8. 有効性の評価

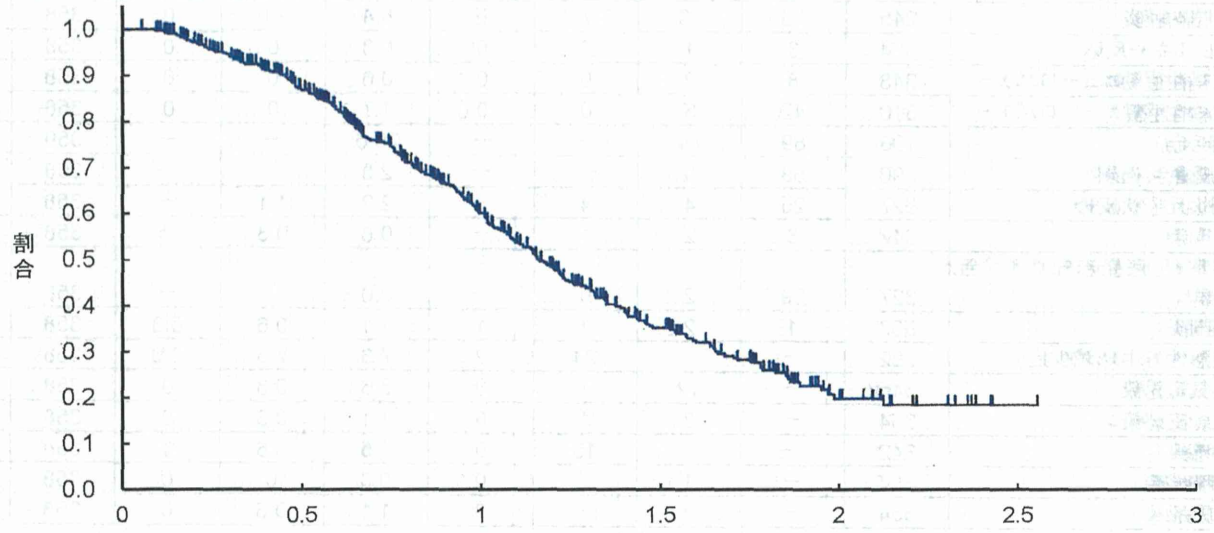
「1 年 = 365.25 日」「1 か月 =(365.25/12)日」で計算

全生存期間

解析対象:2014 年 10 月 31 日までの登録例 541 例のうち、死亡日不明の 1 例(No.179)を除く 540 例
起算日:登録日
イベント:死亡
打ち切り:生存例、追跡不能例は最終生存確認日で打ち切り

Kaplan-Meier 法による推定生存曲線

2014 年 12 月 1 日調査



解析対象	イベント(死亡)	打ち切り例の最長追跡期間	最後の死亡が起こった時点での生存	生存期間中央値(95%信頼区間)
540 例	278 例	2.55 年	14 例	1.16 年 (1.08 年−1.25 年)

1 年生存割合(95%信頼区間)	2 年生存割合(95%信頼区間)
60.0% (55.1%−64.5%)	19.7% (14.5%−25.5%)

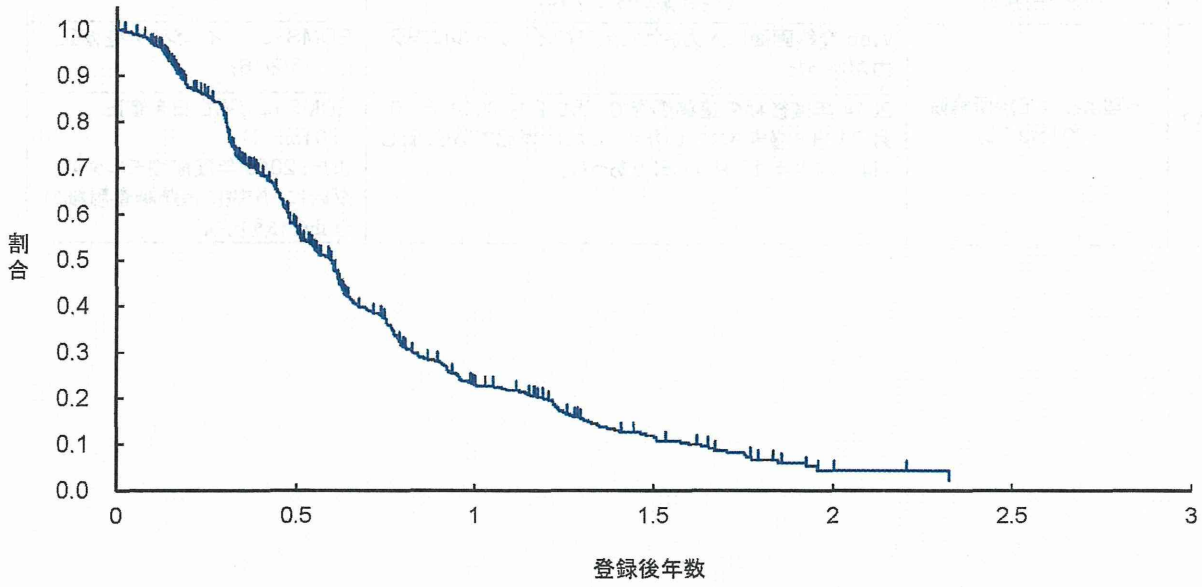
胃がんグループ/研究事務局/効果・安全性評価委員会/JCOG 代表者のみ

無増悪生存期間

解析対象：2014 年 10 月 31 日までの登録例 541 例のうち、増悪判定日不明の 1 例（No.59）と死亡日が不明の 1 例（No.179）除く 539 例
起算日：登録日
イベント：増悪もしくは死亡
打ち切り：無増悪生存例、追跡不能例は最終無増悪生存確認日で打ち切り

Kaplan-Meier 法による推定無増悪生存曲線

2014 年 12 月 1 日調査



解析対象	イベント（死亡・増悪）	打ち切り例の最長追跡期間	最後のイベントが起こった時点での無増悪生存	無増悪生存期間中央値 (95%信頼区間)
539 例	399 例	2.32 年	1 例	0.60 年 (0.51 年－0.62 年)

1 年無増悪生存割合 (95%信頼区間)	2 年無増悪生存割合 (95%信頼区間)
22.9% (19.0%－27.1%)	4.4% (2.1%－7.9%)

追跡調査のデータがアップデートされていない例

2015 年 2 月 28 日現在

No.	群	施設名	最終生存確認日	担当医コメント
24	A	虎の門病院	2013/2/25	なし
33	A	国立がん研究センター東病院	2012/9/6	なし
51	A	天理よろづ相談所病院	2013/12/20	他院へ転院の為追跡できませんでした（2014 年前期）
144	A	国立がん研究センター東病院	2013/3/19	なし
156	A	国立がん研究センター東病院	2013/12/3	なし
338	A	愛知県がんセンター中央病院	2013/11/11	転居先不明。本人、家族とも連絡とれず追跡できません（2014 年後期）
30	B	愛知県がんセンター中央病院	2012/11/13	他院転院のため来院なし（2013 年前期） 追跡できず申し訳ありません（2013 年後期） 追跡できません（2014 年前期） 追跡できません（2014 年後期）

9. 転院患者一覧

No.	登録時施設名	転院先施設名	転院時期
184	神戸大学医学部	兵庫医科大学	2014 年後期

10. 監査委員会からの修正依頼案件

No.	施設名 (監査実施日)	詳細 (報告書からの抜粋)	修正
313	天理よろづ相談所病院 (2015/2/23)	Web 登録画面に入力された患者のイニシャルに誤入力があった	EDMS にて、イニシャルを修正 (2015/2/16)
		2014 年度後期の追跡調査で、死亡日を 2014 年 10 月 24 日と報告されていたが、これは誤記であり、正しくは 2014 年 10 月 17 日であった。	EDMS にて死亡日を修正 (2015/3/4) また、2015 年度前期モニタリング時に、施設に追跡調査用紙の修正を依頼予定

様式第１９

学　会　等　発　表　実　績

委託業務題目「　切除不能進行・再発胃がんに対する個別化治療と最適化標準治療に関する研究」
機関名　　国立がん研究センター中央病院

１．学会等における口頭・ポスター発表

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
学会発表なし				

２．学会誌・雑誌等における論文掲載

掲載した論文（発表題目）	発表者氏名	発表した場所（学会誌・雑誌等	発表した時期	国内・外の別
Phase III study comparing oxaliplatin plus S-1 with cisplatin plus S-1 in chemotherapy-naïve patients with advanced gastric cancer.	Yamada Y, Higuchi K, Nishikawa K, Gotoh M, Fuse N, Sugimoto N, Nishina T, Amagai K, Chin K, Niwa Y, Tsuji A, Imamura H, Tsuda M, Yasui H, Fujii H, Yamaguchi K, Yasui H, Hironaka S, Hamada C,	Ann Oncol 26:141-148	2015	国外
Optimal chemotherapy for advanced gastric cancer: is there a global consensus?	Lordick F, Lorenzen S, Yamada Y, Ilson D	Gastric Cancer 17:213-225	2014	国外
Comparison of advanced adeno-carcinomas of esophagogastric junction and distal stomach in Japanese patients.	Kawano A, Nakajima TE, Oda I, Hokamura N, Iwasa S, Kato K, Hamaguchi T, Yamada Y, Fujii H, Shimada Y.	Gastric Cancer 17:54-60	2014	国外
A phase 1 study of sorafenib in combination with S-1 plus cisplatin in patients with advanced gastric cancer	Yamada Y, Kiyota N, Fuse N, Kato K, Minami H, Hashizume K, Kuroki Y, Ito Y, Ohtsu A	Gastric Cancer 17:161-172	2014	国外
Determination of prognostic factors in Japanese patients with advanced gastric cancer using the date from a randomized controlled trial, Japan Clinical Oncology Group 9912.	Takahari D, Boku N, Mizusawa J, Takashima A, Yamada Y, Yoshino T, Yamazaki K, Koizumi W, Fukase K, Yamaguchi K, Goto M, Nishina T, Tamura T, Tuji A, Ohtsu A	Oncologist 19:358-66	2014	国外
Clinical impact of c-MET expression and genetic mutational status in colorectal cancer patients after liver resection.	Shoji H, Yamada Y, Taniguchi H, Nagashima K, Okita N, Takashima A, Honma Y, Iwasa S, Kato K, Hamaguchi T, Shimada Y.	Cancer Sci 105:1002-1007	2014	国外
Clinicopathological features and prognostic roles of KRAS, BRAF, PIK3CA and NRAS mutations in advanced gastric cancer.	Takahashi N, Yamada Y, Taniguchi H, Fukahori M, Sasaki Y, Shoji H, Honma Y, Iwasa S, Takashima A, Kato K, Hamaguchi T,	BMC Res Notes 7:271-277	2014	国外

（注１）発表者氏名は、連名による発表の場合には、筆頭者を先頭にして全員を記載すること。
（注２）本様式はexcel形式にて作成し、甲が求める場合は別途電子データを納入すること。

Annals of Oncology 26: 141–148, 2015
doi:10.1093/annonc/mdu472
Published online 14 October 2014

Phase III study comparing oxaliplatin plus S-1 with cisplatin plus S-1 in chemotherapy-naïve patients with advanced gastric cancer

Y. Yamada[1*], K. Higuchi[2], K. Nishikawa[3], M. Gotoh[4], N. Fuse[5], N. Sugimoto[6], T. Nishina[7], K. Amagai[8], K. Chin[9], Y. Niwa[10], A. Tsuji[11], H. Imamura[12], M. Tsuda[13], H. Yasui[14], H. Fujii[15], K. Yamaguchi[16], H. Yasui[17], S. Hironaka[18], K. Shimada[19], H. Miwa[20], C. Hamada[21] & I. Hyodo[22]

[1]*Gastrointestinal Oncology Division, National Cancer Center Hospital, Tokyo;* [2]*Department of Gastroenterology, Kitasato University East Hospital, Sagamihara;* [3]*Department of Surgery, Osaka General Medical Center, Osaka;* [4]*Cancer Chemotherapy Center, Osaka Medical College Hospital, Takatsuki;* [5]*Division of Gastrointestinal Oncology and Digestive Endoscopy, National Cancer Center Hospital East, Kashiwa;* [6]*Department of Clinical Oncology, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka;* [7]*Department of Gastrointestinal Medical Oncology, National Hospital Organization Shikoku Cancer Center, Matsuyama;* [8]*Department of Gastroenterology, Ibaraki Prefectural Central Hospital, Kasama;* [9]*Department of Gastroenterology, Cancer Institute Hospital of JFCR, Tokyo;* [10]*Department of Endoscopy, Aichi Cancer Center Hospital, Nagoya;* [11]*Department of Medical Oncology, Kochi Health Sciences Center, Kochi;* [12]*Department of Surgery, Sakai City Hospital, Sakai;* [13]*Department of Gastroenterological Oncology, Hyogo Cancer Center, Akashi;* [14]*Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Sunto-gun;* [15]*Division of Clinical Oncology, Jichi Medical University, Shimotsuke;* [16]*Division of Gastroenterology, Saitama Cancer Center, Kita-adachi-gun;* [17]*Department of Medical Oncology, National Hospital Organization Kyoto Medical Center, Kyoto;* [18]*Clinical Trial Promotion Department, Chiba Cancer Center, Chiba;* [19]*Department of Internal Medicine, Showa University Northern Yokohama Hospital, Yokohama;* [20]*Division of Gastroenterology, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya;* [21]*Faculty of Engineering, Tokyo University of Science, Tokyo;* [22]*Division of Gastroenterology, University of Tsukuba, Tsukuba, Japan*

Received 7 August 2014; revised 25 September 2014; accepted 25 September 2014

Background: We evaluated the efficacy and safety of S-1 plus oxaliplatin (SOX) as an alternative to cisplatin plus S-1 (CS) in first-line chemotherapy for advanced gastric cancer (AGC).

Patients and methods: In this randomized, open-label, multicenter phase III study, patients were randomly assigned to receive SOX (80–120 mg/day S-1 for 2 weeks with 100 mg/m^2 oxaliplatin on day 1, every 3 weeks) or CS (S-1 for 3 weeks with 60 mg/m^2 cisplatin on day 8, every 5 weeks). The primary end points were noninferiority in progression-free survival (PFS) and relative efficacy in overall survival (OS) for SOX using adjusted hazard ratios (HRs) with stratification factors; performance status and unresectable or recurrent (+adjuvant chemotherapy) disease.

Results: Overall, 685 patients were randomized from January 2010 to October 2011. In per-protocol population, SOX ($n = 318$) was noninferior to CS ($n = 324$) in PFS [median, 5.5 versus 5.4 months; HR 1.004, 95% confidence interval (CI) 0.840–1.199; predefined noninferiority margin 1.30]. The median OS for SOX and CS were 14.1 and 13.1 months, respectively (HR 0.958 with 95% CI 0.803–1.142). In the intention-to-treat population (SOX, $n = 339$; CS, $n = 337$), the HRs in PFS and OS were 0.979 (95% CI 0.821–1.167) and 0.934 (95% CI 0.786–1.108), respectively. The most common ≥grade 3 adverse events (SOX versus CS) were neutropenia (19.5% versus 41.8%), anemia (15.1% versus 32.5%), hyponatremia (4.4% versus 13.4%), febrile neutropenia (0.9% versus 6.9%), and sensory neuropathy (4.7% versus 0%).

Conclusion: SOX is as effective as CS for AGC with favorable safety profile, therefore SOX can replace CS.

Clinical trial number: JapicCTI-101021.

Key words: advanced gastric cancer, oxaliplatin, cisplatin, S-1, phase III study

introduction

Combination therapies using cisplatin and fluoropyrimidines with or without epirubicin or docetaxel have been widely used as first-line treatments for advanced gastric cancer (AGC) [1–4]. The German Arbeitsgemeinschaft Internistische Onkologie (AIO) trial showed that 5-fluorouracil (5-FU)/leucovorin plus oxaliplatin treatment was equivalent to 5-FU/leucovorin plus cisplatin treatment [5]. The randomized two-by-two phase III study (REAL-2) of triplet therapy of epirubicin, 5-FU or capecitabine, and cisplatin or oxaliplatin for advanced esophagogastric cancer showed that oxaliplatin was as effective as cisplatin with respect to overall survival (OS) and progression-free survival (PFS) [6].

*Correspondence to: Dr Yasuhide Yamada, Gastrointestinal Oncology Division, National Cancer Center Hospital 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. Tel: +81-3-3542-2511; Fax: +81-3-3545-3567; E-mail: yayamada@ncc.go.jp

© The Author 2014. Published by Oxford University Press on behalf of the European Society for Medical Oncology.
All rights reserved. For permissions, please email: journals.permissions@oup.com.

Downloaded from http://annonc.oxfordjournals.org/ at National Cancer Centre (JMLA) on January 8, 2015

S-1 is an oral anticancer preparation that combines tegafur, a pro-drug of 5-FU, with two modulators, i.e. gimeracil and oteracil [7]. Phase III clinical trials showed that S-1 was noninferior to 5-FU, and that cisplatin plus S-1 (CS) was superior to S-1 (SPIRITS trial) [8, 9]. CS is regarded as a standard first-line treatment of AGC in Japan. A phase III study (FLAGS) suggested that CS could be a substitute for 5-FU plus cisplatin as first-line chemotherapy for AGC [10, 11]. A phase II trial of first-line chemotherapy with S-1 plus oxaliplatin (SOX) yielded promising outcomes, a median PFS and OS of 6.5 and 16.5 months, respectively, with good tolerability [12]. To confirm and extend these results, we carried out a phase III study comparing SOX with CS as first-line chemotherapy for AGC.

methods

patients

The main eligibility criteria included histologically proven, curatively unresectable, advanced or recurrent gastric cancer, age ≥20 years, an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2, the presence of measurable lesions as confirmed by computed tomography (CT), no previous chemotherapy or radiotherapy, oral intake capability, adequate function of the major organs, and written informed consent of the patient. The main exclusion criteria were active infection, serious concurrent disease, markedly impaired cardiac function, gastrointestinal bleeding, sensory neuropathy, serious diarrhea, ascites beyond the pelvic cavity or pleural effusion, a history of blood transfusion within 3 weeks before enrollment, interstitial pneumonia, or previous treatment with platinum as adjuvant chemotherapy.

This study was carried out according to the ethical principles of the Declaration of Helsinki and Good Clinical Practice Guidelines. Each hospital's institutional review board approved this study protocol.

study design

This study was a prospective, multicenter, randomized, open-label, parallel-group phase III clinical trial conducted at 51 centers in Japan. Eligible patients were centrally randomized to CS or SOX in a 1 : 1 ratio, considering the institution, PS, and unresectable or recurrent disease with or without postoperative adjuvant chemotherapy as adjustment factors using the minimization method [13]. The randomization sequence was generated by an independent team from the trial sponsor and investigators. Enrollment was done by a local principal or subinvestigator via a web-based system, which automatically assigned either treatment to a patient. The allocated study treatments were not masked from the patients and investigators.

treatment

In CS, S-1 was given orally twice daily for the first 3 weeks of a 5-week cycle. The dose was 80 mg/day for body surface area (BSA) <1.25 m^2, 100 mg/day for BSA ≥1.25 to <1.5 m^2, and 120 mg/day for BSA ≥1.5 m^2. Cisplatin was administered at 60 mg/m^2 as an i.v. infusion with adequate hydration on day 8 of each cycle [9]. In SOX, S-1 was given as the same way for the first 2 weeks of a 3-week cycle. Oxaliplatin at 100 mg/m^2 was infused for 2 h i.v. on day 1 of each cycle [12]. The treatments were continued until one of the criteria for withdrawal of the study treatment was encountered.

In both treatment groups, the dose of each drug was reduced to ~80%, if the neutrophil count was <500/mm^3, the platelet count was <25 000/mm^3 or ≥grade 3 febrile neutropenia, diarrhea, stomatitis, or hand-foot syndrome developed. In CS, the dose of cisplatin was reduced in the event of grade 3 anorexia suspected to be caused by cisplatin. In SOX, the dose of oxaliplatin was reduced if the platelet count was <75 000/mm^3 on day 29 when the treatment was delayed for a week, or grade 2 sensory neuropathy developed on the first day of a cycle (supplementary Tables S1–S3, available at *Annals of Oncology* online).

assessments

PFS was defined as the time from the randomization to documented progressive disease (PD) or death without prior PD, whichever came first. Patients who were alive and free of progression (i.e. second-line treatment was started due to any cause) were regarded as censored cases at the date of the last assessment. Lesions were evaluated by CT at the baseline and every 6 weeks from the randomization to the initiation of second-line treatment. The assessments were done under the same imaging way as the baseline in all patients. All images for PFS and tumor responses were reviewed by an independent review committee, according to the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.0 [14]. OS was defined as the interval from the date of randomization to the date of death from any cause or the last follow-up date. Adverse events were graded according to the Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE version 3.0).

statistical considerations

We aimed to assess two primary end points. One primary end point was to demonstrate noninferiority in PFS for SOX compared with CS which was used for sample size determination. The other primary end point was to evaluate the relative efficacy in OS between SOX and CS. The noninferiority analysis was carried out in the per-protocol population. The noninferiority margin in PFS was defined at 1.30 in reference to the results of SPIRITS trial and phase II study of SOX (supplementary Appendix A1, available at *Annals of Oncology* online). Since the required number of events was estimated as 456 with a one-sided α value of 0.025 and a power of 80%, we estimated that 600 patients would be needed to achieve the required number of events within the patient accrual (1.5 years) and follow-up periods (1 year after the last patient randomization). In February 2011, it appeared to be difficult to achieve the required number of events within the preplanned timetable, and the target number of patients was revised to 680 according to the predefined procedure in the protocol. For OS, the noninferiority margin was defined to be 1.15 as a guide of evaluation. The number of events required for OS analysis was set as 508 with a one-sided α value of 0.025 and a power of 80% when median OS for SOX and CS were expected as 14.5 and 13.0 months, respectively.

Time-to-events were analyzed using the Kaplan–Meier method. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using the stratified Cox proportional hazards model. The stratification factors were unresectable or recurrent disease, with or without postoperative adjuvant chemotherapy, and PS of 0, 1, or 2, excluding institution from adjustment factors in randomization. We also did the analyses in the intention-to-treat (ITT) population: all randomized patients excluding patients who took no trial medication. In exploratory analyses, subgroup efficacy and multivariate analyses were carried out on stratification factors and demographic factors in the Cox proportional hazards model. Statistical analyses were carried out using SAS v9.1.3.

results

patients disposition and characteristics

From 14 January 2010 through 17 October 2011, 685 patients were enrolled; 343 and 342 patients were randomly assigned to SOX or CS (Figure 1). The demographic characteristics in the per-protocol population were well balanced between SOX and CS (Table 1).

Downloaded from http://annonc.oxfordjournals.org/ at National Cancer Centre (JMLA) on January 8, 2015

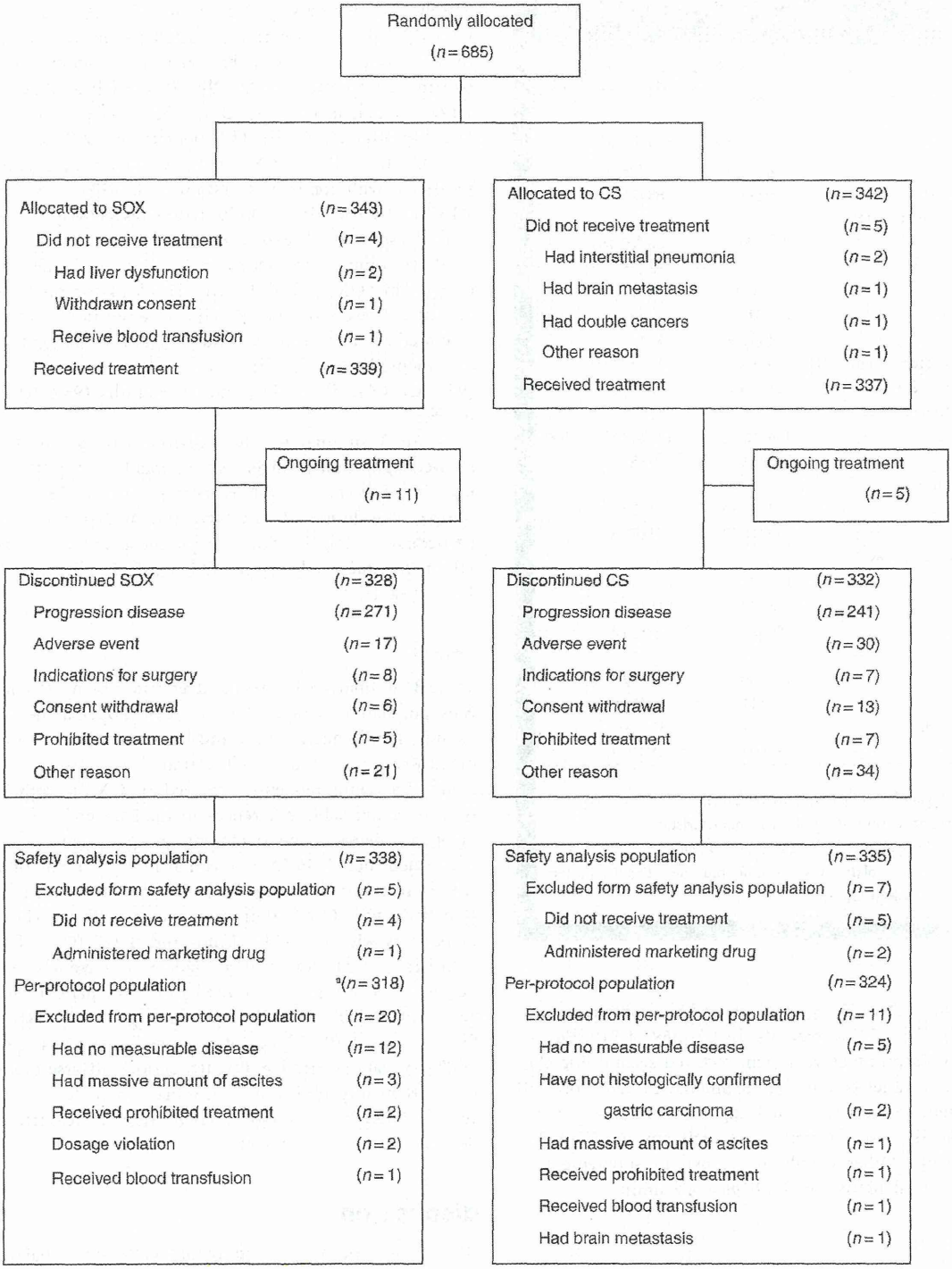


Figure 1. CONSORT diagram. [a]After PFS analysis was fixed, it was verified that one patient did not have gastric carcinoma. This patient was excluded from OS analysis but included in safety analyses because some cycles of assigned treatment were given. SOX, S-1 plus oxaliplatin; CS, cisplatin plus S-1.

treatment delivery

The median treatment cycles in SOX and CS were 7.0 (range 1–43) and 5.0 (range 1–19), respectively. The relative dose intensity was 79.0% [interquartile range (IQR), 62.3–95.1] for oxaliplatin and 78.9% (IQR 65.9–91.3) for S-1 in SOX; it was 80.7% (IRQ 64.2–94.6) for cisplatin and 79.8% (IQR 68.1–90.9) for S-1 in CS.

In SOX, 261 of 308 (84.7%) patients who discontinued treatment received second-line chemotherapies: taxanes-containing regimens in 131 of 261 (50.2%) patients, irinotecan-containing

Downloaded from http://annonc.oxfordjournals.org/ at National Cancer Centre (JMLA) on January 8, 2015

Table 1. Baseline characteristics

	Treatment		
	SOX ($N=318$)	CS ($N=324$)	P^a
Gender			
Male	240 (75.5)	237 (73.1)	0.50
Female	78 (24.5)	87 (26.9)	
Age (years)	65 (21–83)	65 (29–85)	–
ECOG performance status			
0	224 (70.4)	228 (70.4)	0.94
1	91 (28.6)	92 (28.4)	
2	3 (0.9)	4 (1.2)	
Unresectable	261 (82.1)	272 (84.0)	0.78
Recurrent	57 (17.9)	52 (16.0)	
Adjuvant chemotherapy (+)	29 (9.1)	25 (7.7)	
Adjuvant chemotherapy (−)	28 (8.8)	27 (8.3)	
Tumor histology			
Intestinal	144 (45.3)	145 (44.8)	0.89
Diffuse	174 (54.7)	179 (55.2)	
Primary tumor			
−	74 (23.3)	72 (22.2)	0.75
+	244 (76.7)	252 (77.8)	
No. of metastatic sites			
1	102 (32.1)	101 (31.2)	0.97
2	136 (42.8)	141 (43.5)	
≥3	80 (25.2)	82 (25.3)	
Metastatic site[b]			
Liver	124 (39.0)	129 (39.8)	
Lung	36 (11.3)	35 (10.8)	
Lymph node	290 (91.2)	287 (88.6)	
Peritoneal	61 (19.2)	64 (19.8)	

Data are presented as *n* (%) or median (range).
[a]χ^2 test; comparing proportion of each characteristic.
[b]Patients can be included in more than one category.
SOX, S-1 plus oxaliplatin; CS, cisplatin plus S-1; ECOG, Eastern Cooperative Oncology Group.

regimens in 87 of 261 (33.3%) patients, and S-1-containing regimens in 20 of 261 (7.7%) patients. In CS, 269 of 319 (84.3%) patients who discontinued treatment received second-line chemotherapies: taxanes-containing regimens in 102 of 269 (37.9%) patients, irinotecan-containing regimens in 84 of 269 (31.2%) patients, and S-1-containing regimens in 46 of 269 (17.1%) patients. Other details are shown in supplementary Appendix A2, available at *Annals of Oncology* online.

efficacy

The median follow-up for PFS was 6.9 months (IQR 2.9–9.6). The median PFS in SOX and CS were 5.5 months (95% CI 4.4–5.7, 260 events) and 5.4 months (95% CI 4.2–5.7, 249 events), respectively (Figure 2A). The HR was 1.004 (95% CI 0.840–1.199, $P_{\text{noninferiority}} = 0.0044$), and the upper limit of 95% CI was less than the noninferiority margin of 1.30.

The median follow-up for OS was 25.9 months (IQR 21.0–29.2). The median OS in SOX and CS were 14.1 months (95% CI 13.0–15.8, 249 events) and 13.1 months (95% CI 12.1–15.1, 259 events), respectively (Figure 2B). The HR was 0.969 (95% CI 0.812–1.157). However, one eligible patient was not included in the stratified analysis. The analysis including all eligible patients resulted in giving that the HR was 0.958 (95% CI 0.803–1.142) (supplementary Appendix A3, available at *Annals of Oncology* online). In the ITT population (SOX, $n = 339$; CS, $n = 337$), the HRs in PFS and OS evaluated by stratified Cox regression with combining stratum were 0.979 (95% CI 0.821–1.167) and 0.934 (95% CI 0.786–1.108), respectively.

The response rate and disease control rate were 55.7% and 85.2% (2 complete response, 175 partial response, and 94 stable disease) in SOX, and 52.2% and 81.8% (4 complete response, 165 partial response, and 96 stable disease) in CS, respectively. The median time from the randomization to the first date that documented to reach 30% tumor reduction were 1.5 months (95% CI 1.4–2.5) in SOX and 1.5 months (95% CI 1.4–1.6) in CS.

Figure 3 summarizes the subgroup analysis of OS. SOX showed significantly longer OS in patients with peritoneal metastasis. Multivariate analyses showed that ECOG PS (1, 2), unresectable disease, diffuse-type, and sum of tumor diameter (≥median) correlated with poor prognosis in OS. The adjusted HR in treatment efficacy for OS was 0.955 (95% CI 0. 802–1.138) (Table 2).

safety

Table 3 summarizes the main adverse events in the safety analysis population. Grade 3 or worse leukopenia, neutropenia, anemia, febrile neutropenia, and hyponatremia were more frequently seen in CS than in SOX. Grade 3 or worse sensory neuropathy was more frequently observed in SOX than in CS. There were no remarkable differences in the incidence of thrombocytopenia between the treatment groups. Grade 3 or worse febrile neutropenia in CS was seen in 12/111 (10.8%) of patients with a creatinine clearance (Ccr) <70 ml/min and 11/224 (4.9%) of patients with Ccr ≥70 ml/min; and in SOX, in 3/113 (2.7%) of patients with Ccr <70 ml/min and 0/225 (0%) of patients with Ccr ≥70 ml/min. Further, grade 3 or worse febrile neutropenia in CS was seen in 12/234 (5.1%) of patients aged <70 years and 11/101 (10.9%) of patients aged ≥70 years; and in SOX, in 1/224 (0.4%) of patients aged <70 years and 2/114 (1.8%) of patients aged ≥70 years. Serious adverse events were more frequently observed in CS than in SOX [127 (37.9%) versus 99 (29.3%), $P = 0.017$]. There were 12 treatment-related deaths (8 in CS and 4 in SOX).

discussion

This randomized phase III study for AGC showed that SOX was noninferior to CS in terms of PFS and OS. As far as we know, this is the first large comparative study of the oxaliplatin plus S-1 doublet with CS. The results of CS in the present study are similar to those observed in the SPIRITS trial that demonstrated the superiority of CS (median PFS 6.0 months and median OS 13.0 months) to S-1, and this suggests the robustness of our results for noninferiority [9].

The adverse events observed for CS and SOX were consistent with previously reported results. Notably, in the present study,

Downloaded from http://annonc.oxfordjournals.org/ at National Cancer Centre (JMLA) on January 8, 2015

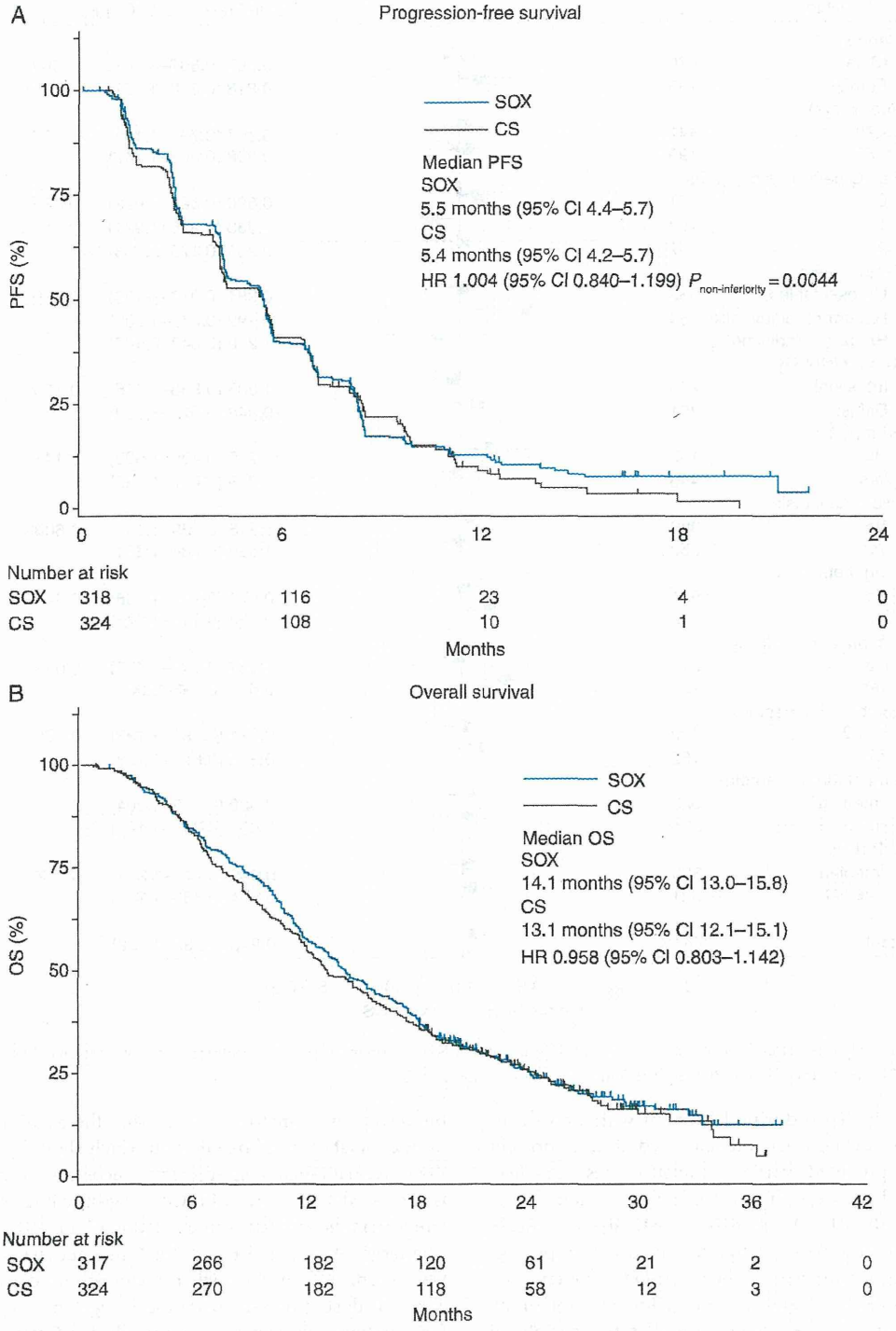


Figure 2. Kaplan–Meier curves for (A) progression-free survival assessed with RECIST and (B) overall survival. SOX, S-1 plus oxaliplatin; CS, cisplatin plus S-1; HR, hazard ratio; CI, confidence interval. Data cut off for PFS was on 1 June 2012 and that for OS was on 16 April 2013 .

SOX provided considerable advantages in safety over CS: ≥grade 3 neutropenia and febrile neutropenia were more frequently observed in CS. All grades of diarrhea, stomatitis, nausea, anorexia, and renal impairment developed more commonly in CS. SOX was safer particularly in patients ≥70 years with Ccr <70 ml/min with respect to febrile neutropenia. In patients with compromised renal function, the decreased renal clearance of gimeracil (a dehydropyrimidine dehydrogenase inhibitor and a component of S-1) increases blood 5-FU concentrations and causes severe adverse effects. Renal

Downloaded from http://annonc.oxfordjournals.org/ at National Cancer Centre (JMLA) on January 8, 2015

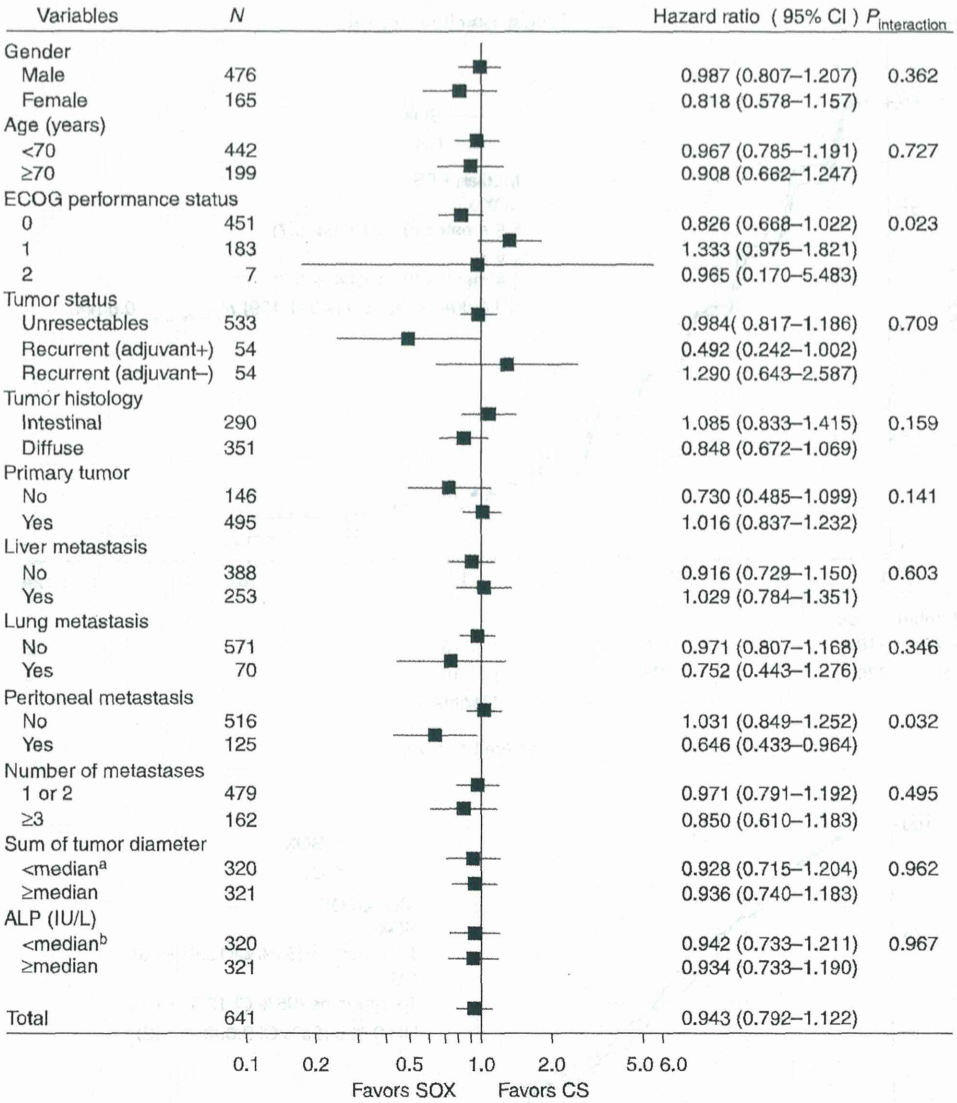


Figure 3. Subgroup analyses of overall survival. SOX, S-1 plus oxaliplatin; CS, cisplatin plus S-1; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group. [a]Median of sum of tumor diameter: 76.5 mm. [b]Median of ALP: 258 IU/l.

function is likely impaired during treatment with a cisplatin-containing regimen, even when adequate hydration to prevent renal toxicity is provided, while oxaliplatin does not affect renal function. These were the probable reasons underlying the favorable results of SOX in elderly patients or patients with renal dysfunction. As expected, the incidence of peripheral sensory neuropathy was higher in SOX. Nonetheless, 50% of patients in SOX received a second-line chemotherapy regimen containing taxanes, suggesting that the peripheral sensory neuropathy induced by oxaliplatin did not clinically hinder the administration of subsequent taxanes-containing chemotherapy.

S-1 has been available for AGC in European and Asian countries. The pharmacokinetics and toxicities of S-1 are different among Caucasian and Asian patients [15, 16]. A couple of the causes are considered as follows; first, the activity of CYP2A6 which is converted to 5-FU from tegafur not only in the liver but also in intestinal mucosa; second, the effect of food intake on the metabolism of oxonic acid which should be localized in the intestinal mucosa and protects mucosal injury by 5-FU, and is converted to cyanuric acid (CA) by gastric juice; third, the difference of folic acid levels in diet among Caucasians and Asians. The larger AUCs of 5-FU and CA in Caucasians than Asians were correlated to the higher incidence of diarrhea by S-1. The oral dosing of S-1 before meal might be one of solutions for avoiding severe diarrhea especially for Caucasians. If dose of S-1 is adequately adjusted by toxicities with enough patient education and self-management, SOX provides considerable improved safety without compromising efficacy for AGC in Caucasians as well.

During the study period, we did not test HER2 expression in tumors and could not know its exact influence on our results. The proportion of patients who received trastuzumab after the study treatment was small (<10%) and similar in both groups.

Downloaded from http://annonc.oxfordjournals.org/ at National Cancer Centre (JMLA) on January 8, 2015