A randomized phase III trial comparing S-1 versus UFT as adjuvant chemotherapy for stage II/III rectal cancer (JFMC35-C1: ACTS-RC)

E. Oki1*, A. Murata2, K. Yoshida3, K. Maeda4, K. Ikejiri5, Y. Munemoto6, K. Sasaki7, C. Matsuda8, M. Kotake9, T. Suenaga10, H. Matsuda11, Y. Emi12, Y. Kakeji13, H. Baba14, C. Hamada15, S. Saji16 & Y. Maehara1

1Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka; 2Department of Gastroenterological Surgery, Hirosaki University Graduate School of Medicine, Aomori; 3Department of Surgical Oncology, Gifu University Graduate School of Medicine, Gifu; 4Department of Surgical Oncology, Osaka City University Graduate School of Medicine, Osaka; 5Department of Surgery, Gastrointestinal Center, National Hospital Organization Kyushu Medical Center, Fukuoka; 6Department of Surgery, Fukui-ken Saiseikai Hospital, Fukui; 7Department of Surgery, Otaru Ekisaikai Hospital, Hokkaido; 8Department of Surgery, Osaka General Medical Center, Osaka; 9Department of Surgery, Kouseiren Takaoka Hospital, Toyama; 10Gastroenterological Surgery, Nanpuh Hospital, Kagoshima; 11Department of Surgery, Hiroshima Red Cross Hospital and Atomic-bomb Survivors Hospital, Hiroshima; 12Department of Surgery, Saiseikai Fukuoka General Hospital, Fukuoka; 13Division of Center, Osaka; 14Department of Surgery, Saiseikai Fukuoka General Hospital, Fukuoka; 15Department of Surgery, Kouseiren Takaoka Hospital, Toyama; 16Faculty of Engineering, Tokyo University of Science, Tokyo; 17Japanese Foundation for Multidisciplinary Treatment of Cancer, Tokyo, Japan

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Backgrounds: Preventing distant recurrence and achieving local control are important challenges in rectal cancer treatment, and use of adjuvant chemotherapy has been studied. However, no phase III study comparing adjuvant chemotherapy regimens for rectal cancer has demonstrated superiority of a specific regimen. We therefore conducted a phase III

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study to evaluate the superiority of S-1 to tegafur–uracil (UFT), a standard adjuvant chemotherapy regimen for curatively resected stage II/III rectal cancer in Japan, in the adjuvant setting for rectal cancer.

**Patients and methods:** The ACTS-RC trial was an open-label, randomized, phase III superiority trial conducted at 222 sites in Japan. Patients aged 20–80 with stage II/III rectal cancer undergoing curative surgery without preoperative therapy were randomly assigned to receive UFT (500–600 mg/day on days 1–5, followed by 2 days rest) or S-1 (80–120 mg/day on days 1–28, followed by 14 days rest) for 1 year. The primary end point was relapse-free survival (RFS), and the secondary end points were overall survival and adverse events.

**Results:** In total, 961 patients were enrolled from April 2006 to March 2009. The primary analysis was conducted in 480 assigned to receive UFT and 479 assigned to receive S-1. Five-year RFS was 61.7% [95% confidence interval (CI) 57.1% to 65.9%] for UFT and 66.4% (95% CI 61.9% to 70.5%) for S-1 [P = 0.0165, hazard ratio (HR): 0.77, 95% CI 0.63–0.96]. Five-year survival was 80.2% (95% CI 76.3% to 83.5%) for UFT and 82.0% (95% CI 78.3% to 85.2%) for S-1. The main grade 3 or higher adverse events were increased alanine aminotransferase and diarrhea (each 2.3%) in the UFT arm and anorexia, diarrhea (each 2.6%), and fatigue (2.1%) in the S-1 arm.

**Conclusion:** One-year S-1 treatment is superior to UFT with respect to RFS and has therefore become a standard adjuvant chemotherapy regimen for stage II/III rectal cancer following curative resection.

**Key words:** adjuvant chemotherapy, local recurrence, rectal cancer, S-1, UFT, total mesorectal excision

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### introduction

Colorectal cancer is one of the most prevalent cancers worldwide, and rectal cancer accounts for 40% of all colorectal cancers [1]. Different Western countries have taken various approaches to its treatment, which includes conducting clinical studies of neoadjuvant chemotherapy without radiotherapy and following the ‘watch and wait’ philosophy [2], but the standard treatment for rectal cancer is to perform total mesorectal excision following preoperative radiation (or chemoradiation) therapy. In Japan, D3 dissection with autonomic nerve preservation, a technique in which the lateral lymph nodes are dissected while preserving the autonomic nerves of the pelvis without neoadjuvant chemoradiotherapy, is carried out to improve treatment outcomes for locally advanced rectal cancer [3]. Preventing distant recurrence and achieving local control are important challenges that the East and West have in common, and use of adjuvant chemotherapy has been studied. Among the clinical trials comparing adjuvant chemotherapy regimens that have been conducted, only the ADORE randomized phase II study showed that adjuvant chemotherapy including oxaliplatin after preoperative chemoradiation therapy (CRT) is useful in treating rectal cancer [4]. However, no phase III study comparing multiple adjuvant chemotherapy regimens for rectal cancer has demonstrated the superiority of a specific regimen.

Oral tegafur–uracil (UFT) is a combination drug that contains tegafur, a prodrug of 5-fluorouracil (5-FU), and uracil, an inhibitor of the 5-FU-degrading enzyme dihydropyrimidine dehydrogenase (DPD). A 1-year regimen of adjuvant chemotherapy with UFT following curative resection for stage III rectal cancer showed benefits compared with surgery alone in a randomized, controlled trial (RCT) [5]. We believe these findings support that, even though 6 months of adjuvant treatment is the typical treatment for colon cancer in Japan, 1-year administration of UFT as adjuvant chemotherapy should be the standard treatment for curatively resected locally advanced rectal cancer.

S-1 combines tegafur, gimeracil, and oteracil potassium in a molar ratio of 1:0.4:1. Oteracil potassium inhibits the phosphorylation of 5-FU in the gastrointestinal tract, thereby reducing gastrointestinal toxicity. As gimeracil is an extremely strong inhibitor of DPD, ~180 times stronger than uracil [6]. The effectiveness of S-1 as adjuvant chemotherapy has been demonstrated in RCTs in patients with stage III colon cancer following curative resection [7]. S-1 has been studied in combination with oxaliplatin or irinotecan for metastatic colorectal cancer, and the noninferiority of regimens including S-1 to standard multidrug chemotherapy has been proved in phase III studies [8, 9].

We therefore conducted an open-label, multicenter, randomized, controlled study, JFMC35-C1 (ACTS-RC), to evaluate the superiority of S-1 to UFT in the adjuvant setting for stage II/III rectal cancer.

### patients and methods

#### patients

The inclusion criteria were histologically proven rectal adenocarcinoma, stage II or stage III rectal cancer (pathological T3-4, N0 or any T, N1-2) (TNM Classification, UICC 6th Edition, 2002), with (systematic) D2 or D3 lymph node dissection, curatively resected, age 20–80 years, no prior chemotherapy or radiation therapy, ability to take oral drugs, and adequate organ function. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and in compliance with Japanese ethical guidelines for clinical studies. The study was approved by the institutional review board of each participating institution. Written informed consent was obtained from all patients before enrollment.

#### randomization and masking

Patients were randomly assigned (1:1) to receive UFT or S-1 at the Data Center of the Japanese Foundation for Multidisciplinary Treatment of Cancer (JMFC) using the minimization method. Stratification factors were institution, tumor location (above the peritoneal reflection versus below the peritoneal reflection and anal canal), depth of invasion (T1, T2 versus T3, T4), and lymph node metastasis (N0 versus N1, N2). Investigators and patients were not masked to treatment allocation.

#### procedures

Patients were enrolled within 42 days after surgery and started study treatment within 7 days after enrollment. UFT was orally administered at one of two dosages according to body surface area (BSA) (500 mg/day for BSA <1.25 m²; 600 mg/day for BSA ≥1.25 m²). The dosage was divided into
two daily doses administered after meals for 5 consecutive days, followed by a 2-day rest period. Follow-up was conducted after 1 year of treatment with UFT. S-1 was orally administered at dosages according to BSA (80 mg/day for BSA <1.25 m²; 100 mg/day for BSA 1.25–1.50 m²; 120 mg/day for BSA ≥1.50 m²). The dosage was divided into two daily doses after meals for 28 consecutive days, followed by a 14-day rest period. Follow-up was conducted after 1 year of treatment with S-1. A complete blood count and liver and renal function tests were required before each cycle of treatment. The dose was reduced when criteria for dose reduction were met. Shortening of the cycle (e.g., to 14 days on and 7 days off) was considered for S-1 arm patients when gastrointestinal toxicities of grade 1 were judged to have occurred due to administration of S-1 for a consecutive period of 14 days or longer. Recurrence was assessed using computed tomography imaging, colonoscopy, and tumor markers. These tests were carried out every 4 months during the first 2 years after surgery and once every 6 months from the third year onward.

**statistical analysis**

For this study, the primary end point was relapse-free survival (RFS) and the secondary end points were overall survival (OS) and adverse events. Assuming a 70% 5-year RFS rate for UFT in this study for stage II/III rectal cancer and a 0.70 hazard ratio (HR) of S-1 to UFT, the necessary enrollment number was calculated to be 762 using Schoenfeld and Richter’s formula with an enrollment period of 3 years, a follow-up period of 5 years, α = 0.05 (two-sided), and statistical power of 80%. The target sample size of 800 was calculated assuming an ineligibility rate of ~5%. The planned enrollment period was 3 years, but the target enrollment number of 800 patients was reached in 2 years and 6 months. Nevertheless, enrollment was continued for 3 years as planned because enrollment of 762–987 patients was necessary to obtain statistical power of 80%–89%. An interim efficacy analysis was carried out in this study. Although the level of significance for the entire study was α = 0.05, the final analysis was carried out at α = 0.049 because α = 0.001 was subtracted at the time of the interim analysis to adjust for multiplicity. RFS was defined as the length of time from the date of surgery until the diagnosis of recurrence or death from any cause, whichever came first. OS was defined as the length of time from the date of surgery until death from any cause. Stratified log-rank tests with all stratification factors except for institution were used to assess superiority in terms of RFS in all enrolled patients (two-sided tests with a significance level of 5%). The RFS and OS curves were estimated using the Kaplan–Meier method. To estimate the cumulative recurrences by each location (local/distant), respective recurrences were considered as events; recurrences other than these and deaths were censored at the time of their occurrence. These were reported as cumulative recurrences using the reverse Kaplan–Meier method. Distant recurrences were defined as hematogenous recurrences and lymphatic recurrences (supplementary Appendix S1, available at **Annals of Oncology** online). Adverse events were evaluated in all treated patients based on the Common Terminology Criteria for Adverse Events v3.0. Data were analyzed using SAS 9.3 (SAS Institute, Cary, NC). This trial is registered with UMIN-CTR [http://www.umin.ac.jp/ctr/] (C000000385).

**results**

A total of 961 patients were enrolled at 222 sites from April 2006 to March 2009. Two patients were excluded from analysis, so 480 patients in the UFT arm and 479 patients in the S-1 arm were included in the primary end point analysis (Figure 1). Patient baseline characteristics were well balanced (Table 1).

The median follow-up time for RFS, which was the primary end point, was 5.02 years (range, 0.00–8.01 years). The 5-year RFS rate was 61.7% [95% confidence interval (CI) 57.1% to 65.9%] in the UFT arm and 66.4% [95% CI 61.9% to 70.5%] in the S-1 arm, demonstrating the superiority of S-1 to UFT (stratified log-rank test; P = 0.0165, HR: 0.77, 95% CI 0.63–0.96) (Figure 2A). The median follow-up time for OS, which was the secondary end point, was 5.55 years (range, 0.30–8.11 years). The 5-year survival rate was 80.2% [95% CI 76.3% to 83.5%] in the UFT arm and 82.0% [95% CI 78.3% to 85.2%] in the S-1 arm, with no significant difference in OS between arms (stratified log-rank test; P = 0.5365, HR: 0.92, 95% CI 0.71–1.20) (Figure 2B).

The safety analysis was carried out in all treated patients excluding one patient in the UFT arm and eight patients in the S-1 arm who did not receive the study drug. The incidence of adverse events of all grades was 73.9% in the UFT arm and 82.3% in the S-1 arm. The incidence of adverse events ≥grade 3 was comparable between the UFT and S-1 arms (11.7% versus 13.4%), indicating that S-1 treatment was tolerable (Table 2). Common adverse events ≥grade 3 in the UFT arm were increased alanine aminotransferase (ALT), diarrhea (each 2.3%), increased aspartate aminotransferase (AST) (1.5%), and decreased hemoglobin (1.3%). Similarly, in the S-1 arm, these were anorexia and diarrhea (each 2.6%), fatigue (2.1%), decreased hemoglobin, increased total bilirubin, and nausea (each 1.3%). The rate of completion of 1 year of treatment was 61.8% for the UFT arm and 61.3% for the S-1 arm. The rate of treatment discontinuation within 6 months was 25.9% for the UFT arm and 23.8% for the S-1 arm. Post-trial treatment for patients with recurrent disease (UFT arm: 174 patients; S-1 arm: 147 patients) was performed after recurrence in 98.3% of UFT arm patients and 93.9% of S-1 arm patients.

The 5-year cumulative local recurrence rate was 13.0% (95% CI 10.0% to 16.7%) in the UFT arm and 9.8% (95% CI 7.2% to 13.1%) in the S-1 arm (HR: 0.72, 95% CI 0.48–1.09), and the 5-year cumulative rate of distant recurrence was 26.9% (95% CI 23.0% to 31.3%) in the UFT arm and 24.7% (95% CI 21.0% to 29.0%) in the S-1 arm (HR: 0.86, 95% CI 0.67–1.11) (Figure 2C). In the subgroup analysis of RFS (Figure 3) and OS, a significant interaction was observed between allocated regimen and age (<70 versus ≥70 years).

**discussion**

A 4.7% increase in the 5-year RFS rate with S-1 treatment was observed in this study, which demonstrates the superiority of S-1 treatment over UFT treatment in terms of RFS as adjuvant chemotherapy for curatively resected stage II/III rectal cancer patients with no preoperative treatment. The reason that no difference in OS of both arms was found is probably that the unexpectedly favorable survival rate achieved through post-trial treatment of patients after recurrence in both arms caused the follow-up period of 5.5 years to be too short and the study to be underpowered.

Though the standard treatment in the West is to perform preoperative radiation (or chemoradiation) therapy, past trials have shown that radiation reduces the rate of local recurrence but does not improve prognosis [10], which is why CRT is not always performed all over the world. The standard treatment in Japan has traditionally been surgery plus adjuvant chemotherapy, and the 5-year survival rate in this study (≥80% in both...
arms) appears comparable with the results of past studies of CRT in the West. It is surprising that such favorable outcomes were achieved just with surgery plus adjuvant chemotherapy.

The results of the subgroup analysis of RFS showed a significant interaction between regimen and age (<70 versus ≥70 years) and marginally significant interactions of regimen with sex (male/female) and with T factor (T1, 2/T3, 4). The higher incidence of adverse events of ≥ grade 3 observed in elderly patients aged ≥70 years may be attributable to increased 5-FU blood levels caused by reduced excretion of gimeracil, a renally excreted ingredient of S-1, due to the decreased renal function of these patients. In addition, patients with advanced T-stage disease are thought to have more micrometastases, which means that intensive adjuvant therapy is more valuable for advanced-stage disease in the case of rectal cancer as well as colon cancer [11]. Thus, S-1 might have been more effective in these patients due to its greater antitumor activity. We cannot identify the reason for the interactions with sex.

Although adjuvant 5-FU-based chemotherapy with or without oxaliplatin following preoperative CRT is recommended in the National Comprehensive Cancer Network guidelines for adjuvant chemotherapy, its benefits remain controversial [12]. The main phase III studies of adjuvant chemotherapy have discontinued enrollment due to poor accrual [13], and no large clinical trials have produced results. One reason why postoperative adjuvant chemotherapy has not been proven effective is poor compliance. In the EORTC 22 921 study, 27% of the eligible patients never started adjuvant chemotherapy [14], and the treatment completion rate was only 43% for patients who received adjuvant chemotherapy. As a result, the 5-year local recurrence rates for the CRT arm and the CRT plus adjuvant chemotherapy arm were 10.9% and 10.7%, respectively, and the 5-year distant recurrence rates were 32.1% and 29.8%, respectively [15], indicating that adjuvant chemotherapy did not contribute to the prevention of recurrence. Preoperative CRT may have decreased compliance with adjuvant chemotherapy, thereby causing adjuvant chemotherapy to not produce the results that would otherwise be expected.

In the S-1 arm of this study, adjuvant chemotherapy was started in 470 patients after excluding 9 patients who discontinued before treatment. The completion rate at 6 months after treatment initiation was 76.2% and the completion rate for 1-year administration was 61.3%, indicating that compliance was favorable. S-1 was more effective in preventing both distant recurrence and local recurrence than UFT. The 5-year
The cumulative local recurrence rate for the S-1 arm was 9.8%, which is not inferior to results from Western studies that include preoperative therapies [15, 16]. In addition, the 5-year cumulative rate of distant recurrence for the S-1 arm was 24.7%, which seems to be superior to 5-year cumulative distant recurrence rates from Western studies [15, 17]. Rectal cancer patients will greatly benefit from being able to undergo surgery without preoperative therapy and taking only oral drugs for adjuvant chemotherapy.

This study was the first randomized phase III trial to compare adjuvant chemotherapy regimens using two 5-FU derivatives in patients with locally advanced rectal cancer and without preoperative CRT, and it demonstrated the superiority of S-1 treatment over UFT treatment in terms of RFS. Future studies must evaluate whether 1-year adjuvant chemotherapy with S-1 can also prevent distant metastases following preoperative CRT.

**Table 1. Baseline patient characteristics (all enrolled patients)**

|                                | UFT (N = 480) | S-1 (N = 479) |
|--------------------------------|---------------|---------------|
| **n (%)**                      |               |               |
| **Age**                        |               |               |
| Median [range]                 | 62 [32–80]    | 63 [27–80]    |
| **Sex**                        |               |               |
| Male                           | 321 (67)      | 322 (67)      |
| Female                         | 159 (33)      | 157 (33)      |
| **Tumor location**             |               |               |
| Upper                          | 252 (53)      | 248 (52)      |
| Lower                          | 221 (46)      | 224 (47)      |
| P                              | 7 (1)         | 7 (1)         |
| **Differentiation assessed by histology** |           |               |
| Well/moderately                | 448 (93)      | 453 (95)      |
| Poorly                         | 32 (7)        | 26 (5)        |
| **Depth of tumor invasion**    |               |               |
| T1                             | 19 (4)        | 13 (3)        |
| T2                             | 43 (9)        | 46 (10)       |
| T3                             | 370 (77)      | 362 (75)      |
| T4                             | 48 (10)       | 58 (12)       |
| **No. of LN examined**         |               |               |
| <12                            | 145 (30)      | 147 (31)      |
| ≥12                            | 335 (70)      | 332 (69)      |
| Median [range]                 | 16 [2–98]     | 16 [1–99]     |
| **LN metastasis**              |               |               |
| N0                             | 164 (34)      | 166 (35)      |
| N1                             | 232 (48)      | 219 (46)      |
| N2                             | 84 (18)       | 94 (19)       |
| **Lateral LN dissection**      |               |               |
| No                             | 335 (70)      | 351 (73)      |
| Yes                            | 145 (30)      | 128 (27)      |
| **Stage**                      |               |               |
| I                              | 2 (0)         | 1 (0)         |
| IIA                            | 144 (30)      | 145 (30)      |
| IIB                            | 18 (4)        | 20 (4)        |
| IIIA                           | 55 (11)       | 47 (10)       |
| IIIB                           | 177 (37)      | 172 (36)      |
| IIIC                           | 84 (18)       | 94 (20)       |
| **Operative procedure**        |               |               |
| AR                             | 348 (72)      | 347 (72)      |
| Hartmann                       | 8 (2)         | 3 (1)         |
| APR                            | 115 (24)      | 119 (25)      |
| Other                          | 9 (2)         | 10 (2)        |
| **Scope of LN dissection**     |               |               |
| D1                             | 4 (1)         | 4 (1)         |
| D2                             | 198 (41)      | 191 (40)      |
| D3                             | 278 (58)      | 284 (59)      |

*aUpper rectum (above the peritoneal reflection); lower rectum (below the peritoneal reflection); P, proctos (anal canal). bUICC-TNM 6th Edition.
LN, lymph node; AR, anterior resection; APR, abdominoperineal resection.

which seems to be superior to 5-year cumulative distant recurrence rates from Western studies [15, 17]. Rectal cancer patients will greatly benefit from being able to undergo surgery without preoperative therapy and taking only oral drugs for adjuvant chemotherapy.

This study was the first randomized phase III trial to compare adjuvant chemotherapy regimens using two 5-FU derivatives in patients with locally advanced rectal cancer and without preoperative CRT, and it demonstrated the superiority of S-1 treatment over UFT treatment in terms of RFS. Future studies must evaluate whether 1-year adjuvant chemotherapy with S-1 can also prevent distant metastases following preoperative CRT. Use
of such relatively mild adjuvant chemotherapy with a single oral anticancer agent to prevent distant recurrence may improve compliance with adjuvant chemotherapy after preoperative CRT.

One potential limitation of our study is that we do not know whether our results can be directly extrapolated to patients of different ethnic origin because the pharmacokinetics and pharmacodynamics of S-1 might vary [6, 18]. For instance, S-1 could potentially cause a high incidence of gastrointestinal toxicities in Caucasian patients if administered at the dose used in this study.

In conclusion, 1-year S-1 treatment has become a standard adjuvant chemotherapy regimen for stage II/III rectal cancer following curative resection. S-1 can be considered an important option, especially for patients who have not received preoperative CRT.

Table 2. Adverse events (all treated patients)

| Characteristics | UFT (N = 479) | S-1 (N = 470) |
|-----------------|--------------|--------------|
|                 | Any (n, %)   | ≥G3 (n, %)   | Any (n, %)   | ≥G3 (n, %)   |
| Any AE          | 354 (73.9)   | 56 (11.7)    | 387 (82.3)   | 63 (13.4)    |
| Laboratory data |              |              |              |
| Leukopenia      | 94 (19.6)    | 3 (0.6)      | 114 (24.3)   | 3 (0.6)      |
| Hemoglobin      | 140 (29.2)   | 6 (1.3)      | 178 (37.9)   | 6 (1.3)      |
| Thrombocytopenia| 88 (18.4)    | 0 (0.0)      | 110 (23.4)   | 4 (0.9)      |
| AST             | 106 (22.1)   | 7 (1.5)      | 105 (22.3)   | 4 (0.9)      |
| ALT             | 118 (24.6)   | 11 (2.3)     | 93 (19.8)    | 4 (0.9)      |
| Bilirubin       | 178 (37.2)   | 5 (1.0)      | 174 (37.0)   | 6 (1.3)      |
| Creatinine      | 17 (3.5)     | 0 (0.0)      | 20 (4.3)     | 0 (0.0)      |
| Symptom         |              |              |              |
| Anorexia        | 90 (18.8)    | 5 (1.0)      | 130 (27.7)   | 12 (2.6)     |
| Diarrhea        | 69 (14.4)    | 11 (2.3)     | 87 (18.5)    | 12 (2.6)     |
| Mucositis/stomatitis | 33 (6.9) | 1 (0.2) | 46 (9.8) | 1 (0.2) |
| Nausea          | 58 (12.1)    | 2 (0.4)      | 82 (17.4)    | 6 (1.3)      |
| Vomiting        | 13 (2.7)     | 1 (0.2)      | 20 (4.3)     | 2 (0.4)      |
| Hyperpigmentation| 48 (10.0) | 0 (0.0) | 134 (28.5) | 0 (0.0) |
| Rash/desquamation| 45 (9.4) | 1 (0.2) | 73 (15.5) | 4 (0.9) |
| Fatigue         | 73 (15.2)    | 3 (0.6)      | 92 (19.6)    | 10 (2.1)     |

Figure 3. Subgroup analysis of relapse-free survival (all enrolled patients). *HR, hazard ratio of S-1 to UFT; upper rectum (above the peritoneal reflection); lower rectum (below the peritoneal reflection); P, proctos (anal canal); LN, lymph node.
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disclosure

EO has received honoraria for lecturing from Taiho Pharmaceutical Co., Ltd, Yakult Honsha Co., Ltd, Merck Serono, Takeda Pharmaceutical Co., Ltd, and Chugai Pharmaceutical Co., Ltd. KY has honoraria from Taiho Pharmaceutical Co., Ltd and La Roche Ltd. YK has honoraria from Taiho Pharmaceutical Co., Ltd, Pfizer Inc., Chugai Pharmaceutical Co., Ltd, Kyowa Hakko Kirin Co., Ltd, and Yakult Honsha Co., Ltd. KY also has a consultant or advisory relationship with Taiho Pharmaceutical Co., Ltd and La Roche Ltd. YK has honoraria from Taiho Pharmaceutical Co., Ltd, Chugai Pharmaceutical Co., Ltd, and Yakult Honsha Co., Ltd. KY also has a consultant or advisory relationship with Taiho Pharmaceutical Co., Ltd and gastroenterology. HB reports grants from Taiho Pharmaceutical Co., Ltd during the conduct of the study and grants from Taiho Pharmaceutical Co., Ltd, Eli Lilly Japan K.K., Pfizer Japan, Inc., Merck Serono Co., Ltd, Coviden Japan, Taisho Toyama Pharmaceutical Co., Ltd, and Eli Lilly Japan K.K. outside the submitted work. HC reports personal fees from Taiho Pharmaceutical Co., Ltd outside the submitted work. YM reports grants from Taiho Pharmaceutical Co., Ltd during the conduct of the study and grants from Taiho Pharmaceutical Co., Ltd. HC reports personal fees from Taiho Pharmaceutical Co., Ltd, Eli Lilly Japan K.K., and Pfizer Japan, Inc., Merck Serono Co., Ltd, Coviden Japan, Taisho Toyama Pharmaceutical Co., Ltd, and Eli Lilly Japan K.K. outside the submitted work. YK has honoraria from Taiho Pharmaceutical Co., Ltd, and Yakult Honsha Co., Ltd, and Yakult Honsha Co., Ltd. HB reports grants from Taiho Pharmaceutical Co., Ltd during the conduct of the study and grants from Taiho Pharmaceutical Co., Ltd, Eli Lilly Japan K.K., Pfizer Japan, Inc., Merck Serono Co., Ltd, Chugai Pharmaceutical Co., Ltd, Kyowa Hakko Kirin Co., Ltd, Sanofi Co., Ltd, Shionogi & Co., Ltd, Johnson & Johnson K.K., Takeda Pharmaceutical Co., Ltd, Chugai Pharmaceutical Co., Ltd, Sanoitomo Dainippon Pharma Co., Ltd, Chugai Pharmaceutical Co., Ltd, Torii Pharmaceutical Co., Ltd, Eli Lilly Japan K.K., Pfizer Japan, Inc., Merck Serono Co., Ltd, Coviden Japan, Taisho Toyama Pharmaceutical Co., Ltd, and Eli Lilly Japan K.K, outside the submitted work. 

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