

Five-Year Outcomes of a Randomized Phase III Trial Comparing Adjuvant Chemotherapy With S-1 Versus Surgery Alone in Stage II or III Gastric Cancer

Mitsuru Sasako, Shinichi Sakuramoto, Hitoshi Katai, Taira Kinoshita, Hiroshi Furukawa, Toshiharu Yamaguchi, Atsushi Nashimoto, Masashi Fujii, Toshifusa Nakajima, and Yasuo Ohashi

See accompanying editorial on page 4348; listen to the podcast by Dr Mayer at www.jco.org/podcast

Mitsuru Sasako, Hyogo College of Medicine, Nishinomiya; Shinichi Sakuramoto, Kitasato University School of Medicine, Sagami-hara; Hitoshi Katai, National Cancer Center Hospital; Toshiharu Yamaguchi and Toshifusa Nakajima, Cancer Institute Hospital, Japanese Foundation for Cancer Research; Masashi Fujii, Nihon University School of Medicine; Yasuo Ohashi, School of Public Health, The University of Tokyo, Tokyo; Taira Kinoshita, National Cancer Center Hospital East, Kashiwa; Hiroshi Furukawa, Sakai Municipal Hospital, Sakai; and Atsushi Nashimoto, Niigata Cancer Center Hospital, Niigata, Japan.

Submitted April 19, 2011; accepted June 30, 2011; published online ahead of print at www.jco.org on October 17, 2011.

Written on behalf of the Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer group.

Supported by Taiho Pharmaceutical, Tokyo, Japan.

Presented in part at the 35th European Society for Medical Oncology Congress, Milan, Italy, October 8-12, 2010.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

Corresponding author: Mitsuru Sasako, MD, PhD, Department of Surgery, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Hyogo, 663-8501, Japan; e-mail: msasako@hyo-med.ac.jp.

© 2011 by American Society of Clinical Oncology

0732-183X/11/2933-4387/\$20.00

DOI: 10.1200/JCO.2011.36.5908

ABSTRACT

Purpose

The first planned interim analysis (median follow-up, 3 years) of the Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer confirmed that the oral fluoropyrimidine derivative S-1 significantly improved overall survival, the primary end point. The results were therefore opened at the recommendation of an independent data and safety monitoring committee. We report 5-year follow-up data on patients enrolled onto the ACTS-GC study.

Patients and Methods

Patients with histologically confirmed stage II or III gastric cancer who underwent gastrectomy with D2 lymphadenectomy were randomly assigned to receive S-1 after surgery or surgery only. S-1 (80 to 120 mg per day) was given for 4 weeks, followed by 2 weeks of rest. This 6-week cycle was repeated for 1 year. The primary end point was overall survival, and the secondary end points were relapse-free survival and safety.

Results

The overall survival rate at 5 years was 71.7% in the S-1 group and 61.1% in the surgery-only group (hazard ratio [HR], 0.669; 95% CI, 0.540 to 0.828). The relapse-free survival rate at 5 years was 65.4% in the S-1 group and 53.1% in the surgery-only group (HR, 0.653; 95% CI, 0.537 to 0.793). Subgroup analyses according to principal demographic factors such as sex, age, disease stage, and histologic type showed no interaction between treatment and any characteristic.

Conclusion

On the basis of 5-year follow-up data, postoperative adjuvant therapy with S-1 was confirmed to improve overall survival and relapse-free survival in patients with stage II or III gastric cancer who had undergone D2 gastrectomy.

J Clin Oncol 29:4387-4393. © 2011 by American Society of Clinical Oncology

INTRODUCTION

In 2008, there were 737,000 deaths from gastric cancer worldwide. Gastric cancer is the second leading cause of cancer-related death, with the highest mortality rates in East Asia, including Japan, Korea, and China (28.1 per 100,000 in males; 13.0 per 100,000 in females).¹ Approximately 60% of gastric cancers in the world are diagnosed in this area. The mainstay of treatment for gastric cancer is surgery. However, in stages II (excluding T1 disease) and III (moderately advanced), an appreciable proportion of patients have recurrence, even after curative resection. Consequently, various regimens for adjuvant chem-

otherapy have been implemented to prevent postoperative recurrence.

Although the results of many randomized, controlled studies conducted to verify the effectiveness of postoperative adjuvant chemotherapy for gastric cancer were negative on an individual study basis, meta-analyses of these results have suggested that postoperative adjuvant chemotherapy is therapeutically useful in patients with gastric cancer.²⁻⁷ However, no regimens have been clearly recommended for adjuvant chemotherapy after gastrectomy with D2 lymphadenectomy (D2 gastrectomy), established as the standard procedure for advanced gastric cancer in East Asia.

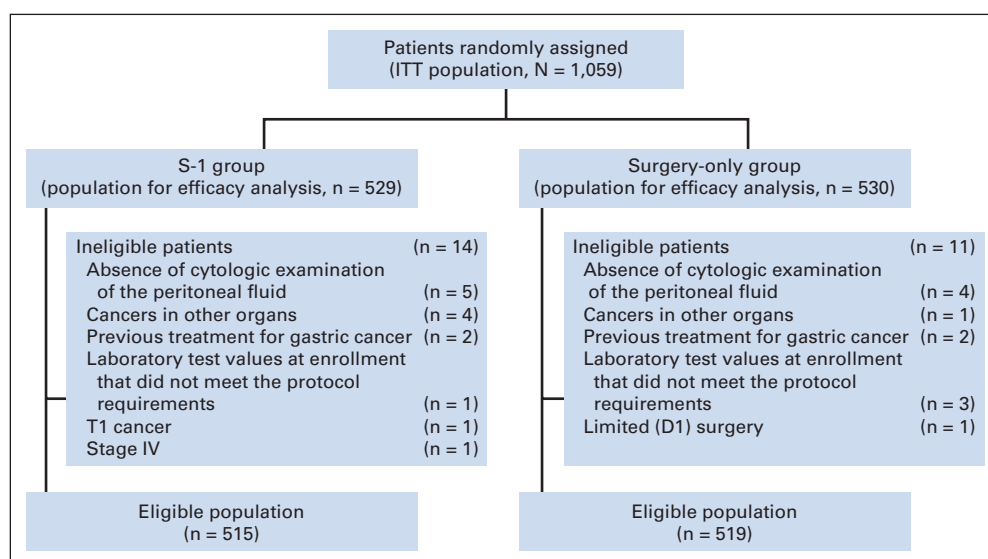


Fig 1. CONSORT diagram. D1 gastrectomy; ITT, intent-to-treat.

The Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC) is a randomized phase III trial to confirm the effectiveness of 1-year postoperative treatment with S-1 compared with surgery alone in patients with stage II or III gastric cancer who underwent D2 gastrectomy. S-1 (TS-1; Taiho Pharmaceutical, Tokyo, Japan) is a dihydropyrimidine dehydrogenase inhibitory fluoropyrimidine preparation combining tegafur, gimeracil, and oteracil potassium in a molar ratio of 1:0.4:1.^{8,9} Two phase II studies^{10,11} in patients with advanced or recurrent gastric cancer obtained high response rates exceeding 40%. Postoperative adjuvant chemotherapy with S-1 was thus expected to be effective.

In this phase III trial, 1,059 patients with histologically confirmed stage II or III gastric cancer who underwent D2 gastrectomy were enrolled. A protocol-based interim analysis performed 1 year after the

completion of enrollment (median follow-up, 3 years) confirmed that S-1 was effective. Because statistical analysis indicated that there was minimal probability that the results of this study would turn out to be negative after 5 years of follow-up, an independent data and safety monitoring committee recommended that the results should be disclosed at that time. An analysis of the results available at that time showed that the 3-year overall survival (OS) was 80.1% in the S-1 group compared with 70.1% in the surgery-only group. S-1 was demonstrated to reduce the risk of death by 32% (hazard ratio [HR], 0.68; 95% CI, 0.52 to 0.87; $P = .003$).¹² Although the study results were disclosed early because of these promising results, we considered it important to have 5-year follow-up data available. Such data would facilitate a comparison of our results for 5-year OS and other outcomes with those of previous trials. Moreover, this analysis may justify

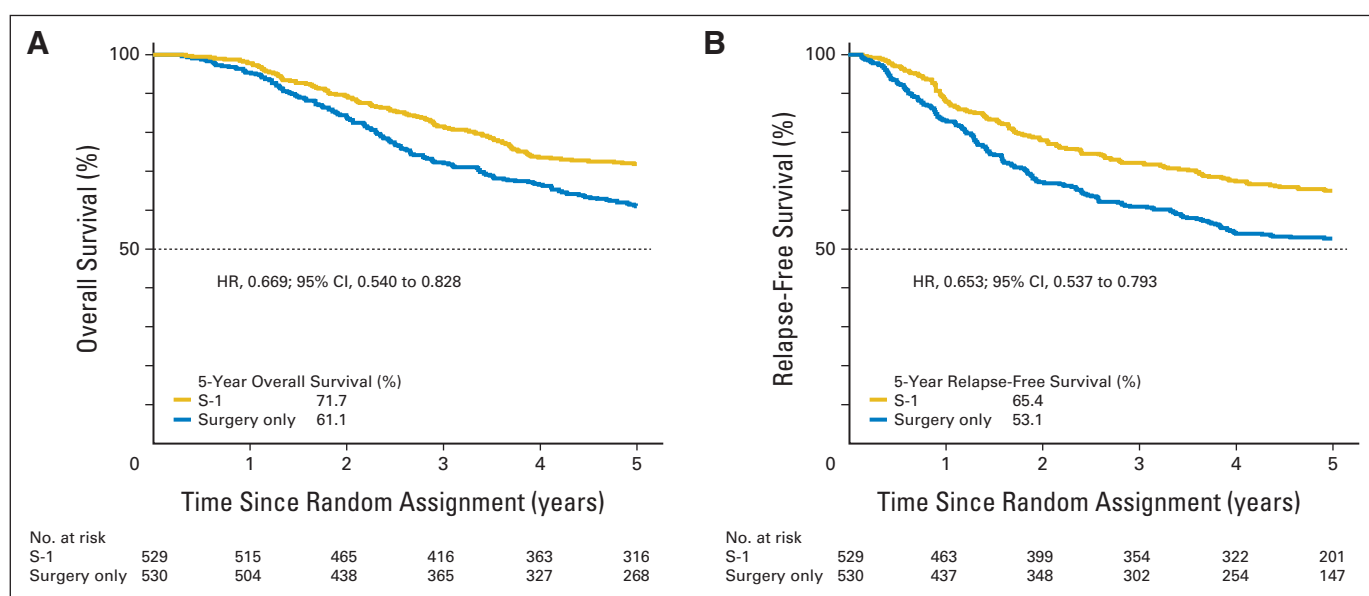


Fig 2. Kaplan-Meier estimates of (A) overall survival and (B) relapse-free survival for all randomly assigned patients. HR, hazard ratio.

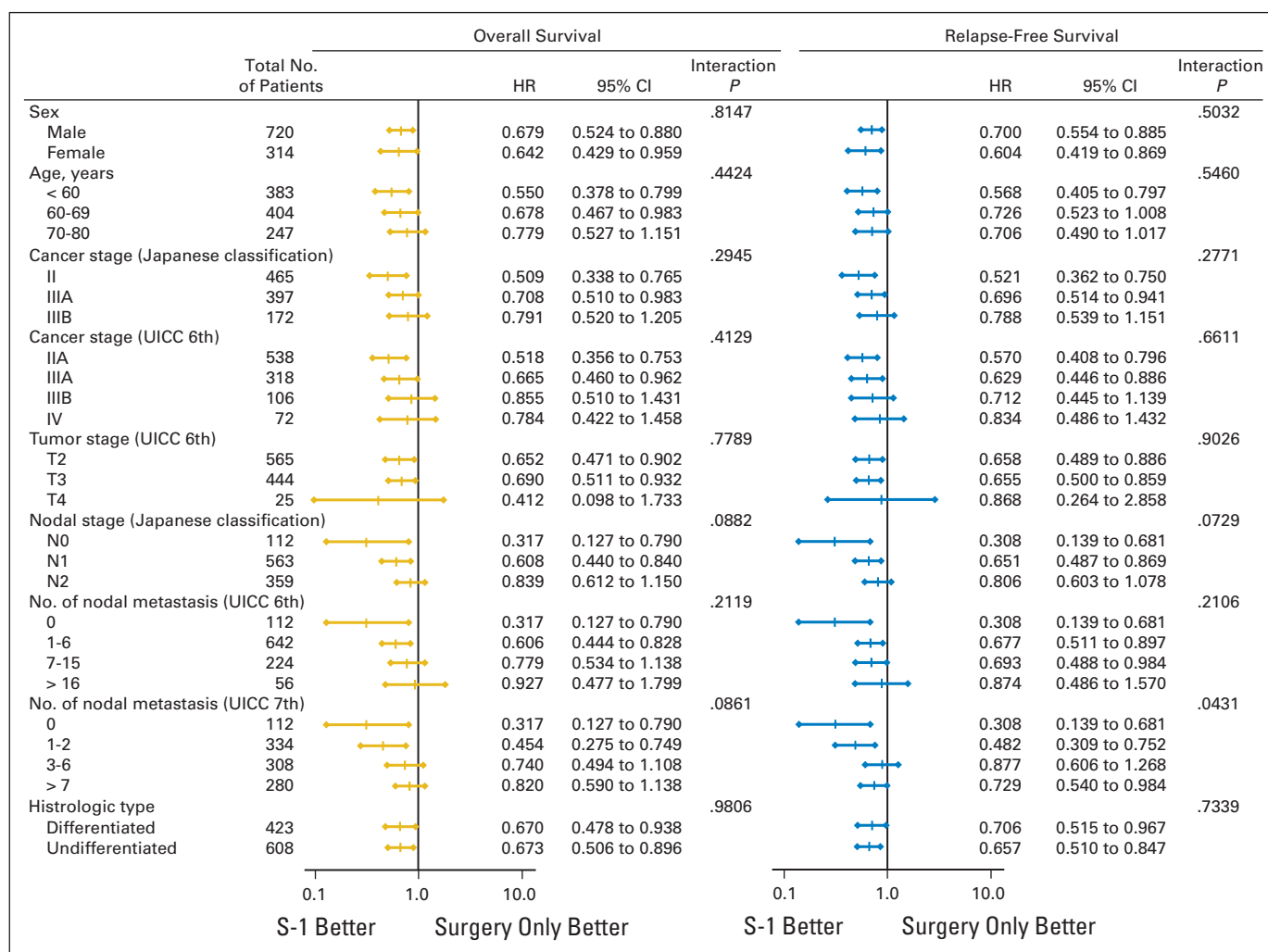


Fig 3. Subgroup analysis: overall survival and relapse-free survival for eligible population. In the surgery-only group, cancers in three patients could not be classified as differentiated or undifferentiated. HR, hazard ratio; UICC, International Union Against Cancer (UICC) TNM Classification of Malignant Tumours.

the present controversial use of 3-year relapse-free survival (RFS) as the primary end point in clinical trials of adjuvant chemotherapy for potentially curable gastric cancer.

PATIENTS AND METHODS

The trial was conducted in accordance with the World Medical Association Declaration of Helsinki and Japanese Good Clinical Practice guidelines. This protocol was approved by the institutional review board of each participating hospital (see Data Supplement). Written informed consent was obtained from all patients. Tumor stage classification and D classification were in accordance with the Japanese Classification of Gastric Carcinoma (Second English Edition).¹³

Patients and Treatment

Eligibility criteria were as follows: a histopathologically confirmed diagnosis of stage II (except for T1 disease), IIIA, or IIIB gastric cancer; R0 resection (with no tumor cells at the margin) with D2 or more extensive lymph node dissection; no evidence of hepatic, peritoneal, or distant metastasis; no tumor cells in peritoneal fluid on cytologic analysis; age 20 to 80 years; no previous treatment for cancer except for the initial gastric resection for the primary lesion; and adequate organ function. Patients were enrolled within 6 weeks

after surgery over the telephone or by means of facsimile. Patients were randomly assigned to either the S-1 group or the surgery-only group. The assignments were made by the minimization method according to disease stage (II, IIIA, or IIIB) at the ACTS-GC data center.

Patients assigned to the S-1 group received S-1 in a daily dose of 80, 100, or 120 mg in two divided doses. The dose of S-1 was assigned on the basis of body surface area. S-1 was given for 4 weeks, followed by 2 weeks of rest. Treatment was continued for 1 year after surgery. Patients assigned to the surgery-only group received no anticancer treatment postoperatively until the confirmation of recurrence. The criteria for dose reduction and toxicity were described previously.¹²

Follow-Up

In the S-1 group, the results of blood tests and clinical findings were assessed at 2-week intervals during treatment with S-1. In the surgery-only group, patients came to the hospital for re-examination at least once every 3 months for the first year after surgery. From the second year onward, all patients were followed up in the same manner. Relapse was confirmed by imaging studies, including ultrasonography, computed tomography, and GI radiography, as well as endoscopy. Patients underwent at least one imaging study at 6-month intervals for the first 2 years after surgery and at 1-year intervals until 5 years after surgery. Individual patients were followed up for 5 years from the date of random assignment.

Statistical Analysis

The sample size was calculated as follows. Given that the 5-year survival rate would be 70% in the surgery-only group, with an HR of 0.70, $\alpha = .05$ (two-sided), and a statistical power of 80%, we estimated that 1,000 patients would be required. OS and RFS were estimated on the basis of all randomly assigned patients. The results in eligible patients were analyzed according to disease stage. OS was defined as the interval from the date of random assignment to the date of death from any cause. RFS was defined as the interval from the date of random assignment to the date of confirming recurrence or death from any cause, whichever came first. Data for up to 5 years from the date of random assignment were analyzed. Data obtained after 5 years were not included in this analysis. The survival rate was estimated by using the Kaplan-Meier method. The Cox proportional hazards model was used to calculate HRs. All statistical analyses were done with SAS, version 9.1 (SAS Institute, Cary, NC).

RESULTS

Patients

From October 2001 through December 2004, a total of 1,059 patients were enrolled at 109 centers throughout Japan; 529 were assigned to the S-1 group and 530 to the surgery-only group (intention-to-treat population; Fig 1). In both groups combined, 474 patients (44.8%) had stage II disease, 409 (38.6%) had stage IIIA disease, and 175 (16.5%) had stage IIIB disease. The numbers of patients with each stage of disease were similar in the two treatment groups. The groups were also well balanced with respect to the type of gastrectomy performed, the combined resection of other organs, and other factors. Details of the patient demographics and baseline characteristics have been reported previously.¹²

Fourteen patients in the S-1 group and 11 in the surgery-only group were ineligible, as shown in Figure 1. In the S-1 group, 12 patients did not receive S-1. In the surgery-only group, four patients received adjuvant treatment at their strong request, violating the protocol.

Safety

Details of the safety analysis have been reported previously.¹² In brief, except for anorexia (incidence, 6%), grade 3 or 4 adverse events occurred in less than 5% of the patients in the S-1 group.

OS and RFS in All Randomly Assigned Patients

Among 1,059 patients, 145 and 199 died, 32 and 42 patients are alive with recurrence, and 352 and 289 patients are alive without recurrence in the S-1 and the surgery-only groups, respectively. Data on 131 patients lost to follow-up within 5 years from the date of random assignment were censored.

OS and RFS were analyzed in all 1,059 randomly assigned patients. The 5-year OS rate was 71.7% (95% CI, 67.8% to 75.7%) in the S-1 group and 61.1% (95% CI, 56.8% to 65.3%) in the surgery-only group. The HR for death in the S-1 group compared with the surgery-only group was 0.669 (95% CI, 0.540 to 0.828), indicating that S-1 reduced the risk of death by 33.1% (Fig 2A). The 5-year RFS rate was 65.4% (95% CI, 61.2% to 69.5%) in the S-1 group and 53.1% (95% CI, 48.7% to 57.4%) in the surgery-only group. The HR for relapse in the S-1 group compared with that in the surgery-only group was 0.653 (95% CI, 0.537 to 0.793). Treatment with S-1 thus reduced the risk of relapse by 34.7% (Fig 2B).

Subgroup Analysis

OS and RFS in eligible patients were analyzed according to sex, age, disease stage (Japanese Classification, 13th edition), and histologic type. There was no interaction between treatment and any of these factors (Fig 3). Kaplan-Meier estimates of OS and RFS are shown according to disease stage, which was used as a stratification factor when patients were randomly assigned (Figs 4, 5, and 6).

The 5-year OS rates of the patients with stage II disease were 84.2% (95% CI, 79.5% to 89.0%) in the S-1 group and 71.3% (95% CI, 65.3% to 77.2%) in the surgery-only group, with an HR of 0.509 (95% CI, 0.338 to 0.765; Fig 4A). Their 5-year RFS rates were 79.2% (95% CI, 73.8% to 84.6%) in the S-1 group and 64.4% (95% CI, 58.1% to 70.7%) in the surgery-only group, with an HR of 0.521 (95% CI, 0.362 to 0.750; Fig 4B). The 5-year OS rates of stage IIIA patients were 67.1% (95% CI, 60.4% to 73.8%) in the S-1 group and 57.3% (95% CI, 50.3% to 64.2%) in the surgery-alone group, with an HR of 0.708 (95% CI, 0.510 to 0.983; Fig 5A). Their 5-year RFS rates were 61.4% (95% CI, 54.5% to 68.4%) in the S-1 group and 50.0% (95% CI, 42.9% to 57.0%) in the surgery-alone group, with an HR of 0.696 (95% CI,

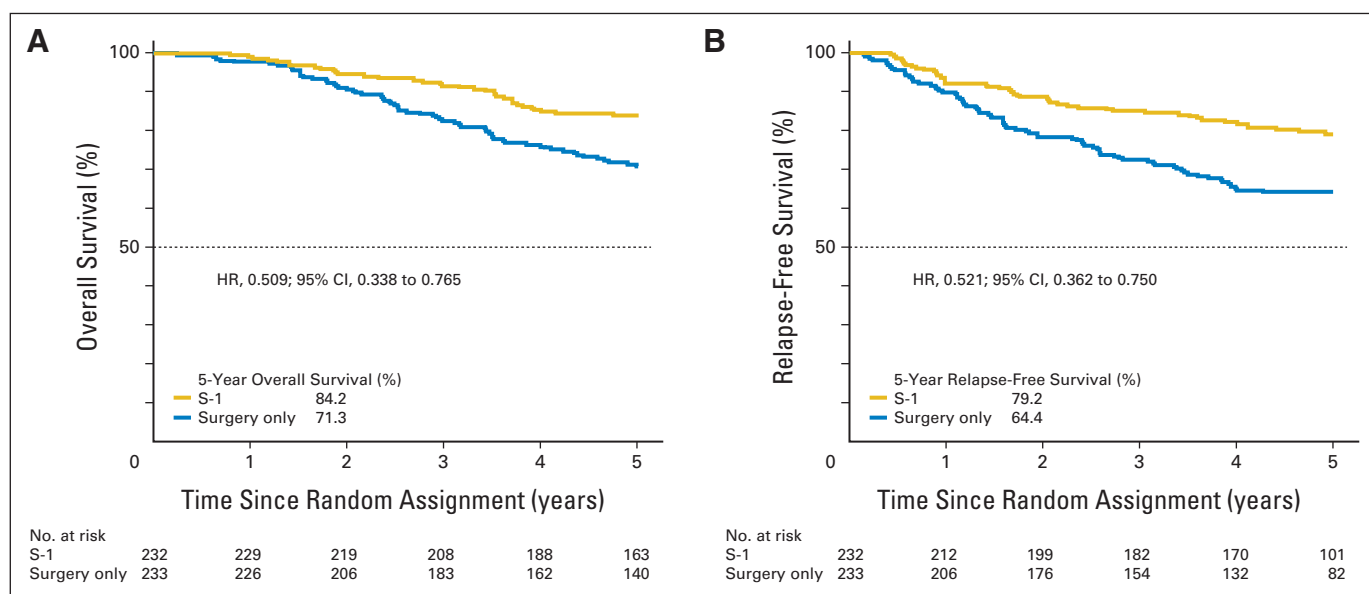


Fig 4. Kaplan-Meier estimates of (A) overall survival and (B) relapse-free survival for eligible patients with stage II gastric cancer. HR, hazard ratio.

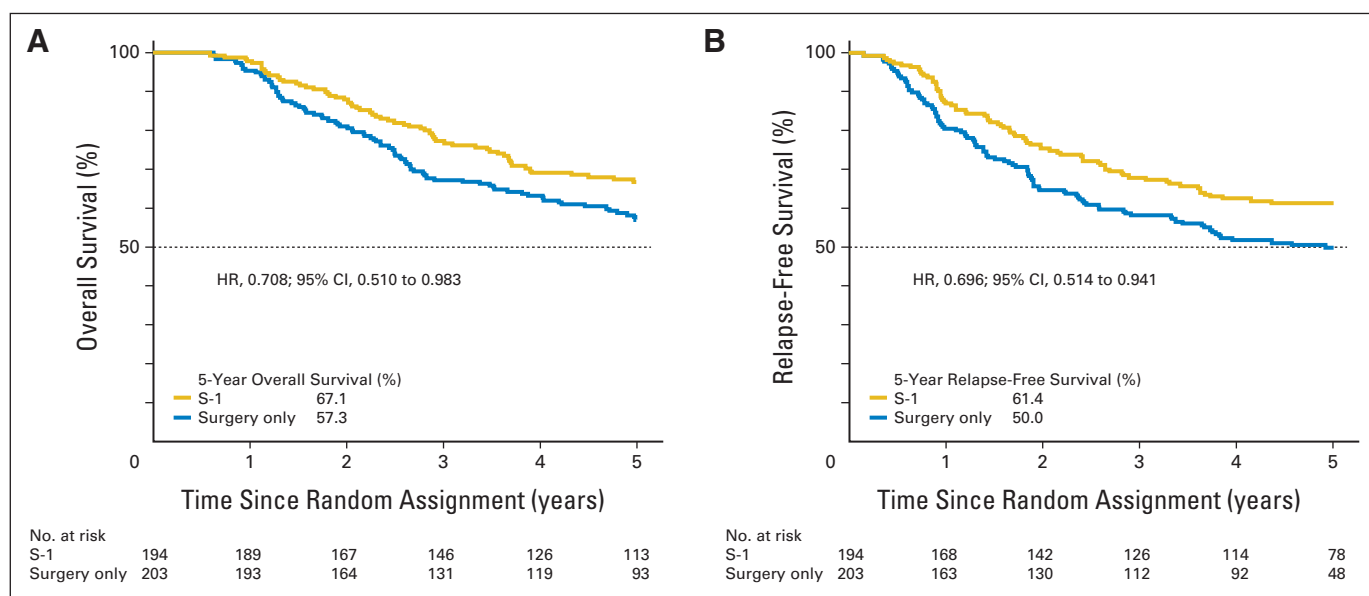


Fig 5. Kaplan-Meier estimates of (A) overall survival and (B) relapse-free survival for eligible patients with stage IIIA gastric cancer. HR, hazard ratio.

0.514 to 0.941; Fig 5B). As for stage IIIB disease, we enrolled 90 patients in the S-1 group and 85 in the surgery-only group; the 5-year OS rates were 50.2% (95% CI, 39.5% to 61.0%) in the S-1 group and 44.1% (95% CI, 33.1% to 55.0%) in the surgery-alone group, with an HR of 0.791 (95% CI, 0.520 to 1.205; Fig 6A). Their 5-year RFS rates were 37.6% (95% CI, 27.0% to 48.2%) in the S-1 group and 34.4% (95% CI, 24.1% to 44.7%) in the surgery-alone group, with an HR of 0.788 (95% CI, 0.539 to 1.151; Fig 6B).

Site of First Relapse

Common sites of first relapse were the peritoneum, hematogenous sites, and lymph nodes (Table 1). Rates of metastasis and relapse were consistently lower in the S-1 group than in the

surgery-only group for all sites. In particular, the rates of recurrence in lymph nodes and of peritoneal relapse were markedly lower in the S-1 group.

DISCUSSION

To the best of our knowledge, the ACTS-GC study is the first large clinical trial of adjuvant chemotherapy enrolling more than 1,000 patients who underwent D2 gastrectomy for gastric cancer. The results of this follow-up study showed that 1-year treatment with S-1 improved OS and RFS at 5 years compared with surgery alone, thus reconfirming the conclusions reached on early publication of the study results after a median follow-up of 3 years.

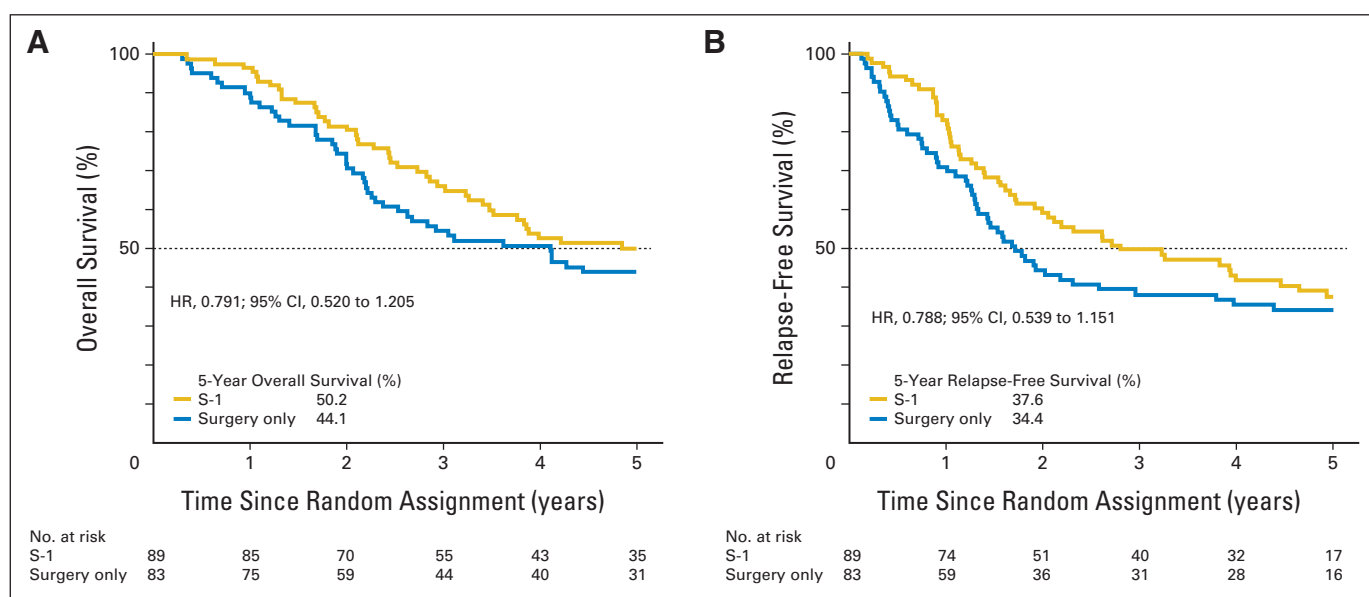


Fig 6. Kaplan-Meier estimates of (A) overall survival and (B) relapse-free survival for eligible patients with stage IIIB gastric cancer. HR, hazard ratio.

Table 1. Site of First Relapse (all randomly assigned patients)*

Site	S-1 (n = 529)		Surgery Only (n = 530)		HR	95%CI
	No.	%	No.	%		
Total No. of relapses	162	30.6	221	41.7	—	—
Local	11	2.1	17	3.2	0.572	0.268 to 1.221
Lymph nodes	30	5.7	54	10.2	0.505	0.323 to 0.789
Peritoneum	77	14.6	100	18.9	0.687	0.511 to 0.925
Hematogenous	61	11.5	71	13.4	0.784	0.557 to 1.105

Abbreviation: HR, hazard ratio.

*Some patients had a first relapse at more than one site.

Our present results confirmed that postoperative adjuvant chemotherapy with S-1 alone reduced the risk of death by 33.1%, thereby demonstrating that effectiveness was maintained since the previous analysis. This reduction in the risk of mortality is comparable with that obtained with combined regimens for adjuvant chemotherapy in the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial¹⁴ and the Intergroup 0116 (INT-0116) trial.¹⁵

Whether the results of this study can be extrapolated to countries outside East Asia remains uncertain because of possible differences in pharmacokinetics of S-1 between whites and East Asians. If S-1 is used as adjuvant chemotherapy in whites, the dose should be carefully adjusted. A second reason is that all patients in this study underwent D2 gastrectomy although more limited surgery (D0/1) is commonly performed in the United States and some parts of Europe. In the surgery-only group, OS at 5 years was 61.1%, which was much better than that of patients undergoing D2 gastrectomy in Europe (33%) in a Dutch trial.¹⁶ One of the reasons for this large difference may be the high level and widespread use of diagnostic technology in Japan, potentially leading to stage migration between Japan and Western countries.¹⁷ Another important reason might be the high quality of D2 gastrectomy in Japan, whereas D0 or D1 gastrectomy remains the standard procedure in the United States and was the standard in Europe until recently. Although a Dutch trial comparing D1 with D2 gastrectomy reported negative results,^{16,18} a 15-year follow-up study showed that the rate of mortality from gastric cancer was significantly lower in the D2 gastrectomy group.¹⁹ Thus, the most recent European Society for Medical Oncology (ESMO) clinical practice guidelines recommend D2 gastrectomy as the standard procedure for curable advanced gastric cancer.²⁰

The primary end point of this study was 5-year OS, although that of an ongoing adjuvant chemotherapy study in Korea and China is 3-year disease-free survival. The latter is designed to evaluate the efficacy of postoperative adjuvant chemotherapy with capecitabine and oxaliplatin compared with surgery alone. To justify the use of RFS or disease-free survival as the primary end point for adjuvant chemotherapy after curative resection of gastric cancer, more evidence is needed, but the results of this study may strongly suggest that RFS can be used as the primary end point of such studies. (In this follow-up analysis, the 3-year RFS rates were 72.4% and 61.1%, and the 5-year OS rates were 71.7% and 61.1% in the S-1 group and surgery-only group, respectively.)

To compare our results with those of other foreign studies, we also report the stage-specific 3- and 5-year OS and RFS according to the International Union Against Cancer (UICC) TNM Classification of Malignant Tumours, Sixth Edition. Three-year OS rates according to UICC

staging in the S-1 and surgery-only groups were 91.1% and 80.9% (stage II), 77.8% and 68.3% (stage IIIA), 66.6% and 56.8% (stage IIIB), and 59.1% and 45.7% (stage IV). Three-year RFS rates were 84.3% and 73.5% (stage II), 69.1% and 56.7% (stage IIIA), 44.8% and 28.9% (stage IIIB), and 46.0% and 37.1% (stage IV). Five-year OS rates were 83.4% and 70.8% (stage II), 68.9% and 56.2% (stage IIIA), 43.7% and 40.1% (stage IIIB), and 45.1% and 42.7% (stage IV). Five-year RFS rates were 77.9% and 65.4% (stage II), 64.3% and 48.7% (stage IIIA), 35.9% and 28.9% (stage IIIB), and 26.8% and 25.0% (stage IV).

The approach for adjuvant chemotherapy differs among East Asian countries, including Japan, in which D2 gastrectomy has long been the standard procedure, and Western countries, in which D0 or D1 gastrectomy used to be or currently is standard. As Cunningham and Chua²¹ stated, “surgery alone” is no longer standard treatment anywhere in the world for advanced gastric cancer. Some type of adjuvant chemotherapy, including the use of radiotherapy after D0/1 resection, can thus be considered standard treatment at present.

A meta-analysis by the Global Advanced/Adjuvant Stomach Tumor Research International Collaboration (GASTRIC) group⁷ showed that some form of postoperative chemotherapy is associated with a higher survival rate than surgery alone; moreover, the use of monotherapy for postoperative adjuvant treatment resulted in good outcomes. The ACTS-GC trial demonstrated that S-1 monotherapy improved OS and RFS. In patients with early-stage (II and IIIA) tumors, the benefits of treatment with S-1 were considerable. However, the 5-year OS rate in patients with stage IIIB disease was 50.2% in the S-1 group and 44.1% in the surgery-only group, suggesting that there remains some room for improvement. Future studies should evaluate the effectiveness of intensive preoperative and/or postoperative chemotherapy with multiple agents in patients at high risk for relapse.

The results of the S-1 plus cisplatin versus S-1 in randomized controlled trial in the treatment for stomach cancer (SPIRITS) trial,²² demonstrating that S-1 plus cisplatin is superior to S-1 alone with respect to survival in patients with unresectable or recurrent gastric cancer, and the V325 study [a randomized, multinational phase II/III trial of patients with untreated advanced gastric cancer],^{23,24} showing that the addition of docetaxel to cisplatin plus fluorouracil prolongs survival, indicated that S-1 plus cisplatin and S-1 plus docetaxel are candidate regimens for postoperative adjuvant chemotherapy. These regimens were confirmed to be feasible in a postoperative setting,^{25,26} and further studies should be performed to examine whether such regimens are superior to S-1 alone.

The Japan Clinical Oncology Group (JCOG) is now performing the JCOG 0501 study to compare S-1 plus cisplatin as neoadjuvant chemotherapy with surgery followed by S-1 monotherapy in patients with clinically resectable Borrmann type 4 (linitis plastica) and large type 3 gastric cancer. This trial is expected to be a landmark study, determining the future direction for preoperative chemotherapy in Japan.

The use of molecular targeted agents for gastric cancer has been studied extensively. In the Trastuzumab in Combination with Chemotherapy Versus Chemotherapy Alone for Treatment of HER2-Positive Advanced Gastric or Gastro-Esophageal Junction Cancer (ToGA) study, trastuzumab combined with cisplatin and either fluorouracil or capecitabine significantly prolonged OS in patients with HER2-positive gastric cancer.²⁷ The effectiveness of adjuvant chemotherapy with molecular targeted agents such as trastuzumab also needs to be assessed in patients with HER2-positive gastric cancer.

In conclusion, this 5-year follow-up study confirmed that adjuvant chemotherapy with S-1 given for 1 year after surgery improved

OS and RFS at 5 years in patients with stage II or III gastric cancer who underwent D2 gastrectomy. Postoperative chemotherapy with S-1 can be recommended for patients with stage II or III gastric cancer who undergo D2 gastrectomy, at least in Asian populations.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** Mitsuru Sasako, sanofi-aventis K.K. (C), Taiho Pharmaceutical (C), Chugai Pharmaceutical (C); Atsushi Nashimoto, Taiho Pharmaceutical (C); Masashi Fujii, Taiho Pharmaceutical (C); Toshifusa Nakajima, Taiho Pharmaceutical (C); Yasuo Ohashi, Taiho Pharmaceutical (C) **Stock Ownership:** Masashi Fujii, Otsuka Holdings **Honoraria:** Mitsuru Sasako, sanofi-aventis K.K., Bayer Yakuhin,

Genzyme Japan K.K., Novartis Pharma K.K., Taiho Pharmaceutical, Bristol-Myers Squibb, Yakult Pharmaceutical Industry; Shinichi Sakuramoto, Taiho Pharmaceutical; Taira Kinoshita, Taiho Pharmaceutical; Hiroshi Furukawa, Taiho Pharmaceutical; Toshiharu Yamaguchi, Taiho Pharmaceutical; Atsushi Nashimoto, Taiho Pharmaceutical; Masashi Fujii, Taiho Pharmaceutical; Toshifusa Nakajima, Taiho Pharmaceutical; Yasuo Ohashi, Taiho Pharmaceutical **Research Funding:** Mitsuru Sasako, Taiho Pharmaceutical, Bristol-Myers Squibb, Chugai Pharmaceutical, sanofi-aventis K.K.; Shinichi Sakuramoto, Taiho Pharmaceutical **Expert Testimony:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Mitsuru Sasako, Taira Kinoshita, Hiroshi Furukawa, Toshiharu Yamaguchi, Atsushi Nashimoto, Masashi Fujii, Toshifusa Nakajima, Yasuo Ohashi

Collection and assembly of data: Mitsuru Sasako, Shinichi Sakuramoto, Hitoshi Katai, Taira Kinoshita, Hiroshi Furukawa, Toshiharu Yamaguchi, Atsushi Nashimoto, Masashi Fujii

Data analysis and interpretation: Mitsuru Sasako, Toshifusa Nakajima, Yasuo Ohashi

Manuscript writing: All authors

Final approval of manuscript: All authors

REFERENCES

1. Ferlay J, Shin HR, Bray F, et al: Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10, 2010. <http://www.iarc.fr/en/publications/eresources/cancerbases/index.php>
2. Hermans J, Bonenkamp JJ, Boon MC, et al: Adjuvant therapy after curative resection for gastric cancer: Meta-analysis of randomized trials. *J Clin Oncol* 11:1441-1447, 1993
3. Piedbois P, Buyse M: Meta-analyses need time, collaboration, and funding. *J Clin Oncol* 12:878-880, 1994
4. Earle CC, Maroun JA: Adjuvant chemotherapy after curative resection for gastric cancer in non-Asian patients: Revisiting a meta-analysis of randomised trials. *Eur J Cancer* 35:1059-1064, 1999
5. Mari E, Floriani I, Tinazzi A, et al: Efficacy of adjuvant chemotherapy after curative resection for gastric cancer: A meta-analysis of published randomised trials—A study of the GISCAD (Gruppo Italiano per lo Studio dei Carcinomi dell'Apparato Digerente). *Ann Oncol* 11:837-843, 2000
6. Panzini I, Gianni L, Fattori PP, et al: Adjuvant chemotherapy in gastric cancer: A meta-analysis of randomized trials and a comparison with previous meta-analyses. *Tumori* 88:21-27, 2002
7. GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) Group, Paoletti X, Oba K, et al: Benefit of adjuvant chemotherapy for resectable gastric cancer: A meta-analysis. *JAMA* 303:1729-1737, 2010
8. Shirasaka T, Shimamoto Y, Ohshimo H, et al: Development of a novel form of an oral 5-fluorouracil derivative (S-1) directed to the potentiation of the tumor selective cytotoxicity of 5-fluorouracil by two biochemical modulators. *Anticancer Drugs* 7:548-557, 1996
9. Diasio RB: Clinical implications of dihydropyrimidine dehydrogenase inhibition. *Oncology (Williston Park)* 13:17-21, 1999
10. Sakata Y, Ohtsu A, Horikoshi N, et al: Late phase II study of novel oral fluoropyrimidine anticancer drug S-1 (1 M tegafur-0.4 M gimestat-1 M otastat potassium) in advanced gastric cancer patients. *Eur J Cancer* 34:1715-1720, 1998
11. Koizumi W, Kurihara M, Nakano S, et al: Phase II study of S-1, a novel oral derivative of 5-fluorouracil, in advanced gastric cancer: For the S-1 Cooperative Gastric Cancer Study Group. *Oncology* 58:191-197, 2000
12. Sakuramoto S, Sasako M, Yamaguchi T, et al: Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med* 357:1810-1820, 2007
13. Japanese Gastric Cancer Association: Japanese Classification of Gastric Carcinoma - 2nd English Edition. *Gastric Cancer* 1:10-24, 1998
14. Cunningham D, Allum WH, Stenning SP, et al: Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 355:11-20, 2006
15. Macdonald JS, Smalley SR, Benedetti J, et al: Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 345:725-730, 2001
16. Bonenkamp JJ, Hermans J, Sasako M, et al: Extended lymph-node dissection for gastric cancer. *N Engl J Med* 340:908-914, 1999
17. Bunt AM, Hermans J, Smit VT, et al: Surgical/pathologic-stage migration confounds comparisons of gastric cancer survival rates between Japan and Western countries. *J Clin Oncol* 13:19-25, 1995
18. Bonenkamp JJ, Songun I, Hermans J, et al: Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. *Lancet* 345:745-748, 1995
19. Songun I, Putter H, Kranenbarg EM, et al: Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. *Lancet Oncol* 11:439-449, 2010
20. Okines A, Verheij M, Allum W, et al: Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 21:v50-v54, 2010
21. Cunningham D, Chua YJ: East meets West in the treatment of gastric cancer. *N Engl J Med* 357:1863-1865, 2007
22. Koizumi W, Narahara H, Hara T, et al: S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): A phase III trial. *Lancet Oncol* 9:215-221, 2008
23. Van Cutsem E, Moiseyenko VM, Tjulandin S, et al: Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: A report of the V325 Study Group. *J Clin Oncol* 24:4991-4997, 2006
24. Ajani JA, Moiseyenko VM, Tjulandin S, et al: Quality of life with docetaxel plus cisplatin and fluorouracil compared with cisplatin and fluorouracil from a phase III trial for advanced gastric or gastroesophageal adenocarcinoma: The V-325 Study Group. *J Clin Oncol* 25:3210-3216, 2007
25. Fujitani K, Tamura S, Kimura Y, et al: Phase II feasibility study of adjuvant S-1 plus docetaxel for stage III gastric cancer patients after curative D2 gastrectomy (OGSG 0604). *J Clin Oncol* 27, 2009 (suppl; abstr e15567)
26. Takahari D, Hamaguchi T, Yoshimura K, et al: Feasibility study of adjuvant chemotherapy with S-1 plus cisplatin for gastric cancer. *Cancer Chemother Pharmacol* 67:1423-1428, 2011
27. Bang YJ, Van Cutsem E, Feyereislova A, et al: Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): A phase 3, open-label, randomised controlled trial. *Lancet* 376:687-697, 2010