myers Squibb, and personal fees from Taiho, Ono Pharmaceutical Co., Bristol-Myers Squibb, Chugai

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Human rights statement and informed consent All procedures followed were in accordance with the ethical standards of the institutional and national committees governing human experimentation and in compliance with the Helsinki Declaration of 1964 and later versions.

Informed consent Informed consent or an appropriate substitute was obtained from all patients prior to their inclusion in the study.

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