Gastric Cancer (2018) 21:811–818
https://doi.org/10.1007/s10120-018-0815-0

ORIGINAL ARTICLE

A phase II trial of capecitabine plus cisplatin (XP) for patients with advanced gastric cancer with early relapse after S-1 adjuvant therapy: XParTS-I trial

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Received: 18 November 2017 / Accepted: 19 February 2018 / Published online: 27 February 2018

Abstract

Backgrounds In Japan, standard regimens for advanced gastric cancer (AGC) include S-1 chemotherapy. The standard treatment for early relapse after adjuvant chemotherapy with fluoropyrimidine alone is platinum-based chemotherapy, while the standard treatment for early relapse after adjuvant chemotherapy with fluoropyrimidine plus platinum is second-line chemotherapy. To evaluate the efficacy and safety of capecitabine plus cisplatin (XP) treatment for AGC patients who relapse within 6 months after S-1-based therapy, we conducted a multicenter phase II trial (NCT01412294).

Methods HER2-negative gastric cancer patients treated with adjuvant chemotherapy including S-1 for more than 12 weeks and relapsed within 6 months were treated with capecitabine 1000 mg/m^2 bid for 14 days plus cisplatin 80 mg/m^2 on day 1 of a 3-week cycle. The primary endpoint was PFS; secondary endpoints were OS, time to treatment failure, overall response rate (ORR) and safety.

Results Forty patients (median age 64) were enrolled; of those, 37 (92.5%) received adjuvant S-1 monotherapy. Median PFS was 4.4 months (95% CI 3.6–5.1), which was longer than the 2-month protocol-specified threshold ($p < 0.001$). Median OS was 13.7 months (95% CI 9.0–17.7) and ORR was 8/30 (26.7%) (95% CI 14.2–44.4). Most common grade ≥ 3 adverse events were neutropenia (23%), anemia (18%), elevated serum creatinine (18%), fatigue (13%), diarrhea (7.5%), and anorexia (7.5%).

Conclusions XP was safe and effective in patients with early relapse after S-1 adjuvant chemotherapy for curatively resected gastric cancers. XP may be a good option for the treatment of patients after early failure after adjuvant S-1.

Trial registration NCT01412294.

Keywords Advanced gastric cancer · Capecitabine plus cisplatin (XP) · S-1 adjuvant therapy · Early relapse · Fluoropyrimidine switching

Introduction

Gastric cancer is the third leading cause of death worldwide [1]. S-1 monotherapy has been considered the standard adjuvant treatment after curative gastrectomy of stage II or III gastric cancer patients in Japan [2]. However, almost half of those patients eventually experience disease relapse, and their long-term prognosis is unfavorable [3]. After the results were reported from the JCOG9912 and SPIRITS trials, S-1 plus cisplatin (SP) became accepted as the standard treatment for patients with advanced gastric cancer (AGC) in Japan [4, 5]. In a retrospective analysis of those patients by Shitara et al., SP was not shown to be effective in patients with recurrent gastric cancer, especially with a relapse-free interval (RFI) of less than 6 months after adjuvant S-1 chemotherapy [6]. In their report, compared with patients with RFI of ≥ 6 months, patients with RFI of < 6 months had a significantly lower objective overall response rate (ORR) (5.0 vs. 37.5%), shorter progression-free survival (PFS) (2.3 vs. 6.2 months), and shorter overall survival (OS) (7.3 vs. 16.6 months). In this regard, establishment of effective

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treatment options for early relapse after S-1 adjuvant chemotherapy is required. Although no prospective study has evaluated chemotherapy specifically for patients who have failed adjuvant S-1, a phase II study of capecitabine plus cisplatin (XP) in 32 patients with gastric cancer that recurred within or more than 6 months after adjuvant chemotherapy with doxifluridine or 5-fluorouracil (5-FU)-containing regimens was reported [7]. In this trial, response rates (39 vs. 21%, $p = 0.427$), time to treatment failure (TTF) (8.3 vs. 5.4 months, $p = 0.072$), and OS (14.1 vs. 9.3 months, $p = 0.075$) tended to be better in patients with an RFI of > 6 months ($n = 13$) than in patients with an RFI < 6 months ($n = 19$), although the differences did not reach statistical significance.

As to the first-line setting, combined administration of fluoropyrimidine and a platinum is the standard chemotherapy for advanced or recurrent gastric cancer, while triplet chemotherapy using docetaxel, cisplatin, and fluorouracil; epirubicin, cisplatin, and fluorouracil; or epirubicin, oxaliplatin, and capecitabine, are other treatment options [8, 9]. In Japan, SP is the most prevalent combination chemotherapy for first-line treatment, as above [5]. Kang and colleagues evaluated the non-inferiority of XP compared with 5-FU plus cisplatin. The median progression-free survival (PFS) showed significant non-inferiority (5.6 months vs. 5.0 months; HR = 0.81, 95% confidence interval (CI) 0.63–1.04, $p < 0.001$) [10]. Based on these results, XP could now be considered one of the standard treatments for AGC [11], and XP was adopted as the reference arm in two recent global studies of molecular targeted agents [12, 13]. However, the usefulness of XP for early relapse after S-1 adjuvant therapy has not yet been assessed.

In this regard, the objectives of this study were to estimate the efficacy and safety of XP in patients with AGC who relapsed within 6 months after S-1-based adjuvant therapy.

Patients and methods

Eligibility

Eligibility requirements included: patients who had received adjuvant chemotherapy for gastric cancer including S-1 for more than 12 weeks, and relapsed within 6 months thereafter; were aged 20–74 years at the time of informed consent; were HER2 negative; and had histologically confirmed gastric adenocarcinoma. Other inclusion criteria were as follows: lesions confirmed by imaging no more than 28 days before registration [not required for measurable lesions as defined in Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1]; no previous chemotherapy or radiotherapy except for S-1-based adjuvant chemotherapy; last dose of anticancer drug in the prior chemotherapy ≥ 14 days before enrollment; Eastern Cooperative Oncology Group performance status (PS) of 0–2; life expectancy of at least 3 months after registration; and adequate organ function [neutrophil count ≥ 1500/mm^3, hemoglobin ≥ 9.0 g/dL, aspartate aminotransferase (AST), alanine aminotransferase (ALT) ≤ 2.5 × upper limit of normal (ULN) in each institution (≤ 5 times in cases of metastases to liver), ALP ≤ 2.5 × ULN in each institution (≤ 5 times in cases of metastases to liver, and ≤ 10 times in cases of metastases to bone), total bilirubin ≤ 1.5 × ULN in each institution, and creatinine clearance ≥ 60 mL/min (as estimated using the Cockcroft–Gault equation)]. Exclusion criteria included: active second primary malignancy; severe or uncontrolled concurrent disease; overt infection or inflammation; psychiatric disorder being treated or requiring an antipsychotic therapy; active hepatitis; previous treatment with cisplatin of more than a total dose of 120 mg/m^2; previous history of serious hypersensitivity to fluoropyrimidines or platinum agents; previous history of adverse reactions suggestive of dihydropyrimidine dehydrogenase (DPD) deficiency; being treated or in need of treatment with flucytosine, phenytoin, or warfarin potassium; chronic diarrhea (watery stools or stools ≥ 4 times/day); active gastrointestinal bleeding; pericardial effusion, or pleural effusion or ascites requiring drainage; unwillingness to practice contraception; poor oral intake; pregnant or lactating females, or females wishing to become pregnant; and otherwise determined by investigators or site principal investigators to be unsuitable for participation in the study. All eligible patients provided written informed consent before enrollment.

Treatment

Within 14 days after enrollment, eligible patients started treatment with XP on a 3-week cycle. Capecitabine was administered orally at a dose of 1000 mg/m^2 twice daily (equivalent to a total daily dose of 2000 mg/m^2) for 2 weeks (day 1–14). Cisplatin 80 mg/m^2 on day 1 of each cycle was given by intravenous infusion over 2 h. Treatments were discontinued at the following events: progressive disease (PD) based on RECIST version 1.1 or clinically determined progression of the primary disease; conversion to resectable disease; an unacceptable adverse event; patient refusal to continue treatment; and death. If treatment continuation with cisplatin was determined to be unfeasible before any progression was confirmed, continuous monotherapy with capecitabine was continued until PD.

Evaluation

At baseline, patient general characteristics and medical history were reviewed, including diagnosis and macroscopic/histologic classification of gastric cancer, imaging to identify

measurable lesions, assessment of subjective and objective symptoms, and laboratory tests.

Tumor responses were classified using RECIST version 1.1 as complete response (CR), partial response (PR), stable disease (SD), or PD, and confirmed by investigators.

Adverse events were evaluated using the CTCAE version 4.0. Contrast-enhanced computed tomography or magnetic resonance imaging and plain chest X-rays were performed within 28 days before enrollment and repeated every 4 weeks after starting treatment, or every 6 weeks from week 16 onwards. During treatment, laboratory tests (hematology and blood chemistry) were performed on the day before every drug administration.

Statistical methods

This was a phase II, open-label, multicenter trial performed at 15 institutions across Japan. The primary endpoint was PFS. Secondary endpoints were OS, time to treatment failure (TTF), ORR, and the incidence and severity of adverse events.

Because the PFS was 2.3 months in recurrent gastric cancer with RFI of less than 6 months after adjuvant S-1 chemotherapy in the previous retrospective analysis [6], the threshold PFS was set at 2 months. The addition of XP was expected to increase PFS by 1 month. At a one-sided significance of 5% and a power of 80%, 37 patients were required for this study. When ineligible patients or dropouts were included, the target sample size was estimated to be 40. All clinical data were held centrally at the ECRIN data center and analyzed using SAS for Windows version 9.3 (SAS Institute Inc., Cary, NC, USA).

This trial was conducted in compliance with the ethical principles of the Declaration of Helsinki and the Ethical Guidelines for Clinical Studies of the Japanese Ministry of Health, Labour and Welfare. This trial was approved by institutional review boards or ethics committees at all participating centers. This trial was registered with ClinicalTrials.gov, number NCT 01412294.

Results

Patient characteristics

Between June 2011 and April 2014, 40 patients were enrolled from 15 institutions in Japan. All patients were included in the final analyses. Median follow-up was 13.7 months (range 0.2–41.9 months). Patient characteristics are summarized in Table 1. Median age was 64, 32 males (80%); adjuvant chemotherapy: regimen, S-1 monotherapy ($N = 37$, 92.5%).

Table 1 Patient characteristics

	N	%
Age, years		
Median (range)	65.5 (43–77)	
Sex		
Male	32	80
Female	8	20
ECOG PS		
0	32	80
1	7	17.5
2	1	2.5
Relapse site		
Local	1	1.9
Lymph node	15	27.8
Peritoneum	18	33.3
Liver	11	20.4
Lung	2	3.7
Bone	2	3.7
Other	5	9.3
Adjuvant regimen		
S-1	37	92.5
S-1 + taxane	3	7.5
Adjuvant courses		
Average (standard deviation)	7.1 (3.2)	
Median (range)	7.0 (3–18)	
Completion of adjuvant		
Completed	11	27.5
Discontinued	29	72.5

ECOG Eastern Cooperative Oncology Group, *PS* performance status

Treatments

The median number of cycles of XP was 5 (1–27). Twenty-two patients (55%) required dose reduction of capecitabine and 26 patients (65%) required dose reduction of cisplatin. The dose intensity for all treatment cycles was 79% for capecitabine, and that for the first six cycles was 62% for cisplatin.

At the time of final analysis, seven patients continued on protocol treatment. Twenty-six patients received subsequent treatments (26/33: 78.8%) following protocol treatment.

Tumor responses

Of the 30 patients with measurable lesions, one achieved CR, seven achieved PR, and 11 achieved SD. Therefore, the ORR (CR plus PR) was 26.7% (95% CI 14.2–44.4%; $N = 8/30$), and the disease control rate (DCR) (CR plus PR plus SD) was 63.3% (95% CI 45.5–78.1%; $N = 19/30$) (Table 2). Maximum % changes in tumor measurements

Table 2 Response rate

N = 30	*N*	95% CI
CR	1 (3.3)	
PR	7 (23.3)	
SD	11 (36.7)	
PD	4 (13.3)	
NE	7 (23.3)	
RR (CR, PR)	8 (26.7)	14.2–44.4
DCR (CR, PR, SD)	19 (63.3)	45.5–78.1

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluable, *RR* response rate, *DCR* disease control rate

from baseline according to best overall response are shown in Fig. 1.

Survival

The median PFS was 4.4 months (95% CI 3.6–5.1), which was longer than the protocol-specified threshold of 2 months ($p < 0.001$) (Fig. 2a). Median OS was 13.7 months (95% CI 9.0–17.7) (Fig. 2b) and median TTF was 4.0 months (95% CI 3.1–5.1).

Adverse events

The incidence of grade 3/4 adverse events was low (Table 3). There was no event of clinically significant cumulative toxicity. There was no death resulting from toxicities. The most common grade 3/4 adverse events were neutropenia in nine patients (22.5%), anemia in seven patients (17.5%), hyponatremia in five patients (12.5%), fatigue in five patients (12.5%), diarrhea in three patients (7.5%), and anorexia in three patients (7.5%). Other grade 3/4 toxicities were thrombocytopenia and febrile neutropenia that occurred in two patients (5.0%), and nausea, oral mucositis, and hand–foot syndrome that occurred in one patient (2.5%).

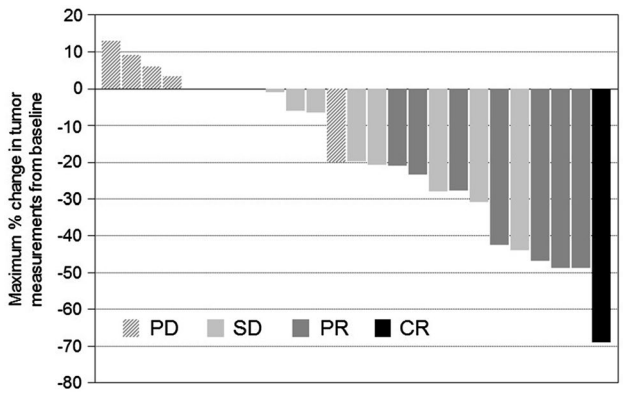

Fig. 1 Waterfall plot of the best overall response in individual patients. *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

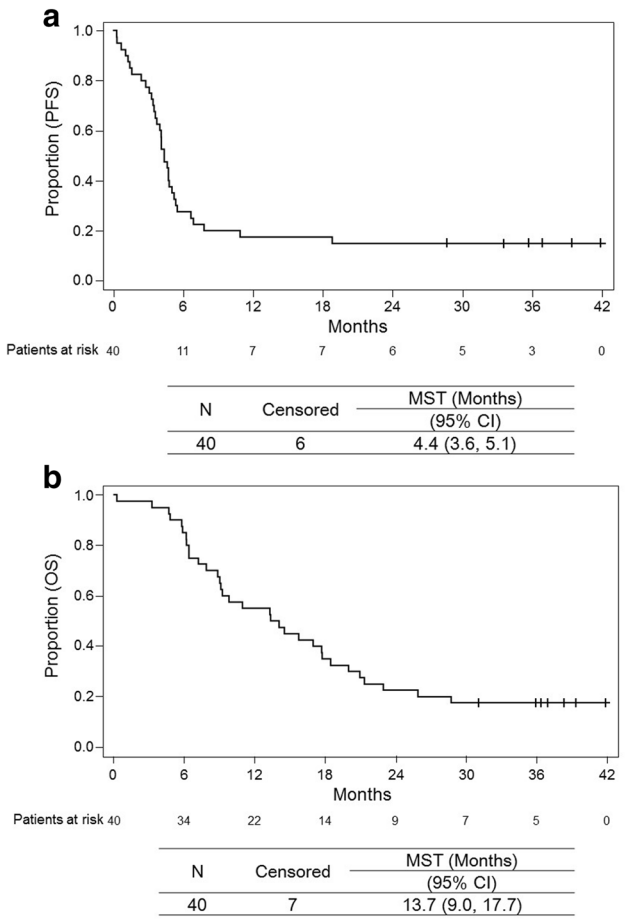

Fig. 2 Kaplan–Meier plots of progression-free survival (**a**), and overall survival (**b**). *CI* confidence interval, *MST* median survival time, *PFS* progression-free survival, *OS* overall survival

Discussion

This is the first report of a phase II study examining the efficacy and safety of XP in patients with AGC, who relapsed within 6 months after S-1-containing adjuvant chemotherapy. XP-treated patients achieved favorable PFS, OS, and ORR compared with SP in this setting [6]. This combination therapy was also tolerable, with a low rate of grade 3/4 adverse events; most adverse events were of grade 1/2. The primary endpoint was met because the median PFS was 4.4 months (95% CI 3.6–5.1) ($p < 0.001$).

It was interesting to evaluate the effects of re-challenge with different types of fluoropyrimidines after the failure of another drug, although fluoropyrimidine switching is still controversial [14, 15]. The response rate of 26.7% in the

Table 3 Adverse events ($N = 40$)

	Grades 1–4		Grade 3/4	
	N	%	*N*	%
Neutropenia	26	65.0	9	22.5
Anemia	36	90.0	7	17.5
Thrombocytopenia	26	65.0	2	5.0
Serum AST value increased	16	40.0	0	0.0
Serum ALT value increased	13	32.5	0	0.0
Serum total bilirubin value increased	5	12.5	0	0.0
Serum creatinine value increased	19	47.5	0	0.0
Hypoalbuminemia	24	60.0	0	0.0
Hyponatremia	25	62.5	5	12.5
Hyperkalemia	18	45.0	0	0.0
Febrile neutropenia	2	5.0	2	5.0
Fatigue	21	52.5	5	12.5
Fever	6	15.0	0	0.0
Weight loss	12	30.0	0	0.0
Anorexia	31	77.5	3	7.5
Nausea	23	57.5	1	2.5
Vomiting	9	22.5	0	0.0
Oral mucositis	15	37.5	1	2.5
Diarrhea	11	27.5	3	7.5
Allergen reaction	1	2.5	0	0.0
Peripheral sensory neuropathy	10	25.0	0	0.0
Hand–foot syndrome	16	40.0	1	2.5

AST aspartate aminotransferase, *ALT* alanine aminotransferase

present study was comparable with that previously reported by Kang et al. for XP after adjuvant chemotherapy (21%) [7]. One possible reason for the high response rate observed in patients with early recurrence of GC is that we did not use the same fluoropyrimidine (capecitabine after S-1 versus capecitabine after doxifluridine or 5-FU) as Kang et al.

S-1 is an oral anticancer drug composed of the 5-FU prodrug, tegafur, and two 5-FU modulators; it has achieved high response rates in patients with gastric cancer in phase II studies [16, 17]. Capecitabine is also an oral fluoropyrimidine that is metabolized primarily in the liver and converted in tumor tissues to 5-FU by the enzyme thymidine phosphorylase (TP), which is found in higher concentrations in tumor than in normal cells [18]. These two types of oral fluoropyrimidines show some different characteristics in the mechanisms of their antitumor effect. A subset analysis of the FLAGS trial showed that S-1 seemed to be better than 5-FU in the subgroup with diffuse-type gastric cancer [19]. This result was consistent with the results of a subset analysis of the JCOG9912 trial, which showed that S-1 was better than 5-FU in patients with diffuse-type gastric cancer or with gastric cancer associated with high dihydropyrimidine dehydrogenase (DPD), with diffuse-type tumors associated more commonly than intestinal types with high DPD [20]. This result was expected, since S-1 consists of tegafur, otastat potassium, and gimestat, a potent competitive inhibitor of DPD. Capecitabine is transformed to 5-FU in several steps, with the final step involving TP, as above [17]. A phase II trial in Japan showed that the response rate (RR) was significantly higher (Fisher's exact test, $p = 0.028$) in patients with TP-positive and DPD-negative tumors (60%, 6/10) than in the remaining patients (13%, 2/15) [21]. In contrast, high expression of TP was reported to be negatively associated with the efficacy of 5-FU or S-1 in gastric cancer [22, 23].

Conventional exclusion criteria in clinical trials in the first-line setting omitted patients who experienced disease recurrence within 6 months after the last adjuvant chemotherapy [4, 5, 10, 13]. The standard treatment for early relapse after adjuvant chemotherapy with fluoropyrimidine alone is platinum-based chemotherapy, such as XP, XELOX and FOLFOX. However, the usefulness of platinum-based chemotherapy in this setting has not been reported much. Besides this, these early relapsed patients after adjuvant therapy sometimes used second-line chemotherapy regimens such as irinotecan, taxane, or irinotecan plus cisplatin [24–26]. These prior reports evaluated other second-line chemotherapies and reported median PFS periods of 2.3–3.8 months, median OS periods of 5.2–10.7 months, and ORRs of 7–22% [24–26]. In contrast, median PFS was 4.4 months (95% CI 3.6–5.1), median OS was 13.7 months (95% CI 9.0–17.7), and ORR was 26.7% (95% CI 14.2–44.4%; $N = 8/30$) in our study. The efficacy of XP compared with other chemotherapies (irinotecan, taxane or irinotecan plus cisplatin) for recurrence after adjuvant S-1 should be evaluated in future clinical trials.

There are two possible explanations for these longer PFS and OS and high ORR. First, all patients in our study received the protocol treatment without prior use of platinum, which resulted in a favorable PFS of 4.4 months and an ORR of 26.7%. Second, the proportion of patients who received subsequent chemotherapy after disease progression (following therapy) was high (26/33 patients, 78.8%). The subsequent therapy might also contribute to the large difference between OS and PFS in this study (13.7 and 4.4 months, respectively).

The incidence of grade 3/4 adverse events in this study was similar to that in an earlier study using the same XP regimen for patients who recurred after adjuvant chemotherapy with doxifluridine or 5-FU-containing regimens. In that study, neutropenia (38%), leukopenia (9%), anemia (16%), diarrhea (5%), anorexia (2%), and peripheral sensory neuropathy (2%) were the most common grade 3/4 adverse events in the cohort of 32 patients treated with XP [7]. In our study of 40 patients, neutropenia (22.5%), anemia (17.5%), hyponatremia (12.5%), fatigue (12.5%), diarrhea (7.5%), and anorexia (7.5%) were the most common grade 3/4 adverse events. These results suggest that XP

was well tolerated in patients with recurrent gastric cancer after fluoropyrimidine-based adjuvant chemotherapy.

However, there are some limitations of this study. First, because this was not a randomized comparative study, the selected population may have been biased toward patients with good performance status (PS) and low tumor burden. Second, the moderate sample size in a single-country study was another limitation. The inclusion of only Japanese patients may also limit the generalizability of this study. Third, the efficacy of XP compared with other chemotherapies (irinotecan, taxane and/or ramucirumab) for recurrence after adjuvant S-1 should be evaluated in future randomized trials.

In conclusion, XP was generally well tolerated and effective in patients with AGC who relapsed within 6 months after S-1-based adjuvant therapy. XP may be a good option for this cohort of patients in Japan.

Acknowledgements We thank the investigators from the following institutions who enrolled patients for this trial: Osaka General Medical Center, Yokohama Municipal Citizen's Hospital, Hiroshima University Graduate School of Medicine, Saitama Cancer Center, Yokohama City University, Yamaguchi University Graduate School of Medicine, Kochi Medical School, Kanagawa Cancer Center, Yokohama City University, Kobe City Medical Center General Hospital, Osaka City General Hospital, Sakai Municipal Hospital, Nagoya University Graduate School of Medicine, Oita University Faculty of Medicine, Hiroshima City Asa Hospital, and Niigata Cancer Center Hospital. Furthermore, we deeply appreciate all patients who participated in the trial. We acknowledge Dr Mark Abramovitz of Edanz Medical Writing for editorial support, which was funded by the non-profit organization Epidemiological and Clinical Research Information Network (ECRIN).

Funding This work was supported by the non-profit organization Epidemiological and Clinical Research Information Network (ECRIN).

Compliance with ethical standards

Conflict of interest The individual conflict of interest disclosure is as follows: K. Nishikawa has received honoraria from Chugai, Taiho, Yakult, Eli Lilly, Tsumura, and EA Pharma, and research funding from Yakult and Taiho, outside the submitted work. T. Yoshikawa has received lecture fees from Chugai, Taiho, Yakult, Eli Lilly and Ono, and for advisory work from Ono and MSD, outside the submitted work. K. Yamaguchi has received personal fees from Chugai, Taiho, Yakult, Takeda, Merck and Eli Lilly, and research funding from MSD, Merck, Bristol, Ono, Dainippon Sumitomo, Taiho, Daiichi-Sankyo and Yakult, outside the submitted work. S. Yoshino has received honoraria from Chugai, Taiho, Ono and Eli Lilly, outside the submitted work. Y. Kodera has received research funding from Chugai, Taiho, Daiichi-Sankyo, Bristol-Myers, Eli Lilly, Otsuka, Takeda, Yakult, CSL Behring, Pfizer, Ono, Kaken, Tsumura, EA Pharma, Novartis, KCI and the Japan Blood Products Organization, outside the submitted work. S. Morita has received honoraria from Chugai and Taiho, outside the submitted work. J. Sakamoto has received consultant fee from Takeda, and Honoraria from Tsumura and Chugai, outside the submitted work. None of the remaining authors have potential conflicts of interest to declare.

Ethical statements This trial was conducted in compliance with the ethical principles of the Declaration of Helsinki and the Ethical Guidelines for Clinical Studies of the Japanese Ministry of Health, Labour and Welfare. This trial was approved by the institutional review boards or ethics committees at all participating centers. This trial was registered with ClinicalTrials.gov (NCT01412294).

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