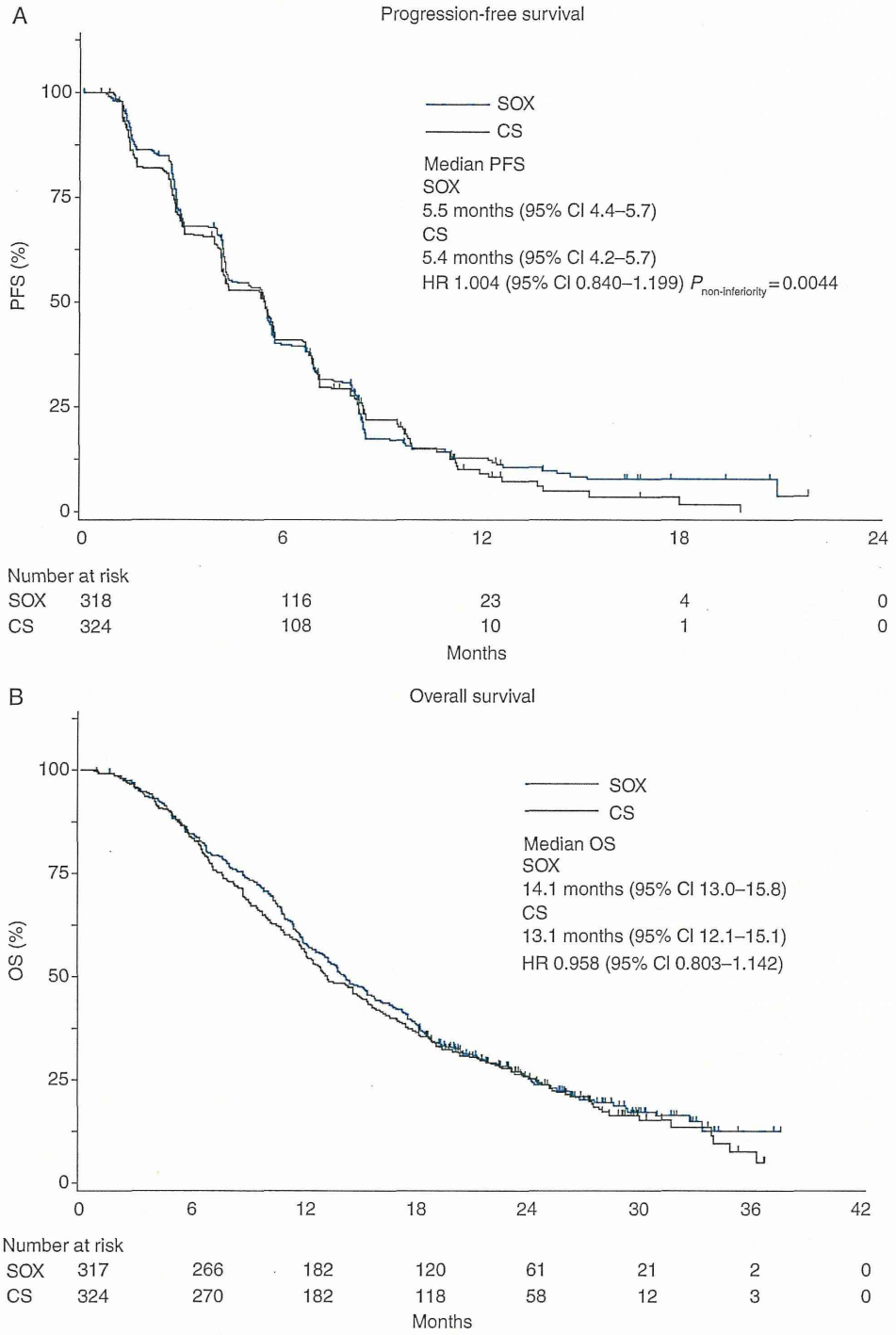

Figure 2. Kaplan–Meier curves for (A) progression-free survival assessed with RECIST and (B) overall survival. SOX, S-1 plus oxaliplatin; CS, cisplatin plus S-1; HR, hazard ratio; CI, confidence interval. Data cut off for PFS was on 1 June 2012 and that for OS was on 16 April 2013 .

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

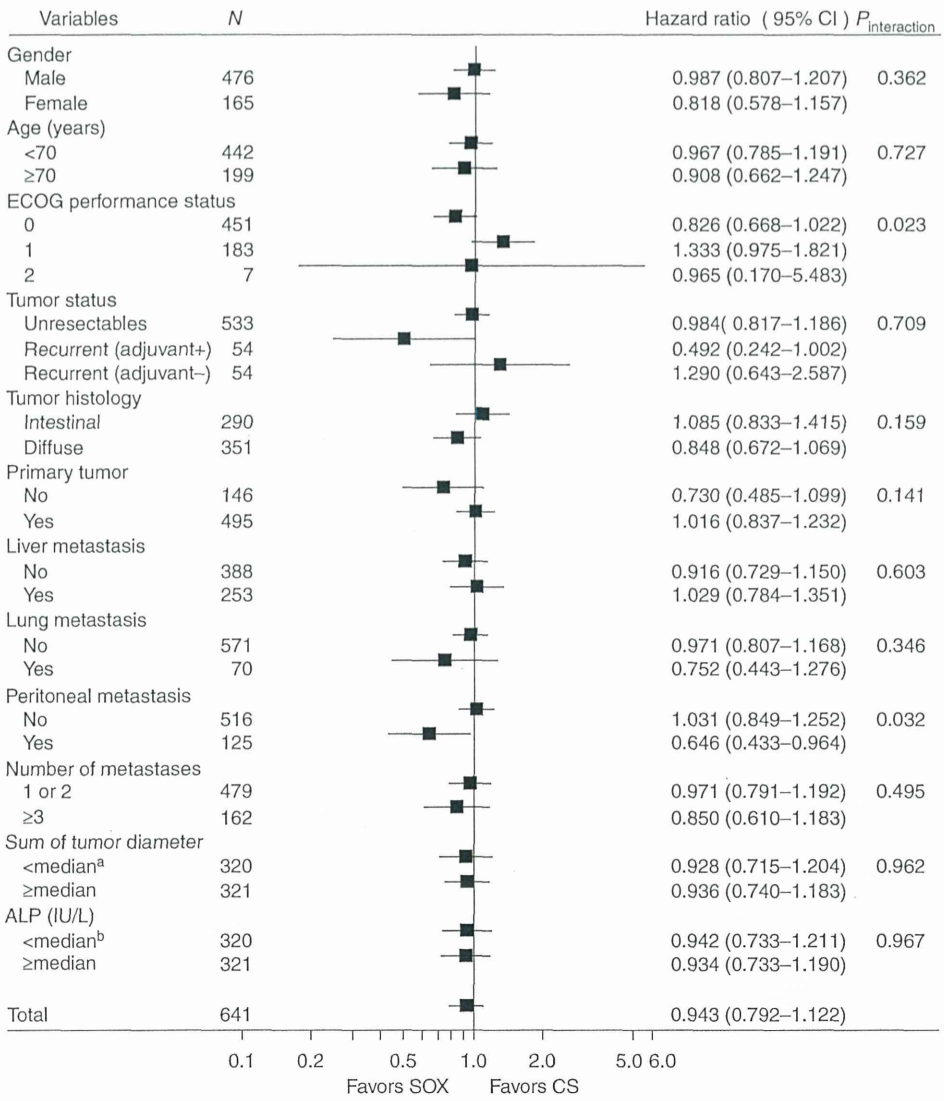

Figure 3. Subgroup analyses of overall survival. SOX, S-1 plus oxaliplatin; CS, cisplatin plus S-1; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group. [a]Median of sum of tumor diameter: 76.5 mm. [b]Median of ALP: 258 IU/l.

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.

Table 2. Multivariate analysis for overall survival

Variables	Category	HR	95% CI	P^a
Regimen	SOX (versus CS)	0.955	0.802–1.138	0.61
Gender	Male (versus female)	1.108	0.904–1.357	0.32
Age (years)	≥70 (versus <70)	0.924	0.762–1.119	0.42
ECOG performance status	1, 2 (versus 0)	1.603	1.328–1.935	<0.0001
Disease status	Recurrent (versus unresectable)	0.588	0.451–0.767	0.0001
Tumor histology	Diffuse (versus intestinal)	1.378	1.151–1.649	0.0005
Peritoneal metastasis	Yes (versus no)	1.099	0.878–1.377	0.41
Sum of tumor diameter[b]	≥Median[c] (versus <median)	1.437	1.195–1.728	0.0001
ALP	≥Median[d] (versus <median)	1.097	0.916–1.315	0.31

Multivariate analyses showed that ECOG performance status (1, 2), unresectable, diffuse-type, and sum of tumor diameter (≥median) correlated with poor prognosis in overall survival.

[a]Wald test.

[b]Sum of tumor diameter, according to the Response Evaluation Criteria In Solid Tumors version 1.0.

[c]Median of sum of tumor diameter : 76.5 mm.

[d]Median of ALP: 258 IU/l.

HR, hazard ratio; CI, confidence interval; SOX, S-1 plus oxaliplatin; CS, cisplatin plus S-1; ECOG, Eastern Cooperative Oncology Group; ALP, alkaline phosphatase.

Table 3. Treatment-related adverse events

	SOX ($N = 338$)				CS ($N = 335$)				P^a	
	Any		≥Grade 3		Any		≥Grade 3		Any	≥Grade 3
Hematological										
Leukopenia	205	60.7	14	4.1	248	74.0	65	19.4	0.0002	<0.0001
Neutropenia	233	68.9	66	19.5	266	79.4	140	41.8	0.0019	<0.0001
Anemia	187	55.3	51	15.1	247	73.7	109	32.5	<0.0001	<0.0001
Thrombocytopenia	265	78.4	34	10.1	232	69.3	35	10.4	0.0069	0.87
Nonhematological										
Febrile neutropenia	3	0.9	3	0.9	23	6.9	23	6.9	<0.0001	<0.0001
Total bilirubin	131	38.8	9	2.7	80	23.9	4	1.2	<0.0001	0.17
AST	205	60.7	10	3.0	77	23.0	4	1.2	<0.0001	0.11
ALT	136	40.2	10	3.0	80	23.9	3	0.9	<0.0001	0.052
Creatinine	30	8.9	1	0.3	132	39.4	6	1.8	<0.0001	0.056
Hyponatremia	74	21.9	15	4.4	154	46.0	45	13.4	<0.0001	<0.0001
Diarrhea	163	48.2	19	5.6	196	58.5	25	7.5	0.0075	0.33
Nausea	208	61.5	13	3.8	231	69.0	13	3.9	0.043	0.98
Vomiting	118	34.9	2	0.6	119	35.5	5	1.5	0.87	0.25
Stomatitis	109	32.2	5	1.5	138	41.2	4	1.2	0.016	0.75
Anorexia	252	74.6	52	15.4	271	80.9	62	18.5	0.048	0.28
Fatigue	195	57.7	22	6.5	203	60.6	29	8.7	0.44	0.29
Sensory neuropathy	289	85.5	16	4.7	79	23.6	0	0	<0.0001	<0.0001

Data are presented as n (%).

[a]χ^2 test; comparing frequency of adverse events of any grades, and grade 3 or higher.

SOX, S-1 plus oxaliplatin; CS, cisplatin plus S-1; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Therefore, trastuzumab treatment would not seem to impact on comparing OS between both groups.

In conclusion, SOX was as effective as CS for AGC. Generally, SOX was less toxic and more convenient clinically, in which forced hydration is not needed unlike cisplatin, than CS. SOX can thus replace CS in the first-line treatment of AGC.

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disclosure

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references

1. Waters JS, Norman A, Cunningham D et al. Long-term survival after epirubicin, cisplatin and fluorouracil for gastric cancer: results of a randomized trial. Br J Cancer 1999; 80: 269–272.
2. Vanhoefer U, Rougier P, Wilke H et al. Final results of a randomized phase III trial of sequential high-dose methotrexate, fluorouracil, and doxorubicin versus etoposide, leucovorin, and fluorouracil versus infusional fluorouracil and cisplatin in advanced gastric cancer: a trial of the European Organization for Research and Treatment of Cancer Gastrointestinal Tract Cancer Cooperative Group. J Clin Oncol 2000; 18: 2648–2657.
3. 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 2006; 24: 4991–4997.
4. Kang YK, Kang WK, Shin DB et al. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. Ann Oncol 2009; 20: 666–673.
5. Al-Batran SE, Hartmann JT, Probst S et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. J Clin Oncol 2008; 26: 1435–1442.
6. Cunningham D, Starling N, Rao S et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 2008; 358: 36–46.
7. Shirasaka T. Development history and concept of an oral anticancer agent S-1 (TS-1): its clinical usefulness and future vistas. Jpn J Clin Oncol 2009; 39: 2–15.
8. Boku N, Yamamoto S, Fukuda H et al. Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomised phase 3 study. Lancet Oncol 2009; 10: 1063–1069.
9. 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 2008; 9: 215–221.
10. Ajani JA, Rodriguez W, Bodoky G et al. Multicenter phase III comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS trial. J Clin Oncol 2010; 28: 1547–1553.
11. Ajani JA, Buyse M, Lichinitser M et al. Combination of cisplatin/S-1 in the treatment of patients with advanced gastric or gastroesophageal adenocarcinoma: results of noninferiority and safety analyses compared with cisplatin/5-fluorouracil in the First-Line Advanced Gastric Cancer Study. Eur J Cancer 2013; 49: 3616–3624.
12. Koizumi W, Takiuchi H, Yamada Y et al. Phase II study of oxaliplatin plus S-1 as first-line treatment for advanced gastric cancer (G-SOX study). Ann Oncol 2010; 21: 1001–1005.
13. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 1975; 31: 103–115.
14. Therasse P, Arbuck SG, Eisenhauer EA et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000; 92: 205–216.
15. Comets E, Ikeda K, Hoff P et al. Comparison of the pharmacokinetics of S-1, an oral anticancer agent, in Western and Japanese patients. J Pharmacokinet Pharmacodyn 2003; 30: 257–283.
16. Chuah B, Goh BC, Lee SC et al. Comparison of the pharmacokinetics and pharmacodynamics of S-1 between Caucasian and East Asian patients. Cancer Sci 2011; 102: 478–483.

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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

A phase 3 non-inferiority study of 5-FU/*l*-leucovorin/irinotecan (FOLFIRI) versus irinotecan/S-1 (IRIS) as second-line chemotherapy for metastatic colorectal cancer: updated results of the FIRIS study

Hirofumi Yasui · Kei Muro · Yasuhiro Shimada · Akihito Tsuji · Shinichi Sameshima · Hideo Baba · Taroh Satoh · Tadamichi Denda · Kenji Ina · Tomohiro Nishina · Kensei Yamaguchi · Taito Esaki · Shinya Tokunaga · Hiroyuki Kuwano · Narikazu Boku · Yoshito Komatsu · Masahiko Watanabe · Ichinosuke Hyodo · Satoshi Morita · Kenichi Sugihara

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Abstract
Purpose The FIRIS study previously demonstrated non-inferiority of IRIS (irinotecan plus S-1) to FOLFIRI (5-fluorouracil/leucovorin with irinotecan) for progression-free survival as the second-line chemotherapy for metastatic colorectal cancer (mCRC) as the primary endpoint. The overall survival (OS) data were immature at the time of the primary analysis.
Methods Between 30 January 2006 and 29 January 2008, 426 patients with mCRC who failed in first-line chemotherapy were randomly assigned to receive either FOLFIRI or IRIS. After the primary analysis, the follow-up survey was cut off on 29 July 2010, and the final OS data were analysed.
Results With a median follow-up of 39.2 months, the median OS was 17.4 months in the FOLFIRI group and 17.8 months in the IRIS group [hazard ratio (HR) 0.900; 95 % confidence interval (CI) 0.728–1.112]. In the pre-planned subgroup of patients who received prior chemotherapy containing oxaliplatin, the median OS was

H. Yasui (✉)
Division of Gastrointestinal Oncology, Shizuoka Cancer Center, 1007 Shimonagakubo, Nagaizumi-cho, Sunto-gun, Shizuoka 411-8777, Japan
e-mail: h.yasui@scchr.jp

K. Muro
Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan

Y. Shimada
Division of Gastrointestinal Oncology, National Cancer Center Hospital, Tokyo, Japan

A. Tsuji
Department of Medical Oncology, Kobe City Medical Center General Hospital, Kobe, Japan

S. Sameshima
Department of Surgery, Dokkyo Medical University Koshigaya Hospital, Koshigaya, Japan

H. Baba
Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan

T. Satoh
Department of Frontier Science for Cancer and Chemotherapy, Osaka University Graduate School of Medicine, Suita, Japan

T. Denda
Department of Gastroenterology, Chiba Cancer Center, Chiba, Japan

K. Ina
Department of Medical Oncology, Nagoya Memorial Hospital, Nagoya, Japan

T. Nishina
Department of Medical Oncology, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan

K. Yamaguchi
Department of Gastroenterology, Saitama Cancer Center, Ina-machi, Kitaadachi-gun, Saitama, Japan

T. Esaki
Department of Gastrointestinal and Medical Oncology, National Kyushu Cancer Center, Fukuoka, Japan

S. Tokunaga
Department of Clinical Oncology, Osaka City General Hospital, Osaka, Japan

H. Kuwano
Department of General Surgical Science, Graduate School of Medicine, Gunma University, Maebashi, Japan

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12.7 months in the FOLFIRI group and 15.3 months in the IRIS group (HR 0.755; 95 % CI 0.580–0.983).
Conclusions IRIS is non-inferior to FOLFIRI for OS as second-line chemotherapy for mCRC. IRIS can be an option for second-line chemotherapy of mCRC. (ClinicalTrials.gov Number: NCT00284258).

Keywords Colorectal cancer · FIRIS · Irinotecan · IRIS · S-1

Introduction

At present, the combination of 5-fluorouracil (5-FU)/leucovorin (LV) with either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) is the mainstream chemotherapy for metastatic colorectal cancer (mCRC) worldwide (O'Neil and Goldberg 2008; National Comprehensive Cancer Network 2014a, b; Tournigand et al. 2004).

In Japan, FOLFOX or FOLFIRI is widely used as the first-line or second-line chemotherapy for mCRC. However, infusional 5-FU-based regimens such as FOLFOX or FOLFIRI are inconvenient because continuous infusion and implantation of an intravenous port system are required. In addition, their use is sometimes complicated by catheter-related infections and thrombosis. Replacement of infusional 5-FU with an oral anticancer drug may be convenient and reduce the burden on patients and healthcare professionals.

In Japan, oral S-1 has been widely used for the treatment of gastrointestinal cancers. In phase 2 studies of IRIS combining S-1 and irinotecan for mCRC, the response rates ranged from 52.5 to 62.5 %, and the median progression-free survival (PFS) was 7.8–8.6 months, suggesting that IRIS may have comparable efficacy to FOLFIRI as a first-line therapy (Goto et al. 2006; Komatsu et al. 2011; Tsunoda et al. 2009; Komatsu et al. 2010: Shiozawa et al. 2010).

The FIRIS study is a phase 3 randomised study to investigate the non-inferiority of IRIS to FOLFIRI, which is a standard second-line chemotherapy for mCRC after failure of fluoropyrimidine chemotherapy with or without oxaliplatin. In the primary analysis, the median PFS was 5.1 months in the FOLFIRI group and 5.8 months in the IRIS group [hazard ratio (HR) 1.077; 95 % confidence interval (CI) 0.879–1.319], demonstrating the non-inferiority of IRIS to FOLFIRI (Muro et al. 2010). Thereafter, in the ESMO Consensus Guidelines for management of patients with colon and rectal cancer, IRIS is listed in the table of the treatment options (Schmoll et al. 2012). However, the survival data of the FIRIS study were immature. In this paper, an updated analysis focusing on overall survival (OS) is reported.

Patients and methods

Study design and treatment

This randomised, open-label, phase 3 study of second-line chemotherapy for patients with mCRC was conducted at 40 institutions in Japan (see "Appendix"). The eligibility criteria and design were described in detail in a previous report (Muro et al. 2010).

The patients were centrally randomised to receive either FOLFIRI or IRIS using the minimisation method with stratification by institution, prior therapy (with oxaliplatin vs. without oxaliplatin), and performance status (PS; 0 vs. 1). In the FOLFIRI group, the patients received *l*-LV (200 mg/m^2) and irinotecan (150 mg/m^2) followed by a bolus injection of 5-FU (400 mg/m^2) on day 1, and then continuous infusion of 5-FU (2,400 mg/m^2) over 46 h, repeated every 2 weeks (4 weeks counted as one course). The dose of irinotecan (150 mg/m^2) given to the FOLFIRI group is the upper limit of the approved dose in Japan (Fuse et al. 2008). The IRIS group received irinotecan (125 mg/m^2) on days 1 and 15 and S-1 [40–60 mg/body, based on the body surface area (BSA): BSA < 1.25 m^2, 40 mg/body; 1.25 m^2 ≤ BSA < 1.5 m^2, 50 mg/body; BSA ≥ 1.5 m^2, 60 mg/body] twice daily for 2 weeks followed by 2 weeks of rest, based on the results of the phase 2 study (Goto et al. 2006). The treatment was continued until one of the following events occurred: disease progression (PD); unacceptable toxicity; or patient's refusal to continue treatment.

The primary objective of the study was to demonstrate the non-inferiority of IRIS to FOLFIRI for PFS.

N. Boku
Department of Clinical Oncology, St. Marianna University School of Medicine, Kawasaki, Japan

Y. Komatsu
Department of Cancer Chemotherapy, Hokkaido University Hospital Cancer Center, Sapporo, Japan

M. Watanabe
Department of Surgery, Kitasato University School of Medicine, Sagamihara, Japan

I. Hyodo
Division of Gastroenterology, Tsukuba University Hospital, Tsukuba, Japan

S. Morita
Department of Biostatistics and Epidemiology, Yokohama City University Medical Center, Yokohama, Japan

K. Sugihara
Department of Surgical Oncology, Tokyo Medical and Dental University Graduate School, Tokyo, Japan

The secondary endpoints included OS, response rate, and safety. In addition, pre-planned subgroup analyses were performed.

The protocol of the study was approved by the institutional review board or ethics committee and was conducted in compliance with the Declaration of Helsinki and Japanese ethical guideline for clinical studies. Written informed consent was obtained from all patients participating in the study.

Study assessments

Physical examinations and laboratory tests were performed at baseline and repeated at least every 2 weeks during the treatment. Tumours were assessed at baseline (within 1 month before enrolment), 2, 3, and 4 months after enrolment, and every 2 months thereafter until progression. Progression was defined when any of the following three events occurred: (1) PD based on the response evaluation criteria in solid tumours (RECIST) version 1.0; (2) clinical progression judged by the investigator; or (3) death from any cause without progression. PFS was calculated from the date of randomisation to the date of the events described above.

OS was calculated from the date of randomisation to the date of death from any cause. Surviving patients, including those lost to follow-up, were censored at the date of last confirmation of survival. Toxicity was evaluated based on the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0).

Statistical analysis

The intent-to-treat (ITT) population consisted of all randomised patients, and the per-protocol set (PPS) population was defined as the ITT population excluding patients who violated protocols to a considerable extent, including major protocol inclusion/exclusion criteria or treatment protocols.

The primary endpoint of PFS was assumed to be 4 months in both groups. By defining a 1-month shorter PFS with IRIS than with FOLFIRI as the acceptance limit for non-inferiority, which was also the minimum difference detected by monthly image examinations, a non-inferiority margin of 1.333 was selected. After the required number of events was calculated with a one-sided α of 0.025 and a power of 80 %, a target sample size of 400 patients was selected.

For the primary endpoint of PFS and the secondary endpoint of OS, the HR for IRIS to FOLFIRI and its 95 % CI were calculated to show the non-inferiority of IRIS to FOLFIRI, respectively. Furthermore, Bayesian analyses were carried out to assess the robustness of these preliminary results. Post hoc analyses for posterior probabilities with log HR within the range of 1.333–1.15 (a stricter threshold) were performed (Spiegelhalter et al. 1994).

For the primary analysis, the collection of the primary endpoint PFS data was cut off on 31 December 2008 and the number of confirmed events was 389 (Muro et al. 2010). The final analysis was performed on 29 July 2010 (2.5 years after the last patient was enrolled, as pre-specified in the protocol).

Subgroup analyses were pre-planned to determine whether therapeutic efficacy interacted with sex, age, histological type, PS, and prior chemotherapy with or without oxaliplatin. PFS and OS were estimated using the Kaplan–Meier method. The 95 % CI for the median PFS and OS was calculated using the method of Brookmeyer and Crowley (Brookmeyer and Crowley 1982). All p values were two-sided. All statistical analyses were performed using SAS version 8.2 (SAS Institute, Cary, NC, USA). This study is registered with ClinicalTrials.gov (Number: NCT00284258).

Results

Patient populations

A total of 426 patients from 40 institutions in Japan were enrolled from January 2006 to January 2008, and randomised to receive either FOLFIRI or IRIS ($n = 213$ in each group; Fig. 1). The PPS population consisted of 203 patients in the FOLFIRI group and 198 in the IRIS group. All patients who received a study treatment [FOLFIRI ($n = 211$) and IRIS ($n = 210$)] were included in the safety evaluation. The baseline characteristics were well balanced between the two groups, as previously reported (Muro et al. 2010).

Treatment

The median number of courses of the protocol treatment was 4.0 (range 1–27) and 4.0 (range 1–23) in the FOLFIRI and IRIS groups, respectively. The median dose intensity relative to the planned dose intensity was irinotecan 78.3 %, bolus 5-FU 76.9 %, and infusional 5-FU 81.5 % in the FOLFIRI group, and irinotecan 78.3 % and S-1 88.9 % in the IRIS group. Treatments were discontinued because of PD in 71.8 % of the FOLFIRI group ($n = 153$) and 67.1 % of the IRIS group ($n = 143$). Treatment discontinuation owing to adverse events was more frequently observed in the IRIS group ($n = 49$, 23.0 %) than in the FOLFIRI group ($n = 28$, 13.1 %). Overall, 179 (84.8 %) patients in the FOLFIRI group and 184 (87.6 %) patients in the IRIS group required at least one dose delay or dose reduction at some point during the treatment course.

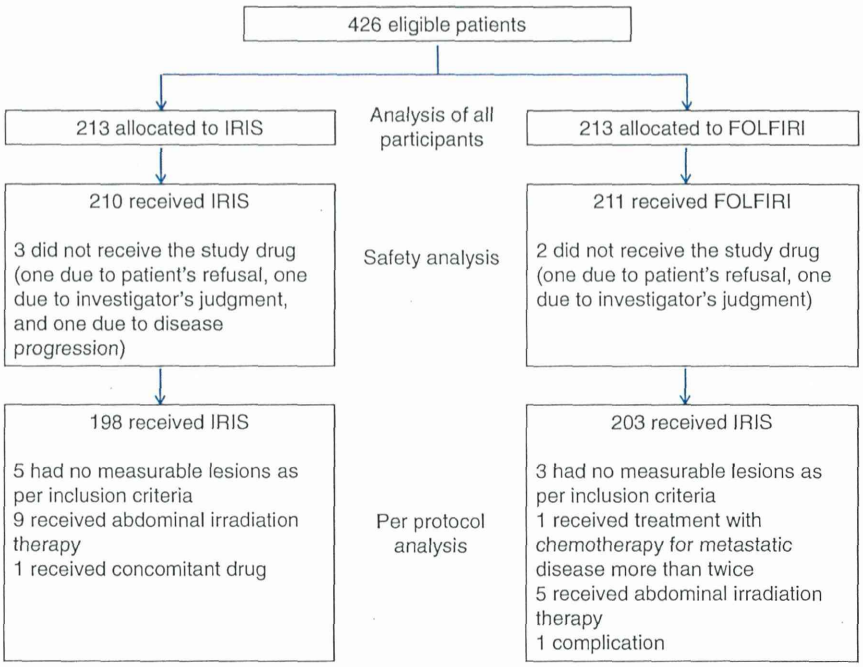

Fig. 1 Consort diagram. *IRIS* irinotecan plus S-1, *FOLFIRI* infusional 5-fluorouracil, folinic acid, and irinotecan

Third-line chemotherapy after failure of the protocol treatment in the second-line therapy was given to 168 (78.9 %) patients in the FOLFIRI group and 153 (71.8 %) patients in the IRIS group. In these patients, molecularly targeted agents were concomitantly used in 58 (27.2 %) patients (bevacizumab, 45; cetuximab, 17) in the FOLFIRI group and 52 (24.4 %) patients (bevacizumab, 38; cetuximab, 16) in the IRIS group, and no marked difference in the use of these agents was evident between the two groups (Table 1).

Table 1 Cancer treatment after discontinuation of the study treatment

Treatment	FOLFIRI *n* (%)	IRIS *n* (%)
No	45 (21.1)	60 (28.2)
Yes	168 (78.9)	153 (71.8)
Bevacizumab		
FOLFOX + bevacizumab	33 (15.5)	29 (13.6)
FOLFIRI + bevacizumab	19 (8.9)	12 (5.6)
5-FU/LV + bevacizumab	8 (3.8)	6 (2.8)
Cetuximab		
FOLFIRI + cetuximab	0 (0)	1 (0.5)
Irinotecan + cetuximab	16 (7.5)	13 (6.1)
FOLFOX	60 (28.2)	61 (28.6)
FOLFIRI	9 (4.2)	25 (11.7)
5-FU/LV	7 (3.3)	10 (4.7)
Irinotecan	8 (3.8)	20 (9.4)
S-1	35 (16.4)	7 (3.3)
Irinotecan + S-1	16 (7.5)	3 (1.4)
Operation	12 (5.6)	11 (5.2)
Radiation therapy	29 (13.6)	18 (8.5)
Other	48 (22.5)	45 (21.1)

FOLFIRI infusional 5-fluorouracil, folinic acid, and irinotecan, *IRIS* irinotecan plus S-1, *FOLFOX* 5-fluorouracil, LV, and oxaliplatin, *5-FU* 5-fluorouracil, *LV* leucovorin

Overall survival

As of 29 July 2010 when the data collection was finally cut off, 352 deaths (FOLFIRI, 178; IRIS, 174) were confirmed with a median follow-up of 39.2 months. A total of 125 censored cases resolved from the last cut-off that we reported. The median OS was 17.4 months in the FOLFIRI group and 17.8 months in the IRIS group (HR 0.900; 95 % CI 0.728–1.112; $p = 0.003$ for a non-inferiority margin of 1.333; Fig. 2a). In the PPS population, the median OS was 17.4 months in the FOLFIRI group and 17.4 months in the IRIS group (HR 0.905; 95 % CI 0.728–1.126). The Bayesian posterior probabilities that the HR of IRIS relative to FOLFIRI would be <1.333 and <1.15 were calculated to be >99.9 % and >98.7 %, respectively.

Progression-free survival

When the data collection was finally cut off, 412 events including an increase of 23 events from the primary analysis were confirmed. The median PFS was 5.1 months in the FOLFIRI group and 5.8 months in the IRIS group. In the ITT population, the HR for IRIS to FOLFIRI was

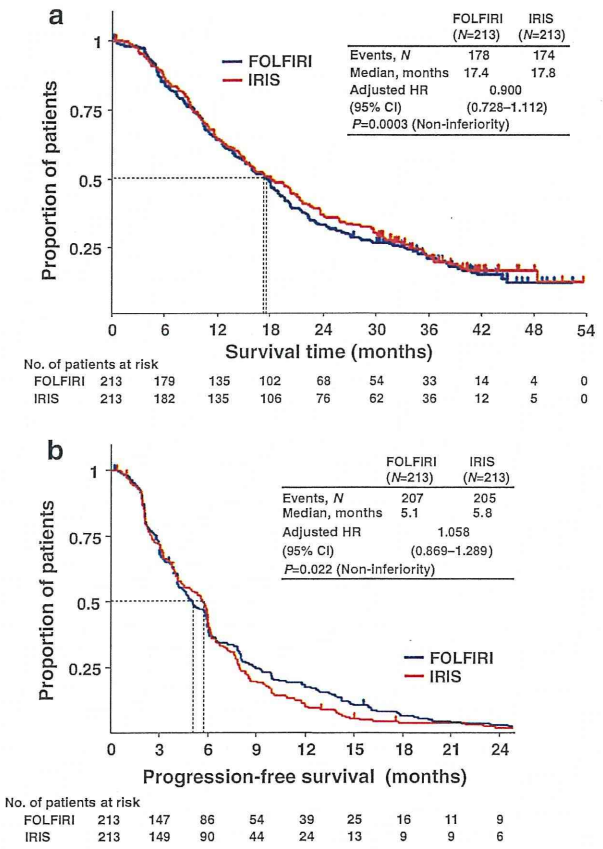

Fig. 2 OS (**a**) and PFS (**b**) in the intention-to-treat population. *IRIS* irinotecan plus S-1, *FOLFIRI* infusional 5-fluorouracil, folinic acid, and irinotecan, *HR* hazard ratio, *CI* confidence interval

1.058 (95 % CI 0.869–1.289; $p = 0.022$) and consistent with the primary analysis (Fig. 2b). In the PPS population, the median PFS was 5.1 months in the FOLFIRI group and 5.7 months in the IRIS group (HR 1.035; 95 % CI 0.843–1.271), being consistent with the primary analysis.

Subgroup analyses

Figure 3 shows the results of the subgroup analyses for OS. Except for the interaction of prior chemotherapy containing oxaliplatin (yes vs. no) and therapeutic effect, no interaction was observed between sex (male vs. female), age (<65 vs. 65–75 years), histological type (adenocarcinoma, well differentiated vs. moderately differentiated vs. poorly differentiated), or PS (0 vs. 1), and the therapeutic effect of IRIS was comparable to that of FOLFIRI.

In the subgroups of patients treated with FOLFIRI ($n = 128$) or IRIS ($n = 129$) who had received prior chemotherapy containing oxaliplatin, the median OS was 15.3 months in the IRIS group and 12.7 months in the FOLFIRI group (adjusted HR 0.755; 95 % CI 0.580–0.983); showing better survival in the IRIS group than in the FOLFIRI group (Fig. 4a). On the other hand, in the subgroups of patients treated with FOLFIRI ($n = 85$) or IRIS ($n = 84$) who had received prior chemotherapy without oxaliplatin, the median OS was more favourable in the FOLFIRI group than in the IRIS group (26.9 vs. 23.6 months; adjusted HR 1.229; 95 % CI 0.866–1.745) (Fig. 4b).

Safety

The results of the updated safety analysis were very similar to those previously reported (Muro et al. 2010). Briefly, specific adverse events were haematological toxicity (grade 3 or 4 neutropenia), which was observed in 52.1 % of the FOLFIRI group and 36.2 % of the IRIS group, and non-haematological toxicity (grade 3 diarrhoea), which was observed in 4.7 % of the FOLFIRI group and 20.5 % of the IRIS group. One treatment-related death from hypotension caused by shock was reported in the FOLFIRI group within 28 days after the end of the protocol treatment, while no treatment-related deaths were reported in the IRIS group.

Discussion

We conducted a phase 3 randomised study to compare FOLFIRI and IRIS as second-line chemotherapies for patients with mCRC. The primary analysis demonstrated the non-inferiority of IRIS to FOLFIRI for PFS as the primary endpoint. The secondary endpoints of OS and response rate were also equivalent between the two groups (Muro et al. 2010), but the data were immature with many cases censored at the primary analysis. In this updated analysis, data obtained 2.5 years after the end of the enrolment period (as pre-specified in the protocol) were included. The non-inferiority of IRIS to FOLFIRI for PFS as the primary endpoint was re-confirmed, and non-inferiority for OS was also demonstrated. In addition, the probabilities of HR < 1.333 and HR < 1.15, which are stricter non-inferiority margins for OS, were estimated to be >99.9 and >98.7 %, respectively, using Bayesian analyses. Our study results are highly robust.

When our study was started, FOLFOX was already one of the standard treatments worldwide, but oxaliplatin had just been launched and was rarely used in an adjuvant setting in Japan. Actually, 85 (39.9 %) patients in the FOLFIRI group and 84 (39.4 %) patients in the IRIS group had received prior chemotherapy without oxaliplatin. Most of these patients received prior chemotherapy in an adjuvant setting including tegafur-uracil with or without LV (27 patients in the FOLFIRI group and 32 in the IRIS group) or 5-FU/LV (11 patients in the FOLFIRI group and 7 in the IRIS group).

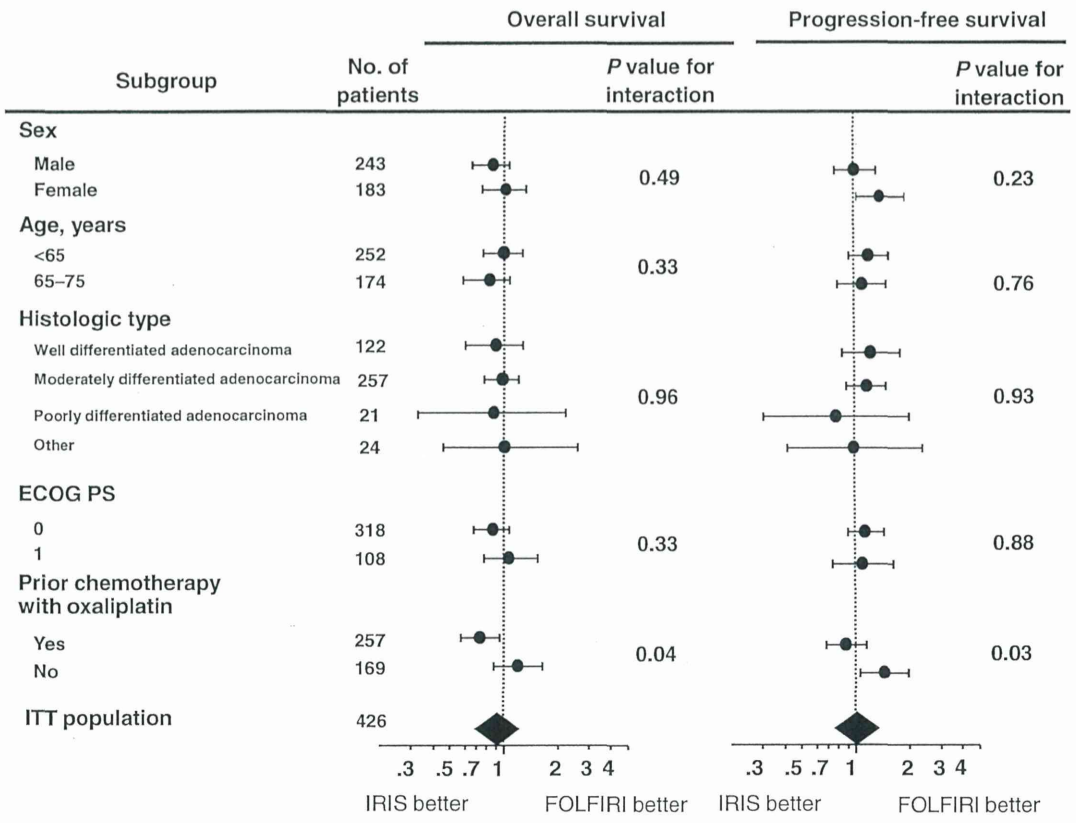

Fig. 3 Subgroup analyses of OS and PFS in the intention-to-treat (ITT) population. *IRIS* irinotecan plus S-1, *FOLFIRI* infusional 5-fluorouracil, folinic acid, and irinotecan

In the subgroup of patients who had received prior oxaliplatin, the adjusted HR for OS of IRIS to FOLFIRI was 0.755 (95 % CI 0.580–0.983), suggesting that IRIS might prolong the survival of patients who failed in first-line chemotherapy with oxaliplatin-containing regimens, compared with FOLFIRI. On the other hand, in the subgroup of patients who had received prior chemotherapy without oxaliplatin, the median OS was longer in the FOLFIRI group than in the IRIS group (adjusted HR 1.229; 95 % CI 0.866–1.745). Interactions between prior chemotherapy and therapeutic effects in the two groups may need to be considered.

There are some possible reasons for the interactions. Resistance to 5-FU/LV shared by patients receiving first-line FOLFOX and second-line FOLFIRI may be overcome to some extent by the dihydropyrimidine dehydrogenase (DPD) inhibitor contained in S-1. On the other hand, it is also speculated that cross-resistance to DPD inhibitory agents may be partly overcome by bolus 5-FU/LV in patients receiving FOLFIRI (Baba et al. 2012), considering the fact that many patients in the subset without prior oxaliplatin received adjuvant chemotherapy with DPD inhibitory agents as a prior therapy. However, further studies, including basic studies, are needed to clarify this finding.

In recent phase 3 trials of molecularly targeted agents used in second-line chemotherapy regimens, the median OS was reported to be 10.7–14.5 months in groups treated with anti-EGFR antibodies. The survival data in the present study seemed to be consistent with the survival data in these recent studies of molecularly targeted agents (Sobrero et al. 2008; Peeters et al. 2010).

In conclusion, this study has demonstrated that IRIS is non-inferior to FOLFIRI not only for PFS, but also for OS as second-line chemotherapy for mCRC. Thus, IRIS should be considered as a treatment option. In particular, IRIS may be a favourable regimen for patients previously treated with chemotherapy containing oxaliplatin. To further improve the outcome, future studies of both first-line and second-line therapies are warranted to evaluate IRIS in combination with molecularly targeted agents such as bevacizumab, cetuximab, and panitumumab.

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