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The SOFT trial: a Phase III study of the dihydropyrimidine dehydrogenase inhibitory fluoropyrimidine S-1 and oxaliplatin (SOX) plus bevacizumab as first-line chemotherapy for metastatic colorectal cancer

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ABSTRACT A combination of oxaliplatin, leucovorin and 5-fluorouracil (FOLFOX) plus bevacizumab has been widely used for the first-line chemotherapy of metastatic colorectal cancer (mCRC). S-1 is an oral fluoropyrimidine preparation that combines tegafur, a prodrug of 5-fluorouracil, with two modulators. Several studies of combination chemotherapy with oxaliplatin plus S-1 (SOX) conducted in Asia have reported promising efficacy and safety in patients with mCRC, suggesting the potential to replace mFOLFOX6. The SOFT trial (JapicCTI-090699) was a randomized Phase III trial designed to evaluate the noninferiority of SOX plus bevacizumab to mFOLFOX6 plus bevacizumab in patients with mCRC. This review summarizes the drug concept of S-1 and the results of clinical trials of S-1 and SOX in CRC and presents an overview of the SOFT trial.

Colorectal cancer (CRC) is one of the most common causes of cancer-related death in the USA, EU and Asia. Developing of chemotherapy and targeting agents have prolonged overall survival (OS) of metastatic colorectal cancer (mCRC) patients. In mCRC, doublet combination chemotherapy plus targeted agents (anti-VEGF antibody or anti-EGF receptor [EGFR] antibody) are widely accepted as first-line treatment. Combination treatment with 5-fluorouracil (5-FU), leucovorin (LV) and oxaliplatin (FOLFOX) plus bevacizumab is one of the standard therapies for mCRC [1,2]. The FOLFOX4 regimen involves two bolus infusion and two 22-h infusions of 5-FU. Although,

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modified FOLFOX regimen (mFOLFOX6) has replaced FOLFOX4 in some countries and these do afford some greater convenience in terms of one bolus infusion and one 2-day infusion instead of two bolus infusions and two 22-h infusions.

However, to administer FOLFOX, patients have to return to the hospital once every 2 weeks and require a central venous (CV) catheter and portable infusion pump. A CV catheter and infusion pump negatively affect the quality of life (QOL) of patients and can cause adverse events such as infection, thrombosis and various catheter-related problems. To overcome this drawback, capecitabine and oxaliplatin (CapeOX) have been widely used to treat mCRC. Capecitabine is another oral fluoropyrimidine derivative, and patients do not require placement of a CV catheter. CapeOX regimen requires still fewer planned hospital visits, with oxaliplatin administered every 3 weeks and capecitabine taken orally. The NO16966 trial showed that CapeOX is noninferior to FOLFOX4 in terms of progression-free survival (PFS) as a first-line treatment for mCRC [3,4]. Although CapeOX is more convenient to administer than FOLFOX, a higher incidence of hand-foot reaction (HFR) is a serious problem impairing the QOL of patients [5]. HFR is characterized by various types of skin reactions, including redness, swelling and pain of the palms of the hands or soles of the feet. The control of HFR may require the use of decreased dose levels or skipping treatment, which can reduce effectiveness. Oral dihydropyrimidine dehydrogenase (DPD) inhibitory fluoropyrimidine S-1 (TS-1[®], Taiho Pharmaceutical Co., Ltd, Tokyo, Japan; Teysuno[®], Nordic Group BV, Hoofddorp, The Netherlands) demonstrated fewer rate of HFR in comparison with capecitabine [6]. Combination chemotherapy of S-1 plus oxaliplatin (SOX) plus bevacizumab showed noninferiority to mFOLFOX6 plus bevacizumab in terms of PFS as a first-line treatment for mCRC in the multicenter Phase III trial in Japan (SOFT trial) [7–9].

In this review, we summarize the drug concept and the results of clinical trials of S-1 for mCRC, and describe an overview of the SOFT trial.

• Drug concept of S-1

From its discovery in 1957, 5-FU has been used for various solid tumors for a long time and it has been established as standard care in a lot of cancers. S-1 was developed to increase antitumor

effect and to decrease gastrointestinal toxicity of 5-FU. S-1 is an oral fluoropyrimidine preparation that combines tegafur, a prodrug of 5-FU, with 5-chloro-2,4-dihydropyridine (CDHP) and oteracil potassium (Oxo) in a molar ratio of 1:0.4:1, based on a biochemical modulation of 5-FU [10–15]. **Figure 1** shows the composition of S-1 and its biochemical modulation. After oral administration of S-1, tegafur is gradually converted into 5-FU by CYP2A6 mainly in the liver and in tumor cells. CDHP reversibly inhibits the activity of DPD, the rate-limiting enzyme for the degradation of 5-FU. Consequently, high concentrations of 5-FU in serum and tumor are maintained for prolonged periods [16]. Although maintained high concentration of 5-FU causes gastrointestinal toxicities, in the case of S-1, Oxo blocks the phosphorylation of 5-FU in the gastrointestinal tract, thereby decreasing gastrointestinal toxic effects. On these mechanisms, S-1 showed excellent antitumor activities against various types of tumors with acceptable toxicities and is approved for the treatment of gastric, colorectal, head and neck, pancreatic, bile duct, breast and non-small-cell lung cancers in Japan and for the treatment of gastric cancer in Asia and Europe [17–23].

• S-1 monotherapy for CRC

Based on the promising preclinical results [14,15], antitumor effect of S-1 for mCRC was investigated as monotherapy in two Phase II studies first of all [22–24]. In these trials, S-1 was administered orally twice daily at a standard dose of 40–60 mg according to body surface area for 28 days followed by a 14-day rest. These two trials showed same tendency that response rates of 35–39.5% and median survival time were 12 months. Toxicities were easily manageable.

Also, in adjuvant setting, S-1 monotherapy showed a noninferiority to tegafur-uracil (UFT) plus LV (UFT/LV) in terms of disease-free survival in patients with stage III colon cancer in a multicenter Phase III trial (ACTS-CC trial). The 3-year disease-free survival rate was 75.5 and 72.5% in the S-1 and UFT/LV group, respectively [25].

• S-1 plus irinotecan for mCRC

After the confirmation of clinical efficacy of S-1 as a single agent, combination therapy of S-1 and irinotecan was investigated. A Phase II study of combined therapy of S-1 and irinotecan (IRIS) was conducted and showed objective

Figure 1. Biochemical action of S-1.

DPD: Dihydropyrimidine dehydrogenase; OPRT: Orotate phosphoribosyltransferase.

response rate of 52.5% that was higher than the results of S-1 monotherapy [26]. Based on this finding, large multicenter Phase III clinical trial (FIRIS trial) was performed to investigate the noninferiority of IRIS to 5-FU, LV and irinotecan (FOLFIRI) as second-line chemotherapy for mCRC [27]. In the IRIS group, patients received irinotecan (125 mg/m²) on days 1 and 15 and S-1 (40–60 mg) twice daily for 2 weeks, repeated every 4 weeks. The primary end point was PFS. The results of this Phase III trial showed that median PFS of FOLFIRI and IRIS were 5.1 months and 5.8 months, respectively, and noninferiority was proved (hazard ratio [HR]: 1.077 [95% CI: 0.879–1.319], $p_{\text{noninferiority}} = 0.039$). The main grade 3 or higher adverse events were neutropenia (52.1% in the FOLFIRI group vs 36.1% in the IRIS group) and diarrhea (4.7 vs 20.5%). Updated results of FIRIS trial showed noninferiority of IRIS to FOLFIRI in terms of OS [28]. Recently, IRIS was stated as a treatment option for mCRC in Japanese and European guideline [29].

Phase II clinical trials evaluating a combination of S-1 and irinotecan plus bevacizumab as first-line chemotherapy have been reported. The response rates were 57.7 and 67.0% with PFS of

16.7 and 12.4 months, respectively, indicating good outcomes [30,31]. Currently, Phase III study to evaluate the S-1 and irinotecan plus bevacizumab to oxaliplatin-based standard treatment in terms of PFS is in progress (TRICOLORE trial; UMIN000007834).

• S-1 plus oxaliplatin for mCRC

Next, the clinical efficacy of combination treatment of S-1 and oxaliplatin (SOX) was evaluated.

First, SOX was evaluated in Phase I/II studies independently performed in Japan and Korea [32,33]. Both studies obtained response rates of 50 and 54%, with PFS of 6.4 and 8.5 months, respectively. The most common grade 3 or higher adverse event was thrombocytopenia (27 and 14%). This event was well managed by adequate dose modification of oxaliplatin and S-1 in subsequent cycles. No treatment related death was observed. No patient had HFR in the Japanese trial.

Overview of the SOFT trial

The SOFT trial was an open-label, prospective, multicenter randomized controlled trial (Figure 2). The inclusion criteria were as follows: an age of 20–80 years; a histologically

Figure 2. SOFT trial design.

5-FU: 5-fluorouracil; Bev: Bevacizumab; BSA: Body surface area; civ: Continuous intravenous infusion; I-LV: I-leucovorin; L-OHP: Oxaliplatin; mCRC: Metastatic colorectal cancer; mFOLFOX6: Modified regimen of leucovorin, 5-fluorouracil and oxaliplatin; PS: Performance status; SOX: S-1 and oxaliplatin.

proven diagnosis of colorectal adenocarcinoma; curatively unresectable, advanced or recurrent CRC; an Eastern Cooperative Oncology Group performance status of 0 or 1; the presence of assessable lesions as confirmed by CT or MRI; no previous chemotherapy or radiotherapy and the ability to receive drugs orally and adequate organ function.

Enrolled patients were randomly assigned to receive mFOLFOX6 plus bevacizumab or SOX plus bevacizumab (7.5 mg/kg of bevacizumab, 130 mg/m² of oxaliplatin on day 1 and 40–60 mg of S-1 twice daily for 2 weeks, followed by a 1-week rest).

The primary end point was PFS. Secondary end points were OS, time to treatment failure, response rate, disease control rate, R0 resection rate and adverse events.

Noninferiority was established if the upper confidence limit of the estimated HR was less than 1.33.

The results of the SOFT trial were first presented at the annual meeting of the American Society of Clinical Oncology in June 2013 [7]. The details were reported by Yamada *et al.* in

the *Lancet Oncology* [8]. A total of 512 patients were enrolled at 82 centers in Japan between February 2009 and March 2011. The median follow-up for PFS analysis was 18.4 months, and 413 events were confirmed at the time of the primary end point evaluation. The median PFS was 11.7 months (95% CI: 10.7–13.2) in the SOX plus bevacizumab group as compared with 11.5 months (95% CI: 10.7–13.2) in the mFOLFOX6 plus bevacizumab group. SOX plus bevacizumab was confirmed to be statistically non-inferior to mFOLFOX6 plus bevacizumab (HR: 1.04 [95% CI: 0.86–1.27]; $p_{\text{noninferiority}} = 0.015$). On updated OS analysis after a median follow-up of 37.7 months, the median survival time was 29.6 months (95% CI: 25.8–34.7) in the SOX plus bevacizumab group and 29.7 months (95% CI: 26.5–33.1) in the mFOLFOX6 plus bevacizumab group (HR: 1.018 [95% CI: 0.823–1.258]; $p_{\text{noninferiority}} = 0.0133$) [9].

The main grade 3 or higher adverse events were neutropenia (9 in the SOX plus bevacizumab group vs 34% in the mFOLFOX6 plus bevacizumab group; $p < 0.0001$), thrombocytopenia (4 vs 1%; $p = 0.063$), anorexia (5 vs 1%;

$p = 0.019$), diarrhea (9 vs 3%; $p = 0.004$), gastrointestinal perforation (2 vs <1%; $p = 0.22$) and febrile neutropenia (0 vs <1%; $p = 0.50$). There were no differences in sensory neuropathy (91 in the SOX plus bevacizumab group vs 90% in the mFOLFOX6 plus bevacizumab group) or HFR (16 vs 18%) between the two treatment groups.

Conclusion

The SOFT trial showed that SOX plus bevacizumab is noninferior to mFOLFOX6 plus bevacizumab in terms of PFS in patients with mCRC. The PFS of 11.7 months and OS of 29.6 months irrespective of Kras status in the SOX plus bevacizumab are consistent with the recently reported results of global multicenter Phase III trials (Table 1) [34–38]. The addition of targeted agents to first-line chemotherapy has improved survival in patients with mCRC. Bevacizumab in combination with oxaliplatin-based doublet chemotherapy, which was first evaluated in the NO16966 trial, was established to be a standard treatment for mCRC [3,4]. The SOFT trial showed that SOX plus bevacizumab is an effective regimen for doublet chemotherapy, which can be used instead of FOLFOX plus bevacizumab or CapeOX plus bevacizumab.

A strong point of the SOX plus bevacizumab regimen is that it combines high effectiveness in terms of PFS and OS with convenience and a good QOL in patients with mCRC; and cost-effectiveness should be discussed. Although the drug fee of CapeOX is expensive than FOLFOX, CapeOX does not need CV catheter insertion and portable infusion pump, and fees related

to adverse events is cheaper [39]. Additionally, patients who received CapeOX returned to the hospital once every 3 weeks rather than once every 2 weeks for patients who received FOLFOX, therefore fees for travel and absenteeism is cheaper in CapeOX than FOLFOX. The cost-effectiveness is different by the country and its medical care system, but the total cost was reduced in CapeOX as compared with FOLFOX in several studies [39–44]. When calculated in drug costs in Japan, CapeOX was proven to significantly reduce treatment costs by JPY 360,000 (about US\$3000; using an exchange rate of 1US\$ = 120JPY) and JPY 270,000 (US\$2300) for first-line and second-line treatments, respectively, as compared with FOLFOX [44]. The drug cost of SOX is about JPY 9700 (about US\$81) cheaper than CapeOX per 1 course in Japan (BSA 1.7 m²). So, we consider SOX plus bevacizumab is more cost effective than FOLFOX or CapeOX.

In the SOFT trial, 16% of the patients had HFR, and <1% had grade 3 HFR. A Phase III trial comparing SOX with CapeOX in Korea reported that the rate of HFR was significantly higher in the CapeOX group (31%) than that in the SOX group (14%), whereas response rate was significantly higher in the SOX group (47%) than that in the CapeOX group (36%) [36]. HFR may restrict activities of daily living and impair the QOL of patients. In this respect, SOX might be more advantageous to patients than CapeOX.

Finally, to maximize antitumor effectiveness and minimize adverse effects in individual patients with mCRC, the identification and analysis of biomarkers are expected to play

Table 1. Recent randomized Phase III studies in metastatic colorectal cancer.

Author	Regimen	n	PFS (months)	OS (months)	p-value (OS)	Ref.
Saltz LB <i>et al.</i> (2008)	FOLFOX4/CapeOX + placebo	701	8.0	19.9	$p = 0.0769$	
NO16966 trial	FOLFOX4/CapeOX + Bev	699	9.4	21.3		[34]
Tol J <i>et al.</i> (2009)	CapeOX + Bev	368	10.7	20.3	$p = 0.16$	[35]
CAIRO2	CapeOX + Bev + Cetu	368	9.4	19.4		
Hong YS <i>et al.</i> (2012)	CapeOX	172	6.7	20.5	$p = 0.18$	
Korean trial	SOX	168	8.5	21.2		[36]
Heinemann V <i>et al.</i> (2014)	FOLFIRI + Bev (<i>Kras</i> wild-type)	295	10.3	25.0	$p = 0.017$	[37]
FIRE-3	FOLFIRI + Cetu (<i>Kras</i> wild-type)	297	10.0	28.7		
Venook AP <i>et al.</i> (2014)	FOLFOX/FOLFIRI + Bev (<i>Kras</i> wild-type)	559	10.8	29.0	$p = 0.34$	[38]
CALGB/SWOG 80405	FOLFOX/FOLFIRI + Cetu (<i>Kras</i> wild-type)	578	10.4	29.9		
Yamada Y <i>et al.</i> (2013)	mFOLFOX6 + Bev	255	11.5	30.9	Not reported	
SOFT trial	SOX + Bev	256	11.7	29.6		[8]

Bev: Bevacizumab; CapeOX: Capecitabine and oxaliplatin; Cetu: Cetuximab; FOLFIRI: Leucovorin, 5-fluorouracil and irinotecan; FOLFOX: Leucovorin, 5-fluorouracil and oxaliplatin; OS: Overall survival; PFS: Progression-free survival; SOX: S-1 and oxaliplatin.

increasingly important roles in selecting the most appropriate regimen for chemotherapy, biologic therapy or both. The CDHP component of S-1 is thought to inhibit DPD activity, resulting in high concentrations of 5-FU in serum and tumor without severe toxicity. S-1 may thus be more effective in patients who have tumors with high DPD expression. We expect that innovations in genomics and proteomics will lead to the identification of new biomarkers for S-1 in the near future.

Financial & competing interests disclosure

M Nakamura has received honoraria from Taiho, Yakult, Chugai and Pfizer. Y Yamada has received honoraria from Taiho, Chugai and Pfizer Japan. K Muro has received honoraria from Taiho, Yakult and Chugai. K Takahashi has received honoraria from Taiho and Chugai. H Baba has received consultant fees from Taiho and honoraria from Taiho, Pfizer, Yakult and Chugai. Y Sasaki has received consulting fees from Taiho and is a stockholder of Taiho, Yakult and Chugai. Y Komatsu has received honoraria from Taiho, Kyowa, Yakult, Chugai and Pfizer. T Satoh has received consulting fees from Taiho, Yakult and Chugai; honoraria from Taiho,

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EXECUTIVE SUMMARY

- S-1 is an oral fluoropyrimidine preparation that combines tegafur, a prodrug of 5-FU, with CDHP, and Oxo in a molar ratio of 1:0.4:1, based on a biochemical modulation of 5-FU. S-1 is approved for colorectal and various other types of cancer in Japan and for gastric cancer in Asia and Europe.
- As adjuvant chemotherapy, S-1 has been demonstrated to be noninferior to UFT/LV in terms of disease-free survival in patients with stage III colon cancer. IRIS was shown to be noninferior to FOLFIRI as second-line chemotherapy for metastatic colorectal cancer (mCRC).

SOFT trial

- The SOFT trial was a randomized Phase III trial designed to evaluate whether SOX plus bevacizumab is noninferior to mFOLFOX6 plus bevacizumab in patients with mCRC. The primary end point was progression-free survival (PFS). Secondary end points were overall survival, time to progression, time to treatment failure, response rate, disease control rate, resection rate and adverse events.
- The median PFS was 11.5 months in the mFOLFOX6 plus bevacizumab group and 11.7 months in the SOX plus bevacizumab group. The hazard ratio for PFS was 1.04 (95% CI: 0.86–1.27), and the p value for noninferiority was 0.015. As a first-line treatment for mCRC, SOX plus bevacizumab was demonstrated to be noninferior to mFOLFOX6 plus bevacizumab in terms of PFS.
- At the final analysis, median survival time was 29.6 months in the SOX plus bevacizumab group and 29.7 months in the mFOLFOX plus bevacizumab group.
- Adverse events differed between the two groups, but were generally tolerable.
- A strong point of the SOX plus bevacizumab regimen is that it combines high antitumor effectiveness with convenience and a good quality of life in patients with mCRC.
- SOX plus bevacizumab was shown to be effective as first-line chemotherapy for mCRC and can replace mFOLFOX6 plus bevacizumab.

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