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A Phase II Trial of Trastuzumab Combined With Irinotecan in Patients With Advanced HER2-positive Chemotherapy-refractory Gastric Cancer (OGSG1203 HERBIS-5): Final Results

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Abstract

Background/Aim: Irinotecan is a key drug for patients with advanced gastric cancer. We assessed the efficacy and safety of combination chemotherapy with trastuzumab and irinotecan in patients with advanced human epidermal growth factor receptor type 2 (HER2)-positive chemotherapy-refractory gastric cancer.

Patients and Methods: Eligibility criteria included unresectable or recurrent HER2-positive gastric cancer patients who were refractory to at least one regimen of chemotherapy. Irinotecan was administered at a dose of 150 mg/m^2 every 2 weeks, and trastuzumab at a dose of 8 mg/kg on day 1 of the first cycle, followed by 6 mg/kg every 3 weeks. The primary endpoint was the disease control rate (DCR). The secondary endpoints were adverse events (AEs), overall response rate (ORR), time-to-treatment failure (TTF), progression-free survival (PFS), and overall survival (OS).

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Results: Thirty patients were enrolled, of whom 18 previously received a single chemotherapy regimen whereas 12 received two or more regimens. As one patient withdrew before the study treatment, 29 patients were assessable for efficacy and safety. The DCR was 65.5%, and the ORR was 20.7%. The median PFS and OS were 3.7 and 7.5 months, respectively. The major grade 3/4 AEs were neutropenia (24%), anemia (24%), leukopenia (21%), anorexia (11%), fatigue (14%), hypoalbuminemia (24%), and hypokalemia (14%). One treatment-related death occurred.
Conclusion: These findings indicate that irinotecan plus trastuzumab is feasible with modest potential efficacy against chemotherapy-refractory advanced HER2-positive gastric cancer.

Keywords: HER2-positive, gastric cancer, chemotherapy, trastuzumab, irinotecan.

Introduction

Gastric cancer is the fifth most commonly diagnosed cancer and the fifth leading cause of cancer-related mortality worldwide, making it an important global health burden (1). Approximately 60% of patients with gastric cancer worldwide are diagnosed in East Asian countries, including Japan, Korea, and China (1). The human epidermal growth factor receptor type 2 (HER2)-positive subtype, characterized by HER2 overexpression or amplification, comprises 10-20% of advanced gastric cancer (AGC) patients (1).

For patients with HER2-positive AGC, adding trastuzumab, anti-HER2 monoclonal antibody, to fluoropyrimidine plus platinum-based chemotherapy is the standard first-line chemotherapy based on the result of the ToGA trial (2). In case of AGC that is refractory to first-line chemotherapy, irrespective of HER2 status, paclitaxel plus ramucirumab based on the results of the RAINBOW trial was recognized as the standard second-line chemotherapy for AGC (3). The Japanese WJOG4007 trial, comparing irinotecan with paclitaxel as second-line chemotherapy, concluded that neither regimen demonstrated superiority in terms of efficacy or tolerability (4). A potential explanation for this could be the high crossover rate to subsequent treatments. Thus, irinotecan could be an option for second- or later-line chemotherapy for AGC.

Evidence from HER2-positive breast cancer demonstrated the benefit of continuing or re-challenging anti-HER2 therapy beyond disease progression after chemotherapies with trastuzumab (5-7). Continuous blockade of HER2 signals is recommended to prolong survival outcomes in HER2-positive advanced breast cancer (8, 9). Retrospective studies evaluating FOLFIRI plus trastuzumab showed a potential efficacy for chemotherapy-refractory HER2-positive AGC (10, 11). Based on these findings, we hypothesized that continuous administration of trastuzumab or re-challenge might be effective in HER2-positive AGC after disease progression on prior chemotherapy with trastuzumab.

Therefore, we conducted this phase II study to assess the efficacy and safety of combination of trastuzumab and irinotecan in patients with HER2-positive chemotherapy-refractory AGC.

Patients and Methods

Study design. This was a multicenter, open-label, single-arm, phase II study in Japan to evaluate the efficacy and safety of a combination of trastuzumab and irinotecan for patients with HER2-positive chemotherapy-refractory AGC. This study was conducted in accordance with the Declaration of Helsinki and the guidelines of Good Clinical Practice. The study protocol was approved by the Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG) Steering Committee and the institutional review boards of all participating hospitals, and was previously described (12). This study was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR, UMIN000008626).

Patients. We enrolled patients with unresectable or recurrent HER2-positive adenocarcinoma in the stomach or gastroesophageal junction from 8 Institutions in Japan: Osaka General Medical Center, Sakai City Medical Center, NHO Osaka National Hospital, Osaka International Cancer Institute, Nishinomiya Municipal Central Hospital, Higashiosaka City Medical Center, Matsushita Memorial Hospital, and Yao Municipal Hospital. In this study, only patients with either immunohistochemistry (IHC) 3+, or IHC 2+ and fluorescence *in situ* hybridization (FISH)-positive according to the gastric cancer scoring system for HER2 (13) were eligible, and HER2 positivity was determined by each participating institution. Patients were required to have received one or more lines of chemotherapy and confirmed disease progression by imaging. Patients were required to have measurable lesions according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (14). Eligibility criteria also included: age 20 years old or older, Eastern Cooperative Oncology Group performance status score of 0, 1, or 2, neutrophil count ≥1,500/mm^3, hemoglobin ≥8.0 g/dl, platelet count ≥100,000/mm^3, serum bilirubin <1.5 mg/dl, serum creatinine ≤2.0 mg/l, serum aspartate aminotransferase and alanine aminotransferase <150 IU/l; and baseline left ventricular ejection fraction (LVEF) ≥50%. Patients were excluded from the study if they were unable to maintain adequate oral intake, or had received prior irinotecan chemotherapy before enrollment. All patients provided written informed consent before enrollment.

Treatment. Patients received irinotecan at a dose of 150 mg/m^2 intravenously every 2 weeks and trastuzumab at a dose of 8 mg/kg intravenously on day 1 of the first cycle, followed by 6 mg/kg every 3 weeks. Uridine diphosphate glucuronosyl-transferase (UGT) 1A1 testing was not mandatory, and if UGT1A1 was found to be homozygous, starting with a 1-level dose reduction (120 mg/m^2) was permissible. Each administration of irinotecan and trastuzumab was repeated according to independent schedules. Treatment was continued until disease progression, unacceptable toxicity or withdrawal of consent. Dose adjustment of irinotecan was allowed based on toxicity. Toxicity from trastuzumab was managed by treatment interruption.

Endpoints and assessments. The primary endpoint of this study was the disease control rate (DCR), defined as the proportion of patients showing a complete response (CR), partial response (PR) or stable disease (SD) as the best overall response according to RECIST version 1.1 (14). The secondary endpoints were the rates of adverse events (AEs), overall response rate (ORR), time to treatment failure (TTF), progression-free survival (PFS), overall survival (OS), and ORR stratified by prior trastuzumab use.

Physical and safety evaluations and laboratory tests were performed before the initiation of treatment. Responses were evaluated every 2 months or earlier if there were indications of treatment failure due to toxicity. Overall response was determined by the investigators' assessment. Toxicities were assessed every cycle and graded according to the Common Terminology Criteria for Adverse Event (CTCAE) version 4.

All eligible patients except those who withdrew consent were included in the assessment of efficacy and safety.

Statistical analysis. All results were analyzed in the full analysis set (FAS), which included all registered patients who received at least one dose of the study treatment, except those who were ineligible or withdrew consent after registration. The FAS is the primary population used for efficacy analyses in clinical trials and follows the intent-to-treat principle as closely as possible, ensuring that the results reflect real-world clinical scenarios. The planned sample size of this study was 30 patients based on the hypothesis of expected and threshold DCRs of 50% and 30%, respectively, using a one-sided exact binomial test with α-error=0.05, and β-error=0.2. The hypothesis in this study was referred to the previous reports of irinotecan in second-line chemotherapy from the AIO trial (15), in which the DCR was 53%. However, the population in this study included not only second-line cases but also third-line or later cases, and therefore, the lower estimate was adopted.

The Kaplan-Meier method was used to analyze PFS and OS. ORR was summarized as a percentage with a 95% confidence interval (CI). The relative dose intensity (RDI) was determined as the percentage of the actual cumulative dose relative to the estimated dose of each drug. Statistical analyses were performed using R version 3.3.1 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients. Between October 2012 and August 2014, a total of 30 patients were enrolled. One patient withdrew consent prior to protocol treatment, leaving 29 patients for the efficacy analysis set. The characteristics of the eligible patients are presented in Table I. The median age was 70.5 years (range=49-86 years). Five patients (16.7%) had recurrent disease, and ten patients (33.3%) underwent gastrectomy. All patients received previous chemotherapies (18 received one prior regimen, 9 received two regimens, and 3 received three or more). Furthermore, all patients had previously received trastuzumab, with 27 having received trastuzumab in their most recent prior treatment. The median trastuzumab-free interval, defined as the time between the last trastuzumab administration during prior chemotherapy and enrollment in this trial was 22 days.

As of the data cutoff in December 2015, 27 patients had discontinued treatment. The main reason for discontinuation was progressive disease (n=23, 85%), followed by adverse events (n=4, 15%).

The median number of trastuzumab cycles administered was 5 (range=1-17), and the median number of irinotecan cycles was 6 (range=1-23). The RDI for trastuzumab was 100% (range=61-103%), whereas the RDI for irinotecan was 91.4% (range=52.9-101.4%).

Efficacy. The median duration of follow-up was 7.1 months. Of the 29 treated patients, 6 (20.7%) achieved PR, and 13 (44.8%) achieved SD, resulting in a DCR of 65.5% (90% CI=48.6-80.0% and 95% CI=45.7-82.1%) and ORR of 20.7% (Table II). The median OS was 7.5 months (95% CI=5.2-12.6 months), with the 1-year OS rate of 29.3% (95% CI=15.7-54.5%) (Figure 1A). The median PFS was 3.7 months (95% CI=3.1-5.5 months), with the 6-month PFS rate of 17.2% (95% CI=7.8-38.3%) (Figure 1B). The median TTF was 3.3

Table I. *Patient characteristics.*

Characteristics		
Sex, n	Male	25
	Female	5
Age	Median (range)	70.5 (49-86)
PS, n	0	15
	1	13
	2	2
Diagnosis status, n	Unresectable	25
	Recurrence	5
Histology, n	Intestinal	20
	Diffuse	8
	Others	1
	Unknown	1
HER2 status, n	IHC3+	20
	IHC2+/FISH(+)	10
Metastatic site[a], n	Lymph node	20
	Liver	14
	Lung	6
	Peritoneum	4
	Other	4
Number of metastatic sites, n	1	14
	2	12
	3	3
	4	1
UGT1A1*28, n	–/–	14
	-/*28	3
	*28/*28	0
	Unknown	13
UGT1A1*6, n	–/–	14
	-/*6	3
	*6/*6	0
	Unknown	13
Previous gastrectomy, n	(–)	20
	(+)	10
Previous treatment[b], n	Trastuzumab	30
	Fluoropyrimidine	26
	Platinum	17
	Taxane	18
	Radiation	2
	Lentinan	1
Previous treatment lines, n	1	18
	2	9
	≥3	3
CEA	Median (range)	10.5 (1.6-1,039)
CA19-9	Median (range)	20.5 (0.86-4,500)

PS: Performance status; FISH: fluorescence *in situ* hybridization; HER2: human epidermal growth factor receptor type 2; IHC: immunohistochemistry; UGT: uridine diphosphate glucuronosyltransferase, CEA: carcinoembryonic antigen; CA: carbohydrate antigen. [a]Some patients had multiple metastatic sites. [b]Some patients had two or more treatments.

months (95% CI=2.6-5.3 months). The efficacy outcomes stratified by prior treatment line are presented in Table III. OS was 6.6 months in the second-line chemotherapy group and 11.7 months in the third-line or later chemotherapy group. PFS was 3.5 months in the second-line chemotherapy group and 6.6 months in the third-line or later chemotherapy group. The median trastuzumab-free interval was 22.5 days for the second-line chemotherapy group and 18 days for the third-line or later chemotherapy group. The post-treatment continuation rates for each group were 9/17 (52.9%) in the second-line chemotherapy group and 7/10 (70%) in the third-line or later chemotherapy group. Additionally, one case from both the second-line chemotherapy group and the third-line or later chemotherapy group continued with the chemotherapy protocol.

Safety. All AEs observed in three or more patients, or those with grade 3 or higher, are listed in Table IV. Among the hematological AEs, the incidences of grade 3-4 neutropenia, anemia, and hypoalbuminemia were 24.1% for each condition. The most common non-hematological toxicities were fatigue (any grade: 75.9%; grade 3-4: 13.8%), followed by anorexia (any grade: 65.5%; grade 3-4: 10.3%). Except for fatigue and anorexia, no grade 3 or 4 toxicities were observed in more than 10% of patients. One treatment-related death occurred due to heart failure.

Discussion

This was a prospective multicenter phase II study evaluating the efficacy and safety of adding trastuzumab to irinotecan in patients with chemotherapy-refractory, HER2-positive AGC. In our study, we observed a DCR of 65.5%, which was higher than the expected DCR of 50%. The incidence and the profile of AEs were generally mild and consistent with the known safety of irinotecan monotherapy in the refractory setting (4, 15), and few additional toxicities related to trastuzumab were observed.

Although our study suggested potential efficacy of trastuzumab with irinotecan in chemotherapy-refractory HER2-positive AGC at the time it was conducted, this did not demonstrate a clinically meaningful improvement when compared to the current standard regimens in second-line or third-line chemotherapy for HER2-positive AGC; paclitaxel plus ramucirumab in second-line chemotherapy with a median PFS of 4.4 months and a median OS of 9.6 months in the RAINBOW trial (3); trastuzumab-deruxtecan, an antibody-drug conjugate comprised of trastuzumab and a topoisomerase I inhibitor payload, in the third or later lines with ORR of 50%, median PFS of 5.6 months, and median OS of 12.5 months in the Destiny-Gastric01 study (16).

Unlike HER2-positive breast cancer, lapatinib (17), an oral anti-HER2 small-molecule agent, and trastuzumab-emtansine (18), an anti-HER2 antibody-drug conjugate, failed to show efficacy in second-line chemotherapy for HER2-positive AGC beyond disease progression with trastuzumab. Additionally, subsequent reports have not supported the broader use of continuing trastuzumab beyond disease progression. A randomized phase II trial (WJOG 7112G/T-ACT trial) showed no statistical significance in PFS, OS, and RR of the adding trastuzumab to second-line paclitaxel in patients with HER2-positive AGC who failed first-line chemotherapy with trastuzumab plus fluoropyrimidine and platinum (19). Moreover, negative result from another trial (HGCSG1201) of continuation of trastuzumab in addition to irinotecan in second-line chemotherapy for HER2 positive gastric cancer was reported with the ORR of 6.7% and the DCR of 53.3% (20).

Several mechanisms of resistance to HER2-targeted therapy in gastric cancer have been identified (21). The alteration of HER2 protein during the first-line trastuzumab treatment is likely responsible for the reduced efficacy of trastuzumab in the second-line setting (22, 23). Indeed, in the WJOG7112 trial, HER2 positivity of tumor tissues was lost after first-line chemotherapy in 11 (69%) of 16 patients (19), suggesting that continued HER2-targeted therapy may not always be beneficial. Similarly, Shu *et al.* (24) reported a high rate of HER2 loss after chemotherapy, with only one of six initially HER2-positive cases remaining positive, further supporting this observation.

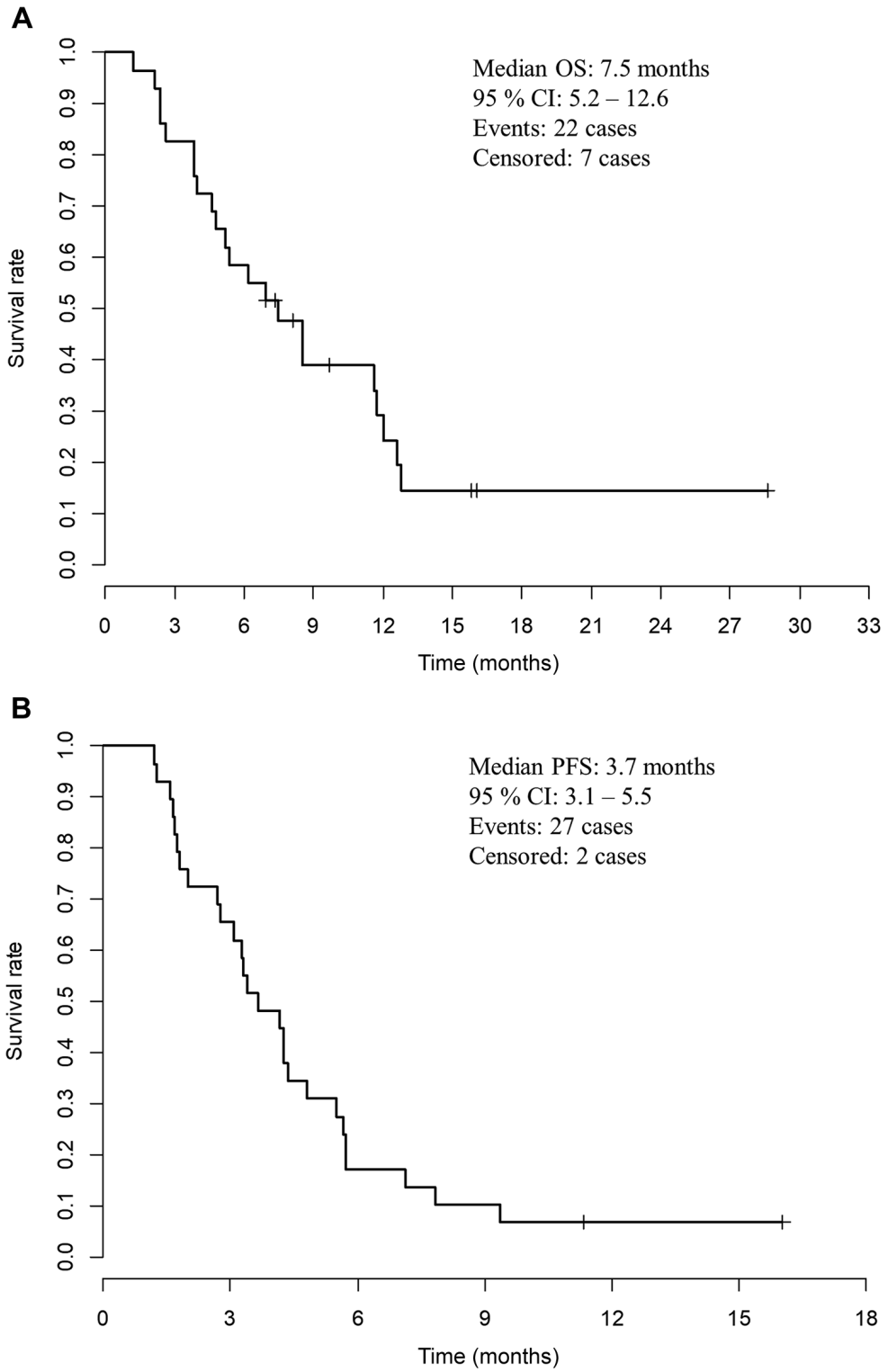

Figure 1. *Kaplan-Meier overall (A) and progression-free (B) survival of the 29 treated patients.*

Table II. *Objective response with confirmation based on RECIST ver. 1.1*

Complete response (CR), n (%)	0 (0.0)
Partial response (PR), n (%)	6 (20.7)
Stable disease (SD), n (%)	13 (44.8)
Progressive disease (PD), n (%)	9 (31.0)
Not evaluable (NE), n (%)	1 (3.4)
Overall Response Rate (CR+PR), %	20.7
Disease Control Rate (CR+PR+SD), % (95% confidence interval)	65.5 (45.7-82.1)

RECIST: Response Evaluation Criteria in Solid Tumors.

Table III. *Efficacy for each treatment line.*

	All patients (n=29)	2nd line (n=18)	3rd or later line (n=11)
OS (months)	7.5	6.6	11.7
PFS (months)	3.7	3.5	6.6
DCR (%)	66	61	72
ORR (%)	21	16	27

OS: Overall survival; PFS: progression-free survival; DCR: disease control rate; ORR: overall response rate.

Table IV. *Main adverse events.*

Events	Any grade, n (%)	≧Grade 3, n (%)
Anemia	28 (96.5)	7 (24.1)
Hypoalbuminemia	26 (89.6)	7 (24.1)
Neutropenia	18 (62.1)	7 (24.1)
Leukopenia	16 (55.2)	6 (20.7)
AST increased	7 (24.1)	1 (3.4)
ALT increased	7 (24.1)	0 (0.0)
Thrombocytopenia	5 (17.2)	1 (3.4)
Creatinine increased	4 (13.8)	0 (0.0)
Total bilirubin increased	3 (10.3)	1 (3.4)
Febrile neutropenia	1 (3.4)	1 (3.4)
Fatigue	22 (75.9)	4 (13.8)
Anorexia	19 (65.5)	3 (10.3)
Nausea	12 (41.4)	0 (0.0)
Diarrhea	13 (44.8)	1 (3.4)
Vomiting	6 (20.7)	0 (0.0)
Stomatitis	6 (20.7)	0 (0.0)
Rash	1 (3.4)	1 (3.4)
Pneumonia	1 (3.4)	1 (3.4)
Heart failure	1 (3.4)	1 (3.4)

AST: Aspartate aminotransferase; ALT: alanine aminotransferase.

In this study, the OS was 1.8 times longer in the third-line or later chemotherapy group compared to the second-line chemotherapy group. The median trastuzumab-free intervals of 22.5 days (second-line chemotherapy group) and 18 days (third-line or later chemotherapy group) were both short, and it does not appear that HER2 positivity was restored during this period. The transition rate to subsequent treatments was 1.3 times higher in the third-line or later chemotherapy group compared to the second-line chemotherapy group, which is thought to be partially related to survival difference.

The primary limitation of this study was its small sample size and single-arm design, which required comparison with historical data. Second, the study only included patients with measurable lesions, which may not represent the entire population of gastric cancer patients, particularly those with peritoneal metastasis. Third, there was a significant delay in submitting this study, which resulted in the emergence of new drugs and changes in treatment trends. Lastly, imaging assessment for DCR, RR, and PFS were evaluated by the investigator.

In conclusion, these findings indicate that irinotecan plus trastuzumab is feasible with modest potential efficacy against chemotherapy-refractory advanced HER2-positive gastric cancer.

Conflicts of Interest

DS received lecture fee from Chugai Pharm, Daiichi Sankyo, and received a research grant from Eli Lilly, Daiichi Sankyo, Chugai Pharm, Ono and Yakult Honsha; KN received lecture fee from Daiichi Sankyo, EA Farma, Eli Lilly, MSD, Ono, Otsuka and Taiho; NS received lecture fee from Chugai Pharm, Daiichi Sankyo, Ono and Eli Lilly, and received a research grant from Chugai Pharm, Daiichi Sankyo, MSD and Pfizer; HK received lecture fee from BMS KK, Ono, Taiho and Daiichi Sankyo, and received a research grant from BMS KK, Chugai Pharm, Eisai, Kobayashi Pharmaceutical, Taiho and Daiichi Sankyo; TSa received lecture fee from Ono, Daiichi Sankyo, Eli Lilly, Taiho and Chugai Pharm, received a research grant from Ono, Dasiichi sankyo, BMS, Eli Lilly, Taiho and Chugai Pharm, received scholarship donations from Daiichi Sankyo and

Taiho, and endowed chairs from Yakult Honsha, Ono and Chugai Pharm. JK, YK, YO, SE, YI, JM, RK, TK, KF, YK and TSh have no conflict of interest. All Authors had full access to all of the data in the study and accepted final responsibility for the decision to submit the article for publication.

Authors' Contributions

JK, DS, SE, KF, YK, HK, and TSa contributed to the conception and design of the work, as well as the acquisition and interpretation of data. KY, KN, NS, YO, YI, JM, RK, and TK contributed to the acquisition of data. TSh contributed to the statistical analysis. All Authors participated in drafting the manuscript, approved the final version to be published, and have agreed to be accountable for all aspects of the work, ensuring that any questions related to the accuracy and integrity of the work are appropriately investigated and resolved.

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