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Exploration of time points and cut-off values for early tumour shrinkage to predict survival outcomes of patients with metastatic colorectal cancer treated with first-line chemotherapy using a biexponential model for change in tumour size

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ABSTRACT

Background Several studies reported that early tumour shrinkage (ETS) was associated with overall survival in patients with metastatic colorectal cancer (mCRC) treated with first-line chemotherapy. However, appropriate time point and cut-off value for ETS remain unclear because these varied in previous studies.

Patients and methods We investigated patients with mCRC who received FOLFOX or FOLFIRI with/without molecular-targeted agents as first-line treatment between 2005 and 2014. Using a biexponential model for change in tumour size, a relative change in the sum of the longest diameters of target lesions from baseline was estimated at a certain time point in each individual patient. Associations of survival outcomes with ETS at various time points based on various cut-off values were evaluated by Cox regression analysis with a landmark approach.

Results Among the 67 patients reviewed, the objective response rate was 73.1% (95% CI 62.5% to 83.7%), the median progression-free survival was 10.9 months (95% CI 8.7 to 13.0 months) and the median overall survival was 25.6 months (95% CI 20.1 to 27.3 months). The model for change in tumour size agreed with the actual measured sizes well. Multivariate Cox regression analysis, including performance status, number of metastatic sites and use of targeted agents, showed that ETS at 8 weeks based on a cut-off value of 20% was most significantly associated with overall survival (HR: 0.404, 95% CI 0.231 to 0.707, P=0.0015).

Conclusion It is suggested that a time point of 8 weeks and a cut-off value of 20% may be optimal criteria for defining ETS.

Key questions

What is already known about this subject?

There have been several studies that described the associations of early tumour shrinkage (ETS) with overall survival (OS) in patients with metastatic colorectal cancer treated with first-line chemotherapy. However, measurement time points and cut-off values to calculate ETS have varied between studies.

What does this study add?

By using a biexponential model for change in tumour size, associations of OS with ETS at various time points based on various cut-off values were evaluated in multivariate Cox regression analyses. This study showed that ETS at 8 weeks based on a cut-off value of 20% was most significantly associated with OS.

How might this impact on clinical practice?

The results could suggest that a time point of 8 weeks and a cut-off value of 20% are optimal criteria for defining ETS. An optimally calculated ETS may serve as a surrogate marker for OS.

INTRODUCTION

Colorectal cancer (CRC) is the third and the second most commonly diagnosed cancer in men and in women worldwide, respectively.[1] The prognosis of patients with unresectable metastatic CRC (mCRC) is poor, with a 5-year survival probability of approximately 10%.[2] Several chemotherapy regimens using cytotoxic and molecular-targeted agents are available for management of patients with mCRC. For first-line treatments, epidermal growth factor receptor-targeting monoclonal antibodies such as cetuximab and panitumumab, as well as vascular endothelial growth factor-targeting monoclonal antibodies such as bevacizumab, have been reported to improve outcomes of patients with mCRC when combined with cytotoxic chemotherapy regimens such as FOLFOX and FOLFIRI.

Tumour response as defined by the Response Evaluation Criteria in Solid Tumors (RECIST)[3] is commonly used as a surrogate marker for evaluating antitumour effects. However, discrepancies between tumour response and overall survival (OS) as true endpoint have been reported with respect to the efficacy of chemotherapy regimens.[4] Recently, early tumour shrinkage (ETS), usually defined by a relative (per cent) reduction in tumour size at a certain time point, has garnered attention as an important clinical marker associated with long survival in the treatment of mCRC.[5–7] Several studies[8–18] showed that achieving ETS during first-line treatments can predict improved OS, suggesting its potential use as a surrogate endpoint.[5 6]

However, the definition of ETS is inconsistent in various studies with respect to time points and cut-off values. Among the studies that adopted ETS at 6 weeks, the cut-off value was 20% in the AIO KRK 0104[15] and FIRE-3 trials.[16] In the FIRE-1 trial, the cut-off value of 20% at 7 weeks was used for ETS.[11] Many studies (the ACCORD 13 trial,[13] CRYSTAL and OPUS trials,[14] PRIME trial,[10] TRIBE trial[9] and a clinical trial that evaluated the impact of ETS in patients with colorectal liver metastases[18]) used the cut-off value of 20% at 8 weeks. Other cut-off values for ETS at 8 weeks were 10% in the NORDIC VI trial[17] and 30% in the PRIME trial.[10] In the N9741 trial, the percentage changes of tumour size at 12 and 24 weeks were evaluated.[12]

Another problem in evaluating the relationship between ETS and survival outcomes is that tumour size cannot usually be measured at an exact time point; therefore, tumour size data for evaluating ETS are often collected within allowable time windows, such as 8±2 weeks. Using a wide time window or excluding patients with no available data within the period may cause biases in the analyses.

Recently, several models that describe tumour regression and progression patterns have been proposed.[19–23] Some of the metrics and parameters estimated by these models were shown to be useful in predicting survival outcomes of patients with mCRC. Furthermore, the models proved useful for the design of phase III trials based on modelling survival outcomes from phase II (or other clinical trial) data.[19 22] Moreover, the models for change in tumour size can be used for estimating ETS at any time point from data of actually measured tumour size.

The objective of this study was to explore the appropriate time point and cut-off value of ETS for predicting survival by using the biexponential model for the change in tumour size.

METHODS

Subjects

The source of the subjects in this retrospective study was the patients with mCRC at Shizuoka Cancer Center and St Marianna University School of Medicine Hospital who met the following criteria: (1) ages 20–80 years; (2) Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2; (3) histologically confirmed adenocarcinoma of the colon or rectum; (4) unresectable metastatic or recurrent disease; (5) having measurable target lesions (according to RECIST version 1.1) confirmed by CT within 30 days before initiating chemotherapy; (6) receiving the first-line chemotherapy with FOLFIRI or FOLFOX alone or combined with targeted agents (bevacizumab, cetuximab or panitumumab) between 2005 and 2014; (7) at least one evaluation of response by CT after initiating chemotherapy; (8) no prior chemotherapy including adjuvant chemotherapy; (9) preserved organ function; (10) no massive ascites or pleural effusion; (11) no brain metastasis; and (12) no serious complications such as infection or heart disease. For exploratory objectives, we targeted a sample size of approximately 60, those with various chemotherapy regimen, such as FOLFOX or FOLFIRI in combination with or without molecular-targeted agent (bevacizumab, cetuximab or panitumumab).

Treatments

FOLFOX comprised biweekly administration of oxaliplatin (85 mg/m^2), *l*-leucovorin (200 mg/m^2), an intravenous bolus of fluorouracil (400 mg/m^2) and continuous infusion of fluorouracil (2400 mg/m^2); FOLFIRI comprised similar administration of fluorouracil and irinotecan (150 mg/m^2) instead of oxaliplatin. Molecular-targeted agents administered in combination with chemotherapy included bevacizumab (5 mg/kg, biweekly), cetuximab (400 mg/m^2 followed by 250 mg/m^2, weekly) or panitumumab (6 mg/kg, biweekly). These treatments were continued until disease progression, unacceptable toxicities or patient refusal. Dose reduction, delay or omission of any agent was decided according to physician's discretion based on any toxicities that arose.

Evaluation

CT was performed at baseline and then repeated approximately every 2–3 months, and objective tumour response was evaluated according to RECIST version 1.1. At baseline, all measurable lesions up to a maximum of 5 (with 2 maximum per organ that were representative of all involved organs) were identified as target lesions. All other lesions were identified as non-target lesions. The tumour size was calculated as the sum of the longest diameters of all target lesions on CT.

Model for change in tumour size

We used the biexponential model (empirical model).[20 22] This model describes the change in tumour size by a function of time, and accounts for the natural growth (tumour progression) and the treatment effect on tumour growth (tumour regression or tumour growth inhibition) as follows:

$$Y(t) = Y_0 \times \left\{\exp\left(K_L * t\right) + \exp\left(-K_D * t\right) - 1\right\},$$

where $Y(t)$ is the tumour size at t weeks, Y_0 is the baseline tumour size, K_L is the tumour growth parameter and K_D is the tumour growth inhibition parameter.

To estimate the parameters for each patient by using the actual tumour size data of each patient and that of all patients in this study, we used the non-linear mixed effects modelling approach where K_L and K_D follow the log-normal distribution. Tumour sizes in particular weeks were calculated from the estimated biexponential models for each patient.

Tumour shrinkage ratio is calculated as the relative change in tumour size at certain weeks from baseline as follows:

$R(t) = \{Y(0) - Y(t)\} / Y(0) \times 100\ (\%)$,

where $R(t)$ is the tumour shrinkage ratio at t weeks. ETS is defined as an $R(t)$ greater than or equal to a cut-off value. Subjects were divided into ETS and non-ETS subgroups according to cut-off values of 10%, 20%, 30% and 40% for $R(t)$ at t=6, 8, 12 and 16 weeks.

Statistical analysis

We summarised continuous variables by median (range), and categorical variables by frequency (%) for patient characteristics and tumour responses as evaluated by RECIST version 1.1. Progression-free survival (PFS) and OS were summarised by the Kaplan-Meier method. Univariate Cox regression was applied for evaluating the relationship between patient characteristics and survival outcomes.

The relationships between survival outcomes and ETS at specified time points based on specified cut-off values were examined by multivariate Cox regression analysis, including the ECOG PS, number of metastatic organs and use of a targeted agent. These variables were selected based on clinical importance. We applied landmark analysis to confirm the impact of the time point and the cut-off value for ETS on the predictability of survival outcomes. Survival curves of PFS and OS by ETS were compared by the log-rank test.

All statistical analyses were performed by R V.3.3.0 (http://www.R-project.org). We used the JAGS (http://mcmc-jags.sourceforge.net/) in R for the non-linear mixed effects model in the biexponential model.

RESULTS

Patient characteristics

Sixty-seven patients with mCRC who received first-line chemotherapy between 2005 and 2014 comprised the study population. The patient characteristics are listed in table 1.

RECIST response and survival outcomes

Of the 67 patients, 49 achieved partial response (PR), 14 had stable disease and 4 had progressive disease. The objective response rate was 73.1% (95% CI 62.5% to 83.7%) and the disease control rate was 94.0% (95% CI 88.4% to 99.7%). The median PFS was 10.9 months (95% CI 8.7 to 13.0 months) and the median OS was 25.6 months (95% CI 20.1 to 27.3 months) (see online supplemental table S1).

Table 1 Patient characteristics (n=67)

Age*	63 (29–77)
Sex	
Male	46 (61.2%)
Female	21 (38.8%)
ECOG PS	
0	44 (65.7%)
1	22 (32.8%)
2	1 (1.5%)
Number of metastatic organs	
0	2 (3.0%)
1	35 (52.2%)
2	18 (26.9%)
≥3	12 (17.9%)
Baseline tumour size (mm)*	92 (10–313)
Chemotherapy	
FOLFOX	42 (62.7%)
FOLFIRI	25 (37.3%)
Targeted agent	
None	31 (46.3%)
Bevacizumab	25 (37.3%)
Anti-EGFR antibody†	11 (16.4%)

*Median (range).
†Cetuximab, panitumumab.
ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor.

In univariate Cox regression analysis, the chemotherapy regimens (FOLFIRI/FOLFOX) were marginally correlated with the OS. However, none of patient characteristics strongly correlated with the OS in this study population (see online supplemental table S2).

Tumour size estimation

The relationship between actual tumour sizes and those estimated by the biexponential models is shown in figure 1, and typical relationships between the actual values and estimated tumour size trends in individuals are shown in figure 2. The biexponential model with mixed effects agreed with the actual changes in tumour size very well (figures 1 and 2A, B), while there were some differences in acute progression when the number of measurements was insufficient (figure 2C). The median number of actual measurements by CT following the baseline measurement was 4 (range: 1–21), and 54 patients (80.6%) showed tumour regression to various extents until 24 weeks. Among five patients whose tumours progressed with no evidence of shrinkage, the estimated progression pattern based on some measurements was adequate (figure 2B); however, having only a single measurement in acute progression was inadequate (figure 2C). With respect to ETS categorisation, however, the deviation of estimates

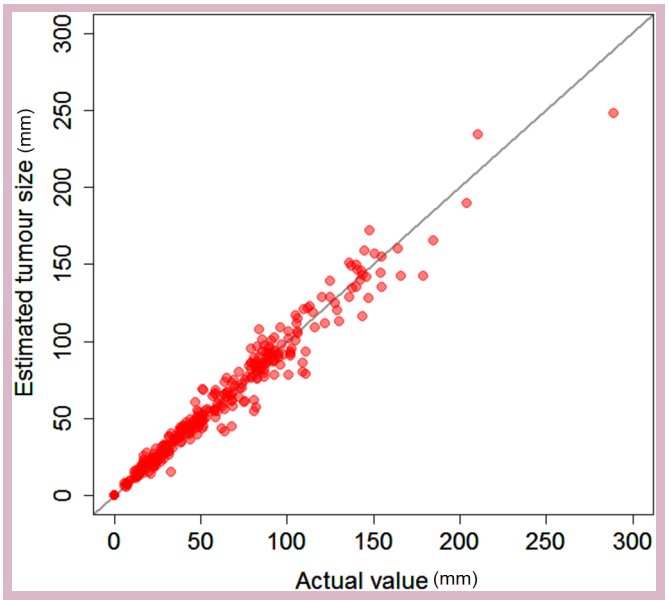

Figure 1 Relationship between actual values and estimated tumour sizes

Table 2 Relationship between ETS and OS by time points and cut-off values

Time point	Cut-off value (%)	HR (95% CI)	P value
6 weeks	10	0.439 (0.247 to 0.779)	0.005
	20	0.637 (0.356 to 1.137)	0.127
	30	0.881 (0.350 to 2.220)	0.788
	40	0.769 (0.263 to 2.243)	0.630
8 weeks	10	0.406 (0.217 to 0.759)	0.005
	20	0.404 (0.231 to 0.707)	0.002
	30	1.387 (0.732 to 2.629)	0.316
	40	0.769 (0.263 to 2.243)	0.630
12 weeks	10	0.536 (0.275 to 1.046)	0.068
	20	0.406 (0.229 to 0.721)	0.002
	30	0.404 (0.231 to 0.707)	0.002
	40	1.287 (0.683 to 2.422)	0.435
16 weeks	10	0.536 (0.275 to 1.046)	0.068
	20	0.476 (0.263 to 0.859)	0.014
	30	0.400 (0.225 to 0.713)	0.002
	40	0.493 (0.276 to 0.878)	0.016

Adjusted by ECOG PS, number of metastatic organs, use of targeted agent.
ECOG PS, Eastern Cooperative Oncology Group performance status; ETS, early tumour shrinkage; OS, overall survival.

from actual measurements at disease progression had no impact on the calculation of tumour shrinkage in this model.

Using the estimated biexponential models, all patients could be categorised as ETS or non-ETS according to the cut-off for tumour shrink age at each evaluation time (see online supplemental figure S1). The number of patients with an ETS at 8 weeks based on a cut-off value of 20% was equal to that of patients with ETS at 12 weeks based on a cut-off value of 30%. Between 6 and 8 weeks, using 20% as a cut-off value produced a 15% discrepancy (ie, 10 patients were categorised differently). All 30 patients showing ≥20% tumour shrinkage at 8 weeks achieved PR, accounting for 61% (30/49) of all patients with PR. On the other hand, 18 of 37 patients (49%) with tumour shrinkage <20% at 8 weeks did not achieve PR.

Relationship between tumour shrinkage and survival outcomes

We investigated the relationship between ETS at various time points based on various cut-off values and OS by multivariate Cox regression analysis (table 2). The ECOG PS, number of metastatic organs and use of a targeted agent were not significantly associated with OS. ETS with a cut-off of 10% at 6 and 8 weeks, a cut-off of 20% at 8 and

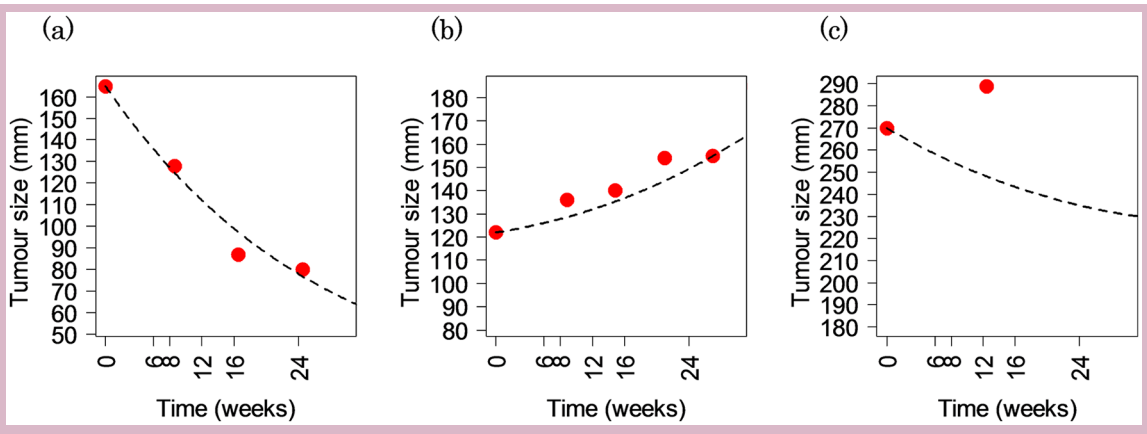

Figure 2 Actual versus estimated trend of tumour size. Dots: actual values; dashed line: estimated trend of tumour size. (A) Well fitted (regression); (B) Well fitted (progression); (C) Poorly fitted (acute progression).

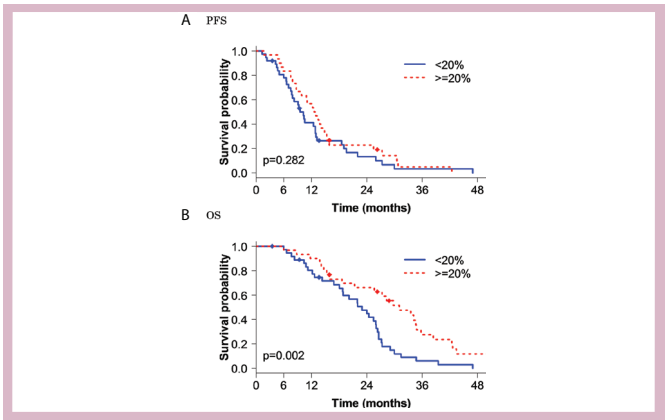

Figure 3 Survival curves by early tumour shrinkage at 8 weeks with a cut-off value of 20%. (A) Progression-free survival (PFS). (B) Overall survival (OS).

12 weeks, and a cut-off of 30% at 12 and 16 weeks were significantly associated with OS (table 2). While the HRs of ETS with a cut-off of 10% and 20% at 8 weeks, 20% and 30% at 12 weeks, and 30% at 16 weeks were very similar (approximately 0.40), ETS with a cut-off of 20% at 8 weeks and a cut-off of 30% at 12 weeks showed the lowest upper CI limit (HR: 0.404, 95% CI 0.231 to 0.707, P=0.0015). PFS and OS curves by tumour shrinkage at 8 weeks with a cut-off value of 20% are shown in figure 3. The difference in PFS curves between ETS and non-ETS was small (median PFS, non-ETS: 9.5 months; ETS: 12.8 months; P=0.282). However, OS curves were largely different after approximately 18 months (median OS, non-ETS: 23.0 months; ETS: 31.0 months; P=0.002).

DISCUSSION

In this retrospective study, we explore the appropriate ETS criteria that would predict OS by using a model for change in tumour size. The subjects of this study were treated with various chemotherapy regimens with and without targeted agents. While the response rates in this study were relatively high, median PFS and OS were similar to those in previous clinical trials. One of the reasons for the favourable response rates in this study may be attributed to their calculation based on the best tumour shrinkage without confirmation of responses. Additionally, all the subjects were chemo-naïve, including for adjuvant chemotherapy. Although there may have been some selection bias in this study owing to the stringent selection criteria, the treatment efficacy and clinical outcomes of the subjects in this study are consistent with those in general clinical trials.

The validity of exploring appropriate time point and cut-off value depends on the model fitting for change in tumour size. In this study, the biexponential model estimated the tumour sizes well except for the case of insufficient number of measurements in acute progression; however, this did not impact ETS categorisation. Other models for change in tumour size[19 21–23] may improve the model fitting. However, considering the number of measurements of tumour size and the number of patients in this study, the differences between the various models may not be substantial. In fact, the biexponential model with mixed effects fit the real change of tumour size very well. Thus, the exploration of appropriate time point and cut-off value in this study was deemed to be warranted.

Our data suggested that a time point of 8 weeks and a cut-off value of 20% are most appropriate for determining the ETS that predicts OS; these values have already been employed in some previous studies.[9 10 13 14 18] While 6 weeks may be sufficient to determine whether a tumour is growing or not, determining tumour shrinkage of ≥10% at 6 weeks may be less evident than that of ≥20% at 8 weeks when considering measurement errors depending on slice thickness on CT image reconstruction. For the same reason, a cut-off value of 20% appears to be more suitable than 10% at 8 weeks. Although cut-off values of 20% at 8 and 12 weeks and of 30% at 12 and 16 weeks showed very similar HRs, a cut-off value of 20% at 8 weeks is better than others as criteria of ETS in consideration of earlier prediction of OS.

While ETS with a cut-off value of 20% at 8 weeks predicted OS well, prediction of PFS was not as profound. Similarly, there was no difference in PFS according to ETS in the FIRE-3 trial.[16] A potential explanation is that tumours may easily grow by more than 20%, which is the definition of progressive disease according to the RECIST, especially after remarkable shrinkage. While actual tumour size and degree of tumour regression may hardly reflect on PFS, they are important parameters for OS as true endpoint.[7] Hence, ETS may simply be unsuitable for predicting PFS.

The depth of response (DpR) is the relative change in tumour size at the nadir of tumour response from baseline, the one of the important candidate surrogate endpoints for prediction of survival outcomes.[5 7 24] In this study, we did not evaluate the relationship between DpR and survival outcomes; the model for change in tumour size could not estimate DpR accurately enough owing to insufficient data on tumour size around the nadir of tumour response. Moreover, because it is impossible to know in advance when the nadir of tumour response will be achieved, and since CT cannot be performed so frequently, there may be errors in measuring DpR during clinical trials. Therefore, ETS appears to be a useful maker that can be measured at fixed time point prospectively. Treatment strategies such as switch maintenance according to ETS can potentially be investigated in future clinical trials.

Our study has some limitations. While we used RECIST version 1.1, some other studies used version 1.0.[9 15 17] Furthermore, the appearance of new lesions was not considered in the analysis. New lesions ought to have some impact on survival as would tumour size and progression. Moreover, we did not evaluate tumour shrinkage by regimen (FOLFOX/FOLFIRI, and bevacizumab/cetuximab/panitumumab) because of the small number of patients. Although the concept of the ETS was

initially proposed in the clinical trial of antiepidermal growth factor receptor antibody, our results suggest that ETS may have an impact on survival regardless of chemotherapy regimens. Future studies should therefore investigate tumour shrinkage according to regimens.

The results of this study should be validated by using the actual tumour size data collected at various time points in different cohorts. Because CT cannot be performed at exactly 8 weeks for all patients as a practical matter, a time window for performing CT should be set for the evaluation of ETS. Considering the difference in tumour shrinkage between 6 and 8 weeks, the allowable range should not exceed ± 2 weeks. The results of this study were validated[25] by using the actual tumour size data that were acquired within such a time window in the WJOG4407G trial,[26] which compared FOLFOX with FOLFIRI in combination with bevacizumab as the first-line chemotherapy in patients with mCRC. In the validation study with 305 patients, ETS with a cut-off value of 20% at 8 weeks±2 weeks (at 6–10 weeks) was significantly associated with OS (HR: 0.53, 95% CI 0.38 to 0.74, P<0.001). Using a narrower allowable range, the relationship of ETS with a cut-off value of 20% at 8 weeks±1 week (at 7–9 weeks) and OS was shown more clearly (HR: 0.47, 95% CI 0.33 to 0.67, P<0.001). It is considered that ETS evaluated at 8 weeks with some allowable ranges might predict long survival.

CONCLUSION

We propose that a time point of 8 weeks and a cut-off value of 20% can be optimal for the definition of ETS. Furthermore, we posit that ETS can be a useful surrogate endpoint of OS in future clinical trials.

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Competing interests KS received honoraria from Chugai Pharma and Taiho Pharmaceutical. KY received honoraria from Chugai Pharma, Daiichi Sankyo, Yakult Honsha, Takeda, Bayer, Merck Serono, Bristol-Myers Squibb Japan, Lilly, and Taiho Pharmaceutical. SM received honorarium from Chugai Pharma. All remaining authors have declared no conflicts of interest.

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