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Phase II Study of the Reuse of Trastuzumab with Docetaxel beyond Progression after First-Line Treatment in Second-Line Treatment for Unresectable, Metastatic Gastric Cancer (T-CORE1203)

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Whether trastuzumab use beyond disease progression is beneficial in second-line treatment for patients with unresectable human epidermal growth factor receptor 2 (HER2)-positive gastric cancer remains to be elucidated. We conducted this phase II study to assess whether trastuzumab plus docetaxel was effective for patients with previously treated advanced HER2-positive gastric cancer. This trial was a single-arm, open-label, multicenter, phase II study, conducted by Tohoku Clinical Oncology Research and Education Society (T-CORE). Patients aged 20 years or older who had advanced HER2-positive gastric cancer and were refractory to trastuzumab, fluoropyrimidine, and cisplatin were enrolled. Patients were treated with 6 mg/kg trastuzumab and 60 mg/m^2 docetaxel every 3 weeks. The primary endpoint was the overall response rate. The threshold overall response rate was estimated to be at 15%. Secondary endpoints were progression-free survival, 6-month survival rate, overall survival, and toxicities. A total of 27 patients were enrolled from 7 hospitals. The median age was 67 years. Partial response was seen in 3 patients among the 26 evaluated patients. The overall response rate was at 11.5% (90% confidence interval 1.2%-21.8%). The median progression-free survival was 3.2 months, the 6-month survival rate was 85%, and the median overall survival was 11.6 months. Febrile neutropenia was observed in 14.8%. The most frequently observed grade 3 non-hematologic toxicity was anorexia (14.8%). The primary endpoint was not achieved. The results support a current consensus that the continuation of trastuzumab in second-line therapy for gastric cancer is not a recommended option.

Keywords: docetaxel; gastric cancer; HER2; reuse beyond progression; trastuzumab
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Introduction

Gastric cancer has been ranked fifth as the most frequently diagnosed cancer and the third leading cause of death worldwide (Bray et al. 2018). Gastric cancer is estimated to be newly diagnosed in 1,030,000 individuals and responsible for 782,000 deaths (Bray et al. 2018). For patients with nonresectable, advanced, or metastatic gastric cancer, chemotherapy is the first treatment option. The combination of fluoropyrimidine and platinum drugs is the first-line standard therapy for these patients (Mizrak Kaya et al. 2017).

The ToGA study showed that adding trastuzumab, an anti-human epidermal growth factor receptor 2 (ant-HER2) antibody, to capecitabine plus cisplatin or fluorouracil plus cisplatin as the first-line treatment improved the overall survival (OS) of patients with HER-2-overexpressed advanced gastric cancer (Bang et al. 2010). The median OS was 13.8 months (95% confidence interval [CI] 12-16) in the trastuzumab plus chemotherapy arm compared with 11.1 months (95% CI 10-13) in the chemotherapy alone arm (hazard ratio [HR] 0.74, 95% CI 0.60.91, p = 0.0046) (Bang et al. 2010). The median progression-free survival (PFS) was 6.7 months versus 5.5 months (HR 0.71, 95% CI 0.59-0.85, p = 0.0002). According to these results, trastuzumab combined with fluoropyrimidine and platinum has become the most recommended regimen in previously untreated patients with gastric cancer (Boku 2014). As second-line therapy, ramucirumab, an anti-vascular endothelial growth factor receptor 2 (anti-VEGFR2) antibody, plus paclitaxel is a standard regimen for patients with advanced gastric cancer regardless of HER2 expression status (Wilke et al. 2014). The RAINBOW trial showed that OS (median 9.6 months vs. 7.4 months, HR 0.807, 95% CI 0.68-0.96) and PFS (median 4.4 months vs. 2.9 months, HR 0.64, 95% CI 0.54-0.75) were significantly longer in the ramucirumab plus paclitaxel group than in the placebo plus paclitaxel group (Wilke et al. 2014). The objective response rate (ORR) was also greater in the ramucirumab plus paclitaxel group (28% vs. 16%, P = 0.0001) (Wilke et al. 2014).

It is still unclear whether patients with HER2-positive gastric cancer would benefit from the sequential use of trastuzumab in second-line therapy beyond progression after first-line use of trastuzumab. In HER2-positive breast cancer, second-line use of anti-HER2 therapy, mainly trastuzumab emtansine (T-DM1), beyond progression on first-line therapy is a recommended option (Ponde et al. 2018). At the time we planned this study in 2012, there were no clinical trials that showed the efficacy of continuing anti-HER2 therapy in second-line therapy in gastric cancer patients. In addition, which treatment was best among taxanes, irinotecan, other drugs, or combinations in second-line therapy for patients with gastric cancer, regardless of HER2 status, had not been fully established until the WJOG4007 trial (Hironaka et al. 2013) and the RAINBOW trial (Wilke et al. 2014) were reported. On the other hand, in HER2-positive breast cancer, a combination of docetaxel and trastuzumab was regarded as a promising treatment options (Inoue et al. 2010, Valero et al. 2011).

The aim of the present phase II study was to evaluate the efficacy and toxicity of trastuzumab plus docetaxel in patients with HER2-positive advanced gastric cancer who had previously received trastuzumab, fluoropyrimidine, and cisplatin.

Methods

Ethics

This single-arm, phase II trial (UMIN000010869) enrolled patients at seven institutions that participate in the Tohoku Clinical Oncology Research and Education Society (T-CORE) in Japan. The study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by institutional ethics committees and/or institutional review boards at all sites that participated. Written informed consent was obtained from all patients.

Patients

Patients were regarded eligible if they were aged 20 years or older; had histologically confirmed unresectable, recurrent, or metastatic gastric adenocarcinoma with HER2 overexpression (immunohistochemistry [IHC] score 3+ or IHC score 2 and fluorescence-in-situ-hybridization-positive [FISH-positive] before first-line treatment) and measurable lesions according to the Response Evaluation Criteria in Solid Tumors version 1.1; an Eastern Oncology Group Performance Status (ECOG-PS) of 0-2; received one chemotherapeutic regimen, including trastuzumab; did not receive docetaxel; estimated to be alive at least 3 months since enrollment in the study; and had appropriate bone marrow and liver functions [white blood count (WBC) 3,000-12,000/mm^3, neutrophil ≥ 1,500/mm^3, hemoglobin ≥ 8.0 g/dl, platelet ≥ 7.5 × 10^4/mm^3, aspartate aminotransferase (AST) ≤ 100 U/l, alanine aminotransferase (ALT) ≤ 100 U/l, and creatinine (Cr) ≤ 1.5 mg/dl].

Treatment

Eight mg/kg of trastuzumab was administered intravenously on day 1 for 90 min, and then 6 mg/kg was administered intravenously for 30 min every 3 weeks. Sixty mg/m^2 of docetaxel was administered intravenously for 60 min on day 1 and continuously administered every 3 weeks.

Endpoints

The primary endpoint was ORR. Secondary endpoints were PFS, 6-month survival rate, OS, and toxicities. PFS was defined as the time from the initiation of protocol treatment to the first radiologic confirmation of disease progression or death from any cause. OS was defined as the time from the initiation of protocol treatment to death from any cause. Tumor response was evaluated based on investigator assessment by using computed tomography taken every 6 weeks according to the Response Evaluation Criteria in

Solid Tumors version 1.1. The ORR was defined as the number of patients with a complete response (CR) or partial response (PR) divided by the number of all patients with measurable lesions. The disease control rate (DCR) was defined as the number of patients with CR, PR, or stable disease (SD) divided by the number of response-evaluable patients.

Statistical analysis

In 2012, at the time this study was planned, there was only one phase III study that analyzed the efficacy of second-line treatment in gastric cancer (Thuss-Patience et al. 2011). In the AIO study, OS was superior in the irinotecan arm to the best supportive care arm, but no ORR was observed in the irinotecan arm (Thuss-Patience et al. 2011). In contrast, a phase II study showed an ORR of 16% in patients who received docetaxel in second-line therapy after failure of fluoropyrimidine and platinum (Lee et al. 2008). In light of these reports, the threshold ORR was set to 15%, and the expected ORR was set to 35%. At a one-sided significance of 0.05 and power of 80%, the minimum number of patients required was estimated to be 28. Considering ineligible cases, we decided that 30 patients were to be enrolled in this study. Patient registration period was planned to be 2 years from Mar 2013, and follow-up period was planned to be 2 years.

Results

Patient characteristics

A total of 27 patients were enrolled from 7 institutions in Japan between May 2013 and June 2016. The patient recruitment period was initially planned to be two years. However, due to poor accrual, patient registration was extended to June 2016, and then stopped. The median follow-up period was 11.8 months.

The clinicopathological characteristics of the patients are shown in Table 1. The median age was 67 (range, 38-79 years). There were 22 men and 5 women. The ECOG-PS score was 0 in 19 patients and 1 in 8 patients. HER2 status before first-line treatment was IHC score 3+ in 25 patients and IHC score 2+/FISH-positive in 2 patients. Previous chemotherapeutic regimens were capecitabine, cisplatin, and trastuzumab in 14 patients; S-1, cisplatin, and trastuzumab in 12 patients; and another in 1 patient. Seven patients had received postoperative adjuvant chemotherapy.

Efficacy

Among the 27 patients enrolled in this study, 1 patient without measurable lesions was excluded from the analysis for ORR and PFS. The reason for the cessation of the treatment protocol was disease progression in 23 patients and toxicities in 4 patients.

PR was obtained in three patients, and no CR was observed (Table 2). The ORR was 11.5% (90% CI 1.2-21.8%), which was not statistically significantly superior to the pre-planned threshold of 15%. SD was observed in 12 patients (46%) (Table 2). One patient was not evaluable because of disease progression before CT evaluation. Median PFS was 3.2 months (95% CI 1.8-4.6 months, Fig. 1A). The 6-month survival rate was 85% (95% CI 65-94%,

Table 1. Characteristics of patients enrolled in this study (n = 27).

Factor		n	%
Sex	Men	22	81
	Women	5	19
Age	Median	67	
	Range	38-79	
HER2 status	IHC 3+	25	93
	IHC 2+ and FISH+	2	7
Recurrent or metastatic site	Liver	19	70
	LN	14	52
	Peritoneum	6	22
	Lung	2	7
	Local	2	7
	Others	2	7
History of Surgery	Yes	15	56
	No	12	44
Histology	Intestinal	17	63
	Diffuse	10	37
Previous regimens	XP + Trastuzumab	14	52
	SP + Trastuzumab	12	44
	Others	1	4

IHC, immunohistochemistry; LN, lymph node; XP, capecitabine plus cisplatin; SP, S-1 plus cisplatin.

Table 2. Best tumor response and overall response rate.

Factor		n	%
Best tumor response	CR	0	0
	PR	3	11.5
	SD	12	46.2
	PD	10	38.5
	NE	1	3.8
ORR			11.5
DCR			57.7

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; ORR, overall response rate; DCR, disease control rate.

Fig. 1B), and the median OS was 11.6 months (95% CI 8.3-18.5 months, Fig. 1B).

Adverse events

Among the 27 patients, toxicities of all grade by CTC-AE included anorexia (55.6%), fatigue (55.6%), nausea (33.3%), stomatitis (29.6%), neuropathy (29.6%) and others (Table 3). Grade 3 or higher toxicities included anorexia (14.8%), febrile neutropenia (14.8%), fatigue (7.4%), and others (Table 3). No treatment-related death was observed.

Discussion

This phase II trial did not demonstrate that trastuzumab plus docetaxel therapy was an effective regimen in

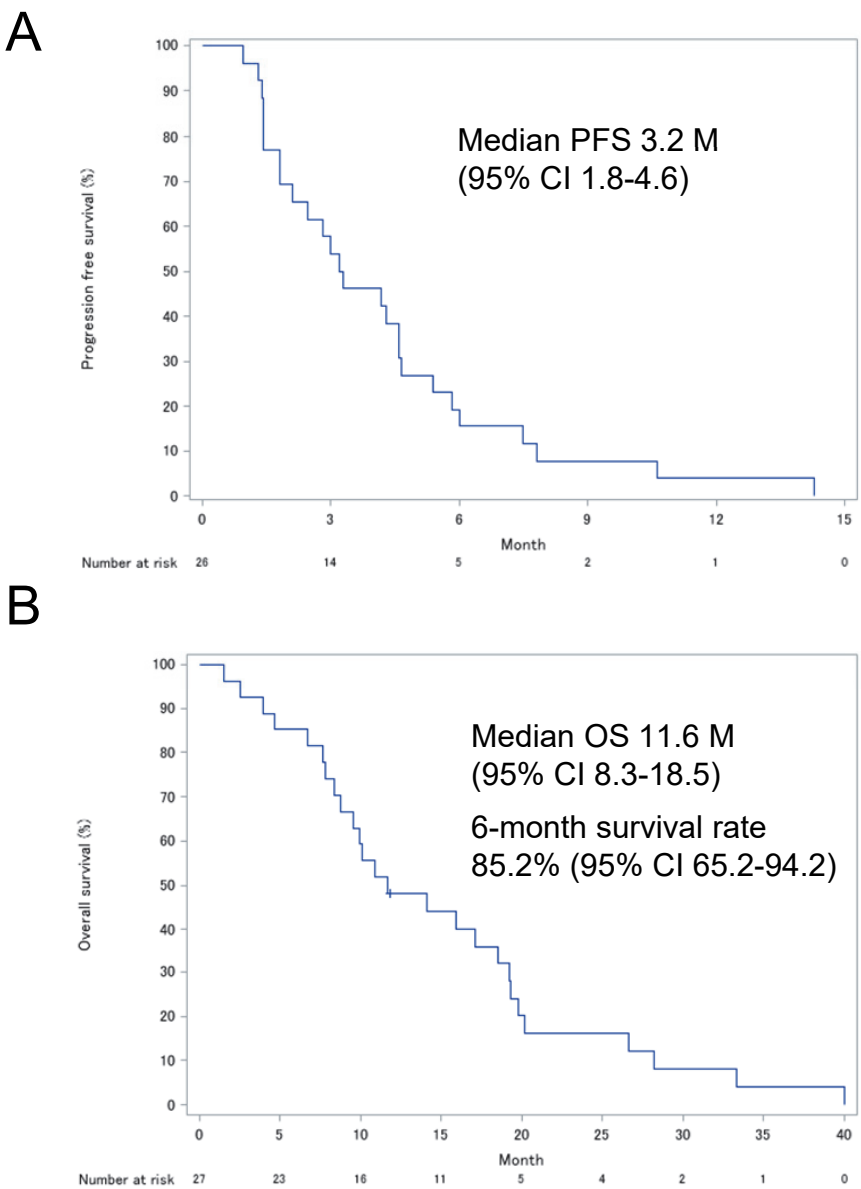

Fig. 1. Clinical outcome of the patients enrolled in this study.
(A) Kaplan-Meyer curve for progression-free survival of patients enrolled in this study.
(B) Kaplan-Meier curve for overall survival of patients enrolled in this study.

Table 3. Adverse events observed in > 5% of all enrolled patients (n = 27).

Factor		Grade 1		Grade 2		Grade 3		Grade 4		All		Grade 3-4	
		n	%	n	%	n	%	n	%	n	%	n	%
Hematological	Febrile neutropenia	n.a.	n.a.	n.a.	n.a.	3	11.1	1	3.7	4	14.8	4	14.8
Non-hematological	Anorexia	5	18.5	6	22.2	4	14.8	0	0.0	15	55.6	4	14.8
	Fatigue	7	25.9	6	22.2	2	7.4	0	0.0	15	55.6	2	7.4
	Nausea	5	18.5	3	11.1	1	3.7	0	0.0	9	33.3	1	3.7
	Stomatitis	5	18.5	2	7.4	1	3.7	0	0.0	8	29.6	1	3.7
	Neuropathy	7	25.9	1	3.7	0	0.0	0	0.0	8	29.6	0	0.0
	Fever up	4	14.8	1	3.7	0	0.0	0	0.0	5	18.5	0	0.0
	Diarrhea	2	7.4	1	3.7	0	0.0	0	0.0	3	11.1	0	0.0
	Abdominal pain	3	11.1	1	3.7	0	0.0	0	0.0	4	14.8	0	0.0
	Hand-foot syndrome	1	3.7	1	3.7	0	0.0	0	0.0	2	7.4	0	0.0

evaluated by CTC-AE ver 4.0. n.a., not available.

patients with advanced HER2-positive gastric cancer who were refractory to trastuzumab, fluoropyrimidine, and cisplatin.

Some recent retrospective and phase II studies have suggested the potent efficacy of continuing trastuzumab beyond progression on first-line treatment. Li et al. (2016) reported in their retrospective analysis that 32 patients treated with trastuzumab plus second-line chemotherapy had longer PFS of the second-line therapy compared with 27 patients treated with second-line chemotherapy alone (median 3.1 vs. 2.0 months, P = 0.008) but did not have statistically significantly longer OS after the second-line therapy (median 10.5 vs. 6.5 months, P = 0.172). Palle et al. (2017) also performed a retrospective study analyzing 104 patients and showed that continuing trastuzumab was statistically significantly associated with longer PFS (median 4.4 vs. 2.3 months, P = 0.002) and OS (median 12.6 vs. 6.1 months, P = 0.01). They also demonstrated that in the multivariate analysis incorporating ECOG-PS, the continuation of trastuzumab remained significantly associated with longer PFS and OS (Palle et al. 2017). Furthermore, Narita et al. (2017) reported in their retrospective analysis that PFS tended to be longer in the continuation of the trastuzumab group but with no significance (median 4.0 vs. 2.3 months, P = 0.14). In a meta-analysis of five reports, including the aforementioned ones, the addition of trastuzumab to second-line chemotherapy beyond progression at first-line therapy, including trastuzumab, was not associated with longer OS or higher ORR but was associated with longer PFS compared with chemotherapy alone (HR 0.64, 95% CI 0.45-0.91, P < 0.05) (Ter Veer et al. 2018).

More recently, Horita et al. (2019) reported the results of their phase II study in which the ORR was 21.4% among 28 patients who received trastuzumab plus weekly paclitaxel as second-line therapy regardless of trastuzumab use in first-line therapy. Of all patients, the median PFS was 4.6 months, and the median OS was 9.6 months (Horita et al. 2019). However, there were no significant differences in ORR, PFS, or OS between the 20 patients who received trastuzumab beyond progression and the 8 patients without trastuzumab use in first-line therapy (Horita et al. 2019). In addition, Makiyama et al. (2020) have recently shown in their randomized phase II study that the PFS of patients with HER2-positive gastric or gastroesophageal cancer in the paclitaxel plus trastuzumab arm (median 3.7 vs. 3.2 months, HR 0.91, 80% CI 0.67-1.22) and ORR (33% vs. 32%, P = 1.00) were not superior to those in the paclitaxel arm. In light of the results of their retrospective and phase II studies, the efficacy of trastuzumab beyond progression in gastric cancer seems quite modest.

In our single-arm phase II study, the ORR, median PFS, and OS were 11.5%, 3.3 months, and 11.8 months, respectively. The primary endpoint ORR was not only achieved but also observed to be relatively low despite the use of combination with docetaxel in second-line therapy. The reason for this is yet to be determined. One speculation is that this may be due to the small sample size of this study. In contrast, PFS and OS were comparable to those of other retrospective or phase II studies (Li et al. 2016; Narita et al. 2017; Palle et al. 2017; Ter Veer et al. 2018; Horita et al. 2019; Makiyama et al. 2020). The RAINBOW trial showed that the median PFS and OS of patients treated with ramucirumab plus paclitaxel at second-line therapy were 4.4 and 9.6 months, respectively (vs. 2.9 and 7.4 months of those with placebo plus paclitaxel) (Wilke et al. 2014). The PFS and OS in our study were comparable to those in the RAINBOW trial, but it cannot be concluded that trastuzumab beyond progression is an optimal approach in second-line treatment for patients with HER2-positive gastric cancer.

In HER2-positive gastric cancer, anti-HER2 therapy at second-line therapy, other than trastuzumab, has not shown promising results, either. The phase III Tytan trial showed that lapatinib plus paclitaxel did not significantly prolong

the OS or PFS (11.0 vs. 8.9 months, P = 0.10, 5.4 vs. 4.4 months, P = 0.24) of patients with HER2-amplified gastric cancer previously treated with trastuzumab, although lapatinib plus paclitaxel significantly improved the ORR (27% vs. 9%, P < 0.001) (Satoh et al. 2014). The phase II/III GATSBY trial showed that T-DM1 was not superior to taxane as second-line therapy for patients with previously treated HER2-positive metastatic gastric cancer, approximately three quarters of whom had received trastuzumab in the first-line therapy (median OS 7.9 vs. 8.6 months, HR 1.15, 95% CI 0.87-1.51, P = 0.86) (Thuss-Patience et al. 2017). At present, the continuation of anti-HER2 therapy, not just trastuzumab, in second-line therapy beyond progression on first-line therapy is not an attractive option for treating patients with HER2-positive gastric cancer.

The reason why anti-HER2-therapy beyond progression is not effective in second-line therapy in gastric cancer remains to be fully elucidated. Saeki et al. (2018) recently provided a clue to address this issue. They re-analyzed HER2 expression status in gastric cancer tissues from 33 patients who showed progression within 3 months after the completion of a trastuzumab-containing regimen. Of the 33 patients, 20 patients (60.6%) showed a loss of HER2 (Saeki et al. 2018). A recent phase II trial has supported their result by showing that HER2 positivity in tumor tissues was lost after first-line therapy in 11 of 16 patients (69%) (Makiyama et al. 2020). We did not re-analyze HER2 expression after first-line trastuzumab-containing regimen, however, the frequency of loss of HER2 expression reported in the two previous other studies appear higher than those observed in breast cancer (15-32%) (Ignatov et al. 2019, Oh and Bang 2020), which might be one of the reasons why most patients with gastric cancer are resistant to the continuation of anti-HER2 therapy.

On the other hand, more recently, Shitara et al. (2020) have shown that trastuzumab deruxtecan, an antibody-drug conjugate consisting of an anti-HER2 antibody and a topoisomerase inhibitor, is a promising drug in patients with HER2-positive gastric cancer treated with two or more lines of chemotherapy. In their randomized phase II trial, ORR was 51% in the trastuzumab deruxtecan group (n = 125), which was higher than 14% in the physician's choice chemotherapy group (n = 62, P < 0.001). OS was significantly longer in the trastuzumab deruxtecan group compared with in the chemotherapy group (median, 12.5 vs. 8.4 months, HR 0.59, 95% CI 0.39-0.88) (Shitara et al. 2020). Although trastuzumab deruxtecan was used in third-line or later setting, not soon after PD by trastuzumab therapy (Shitara et al. 2020), this drug is currently an only drug that has shown meaningful efficacy after PD by trastuzumab in HER2-positive gastric cancer.

Our study has several limitations. First, this study is a single-arm setting. Second, the planned sample size was 30, but the enrollment had to be terminated when 27 patients were enrolled since the pace of enrollment was slower than initially expected. Nevertheless, we consider less likely the possibility that the main interpretation was changed because we set the minimal sample size to 28 with a threshold ORR of 15% at a one-sided significance of 0.05 and power of 80%. Therefore, just one sample was missing, and even if one more patient was enrolled and PR was obtained, the ORR would be 14.8%, which would mean that ORR was not significantly superior to the pre-planned threshold of 15%.

In conclusion, our phase II study did not demonstrate the efficacy of trastuzumab plus docetaxel therapy beyond trastuzumab-resistant HER2-positive gastric cancer. The results support a current consensus that the continuation of trastuzumab in second-line therapy for gastric cancer is not a recommended option.

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Author Contributions

M.T., H.S., T. Yoshioka, and C.I. conceived the design of this study. M.T., Y.S., K.O., M.K., H.O., Y.S., H.H., K.S., K.O., Y.M., H.T., S.K., T. Yoshioka, and H.S. obtained informed consent from the patients. T. Yamaguchi performed the data analysis. M.T., T. Yoshioka, and C.I. wrote the manuscript.

Conflict of Interest

Masanobu Takahashi reports receiving research funding from Ono Pharmaceutical Company. Chikashi Ishioka reports receiving lecture fees from Taiho, Chugai, Takeda, Bayer, Pfizer, Mochida, Asahi Kasei, Bristol-Myers Squibb, Daiichi-Sankyo, Merck Serono, and Novartis, and research funding from Chugai, Taiho, Bristol-Myers Squibb, Daiichi-Sankyo, Merck Serono, Yakult, Ono, and Novartis. The other authors have no conflict of interest.

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