

Rationale and Study Protocol of the J-SAVER Study: A Phase II Study of S-1 on Alternate Days Combined with Bevacizumab in Patients Aged ≥ 75 Years with Metastatic Colorectal Cancer

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Abstract

Fluoropyrimidine combined with bevacizumab is commonly used in elderly patients with metastatic colorectal cancer worldwide. However, the proportion of elderly patients who discontinued treatment due to toxicities was higher than that of younger patients. The aim of this study is to develop a less toxic schedule of S-1, while maintaining the anti-tumor effect. This phase II study is aimed to evaluate an alternate-day administration of S-1 combined with bevacizumab in untreated elderly patients (aged ≥ 75 years) with metastatic colorectal cancer. The primary endpoint is progression-free survival, and the secondary endpoints are safety, response rate, and overall survival. The expected median progression-free survival is 8.5 months, and the minimum efficacy threshold is 5.0 months. The total required sample size is calculated as 50 patients, with a 2-sided type I error of 0.10 and a power of more than 80%. This study is ongoing, and fifty-four patients were enrolled until October 2016. We hope that S-1 on alter-

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nate days combined with bevacizumab for elderly patients with colorectal cancer is well tolerated and can maintain effectiveness. Trial registration: UMIN clinical trials UMIN000010402.

Keywords

Alternate Days, Bevacizumab, Colorectal Cancer, Fluoropyrimidine, Elderly, Older, S-1

1. Introduction

Colorectal cancer (CRC) is one of the most common causes of cancer-related deaths worldwide [1], and the mortality from CRC among all cancers in Japan is the third highest for men and the highest for women [2]. Among patients with CRC, those aged 75 years and older account for more than 70% of the total mortality in men and women combined. Chemotherapy opportunities for metastatic CRC (mCRC) in elderly patients are therefore increasing [2]. Doublet [fluoropyrimidine (FP) plus oxaliplatin or irinotecan] chemotherapy combined with a targeted agent (e.g., bevacizumab, cetuximab, or panitumumab) is recognized as the standard treatment for patients with mCRC [3] [4] [5]. Younger patients can tolerate the doublet regimen combined with a targeted agent, whereas elderly patients often cannot tolerate this combination because many of them develop comorbidity and/or functional disorders. Therefore, a combination of FP and bevacizumab is selected when physicians determine that a patient is unable to tolerate doublet therapy with/without a targeted agent or if the patient refuses those regimens. In several previous trials, FP plus bevacizumab significantly improved the progression-free survival (PFS) (8.8 - 9.2 months versus 5.1 - 5.6 months) as well as the overall survival (OS) (15.5 - 20.7 months versus 12.9 - 16.8 months), compared to FP monotherapy [6] [7] [8]. FP plus bevacizumab has been recognized as one of the standard chemotherapies in elderly patients with mCRC.

In Japan, S-1, which is one of the FPs, was also evaluated in two phase II trials for patients with mCRC [9] [10]. The response rate was 39.5% and 35.5%, and median OS was 11.9 months and 12.0 months, respectively. Based on these results, a phase II trial of S-1 plus bevacizumab was conducted in patients with mCRC aged ≥ 65 years (BASIC trial) [11]. The schedule consisted of a 6-week cycle. S-1 was administered orally twice daily for the first 28 days of each cycle, at a dose determined by body surface area (BSA) (<1.25 m², 40 mg; $1.25 - 1.50$ m², 50 mg; and >1.50 m², 60 mg). Bevacizumab at 5 mg/kg was administered intravenously on day 1, day 15, and day 29 of each cycle. This regimen produced promising results with a response rate, median PFS, and median OS of 43%, 9.9 months, and 27.5 months, respectively.

S-1 on alternate days was conducted as a new administration schedule [12]. A clear difference in the cell cycles of human normal and tumor cells has been dis-

covered [13] [14] [15]. The normal cell cycle was as short as approximately 0.5 to 1.5 days, whereas a tumor cell cycle ranged from 3 to 5 days, and the duration of the S-phase that 5-fluorouracil acted predominantly on was ≥ 1 day in most cancer cells. Based on this difference in cell cycles, a regimen with S-1 administration on alternate days was designed. In a preclinical study, the anticancer activity of S-1 was comparable to or better than that of daily dosing [16]. In a retrospective study, that regimen was conducted in patients with gastric cancer who refused daily dosing of S-1 for 4 weeks followed by 2 weeks of rest, to cope with grade 1 and higher non-hematologic toxicities. The incidence of grade 2 and more non-hematologic toxicities was observed in only 2.8% of the patients, and median time to treatment failure and median OS were 6 months and 11 months, respectively [17]. Thus, it is expected that S-1 on alternate days is well tolerated and the anti-tumor activity might be equivalent to or better than that of daily dosing of S-1 for elderly patients because the compliance improves.

2. Patients and Methods

2.1. Study Design

This is a multi-institutional (27 institutions) study by the NPO Tsukuba Cancer Clinical Trial Group (TCTG) and the Shikoku Gastrointestinal Oncology Study Group (SGOSG), prospective, open labeled, single-arm phase II trial (J-SAVER: Joint study of S-1 on Alternate days combined with bevacizumab in Elderly patients with metastatic colorectal cancer) in Japan. Patients must fulfill all the inclusion and exclusion criteria before enrollment in the study. The inclusion and exclusion criteria are listed in **Table 1**. After confirmation of the eligibility, registration is made via a fax to the Registration Center in the TCTG. Enrolled patients will be started on the study treatment within 14 days from the day of enrollment.

2.2. Ethical Aspects

The study will be conducted according to the Declaration of Helsinki/Tokyo and to the Japanese Clinical Research Guidelines. The protocol has been approved by the ethics committee of each participating institution. An informed consent form is signed by all study participants. This study protocol has been registered at the University Hospital Medical Information Network, UMIN000010402, on 2nd April 2013.

2.3. Treatment Schedule

The following treatment methods will be repeated until tumor progression, severe adverse events, or patients' refusal. Dose modification will depend upon the toxicities. Patients will receive 40 mg (BSA ≤ 1.25 m²), 50 mg (BSA >1.25 to ≤ 1.50 m²), or 60 mg (BSA >1.50 m²) of S-1 orally, twice a day, on Monday, Wednesday, Friday, and Sunday every week. Bevacizumab at 7.5 mg/kg will be administered every 3 weeks (**Figure 1**).

Table 1. Inclusion and exclusion criteria.

Inclusion criteria	<ol style="list-style-type: none"> 1) Histologically confirmed colorectal adenocarcinoma. 2) Confirmed measurable disease as per the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. 3) No previous chemotherapy except for adjuvant chemotherapy completed 6 months or more before enrollment. 4) Age ≥ 75 years at the time that informed consent is obtained. 5) Eastern Cooperative Oncology Group (ECOG) performance status of 0 - 1. 6) Patients with expected survival for at least 3 months. 7) Adequate bone marrow reserve and hepatic and renal function—white blood cell count $\geq 3000/\text{mm}^3$, neutrophil count $\geq 1500/\text{mm}^3$, hemoglobin level ≥ 9.0 g/dl, platelet count $\geq 100,000/\text{mm}^3$, serum aspartate aminotransferase ≤ 100 IU, serum alanine transaminase ≤ 100 IU, total bilirubin level ≤ 1.5 mg/dl, serum creatinine level ≤ 1.2 mg/dl and creatinine clearance ≥ 50 ml/min. 8) Normal electrocardiogram. 9) Provision of signed written informed consent. 10) Capability of oral intake.
Exclusion criteria	<ol style="list-style-type: none"> 1) Concurrent treatment with prohibited medications, including phenytoin and flucytosine. 2) Administration contraindication of fluoropyrimidines and bevacizumab. 3) Serious infection. 4) Hepatitis B virus S antigen positive. 5) Active double cancer. 6) Uncontrolled hypertension. 7) Severe comorbidity such as intestinal tract paralysis, ileus, interstitial lung disease, uncontrolled diabetes, heart failure, renal failure, and liver failure. 8) Past history of radiation therapy over the pelvic cavity. 9) Massive pleural effusion or ascites. 10) Severe diarrhea (diarrhea affecting daily life in patients having an artificial anus). 11) Brain metastasis with symptoms. 12) Uric protein $\geq 2+$. 13) Men of childbearing potential that do not accept to use an adequate method of contraception or pregnant or lactating women at any time during study. 14) Systemic administration of corticosteroids. 15) Past history of thrombosis, cerebral infarction, cardiac infarction, or pulmonary infarction. 16) History of surgery or biopsy via a great incision within 4 weeks before the registration. 17) Systemic administration of anti-platelet drug (≥ 325 mg/day) except for the administration for pain. 18) Bleeding disorders including congenital bleeding factor, clotting disorder (prothrombin time-international normalized ratio ≥ 1.5 within 2 weeks before the registration), or anti-coagulation drug. 19) Severe mental illness. 20) Judged inappropriate for the entry into the study by the investigator.

2.4. Follow-Up

Patients are assessed according to the Common Terminology Criteria for Adverse Events version 4.0 to detect any adverse events that develop during the treatment. The blood tests include a complete blood cell count, measurement of liver and renal function, and tumor markers (carcinoembryonic antigen and carbohydrate antigen 19 - 9), and the urine test includes uric protein. Observation, assessment, and testing are performed every week until the second administration of

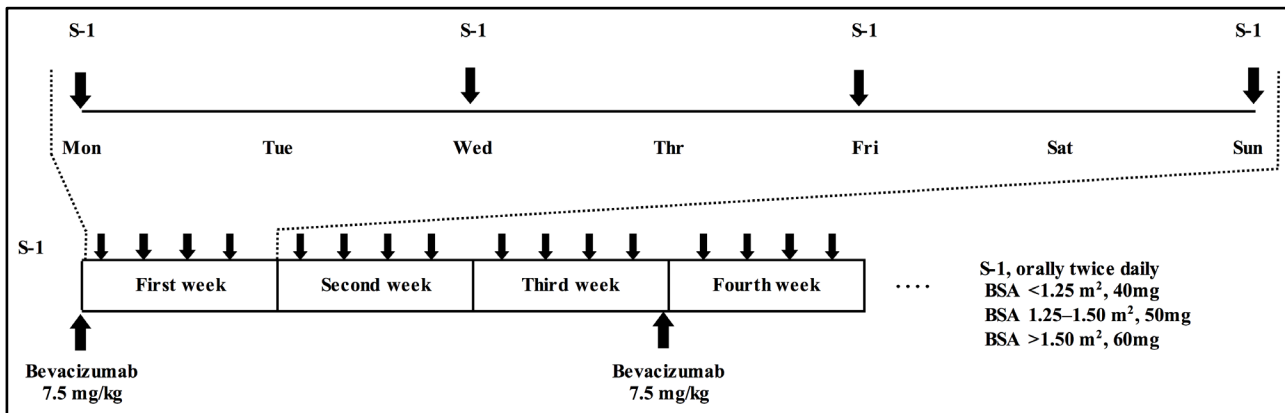


Figure 1. Treatment schedule: BSA—body surface area.

bevacizumab, and at every 3 weeks (the date of administration of bevacizumab) thereafter. Tumor assessments are performed according to RECIST version 1.1. Computed tomography (or magnetic resonance imaging) will be performed every 8 weeks for measurements and evaluation.

2.5. Statistical Methods

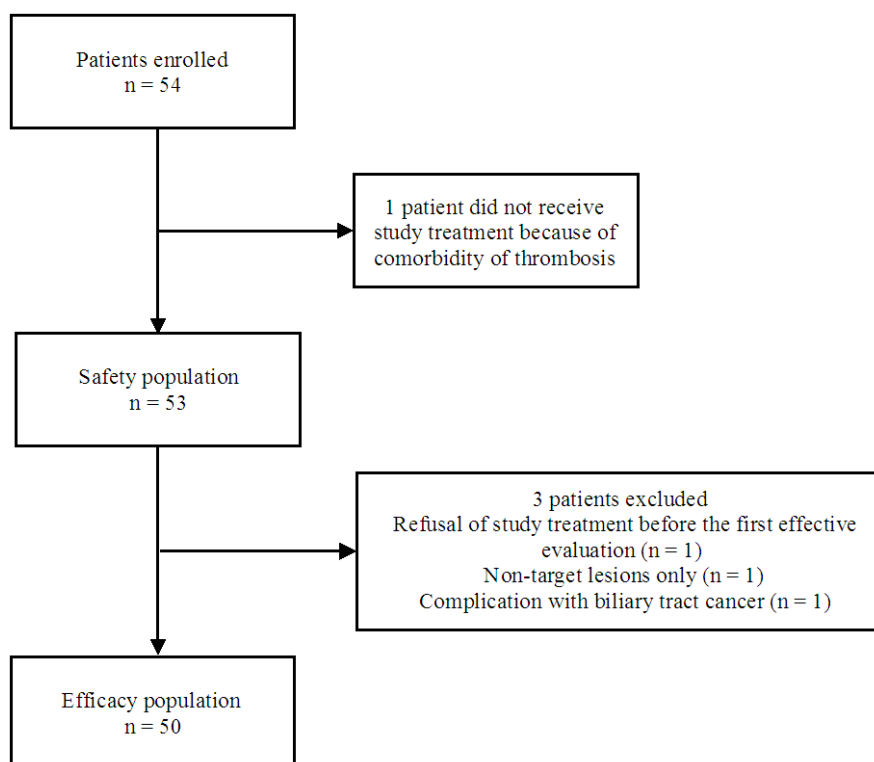
The primary endpoint is PFS. The secondary endpoints are safety, response rate, and OS. PFS is defined as the time from enrollment till disease progression or death from any cause. OS is defined as the time from enrollment till death from any cause.

In the previous phase II study of S-1 monotherapy, the median PFS was 5.1 months in patients with mCRC [9] [12]. The median PFS of 5-fluorouracil and leucovorin plus bevacizumab therapy was improved by 3.7 months compared with 5-fluorouracil and leucovorin monotherapy in a randomized phase II study [18]. Thus, the expected median PFS is 8.5 months, and the minimum efficacy threshold is 5.0 months. The total required sample size is calculated as 50 patients, with a 2-sided type I error of 0.10 and a power of $\geq 80\%$. If the enrollment of patients is fulfilled early on, the total required sample size will be increased to 67 patients. As the result, the accuracy of median PFS is with a 2-sided type I error of 0.05 and a power of $\geq 80\%$.

3. Results

Enrollment started in April 2013. Although the enrollment period was scheduled for two years, it was extended to 3.5 years because of slow accrual. Fifty-four patients were enrolled until October 2016. Of 54 enrolled patients, the following patients were excluded: 1 patient with thrombosis was excluded from this study; 1 patient refused study treatment continuation before the first effective evaluation; 1 patient had only non-target lesion; and 1 patient was found out that was complicated with biliary tract cancer after start of study treatment. Therefore, 50 patients for efficacy and 53 patients for safety will be evaluated (Figure 2).

Patient characteristics list in Table 2. Median age was 79 years (range, 75 - 88

**Figure 2.** Patients flow.**Table 2.** Patient characteristics.

Parameter		N	%
Age, years	Median (range)	79	(75 - 88)
Gender	Male	25	50
	Female	25	50
ECOG PS	0	28	56
	1	22	44
Primary tumor site	Right side ^a	15	30
	Left side ^b	35	70
Surgery on primary tumor	Yes	39	78
Metastatic organ site	Liver	28	56
	Lung	19	38
	Peritoneum	15	30
	Lymph node	11	22
	Others	12	24
Number of metastatic organ site	1	26	52
	2	17	34
	≥3	7	14

^aCecum, ascending colon, and transverse colon; ^bDescending colon, sigmoid colon, and rectum.

years). ECOG PS was 0 in 28 patients and 1 in 22 patients. Main of metastatic organ was liver in 28 patients, lung in 19 patients, peritoneum in 15 patients, and lymph node in 11 patients. A half of patients had one metastatic organ site. The

median follow-up time was 34.5 months (range, 25.6 - 44.9 months). The primary endpoint will be analyzed by the end of 2017.

4. Discussion

Although the elderly patients tolerated FP plus bevacizumab well in the trials, the incidence of adverse events did not decrease when compared to the younger patients. In a subgroup analysis by age from a randomized trial of capecitabine, bevacizumab and mitomycin C (AGITG MAX trial), incidences of grade 3 or more diarrhea, hand-foot skin reaction, and fatigue were observed in 21%, 27%, and 13%, respectively, in elderly patients who received capecitabine plus bevacizumab, compared to 15%, 27%, and 11%, respectively, in the younger patients who received the same regimen [8]. In a randomized trial of capecitabine plus bevacizumab versus capecitabine monotherapy in elderly patients with mCRC (AVEX trial), the incidence of grade 3 or more toxicities was observed in 40% patients [7]. In the BASIC trial, the incidence of grade 3 or more toxicities was observed in less than 10% patients; however, 36% of the patients discontinued treatment due to toxicities [11]. Similar results were observed in a phase II study of uracil-tegafur plus oral leucovorin combined with bevacizumab in elderly patients with mCRC (grade 3 or more toxicities in less than 10% patients and discontinuation of study treatment due to any of the toxicities in 25% patients) [19]. A novel FP-containing regimen that is better tolerated should be developed for the elderly patients.

5. Conclusion

We hope that S-1 on alternate days combined with bevacizumab for elderly patients with metastatic colorectal cancer is well tolerated and can maintain effectiveness when comparing to FP combined with bevacizumab regimens which are previous reported.

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Conflict of Interest

The authors declare that they have no conflict of interest regarding the publication of this article.

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