S-1 and oxaliplatin (SOX) plus bevacizumab versus mFOLFOX6 plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer: updated overall survival analyses of the open-label, non-inferiority, randomised phase III: SOFT study

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ABSTRACT
Objective: The SOFT study previously demonstrated that S-1 and oxaliplatin (SOX) plus bevacizumab was non-inferior to l-leucovorin, fluorouracil and oxaliplatin (mFOLFOX6) plus bevacizumab in terms of the primary end point of progression-free survival (PFS) as first-line chemotherapy for metastatic colorectal cancer (mCRC). The overall survival (OS) data were immature at the time of the primary analysis.

Methods: A total of 512 patients were enrolled and randomly assigned to receive either mFOLFOX6 plus bevacizumab (5 mg/kg of bevacizumab, followed by 200 mg/m^2 of l-leucovorin given simultaneously with 85 mg/m^2 of oxaliplatin, followed by a 400 mg/m^2 bolus of 5-FU on day 1 and then 2400 mg/m^2 of 5-FU as an intravenous infusion over the course of 46 hours, every 2 weeks) or SOX plus bevacizumab (7.5 mg/kg of bevacizumab, 130 mg/m^2 of oxaliplatin on day 1 and 40–60 mg of S-1 two times per day for 2 weeks, followed by a 1-week rest). The primary end point was PFS. After the primary analysis, the follow-up survey was cut-off on 30 September 2013, and the final OS data were analysed.

Results: With a median follow-up of 37.7 months, the median survival time (MST) was 29.7 months with mFOLFOX6 plus bevacizumab and 29.6 months with SOX plus bevacizumab (HR, 1.018; 95% CI 0.823 to 1.258). Median PFS was 11.7 months in the mFOLFOX6 group and 12.2 months in the SOX group (HR, 1.051; 95% CI 0.876 to 1.262; p_{non-inferiority}=0.0115).

Conclusion: Our results reconfirmed that SOX plus bevacizumab is non-inferior to mFOLFOX6 plus bevacizumab in terms of progression-free survival (PFS). MST did not differ between the groups. SOX plus bevacizumab is considered an effective regimen for first-line chemotherapy in patients with mCRC and can be used instead of mFOLFOX6 plus bevacizumab.

Trial registration number: JapicCTI-090699.

INTRODUCTION
Fluorouracil and leucovorin combined with either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) plus bevacizumab has been widely used as first-line or second-line chemotherapy for metastatic colorectal cancer (mCRC). However, these regimens require visits to the hospital every 2 weeks, placement of a central venous (CV) port, and a portable infusion pump. Such devices can increase the risk of adverse events such as infection, thrombosis and catheter-related problems. Replacement of infusional fluorouracil with an oral anticancer agent (capecitabine or S-1) might be more convenient and reduce the burden on patients and physicians. The NO16966 trial showed that capecitabine and oxaliplatin (CapeOX) plus bevacizumab is non-inferior to FOLFOX plus bevacizumab in terms of progression-free survival (PFS).

S-1 is an oral anticancer agent that combines tegafur (a prodrug of fluorouracil) with two modulators: gimeracil, which reversibly inhibits dihydropyrimidine dehydrogenase (the primary metabolising
enzyme of fluorouracil) and thereby maintains effective fluorouracil concentrations in the blood for prolonged periods; and oteracil potassium, which suppresses the activity and toxicity of fluorouracil in gastrointestinal tissue.3

The SOFT study was a phase III trial designed to validate the non-inferiority of S-1 and oxaliplatin (SOX) plus bevacizumab to mFOLFOX6 plus bevacizumab in terms of PFS in patients with mCRC who had not previously received chemotherapy. In the primary analysis, median PFS was 11.5 months (95% CI 10.7 to 13.2) in the mFOLFOX6 plus bevacizumab group and 11.7 months (95% CI 10.7 to 12.9) in the SOX plus bevacizumab group (HR, 1.04; 95% CI 0.86 to 1.27; less than non-inferiority margin of 1.33, p non-inferiority =0.014), thereby demonstrating the non-inferiority of SOX plus bevacizumab to mFOLFOX6 plus bevacizumab.4 We now report the results of updated analyses of overall survival (OS), which was based on immature data at the primary analysis, and waterfall plots (WFP).

METHODS

Study design

The SOFT study was an open-label, non-inferiority, randomised phase III trial performed in 82 institutions in Japan. The methods of this study have been described in detail previously.4 This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and complied with Japanese ethical guidelines for clinical studies.

Patients

The main inclusion criteria were an age of 20–80 years, histologically confirmed adenocarcinoma of the colorectum, curatively unresectable, advanced or recurrent colorectal cancer; an Eastern Cooperative Oncology Group performance status of 0 or 1, assessable lesions and no previous chemotherapy or radiotherapy for mCRC. The main exclusion criteria were exposure to oxaliplatin-based regimens as adjuvant chemotherapy, the presence of a primary lesion associated with a severe stricture, precluding passage of an endoscope and substantial peritoneal metastasis as confirmed on imaging studies.4

Randomisation and blinding

Participants were randomly assigned (1:1) to receive either mFOLFOX6 plus bevacizumab or SOX plus bevacizumab. Randomisation was done centrally using the minimisation method, with stratification according to institution and whether postoperative adjuvant chemotherapy had been given. Investigators and patients were not blinded to the treatment assignments.

Treatment

On day 1 of each 2-week period during the study, patients in the mFOLFOX6 plus bevacizumab group received a 5 mg/kg intravenous infusion of bevacizumab and a simultaneous intravenous infusion of 85 mg/m² oxaliplatin, 200 mg/m² leucovorin, 400 mg/m² bolus fluorouracil and 2400 mg/m² infusional fluorouracil (46 hours), delivered with an infusion pump. On day 1 of each 3-week period during the study, patients in the SOX plus bevacizumab group received a 7.5 mg/kg intravenous infusion of bevacizumab, followed by an intravenous infusion of 130 mg/m² oxaliplatin, S-1 (40–60 mg, based on the body surface area (BSA): BSA <1.25 m², 50 mg; BSA ≥1.25 m² to <1.5 m², 60 mg; BSA ≥1.5 m², 60 mg) was administered orally two times per day from after dinner on day 1 to after breakfast on day 15, followed by a 7-day rest. Maintenance chemotherapy with fluorouracil/leucovorin or S-1 was permitted after discontinuing oxaliplatin, bevacizumab or both. Cycles were repeated until the criteria for withdrawal of the study treatment were met. Additional details, that is, dose modifications, have been previously reported.4

Assessments

Tumour assessments (eg, CT or MRI) were performed within 30 days before starting the study treatment and were repeated at 8-week intervals in both groups. The attending physicians assessed response according to the Response Evaluation Criteria in Solid Tumours (RECIST, V.1.0). Safety assessments were performed on day 1 of each cycle. (Safety was also evaluated in week 2 of the first cycle.) Adverse events were graded according to the Common Terminology Criteria for Adverse Events (V.3.0).
Outcomes

The primary end point was PFS, defined as the interval from the date of enrolment to the date on which progressive disease was first confirmed or the date of death from any cause, whichever came first. Progressive disease, defined as a greater than 20% increase in the sum of the longest diameters of target lesions from baseline, was assessed solely by the responsible investigator and was included in the assessment of disease progression for target lesions. Exacerbation of underlying disease and the appearance of new lesions were included in the assessment of disease progression for new non-target lesions. Secondary end points were OS, time to treatment failure, response rate (RR), disease control rate, curative resection rate and adverse events.

Statistical analysis

On the basis of previous studies, the median PFS associated with mFOLFOX6 plus bevacizumab was estimated to be 10 months. Non-inferiority was established if the upper confidence limit of the estimated HR was less than 1.33. We estimated that the required number of progression events would be 388. With a two-sided α of 0.05 and a power of 80%, we estimated that we would need 250 patients in each group to achieve the required number of events by 1.5 years after enrolment of the last patient. For the primary analysis, collection of the primary end point data was cut-off on 30 June 2012, and the number of confirmed events was 413. The cut-off date for this updated analysis was 30 September 2013 (2.5 years after the last patient was enrolled, as specified in the protocol). We estimated time-dependent events with the Kaplan-Meier method. We calculated HRs and their CIs with a Cox proportional-hazards model, adjusted for whether postoperative adjuvant chemotherapy had been given and the treatment groups as covariates. The follow-up periods for PFS and OS were calculated separately for censored patients only. In addition, we performed interaction tests to assess treatment effects according to baseline characteristics, such as history of adjuvant chemotherapy. Early tumour shrinkage (ETS) was defined as ≥20% decrease in the sum of the longest diameters of RECIST target lesions at 8 weeks as compared with the baseline value. Depth of response (DpR) was defined as the percentage of tumour shrinkage, based on the longest diameters or reconstructed volume at the lowest point (nadir) as compared with the baseline value. In our study, DpR was calculated using the longest diameters, as done in the TRIBE study. All statistical analyses were performed using SAS V.9.2 software. This trial is registered with the Japan Pharmaceutical Information Center (No. JapicCTI-090699).

RESULTS

Between February 1, 2009 and March 31, 2011, a total of 512 patients were enrolled and randomly assigned to receive either mFOLFOX6 plus bevacizumab or SOX plus bevacizumab (figure 1). One patient assigned to mFOLFOX6 plus bevacizumab was found not to have colorectal adenocarcinoma after randomisation and was therefore excluded from the primary analyses. The baseline characteristics were well balanced between the two groups, as reported previously.

As of September 30, 2013, the final cut-off date for data collection, median follow-up for the OS analysis was 37.7 months (range, 0.3–52.8). In the mFOLFOX6 plus bevacizumab group, 169 patients (66.3%) had died. The causes of death were progressive disease in 161 patients, other diseases in 2 patients, other reasons in 3 patients and unknown in 3 patients. In the SOX plus bevacizumab group, 174 patients (68.0%) were confirmed to have died. The causes of death were progressive disease in 165 patients, other diseases in 5 patients, other reasons in 2 patients and unknown in 2 patients. In both groups combined, a total of 343 patients had died, representing an increase of 129 deaths as compared with the primary analysis.

Median survival time (MST) was 29.7 months (95% CI 26.5 to 33.1) in the mFOLFOX6 plus bevacizumab group and 29.6 months (25.8–34.7) in the SOX plus bevacizumab group (HR, 1.018; 95% CI 0.823 to 1.258; p<0.0133; figure 2). MST did not differ between the groups. In the subgroup analysis of OS, a significant interaction was observed between assigned regimen and number of metastases (1 vs ≥2) (figure 3). When data collection was finally cut-off, the median follow-up for PFS analysis was 31.2 months (range, 0.0–51.6), and 465 events were confirmed. Median PFS was 11.7 months (95% CI 10.9 to 13.3) in the mFOLFOX6 plus bevacizumab group and 12.2 months (10.7–13.0) in the SOX plus bevacizumab group (HR, 1.051; 95% CI 0.876 to 1.262; p=0.0115; figure 4). The RRs (62.7% for mFOLFOX6 plus bevacizumab, 61.5% for SOX plus bevacizumab) were similar to those in the primary analysis.

The WFP represents the individual responses of target lesions evaluated according to RECIST in each group (figure 5). At the first evaluation at 8 weeks, the number of patients with ETS was 149 (65.9%) of 226 in the mFOLFOX6 plus bevacizumab group and 145 (64.2%) of 226 in the SOX plus bevacizumab group (p=0.6932). The median DpR was 44.4% in the mFOLFOX6 plus bevacizumab group (231 patients) and 43.5% in the SOX plus bevacizumab group (231 patients).

The median number of administered treatment cycles, including cycles in which protocol treatment continued but oxaliplatin (L-OHP) was omitted, was 12 (range, 1 to 97+) in the mFOLFOX6 plus bevacizumab group and 8 (range, 1–58) in the SOX plus bevacizumab group. Two patients continued to receive mFOLFOX6 plus bevacizumab at the time of data cut-off.

Among patients who discontinued the study treatment, second-line treatment was given to 203 (80.2%) of the 253 patients in the mFOLFOX6 plus bevacizumab group and 209 (81.6%) of the 256 patients in the SOX plus bevacizumab group.
Figure 1 CONSORT diagram. *After randomisation, it was verified that this patient did not have colorectal carcinoma and so was excluded from primary analysis; however, this patient was included in safety analyses because some cycles of assigned treatment were received. mFOLFOX6, modified regimen of l-leucovorin, fluorouracil and oxaliplatin; pts, patients; SOX, S-1 and oxaliplatin.

Figure 2 Kaplan-Meier curves for OS. mFOLFOX6, modified regimen of l-leucovorin, fluorouracil and oxaliplatin; MST, median survival time; OS, overall survival; SOX, S-1 and oxaliplatin.
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The results of the updated safety analyses were very similar to those reported previously. The incidences of grade 3 or higher leucopenia and neutropenia were significantly higher in the mFOLFOX6 plus bevacizumab group (8.4% and 33.7%, respectively) than in the SOX plus bevacizumab group (2.4% and 8.8%, respectively). The incidences of grade 3 anorexia and diarrhoea were significantly higher in the SOX plus bevacizumab group (5.2% and 9.2%, respectively) than in the mFOLFOX6 plus bevacizumab group (1.2% and 2.8%, respectively). The incidence of alopecia was significantly higher in the mFOLFOX6 plus bevacizumab group (24.5%) than in the SOX plus bevacizumab group (6.0%). The incidences of sensory neuropathy and hand-foot syndrome (HFS) of any grade did not differ significantly between the mFOLFOX6 plus bevacizumab group (90.0% and 17.7%, respectively), and the SOX plus bevacizumab group (90.0% and 17.7%, respectively).
and the SOX plus bevacizumab group (91.2% and 15.6%, respectively). In the updated results of the safety analyses, there were no cases of gastrointestinal perforation, which had occurred in one patient in the mFOLFOX6 plus bevacizumab group and five patients in the SOX plus bevacizumab group at the time of the primary analysis.¹

**DISCUSSION**

The previously reported primary analysis of the present study demonstrated that SOX plus bevacizumab is non-inferior to mFOLFOX6 plus bevacizumab in terms of PFS, the primary end point.¹ As for the secondary end point of OS, SOX plus bevacizumab was shown to be equivalent to mFOLFOX6 plus bevacizumab. However, at the primary analysis, the median follow-up time was 23.4 months, and many patients had censored data; the OS data were thus immature. In the present updated analysis, the median follow-up time was 37.7 months. Nonetheless, OS was similar for SOX plus bevacizumab and mFOLFOX6 plus bevacizumab. Moreover, SOX plus bevacizumab was reconfirmed to be non-inferior to mFOLFOX6 plus bevacizumab in terms of PFS, the primary end point.

The results of subgroup analyses of OS showed a significant interaction between regimen and number of metastases (1 vs ≥2) and marginally significant interactions between regimen and lung metastases. SOX plus bevacizumab might have been more effective in these patients, but the reason for the interactions is unclear.

Recent phase III studies of patients with wild-type K-ras tumours have reported a MST of about 30 months.⁹⁻¹⁰ In the TRIBE study, the MST of patients who received FOLFOXIRI plus bevacizumab was 29.8 months.¹¹ In our study, the MST in the SOX plus bevacizumab group was 29.6 months irrespective of K-ras status, which was non-inferior to that in patients who received FOLFOXIRI plus bevacizumab, a regimen combining three chemotherapeutic drugs with bevacizumab. Molecular-targeted agents and investigational drugs were used for third-line and subsequent treatment. Such subsequent treatment is considered one factor contributing to the prolonged survival. Recently, considerable attention has focused on ETS and DpR as prognostic factors for PFS and OS after first-line treatment of mCRC.¹² ETS was similar in patients who received SOX plus bevacizumab and those who received mFOLFOX6 plus bevacizumab. Previous studies reported an ETS rate of 60%–70% for FOLFOX or FOLFIRI plus an anti-epidermal growth factor receptor (EGFR antibody.¹² In contrast, the ETS rate was about 50% for FOLFIRI plus bevacizumab.⁸⁻¹² The ETS rate was thus lower in patients who received a two-drug chemotherapy regimen plus bevacizumab than in those who received chemotherapy plus an anti-EGFR antibody. However, the ETS rate in patients who received SOX...
plus bevacizumab was 64.2%, which was comparable to that in patients given chemotherapy plus an anti-EGFR antibody. In the TRIBE study, the median DpR rate was 37.8% for FOLFIRI plus bevacizumab and 43.4% for FOLFOXIRI plus bevacizumab. In our study, the median DpR rate was 43.5% in the SOX plus bevacizumab group, which was similar to that in the mFOLFOX6 plus bevacizumab group (44.4%) and comparable to the median DpR obtained after FOLFOXIRI plus bevacizumab. Good ETS and DpR were thus obtained in our study, which might have also contributed to OS. SOX plus bevacizumab can be given on an outpatient basis, with patients presenting at the hospital once every 3 weeks, and does not require placement of a CV port. It is thus more convenient for patients than mFOLFOX6 plus bevacizumab. In addition, the incidence of grade 3 or higher neutropenia was distinctly lower with SOX plus bevacizumab than with mFOLFOX6 plus bevacizumab, making the former an easy-to-use regimen. A phase III study in South Korea showed that SOX is non-inferior to CapeOX as first-line treatment for mCRC.13 The incidence of HFS was lower in patients who received SOX (14%) than in those who received CapeOX (31%), whereas the RR was significantly higher in the SOX group (47%) than that in the CapeOX group (36%). This finding also suggests that SOX plus bevacizumab can contribute to maintaining a good quality of life among patients. In this respect, SOX might be more advantageous to patients than CapeOX.

In conclusion, our updated analysis reconfirmed that SOX plus bevacizumab is non-inferior to mFOLFOX6 plus bevacizumab in terms of PFS in patients with mCRC who had not previously received chemotherapy. The MST was about 30 months and was similar in the SOX plus bevacizumab group and the mFOLFOX6 plus bevacizumab group. SOX plus bevacizumab is considered an effective regimen for first-line chemotherapy in patients with mCRC and can be used instead of mFOLFOX6 plus bevacizumab.

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Contributors HB, YY, YS, TS, KT, HM, KM, MW, YS and KS formed the coordinating committee, designed and wrote the ancillary protocol, analysed and interpreted the data, and prepared the report. SM analysed the data. All authors collected the data, reviewed and helped revise the manuscript draft, and approved the final manuscript ahead of submission.

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Patient consent All patients provided written informed consent before enrolment.

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REFERENCES
1. Tournycaig C, André T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 2004;22:229–37.
2. Cassidy J, Clarke S, Diaz-Rubio E, et al. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/leucovorin plus oxaliplatin as first-line therapy for metastatic colorectal cancer. J Clin Oncol 2008;26:2006–12.
3. Satoh T, Sakata Y. S-1 for the treatment of gastrointestinal cancer. Expert Opin Pharmacother 2012;13:1943–9.
4. Yamada Y, Takahari D, Matsumoto H, et al. Leucovorin, fluorouracil, and oxaliplatin plus bevacizumab versus S-1 and oxaliplatin plus bevacizumab in patients with metastatic colorectal cancer (SOFT): an open-label, non-inferiority, randomised phase 3 trial. Lancet Oncol 2013:14:1278–86.
5. Saltz LB, Clarke S, Díaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol 2008;26:2013–9.
6. Hochster HS, Hart LL, Ramanathan RK, et al. Safety and efficacy of oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer: results of the TREE study. J Clin Oncol 2008;26:3523–9.
7. Piessevaux H, Buyse M, Schlichting M, et al. Use of early tumor shrinkage to predict long-term outcome in metastatic colorectal cancer treated with cetuximab. J Clin Oncol 2013;31:3764–75.
8. Cremolini C, Loupakis F, Antoniotti C, et al. Early tumor shrinkage and depth of response predict long-term outcome in metastatic colorectal cancer patients treated with first-line chemotherapy plus Bevacizumab: results from phase III TRIBE trial by the Gruppo Oncologico del Nord Ovest. Ann Oncol 2015;26:1188–94.
9. Heinemann V, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. Lancet Oncol 2014;15:1065–75.
10. Elez E, Argilés G, Tabernero J. First-line treatment of metastatic colorectal cancer: Interpreting FIRE-3, PEAK, and CALGB/SWOG 80405. Curr Treat Options Oncol 2015;16:52.
11. Cremolini C, Loupakis F, Antoniotti C, et al. FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study. Lancet Oncol 2015;16:1306–15.
12. Heinemann V, Stintzing S, Modest DP, et al. Early tumour shrinkage (ETS) and depth of response (DpR) in the treatment of patients with metastatic colorectal cancer (mCRC). Eur J Cancer 2015;51:1927–36.
13. Hong YS, Park YS, Lim HY, et al. S-1 plus oxaliplatin versus capecitabine plus oxaliplatin for first-line treatment of patients with metastatic colorectal cancer: a randomised, non-inferiority phase 3 trial. Lancet Oncol 2012;13: 1125–32.