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ORIGINAL ARTICLE

Phase II study of S-1 plus docetaxel as first-line treatment for older patients with advanced gastric cancer (OGSG 0902)

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Abstract

Background Although there is insufficient evidence for the treatment of older patients with advanced gastric cancer, fluorouracil combined with platinum chemotherapy has been recognized as a standard first-line treatment for such populations in Japan despite the lack of efficacy and toxicity data.

Methods Patients aged 75 years or older with advanced gastric cancer were enrolled. S-1 plus docetaxel (docetaxel: 40 mg/m^2, day 1; S-1: 80 mg/m^2, days 1–14; q21 days) was repeated every 3 weeks. The primary endpoint was overall response rate. Secondary endpoints were safety, progression-free survival, time to treatment failure, and overall survival. The sample size was calculated as 30 under the hypothesis of an expected response rate of 40% and a threshold response rate of 20%, at a power of 90% and a two-sided alpha value of 5%.

Results From February 2010 to January 2015, 31 patients were enrolled and assessed for efficacy and toxicity. The response rate was 45.2% (95% CI 27.3%–64.0%; p = 0.001) and it exceeded the expected response rate set at 40%. Median progression-free survival was 5.8 months, the 1-year survival rate was 58.1%, and the median survival time was 16.1 months. The major grade 3/4 adverse events were neutropenia (58%), febrile neutropenia (13%), anemia (10%), anorexia (10%), and fatigue (6%).

Conclusions These findings indicate that S-1 plus docetaxel as first-line treatment for older patients is feasible and that it has promising efficacy against advanced gastric cancer.

Keywords Gastric cancer · Older patients · Docetaxel · S-1

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Introduction

Gastric cancer is predominantly a disease of older people. The number of newly diagnosed patients with gastric cancer aged ≥ 75 years is 65,672 per year, which is equivalent to 53% of all newly diagnosed patients, and the number of gastric cancer deaths in patients aged ≥ 75 years accounts for 67% of all gastric cancer deaths in Japan [1]. Given that is readily available to chemotherapy older patients, it is important to establish a consensus for chemotherapy regimens for older patients with advanced gastric cancer. Importantly, the National Comprehensive Cancer Network guidelines suggest that for older patients, treatment should be selected according to life expectancy, decision-making ability, treatment goals, and side effect risk [2].

Fluorouracil combined with platinum chemotherapy is recognized as the standard first-line treatment for advanced gastric cancer in Japan [3–6]. However, the efficacy and safety of such chemotherapy have not been established for older patients. For advanced gastric cancer patients aged ≥ 70 years treated with S-1 alone or S-1 plus cisplatin (SP) as first-line treatment in propensity score-matched cohorts [7], the survival benefit of SP over S-1 was not observed, and severe adverse events (AEs) were more frequent in the SP group than in the S-1 group. Furthermore, renal function is likely to be impaired during treatment with SP in older patients, even when adequate hydration is provided to prevent renal toxicity. While oxaliplatin does not affect renal function, a phase III study in Japan [8] showed that S-1 plus oxaliplatin (SOX) was as effective as SP for advanced gastric cancer and SOX was less toxic and more convenient clinically, in which forced hydration is not needed, than SP. However, oxaliplatin-containing regimens have a high rate of cumulative peripheral neurotoxicity and gastrointestinal toxicity, which may seriously affect the quality of life of older patients. Although S-1 monotherapy showed good tolerability, a doublet regimen is needed to improve treatment efficacy in older patients with advanced gastric cancer.

Although not considered as a standard of care, but conditionally recommended as first-line treatment in Japan [6], combination therapy of docetaxel plus S-1 (DS) has demonstrated clinically meaningful efficacy compared with S-1 monotherapy as first-line treatment for advanced gastric cancer. In previous studies, overall response rate (ORR) ranged from 46.0% to 56.3% and overall survival (OS) ranged from 14.0 to 14.3 months [9, 10]. DS seemed to be more feasible rather than SP based on the findings that docetaxel is effective and safe in older patients with non-small cell lung cancer [11], prostate cancer [12], and breast cancer [13].

Thus, the Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG) conducted a multicenter phase II trial (OGSG0902) to examine the efficacy and safety of DS as a first-line treatment for older patients with unresectable advanced or recurrent gastric cancer.

Patients and methods

Patient eligibility

Eligible patients were aged ≥ 75 years with histologically confirmed metastatic or recurrent gastric adenocarcinoma with measurable lesions based on Response Evaluation Criteria In Solid Tumors (RECIST), version 1.1 [14]. Other inclusion criteria were an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 1, no previous chemotherapy or more than 6 months after perioperative adjuvant chemotherapy completion, capable of oral intake, adequate organ function creatine clearance (Ccr) ≥ 40, and expected survival of at least 3 months. Written informed consent was obtained from all patients.

Major exclusion criteria were severe ascites or pleural effusion, uncontrolled cardiac disease, other clinically significant, uncontrolled coexisting illness, or concurrent cancer.

Study design

OGSG0902 was a prospective, multicenter, phase II clinical trial that was conducted at nine institutions in Japan. The protocol was approved by the independent ethics committee or institutional review board of each participating institution. This trial was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent before study entry. The trial was registered with the University Hospital Medical Information Network.

The primary endpoint was ORR. Secondary endpoints were OS, defined as the time from the date of registration to the date of death from any cause, progression-free survival (PFS), defined as the time from the date of registration to the date of progressive disease or death from any cause, time to treatment failure (TTF), defined as the time from the date of registration to the date of treatment failure from any cause, and incidence of AEs.

Treatment plan

Although the dose of docetaxel (40 mg/m^2) in phase II and phase III studies of DS in Japanese patients with advanced gastric cancer [9, 10, 15] was lower than that used in Western countries, treatment was well tolerated and showed efficacy. In this study, the dose of docetaxel was in accordance with these previous studies. Docetaxel (40 mg/m^2) was administered intravenously on day 1 and S-1 was administered orally twice daily on days 1–14, every 3 weeks.

The dose of S-1 administered each time was determined based on the body surface area (BSA) and Ccr as follows: in patients with CCr ≥ 60 ml/min, 40 (BSA < 1.25 m^2), 50 (BSA ≥ 1.25 to < 1.5 m^2) or 60 mg (BSA ≥ 1.5 m^2) S-1 was administered, and in patients with CCr ≥ 40 to < 60 ml/min, 25 (BSA < 1.25 m^2), 40 (BSA ≥ 1.25 to < 1.5 m^2) or 50 mg (BSA ≥ 1.5 m^2) S-1 was administered. Dose reduction and/or cycle delays were permitted based on predefined toxicity criteria. The treatment continued until disease progression, occurrence of unacceptable serious toxicity, or patient refusal of further treatment. Subsequent chemotherapy was not specified.

Assessment and data collection

Physical examinations and hematology and biochemistry tests were conducted during drug administration throughout the treatment course. Tumor assessments using computed tomography (CT) scanning of the chest, abdomen, and pelvis were performed every 6 weeks after treatment initiation. RECIST (version 1.1) [14] was used to evaluate treatment responses. When complete response (CR) or partial response (PR) was observed, another CT scan was performed at least 4 weeks after the previous images to confirm the evaluation. Tumor assessments were also continued in patients who discontinued DS therapy for reasons other than disease progression. Safety assessments were repeated at each chemotherapeutic agent administration. The AE severity was graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). Extramural review of patient eligibility, response, and disease progression were performed.

Statistical analysis

The ORR of DS in patients under 75 years of age was reported to be 46.0% by Yamaguchi et al. [9] and 56.3% by Yoshida et al. [10]. Therefore, the ORR for this study in older patients was set at 40.0%, assuming that it would be approximately 5% lower than in these papers. The threshold response rate was set at 20.0% based on the response rate of 14.3% in the OGSG0404 study of S-1 alone in patients aged 75 years and older [16]. Under these settings, the required sample size was then calculated as 28 patients, with a one-sided alpha error of 0.10 and a power of 0.85. Taking into account the possibility of ineligibility, we planned to include 30 patients in this study.

Background data were summarized as the frequency with proportion for categorical variables, and the median with range for continuous variables. The ORR was evaluated using an exact binomial test with 20.0% as the threshold rate. The 95% confidence intervals (CIs) of the ORR and disease-control rate (DCR) were estimated by the Clopper–Pearson method. OS, PFS, and TTF were determined using the Kaplan–Meier method to estimate survival curves and Greenwood's formula to calculate 95% CIs for survival rate.

A p-value of < 0.05 was considered statistically significant. Statistical analyses were performed with R version 4.2.0 (the R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients

From February 2010 to January 2015, 31 patients were enrolled at 9 centers in Japan. Patient demographics and characteristics are shown in Table 1. Disease status included unresectable in 24 patients (77%) and recurrence in 7 patients (23%). Metastatic sites were lymph nodes in 19

Table 1 Baseline patient demographics and characteristics

	n = 31(%)
Sex	
Male	28 (90)
Female	3 (10)
Age	
Median	78
Range	75–85
ECOG performance status	
0	18 (58)
1	13 (42)
Histology	
Intestinal type	23 (74)
Diffuse type	8 (26)
Disease status	
Unresectable	24 (77)
Recurrent	7 (23)
Primary tumor	
Present	21 (68)
Absent	10 (32)
Prior treatment	
None	26 (84)
Surgery	5 (16)
Metastatic site	
Lymph node	19 (61)
Liver	14 (45)
Peritoneal	4 (13)
Lung	2 (6)
Adrenal	1 (3)
Number of organs involved	
0 or 1	22 (71)
≥ 2	9 (29)

Table 2 Reason for treatment discontinuation

	n = 31(%)
Disease progression	19 (61.3%)
Adverse event	2 (6.5%)
Withdrawal	5 (16.1%)
Operation	3 (9.7%)
Other	2 (6.5%)

Table 3 Posterior cancer treatment

	n = 31(%)
None	8 (25.8%)
Surgery	1 (3.2%)
Surgery + chemotherapy	2 (6.5%)
Chemotherapy	20 (64.5%)
CPT-11	9 (29.0%)
wPTX	5 (16.1%)
CPT-11 + CDDP	4 (12.9%)
nab-PTX	2 (6.5%)
S-1	1 (3.2%)
S-1 + DTX	1 (3.2%)

CPT-11 irinotecan, *wPTX* weekly paclitaxel, *CDDP* cisplatin, *nab-PTX* nab-paclitaxel, *DTX* docetaxel

patients (61%), liver in 14 (45%), peritoneum in 4 (13%), lung in 2 (6%), and adrenal in one (3%).

Exposure to chemotherapy

The median number of treatment cycles was 5 (range, 1–20). Treatment was discontinued due to disease progression in 19 patients (61.3 %), AEs in 2 (6.5%), withdrawal of consent in 5 (16.1 %), further surgery in 3 (9.7 %), and other reasons in two (6.5%) (Table 2).

Regarding subsequent therapy, 20 patients (64.5%) received second-line treatment: 13 patients received CPT-11-based regimens and 7 patients received paclitaxel (Table 3). Radical surgery was performed in two patients and reduction surgery was performed in one patient. Eight patients (25.8%) did not receive any posterior cancer treatment.

Efficacy

Objective response rate (ORR), the primary endpoint, was 45.2% (95% CI 27.3%–64.0%) including one CR and 13 PRs. Ten patients (37.5%) had stable disease (SD); hence, the overall tumor control rate (CR + PR + SD) was 77.4%. The median duration of PR was 3.8 months (95% CI 2.5–6.0 months). Seven patients (22.6%) had progressive disease as the best response (Table 4).

With regard to secondary endpoints, median OS was 16.1 months (95% CI 11.4–28.2) (Fig. 1a), median PFS was 5.8 months (95% CI 4.2–7.1) (Fig. 1b), and median TTF was 4.0 months (95% CI 2.9–6.2) (Fig. 1c).

Safety

Table 5 lists the main AEs and the proportion of patients experiencing AEs during treatment. The most common grade 3 or 4 adverse events were neutropenia (58%), leukopenia (45%), febrile neutropenia (13%), anemia (10%), and anorexia (10%). No treatment-related deaths occurred. Nine of 31 patients (29%) were administered chemotherapy without dose reduction. Because of AEs, both the docetaxel and the S-1 doses were reduced in 17 patients, and in 10 of these patients at the start of the second course. Of 19 patients who had a dose reduction of S-1, the dose reduction was undertaken at the beginning of the second course in 11 patients, and 6 patients needed two levels of dose reduction. Of 20 patients who had a dose reduction of docetaxel, the dose was reduced at the start of the second course for 14 patients, and 7 patients needed two levels of dose reduction. Seventeen of 31 patients (55%) were administered chemotherapy without delay until treatment discontinuation, while either the docetaxel or the S-1 dose was reduced in 12 of these patients. Among 14 patients, there was a delay in the administration of 1 course in 10 patients, 2 courses in 2 patients, 3 courses in 1 patient, and 5 courses in 1 patient.

Table 4 Response rate

	Patients, n						
	Total	CR	PR	SD	PD	NE	RR, %
	31	1	13	10	7	0	45.2%
[95% CI]							p = 0.001 [27.3–64.0]

RR response rate, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluable, without measurable lesions according to RECIST (version 1.1)

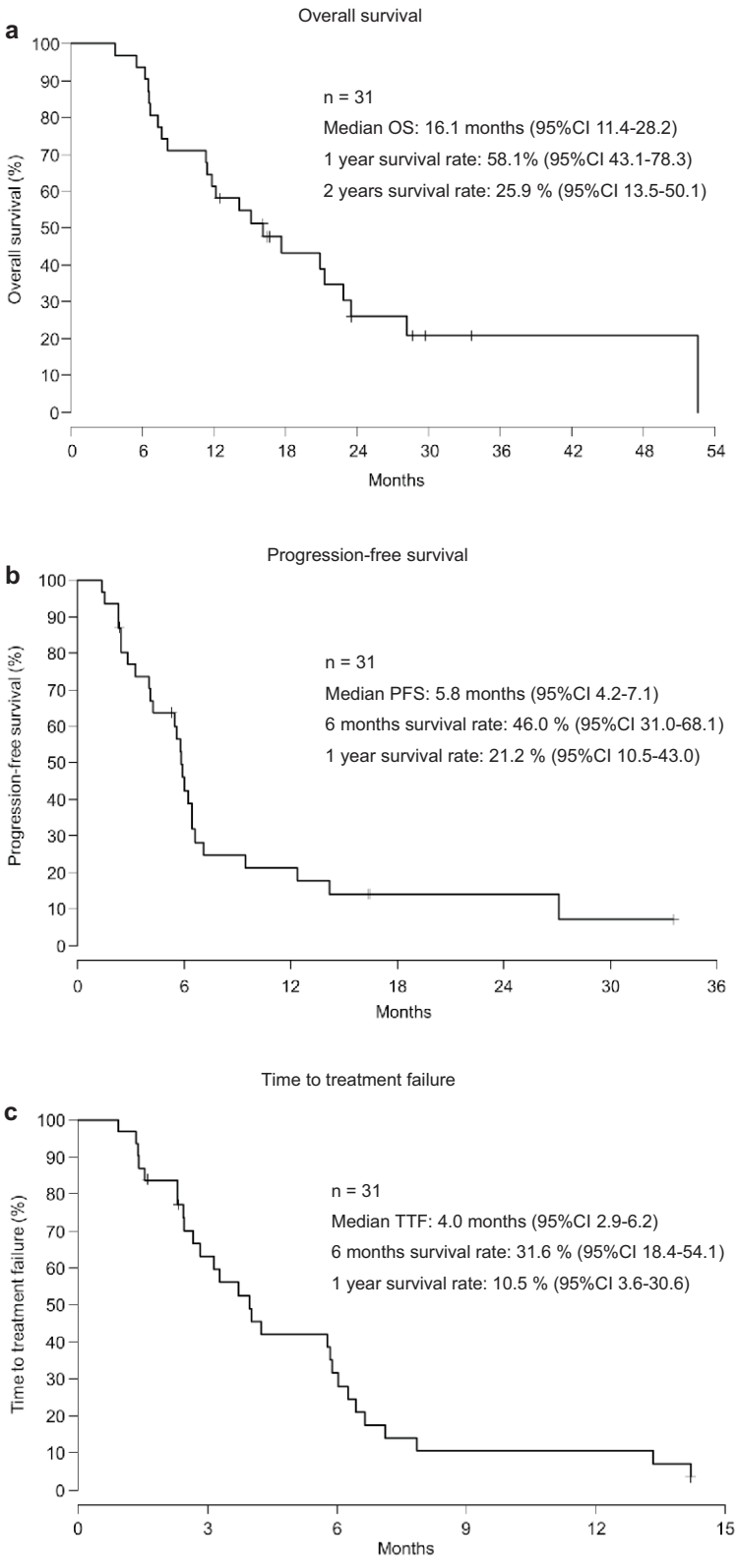

Fig. 1 **a** Overall survival curve. **b** Progression-free survival curve. **c** Time to treatment failure curve

Table 5 Adverse events

	n = 31			
	All grades		Grade 3–4	
	No	(%)	No	(%)
Leukopenia	25	81	14	45
Neutropenia	24	77	18	58
Anemia	22	71	3	10
Thrombocytopenia	9	29	0	0
AST	10	32	0	0
ALT	4	13	0	0
Creatinine	7	23	0	0
Febrile neutropenia	0	0	4	13
Anorexia	22	71	3	10
Fatigue	23	74	2	6
Nausea	6	19	1	3
Vomiting	1	3	0	0
Diarrhea	4	13	0	0
Peripheral sensory neuropathy	6	19	0	0

Discussion

This was a phase II trial that examined the efficacy and safety of DS as first-line treatment in patients aged 75 years or more with advanced gastric cancer. Few prospective studies have been conducted using combination chemotherapy for patients aged 75 years or over with advanced gastric cancer. Suitable evidence has not been provided for older patients with advanced gastric cancer in daily clinical practice thus far, possibly because older patients are often excluded from clinical trials or because the number of older patients in clinical trials is small [3–5, 17].

When we planned this study, SP was widely used as a first-line treatment for advanced gastric cancer in Japan based on the results of the SPIRITS trial [5]. However, the usefulness of SP was not fully evaluated for older patients because only patients aged 20–74 years were eligible for the SPIRITS trial and because cisplatin can result in renal dysfunction, which is not ideal for older patients who generally have renal impairment. In the SPIRITS trial [5], grade 3 or 4 adverse events including leukopenia, neutropenia, anemia, nausea, and anorexia were found more frequently for SP than for S-1. Moreover, in exploratory subgroup analyses, SP did not show superiority to S-1 on OS in older patients aged ≥ 60 years. Subsequently, the REAL2 study confirmed that capecitabine could replace 5-FU and oxaliplatin could replace cisplatin for advanced gastric cancer [3]. Moreover, a phase III study confirmed that S-1 plus oxaliplatin (SOX) was as effective as SP in patients with advanced gastric cancer including older patients, with a favorable safety profile [18]. Recently, the results of several trials of fluorouracil combined with oxaliplatin chemotherapy for frail or older patients with advanced gastroesophageal cancer were published. A phase II trial of CapeOx for 20 older patients with advanced gastric cancer showed that 9 of 19 patients (47%) who could undergo a second course needed a dose reduction, 8 of 19 patients (42%) needed a course delay, and 5 of 20 patients (25%) were unable to complete the initial two courses of chemotherapy due to withdrawal, AEs, or progressive disease [19]. Indeed, relatively high toxicities (any grade and grade ≥ 3) were reported for peripheral neuropathy (60% and 0%), nausea (55% and 10%), vomiting (10% and 0%), and thrombocytopenia (55% and 0%), respectively [19]. The GO2 phase III trial of CapeOX for frail or older patients comparing three doses of CapeOX (100%, 80%, and 60%) concluded that PFS for the reduced-dose groups compared with the full-dose group as the primary endpoint showed non-inferiority [20]. A phase II trial of biweekly SOX for older patients showed that a modified SOX treatment schedule seemed to have favorable tolerance without compromising the efficacy [21]. From the results of these trials, an initial dose reduction or schedule modification of fluorouracil combined with oxaliplatin might be necessary to prevent toxicity in older patients with advanced gastric cancer.

In the current study, the ORR was 45.2%, which exceeded the expected response rate set at 40%, and accordingly, the primary endpoint was met. As secondary endpoints, the median OS was 16.1 months and median PFS was 5.8 months. The efficacy of DS in our study was comparable to that in a previous SOX study, in which the ORR was 55.7%, median OS was 14.1 months, and median PFS was 5.5 months [18]. Several phase II studies have shown the combination of capecitabine and oxaliplatin as effective, with an ORR of 22–42%, PFS of 4.0–5.8 months, and OS of 6.4–12.2 months [22–24].

Compared with oxaliplatin, docetaxel has some advantages in tolerability, such as cumulative peripheral neurotoxicity, gastrointestinal toxicity, which may seriously affect patients' quality of life, and thrombocytopenia. The occurrence of any grade and grade ≥ 3 peripheral neuropathy (19% and 0%), nausea (19% and 3%), vomiting (3% and 0%), and thrombocytopenia (29% and 0%) in the current study suggests that those toxicities were moderate compared with platinum doublet regimens [19], possibly because of the use of docetaxel. Our data thus suggest that DS regimens could be suitable alternatives for older patients who may have difficulty continuing chemotherapy due to peripheral neuropathy and gastrointestinal toxicity. However, caution is warranted for higher toxicities of neutropenia and febrile neutropenia, although no treatment-related deaths were reported in this study. It might be worthwhile to assess survival benefit and quality of life in a phase III trial comparing the efficacy and safety of DS and oxaliplatin-containing regimens in the

first-line treatment of older patients with advanced gastric cancer.

There are some limitations of this study. First, the results might be better than those that could be obtained in daily practice because only 13% of patients had peritoneal dissemination, which is a common and well-known poor prognostic factor in gastric cancer. Second, our study was not randomized. Therefore, our preliminary findings remain to be further verified by well-designed randomized studies. Finally, at the beginning of our study, Herceptin was not approved for HER2-positive gastric cancer in Japan, and hence HER2 status was not examined in these patients. Therefore, potential HER2-positive patients did not receive anti-HER2 therapy.

Conclusions

DS as first-line treatment for older patients is feasible and shows promising efficacy against advanced gastric cancer. Further investigation in randomized studies is needed for older patients.

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Author contributions All authors contributed to the study conception and design. Hiroshi Imamura designed and supervised the research. Material preparation, data collection and analysis were performed by TS. The first draft of the manuscript was written by TK, HK: reviewed and modified the manuscript and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations

Conflict of interest Hiroshi Imamura has received honoraria from Taiho Pharmaceutical Co., Ltd. Kazuhiro Nishikawa has received honoraria from Bristol-Myers Squibb Co., Ltd., Daiichi Sankyo, Co., Ltd., EA Pharma Co., Ltd., Eli Lilly Japan K.K., MSD K.K., Ono Pharmaceutical Co., Ltd., and Taiho Pharmaceutical Co., Ltd. Hisato Kawakami has has received honoraria from BMS K.K., ONO Pharmaceutical Co., LTD., Eli Lilly Japan K.K., MSD K.K., and Daiichi Sankyo, Co., Ltd., fees for promotional materials from ONO Pharmaceutical Co., LTD., üMSD K.K., and Daiichi Sankyo, Co., Ltd., and research funding from BMS K.K., Eisai Co., Ltd., and Kobayashi Pharmaceutical Co. Ltd. Daisuke Sakai has received honoraria from Daiichi Sankyo Co. Ltd., and Chugai Pharmaceutical Co., Ltd., and research funding from Eli Lilly Japan K.K., Daiichi Sankyo Co., Ltd., and Taiho Pharmaceutical Co., Ltd. Yukinori Kurokawa has received lecture fees and research grant from Taiho Pharmaceutical Co., Ltd. Taroh Satoh has received honoraria from ONO Pharmaceutical Co., Yakult Honsha Co., Ltd., Chugai Pharmaceutical Co., Eli Lilly Japan K.K., Bristol-Myers Squibb Co. Ltd., MSD K.K., and Taiho Pharmaceutical Co., Ltd., research funding from ONO Pharmaceutical Co., Chugai Pharmaceutical Co., Eli Lilly Japan K.K., Bristol-Myers Squibb Co. Ltd., MSD K.K., Taiho Pharmaceutical Co., Ltd., and Hutch Med Co., Ltd., scholarship donations from Taiho Pharmaceutical Co., Ltd., and endowed chairs from ONO Pharmaceutical Co., Yakult Honsha Co., Ltd., and Chugai Pharmaceutical Co. All the remaining authors have no conflicts of interest to declare.

Ethical approval All procedures in this study were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants before entry into the study.

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