



Phase II study of S-1 on alternate days plus bevacizumab in patients aged ≥ 75 years with metastatic colorectal cancer (J-SAVER)

Toshikazu Moriwaki¹ · Yoshinori Sakai² · Hiroyasu Ishida³ · Yoshiyuki Yamamoto¹ · Shinji Endo⁴ · Hideaki Kuramochi⁵ · Mikio Sato⁶ · Yukimasa Hatachi⁷ · Yoshiaki Bando⁸ · Takashi Maeba⁹ · Kazuto Ikezawa¹⁰ · Mitsuo Shimada¹¹ · Kenji Amagai¹² · Masamitsu Morimoto¹³ · Kazuma Kobayashi¹⁴ · Akihito Tsuji¹⁵ · Tomohiro Nishina¹⁶ · Ichinosuke Hyodo¹

Received: 28 January 2019 / Accepted: 4 May 2019 / Published online: 14 May 2019
© Japan Society of Clinical Oncology 2019

Abstract

Background Alternate-day administration of S-1 is thought to reduce toxicities. This phase II study evaluated S-1 on alternate days combined with bevacizumab as first-line treatment for elderly patients with metastatic colorectal cancer.

Patients and methods Eligible patients had histologically proven colorectal adenocarcinoma, measurable metastatic lesions, age ≥ 75 years, Eastern Cooperative Oncology Group performance status ≤ 1 , no previous chemotherapy, and refused oxaliplatin- or irinotecan-containing regimens. Patients received 40 mg, 50 mg, or 60 mg (body surface area ≤ 1.25 m², > 1.25 to ≤ 1.50 m², or > 1.50 m², respectively) of S-1 twice orally on Sunday, Monday, Wednesday, and Friday every week. Bevacizumab (7.5 mg/kg) was administered every 3 weeks. The primary endpoint was progression-free survival.

Results Of 54 enrolled patients, 50 patients were evaluated for efficacy and 53 for safety. The median age was 79 years (range 75–88 years). The median progression-free survival was 8.1 months (95% confidence interval (CI) 6.7–9.5 months). The median overall survival was 23.1 months (95% CI 17.4–28.8 months). The response rate was 44% (95% CI 30.2–57.8%), and the disease control rate was 88% (95% CI 79.0–97.0%). Grade 3 or higher hematologic, non-hematologic, and bevacizumab-related adverse events occurred in 9%, 11%, and 25% of patients, respectively. The most common grade 3 and 4 treatment-related adverse events were hypertension (11%), nausea (6%), fatigue (6%), anemia (6%), and proteinuria (6%). Only 6 patients discontinued treatment due to adverse events.

Conclusion S-1 on alternate days combined with bevacizumab showed better tolerability and comparable survival compared with the results of similar studies.

Keywords Bevacizumab · Colorectal cancer · Elderly · Fluoropyrimidine · S-1

Introduction

Colorectal cancer (CRC) is a common cause of cancer-related death worldwide [1, 2]. In Japan, more than 70% of mortality occurs in patients over 75 years old. The proportion and number of elderly patients with metastatic CRC (mCRC) who are treated with chemotherapy is increasing [2].

The first-line standard treatment for patients with mCRC is doublet (fluoropyrimidine [FP] plus oxaliplatin or irinotecan) chemotherapy combined with a molecular targeted

agent (bevacizumab, cetuximab, or panitumumab) [3–5]. However, elderly patients often cannot tolerate this combination chemotherapy because of emerging adverse events, comorbidity, and decreased organ function. Therefore, FP combined with bevacizumab has been recognized as a favorable treatment for elderly patients with mCRC [6–8].

S-1, an oral FP, showed promising results in two phase II trials for chemo-naïve patients with mCRC [9, 10]. The standard treatment schedule of S-1 was twice daily administration for 4 weeks followed by 2 weeks' rest. To increase safety, S-1 on alternate days was studied as a new administration schedule, utilizing the difference in cell cycles between normal gastrointestinal epithelium and tumor cells: the normal cell cycle is approximately 0.5–1.5 days, whereas the tumor cell cycle ranges from 3 to 5 days, and duration

✉ Toshikazu Moriwaki
tmoriwak@gmail.com

Extended author information available on the last page of the article

of the S-phase, where 5-fluorouracil is most active, is a few days in most cancer cells [11–15]. In a retrospective study, this alternate-day S-1 schedule was studied in 92 patients with advanced gastric cancer. Grade 2 and higher non-hematologic toxicities were observed in only 3% of the patients, and the median time to treatment failure and median overall survival (OS) were 6 and 11 months, respectively, which was similar to those in a previous study of the standard S-1 treatment schedule [16].

We herein report a phase II study of S-1 on alternate days combined with bevacizumab as a first-line treatment in elderly patients with mCRC.

Material and methods

Study design

This study was designed as a prospective, open-labeled, single-arm, multicenter phase II trial (J-SAVER: Joint study of S-1 on Alternate days combined with beVacizumab in Elderly patients with metastatic coloRectal cancer) by the nonprofit organization Tsukuba Cancer Clinical Trial Group and the Shikoku Gastrointestinal Oncology Study Group in Japan [17]. The study was conducted according to the Declaration of Helsinki/Tokyo and the Japanese Clinical Research Guidelines. The study protocol was approved by the ethics committee of each participating institution. Informed consent forms were signed by all patients before study entry. The study treatment was started within 14 days from the date of enrollment. The study protocol was registered at the University Hospital Medical Information Network, UMIN000010402, on April 2, 2013.

Patients

The main inclusion criteria were as follows: pathologically confirmed colorectal adenocarcinoma; age ≥ 75 years; Eastern Cooperative Oncology Group performance status (ECOG PS) ≤ 1 ; no previous chemotherapy except for adjuvant chemotherapy with FP completed 6 months or more before enrollment; presence of measurable lesions as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; and adequate bone marrow, hepatic, and renal function. The main exclusion criteria included inability to take oral medication, uncontrolled hypertension, previous radiation therapy over the pelvic cavity, urine protein $\geq +2$ with a stick kit for routine urinary analyses, and history of severe thrombosis. The details of the eligibility criteria have been previously reported [17]. *RAS* mutation was examined in paraffin-embedded tumor tissues at individual institutions using validated methods approved by the Japanese Ministry of Labor and Welfare [18, 19]. In

Japan, *RAS* mutation analysis was performed at only *KRAS* exon 2 (codons 12 and 13) until Apr 2015, and expanded to *KRAS/NRAS* exons 2, 3, and 4 thereafter.

Treatment schedule

Patients received 40 mg (body surface area [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 Sunday, Monday, Wednesday, and Friday every week. The protocol treatment was repeated until tumor progression, development of severe adverse events, or patient refusal. Bevacizumab was administered at 7.5 mg/kg every 3 weeks (Fig. 1). S-1 was postponed if the blood neutrophil count was $< 1000/\text{mm}^3$ or the platelet count was $< 75,000/\text{mm}^3$. Re-initiation of S-1 required non-hematological toxicities, including infection, diarrhea, oral mucositis, nausea, or vomiting, to be grade ≤ 1 . S-1 was discontinued in cases of serum creatinine level ≥ 1.2 mg/dL, serum total bilirubin level ≥ 2.5 mg/dL, serum aspartic aminotransferase (AST) level or serum alanine aminotransferase (ALT) level > 100 IU (> 200 IU in patients with liver metastasis), and grade 2 or higher diarrhea, mucositis, nausea, or vomiting. S-1 was re-initiated at a reduced dose if patients recovered from these adverse events. The dosage of S-1 was reduced by 20% in patients who experienced a neutrophil count $< 500/\text{mm}^3$, platelet count $< 50,000/\text{mm}^3$, serum creatinine level ≥ 1.5 mg/dL, serum total bilirubin level ≥ 4.0 mg/dL, serum AST or ALT level > 200 IU, or grade 3 or higher diarrhea, mucositis, nausea, or vomiting. In addition, dose reduction and treatment delay by physician's determination were allowed, taking into account patient safety.

Assessment

Adverse events during treatment were assessed according to the Common Terminology Criteria for Adverse Events version 4.0. Blood tests included complete blood cell counts, liver and renal function tests, and tumor markers (carcinoembryonic antigen and carbohydrate antigen 19–9), and the urine test included a semi-quantitative protein test. Observation, assessment, and blood and urinary tests were performed every week until the second administration of

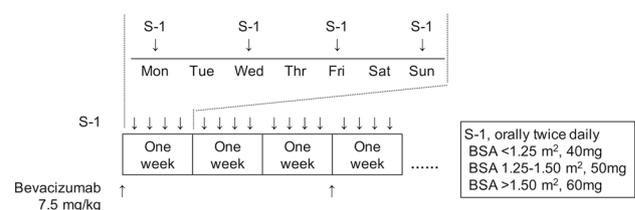


Fig. 1 Treatment schedule. BSA, body-surface area

bevacizumab, and every 3 weeks on the day of bevacizumab administration thereafter. Tumor assessments were performed according to RECIST version 1.1. Computed tomography or magnetic resonance imaging was performed every 8 weeks for evaluation of tumors. The relative dose intensities (RDIs) of S-1 and bevacizumab were calculated as the actual total dose divided by the pre-planned total dose during study treatment. A dedicated schedule calendar was used by patients or family members to record whether the patient orally took S-1.

Statistical analysis

The primary endpoint was progression-free survival (PFS). The secondary endpoints were safety, response rate, and OS. In a previous phase II study of standard S-1 monotherapy for patients with mCRC, the median PFS was 5.1 months [9, 10]. The median PFS of 5-fluorouracil and leucovorin plus bevacizumab therapy was 3.7 months longer than that of 5-fluorouracil and leucovorin monotherapy in a randomized phase II study [6]. Therefore, we set the expected median PFS at 8.5 months and the minimum efficacy threshold at 5.0 months. The required sample size was calculated as 50 patients, with a two-sided type I error of 0.10 and a power of $\geq 80\%$. As post hoc analyses, PFS and OS were evaluated according to *RAS* mutation status: exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146) of *KRAS* and *NRAS*. PFS was defined as the time from enrollment to disease progression or death from any cause. OS was defined as the time from enrollment to death from any cause. The PFS and OS with 95% confidence interval (CI) were estimated using the Kaplan–Meier method. The response rate with 95% CI was calculated using normal approximation based on the best response by the investigator. *P* value of < 0.05 was considered to indicate statistical significance. All analyses were performed using SPSS software, version 22.0 (IBM Japan, Tokyo).

Results

Patients

Fifty-four patients were enrolled from April 2013 to October 2016. Among them, 50 and 53 patients were evaluated for efficacy and safety, respectively. The flowchart of patient selection is shown in Fig. 2.

The median patient age was 79 years (range 75–88 years) (Table 1). The ECOG PS was 0 in 28 patients (56%) and 1 in 22 patients (44%). Primary tumors were located in the cecum, ascending colon, and transverse colon in 15 patients (30%) (right side), and in the descending colon, sigmoid colon, and rectum in 35 patients (70%) (left side). Half of

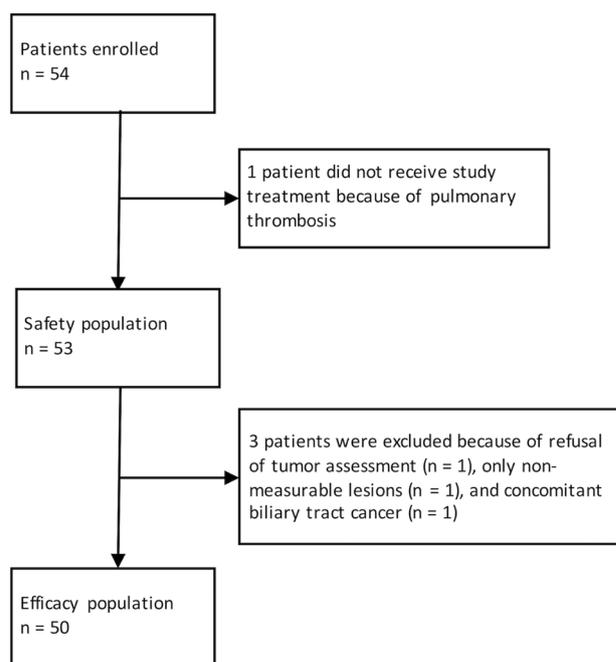


Fig. 2 Flow diagram indicating patient enrollment

the patients had one metastatic site. The tumor *RAS* mutation status was examined in 44 patients (21 wild type and 23 mutant *RAS*).

Efficacy

The median follow-up times for PFS and OS were 34.5 and 44.9 months, respectively. PFS events occurred in 40 patients (80%). The median PFS was 8.1 months (95% CI 6.7–9.5 months) (Fig. 3a). Thirty-nine patients (78%) died. The median OS was 23.1 months (95% CI 17.4–28.8 months) (Fig. 3b). One patient showed complete response, and 21 had partial responses. The response rate was 44% (95% CI 30.2–57.8%), and the disease control rate was 88% (95% CI 79.0–97.0%). Waterfall plots of the best responses are shown in Fig. 4. Tumor shrinkage was observed in 37 patients (74%). Four patients showed 100% tumor regression, but 2 patients with partial response had non-measurable lesions and 1 patient with stable disease had a new lesion when the measurable lesions had disappeared.

In post hoc survival analyses according to *RAS* mutation status, the median PFS was 7.9 months (95% CI 7.1–8.7 months) for patients with wild-type *RAS* and 7.8 months (95% CI 6.6–8.9 months) for those with mutant *RAS* ($P=0.80$). The median OS was 24.2 months (95% CI 17.3–31.0 months) for patients with wild-type *RAS* and 23.8 months (95% CI 8.9–38.7 months) for those with mutant *RAS* ($P=0.80$).

Table 1 Patient characteristics

Characteristics	<i>n</i> = 50	%
Age (years)		
Median (range)	79 (75–88)	
Gender		
Male	25	50
Female	25	50
ECOG performance status		
0	28	56
1	22	44
Histology		
Well differentiated adenocarcinoma	10	20
Moderately differentiated adenocarcinoma	35	70
Poorly differentiated adenocarcinoma	2	4
Mucinous adenocarcinoma	3	6
Primary tumor site		
Cecum/ascending colon/transverse colon	15	30
Descending colon/sigmoid colon/rectum	35	70
Metastasis		
Synchronous	33	66
Metachronous	17	34
Primary therapy		
Resection of primary tumor	39	78
Adjuvant chemotherapy	5	10
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
RAS status		
<i>KRAS</i> exon 2 ^a wild-type	9	18
<i>KRAS/NRAS</i> ^b wild-type	12	24
<i>KRAS/NRAS</i> ^b mutant-type	23	46
Unkown	6	12

ECOG PS Eastern Cooperative Oncology Group Performance Status

^aCodons 12 and 13

^bExon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (117 and 146) of *KRAS* and *NRAS*

Safety

The adverse events are summarized in Table 2. Grade 3 or higher hematologic, non-hematologic, and bevacizumab-related adverse events were observed in 5 (9%), 6 (11%), and 13 (25%) patients, respectively. The most common grade 3 and 4 treatment-related adverse events were hypertension

(11%), anemia (6%), nausea (6%), fatigue (6%), and proteinuria (6%). Treatment-related death caused by cerebral infarction was observed in one patient. The patient experienced several grade 2 non-hematologic toxicities, and the dose of S-1 was reduced to 60% of the initial dose. He developed cerebral infarction after 13 doses of bevacizumab and died 12 months after the start of the study treatment.

The median duration of treatment was 7.8 months (range 0.5–31.5 months). The median cumulative dose of S-1 was 13,060 mg (range 280–54,250 mg) and that of bevacizumab was 3980 mg (range 270–24,910 mg). Seventeen patients (32%) required dose reduction or treatment delay of S-1, and 14 patients (26%) required treatment delay of bevacizumab. The median RDI was 92% (range 20–100%) for S-1 and 89% (range 34–100%) for bevacizumab. The median RDI according to the original S-1 treatment schedule was 79% (range 18–84%).

Subsequent treatments

Among the patients who received study treatment (*n* = 53), discontinuation of the study treatment was reported in 50 patients (94%), and the reason for discontinuation was disease progression in 40 patients (75%), adverse events in 6 patients (11%) (1 patient each: grade 2 anorexia, grade 2 anorexia and fatigue, grade 3 anorexia, grade 3 wound dehiscence, grade 3 colonic perforation, and grade 5 cerebral infarction), withdrawal of consent in 1 patient, and other in 3 patients (1 patient each: sepsis due to aspiration pneumonia, dementia, and unknown) (Table 3). After discontinuation of the study treatment, 14 patients (26%) received best supportive care alone, and 33 patients (62%) were treated with any chemotherapy, including oxaliplatin- and irinotecan-containing therapy (*n* = 14 and 8, respectively). In 22 patients who received oxaliplatin- or irinotecan-containing therapy, the median age was 78 years (range 75–86 years), and 14 patients (64%) had an ECOG PS of 0. No complete response was observed, and 10 patients achieved partial response (45%). The incidences of grade 3 or higher hematologic-, non-hematologic-, and bevacizumab-related toxicities were 5%, 9%, and 14%, respectively. The median RDIs were 95% (range 46–98%) for S-1 and 93% (34–100%) for bevacizumab.

Discussion

We studied S-1 administration on alternate days combined with bevacizumab as first-line treatment for elderly (≥ 75 years) patients with mCRC in a multicenter phase II trial, and showed modest activity and well-tolerated toxicities, while keeping dose intensities of S-1 and bevacizumab as high as approximately 90%.

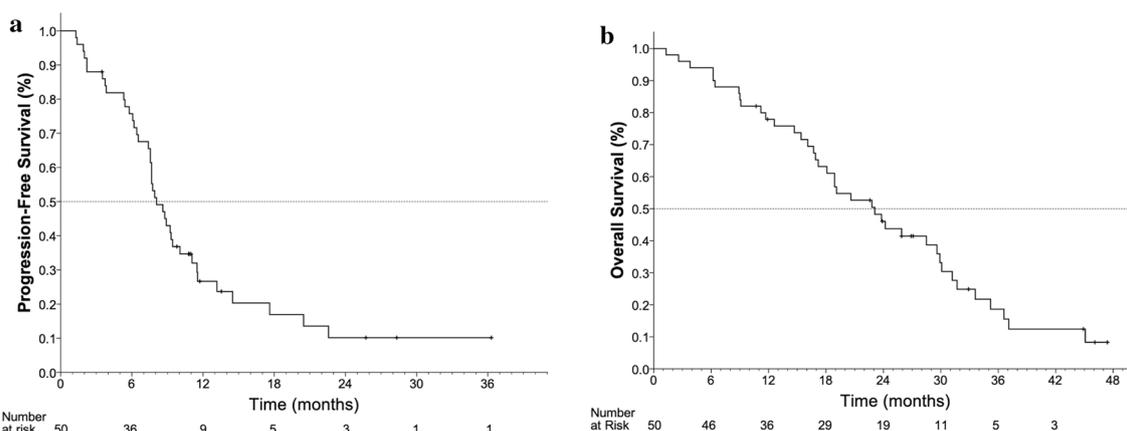


Fig. 3 Kaplan–Meier curves of progression-free survival (a) and overall survival (b). The median progression-free survival was 8.1 months (95% CI 6.7–9.5). The median overall survival was 23.1 months (95% CI 17.4–28.8). *CI* confidence interval

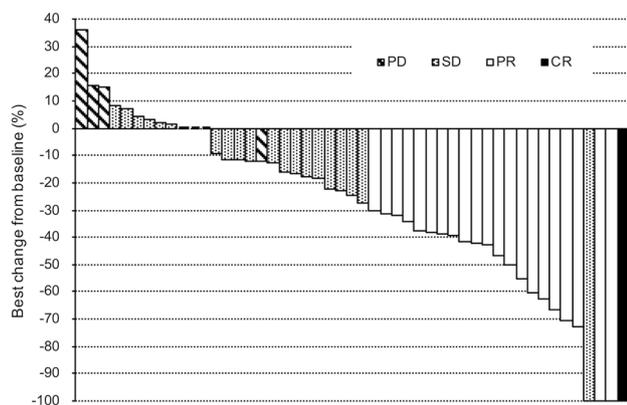


Fig. 4 Waterfall plots according to the best response. *CR* complete response, *PD* progressive disease, *PR* partial response, *SD* stable disease

The main results reported in similar studies of elderly patients with mCRC are summarized in Table 4. The PFS in our study was comparable to those in previous studies of other FPs combined with bevacizumab [7, 20–22]. The dose intensity of S-1 on alternate days corresponded with approximately 86% of the standard daily S-1 dose, and the actual median dose in alternate-day S-1 administration was 79% of the standard dose in the present study. In general, FP plus bevacizumab has been reported to be well tolerated in elderly patients. However, the incidence of grade 3 or higher toxicities was reported as 30% in two studies [7, 23]. Even in other studies in which grade 3 or higher toxicities were observed in less than 10% of patients, treatment was discontinued due to relatively mild to moderate toxicities in approximately 30% of patients [20, 22]. In contrast, the incidence of grade 3 or higher toxicities in our study was low, as expected, and only 11% of patients

discontinued treatment due to toxicities. In addition, incidences of lacrimal disorder and skin disorder, including hand–foot skin reaction, were lower than those in previous studies in elderly patients [7, 22]. This suggests that an alternate-day S-1 schedule had better tolerability than previously reported FP plus bevacizumab regimens.

Recently, two randomized phase II studies of alternate-day S-1 therapy were reported in advanced gastric and pancreatic cancers [24, 25]. This regimen was inferior in efficacy to the standard daily S-1 regimen, although adverse events were mild. One plausible reason for these negative results is the insufficient anti-tumor activity of S-1 due to underdosing in the alternate-day schedule. Nevertheless, these results in advanced gastric and pancreatic cancer do not undermine our favorable results in elderly mCRC patients. These studies included younger patients who could have tolerated the standard daily S-1 regimen, and elderly patients accounted for less than half of the population. Starting with a reduced dose of FP was often adopted in previous studies for elderly patients with mCRC [6, 20, 21, 23]. In a phase II study, aggressive dose modification of capecitabine plus bevacizumab provided rather favorable results in elderly mCRC patients [26]. In the FOCUS2 trial for elderly/frail patients in which FP alone or FP combined with oxaliplatin was started at a reduced dose, only 37% of patients could tolerate a dose increased to the standard level. In contrast, doublet regimens have been reported to demonstrate promising activity and tolerability in elderly patients with mCRC [23, 27–30]. Although doublet regimens should be considered first for elderly patients, not all elderly patients can continue those treatments because of toxicities, and a considerable number of patients actually refuse them to avoid treatment-related toxicities. Our regimen may be a good option as an introductory treatment for such patients.

Table 2 Treatment-related adverse events

Toxicities	Toxicity grade ^a (n = 53)						
	0	1	2	3	4	Any (%)	≥ 3 (%)
Hematologic							
Any	21	15	12	5	0	60	9
Neutropenia	43	3	5	2	0	19	4
Anemia	25	14	7	3	0	53	6
Thrombocytopenia	29	10	4	0	0	45	0
Non-hematologic							
Any	14	17	16	6	0	74	11
Oral mucositis	39	10	4	0	0	26	0
Nausea	34	10	6	3	–	36	6
Vomiting	47	3	3	0	0	11	0
Diarrhea	42	6	3	2	0	21	4
Fatigue	31	14	5	3	–	42	6
Anorexia	44	3	5	1	0	17	2
Lacrimal disorder	47	4	2	0	0	11	0
Skin disorder	38	13	2	0	0	28	0
Febrile neutropenia	53	–	–	0	0	0	0
Bevacizumab related							
Any	15	11	14	11	2 ^b	72	25
Hypertension	33	6	8	6	0	38	11
Bleeding	37	13	1	2	0	30	4
Proteinuria	27	8	15	3	0	49	6
Thrombosis	51	0	1	0	1 ^b	4	2
Wound dehiscence	52	0	0	1	0	2	2
Colonic perforation	52	0	0	0	1	2	2

– Grade is not available

^aToxicity grade was done according to the National Cancer Institute Common Terminology Criteria version 4.0

^bTreatment-related death was observed in one patient

Table 3 Subsequent treatment

	(n = 53)	%
Study treatment continued	3	6
Study treatment discontinued	50	94
Best supportive care	14	26
Any chemotherapies	32	60
Oxaliplatin containing	14	26
Irinotecan containing	8	15
Fluoropyrimidine alone or with bevacizumab	7	13
Anti-EGFR antibody alone	1	2
Trifluridine/tipiracil	2	4
Other	1	2
Radiotherapy	2	4
Treatment-related death	1	2

EGFR epidermal growth factor receptor

Our study suggested that *RAS* mutation had no impact on PFS in patients administered FP plus bevacizumab, similar to the results of a previous report [31]. Anti-epidermal growth factor receptor (EGFR) antibody-containing therapy is recommended for mCRC patients with wild-type *RAS*, and bevacizumab-containing therapy is an optional treatment. In a previous report, the median PFS was 6.4 months in elderly patients with wild-type *KRAS* and 8.4 months in those with wild-type *KRAS/NRAS* [32–34]. The median PFS in our patients with wild-type *KRAS* or *KRAS/NRAS* was similar to these previously reported values. If elderly patients want to avoid anti-EGFR antibody-related skin toxicities, our regimen would be a good substitute.

Elderly patients are extremely diverse. Therefore, the present study had several limitations. The tolerability of chemotherapy for elderly patients is often associated with polypharmacy, comorbidity, renal function, psychological state, and family support [35, 36]. We could not assess these important factors; however, they are very difficult to investigate in all clinical trials. Geriatric function

Table 4 Summary of studies of oral fluoropyrimidine with bevacizumab as first-line therapy for elderly patients with metastatic colorectal cancer

	J-BLUE ¹⁸	Osaka ¹⁹	BASIC ²⁰	AVEX ⁷	Present study
Trial phase	II	II	II	III	II
FP combined with bevacizumab	UFT/LV	UFT/LV	S-1	Capecitabine	Alternate-day S-1
Schedule of FP	300 mg/m ² /day for 3 weeks on, 1 week off	300 mg/m ² /day for 3 weeks on, 1 week off	80 mg/m ² /day for 4 weeks on, 2 weeks off	2000 mg/m ² /day for 2 weeks on, 1 week off	80 mg/m ² /day on Sun, Mon, Wed, and Fri
Number of patients ^a	52	40	56	134	50
Age (years), median (range)	80 (75–87)	81 (75–90)	75 (66–85)	76 (70–87)	79 (75–88)
ECOG PS \geq 1, %	27	13	50	48	44
Median PFS, month	8.2	8.9	9.9	9.1	8.1
Median OS, month	23.0	21.7	25.0	20.7	21.0
Any AEs grade \geq 3, %	29	NR	NR	40	36
Discontinuation due to AEs ^b , %	25	NR	32	17	11

AEs adverse events, ECOG PS Eastern Cooperative Oncology Group Performance Status, FP fluoropyrimidine, LV oral leucovorin, NR not reported, OS overall survival, PFS progression-free survival, UFT uracil–tegafur

^aEfficacy analysis population

^bOf the number of patients who received study treatment

assessment was lacking in our study. Various tools have been attempted for geriatric assessment in oncology trials, but a convenient, useful, and validated tool has not yet been established [35, 36]. That the adherence rate of oral anti-cancer drugs is lower than that of intravenous anti-cancer drugs also needs to be considered [37]. To maintain the dose intensity of S-1 in this study, we asked the patients and their family members to record the day and dose of orally administered S-1 using a dedicated schedule calendar, and we checked the adherence.

In conclusion, alternate-day S-1 combined with bevacizumab was well tolerated and maintained activity in elderly patients (\geq 75 years old) with mCRC and might be recommended as an optional treatment. Further studies are needed to evaluate the influence of different FP toxicities on patients' quality of life and to find the optimal treatment for individual patients based on geriatric assessment.

Acknowledgements We are grateful to Kentaro Yamazaki, Takako E. Nakajima, and Takehiro Oikawa for their important contributions to this study as part of the Data and Safety Monitoring Committee and Miss Mizuki Aida for data management. The participating investigators are as follows: T. Masuishi and T. Eto (Tsuchiura Kyodo General Hospital); S. Yoshida, Y. Ito, and M. Shimoyamada (National Hospital Organization Mito Medical Center); T. Murashita (Ryugasaki Saiseikai Hospital); H. Satake (Kobe City Medical Center General Hospital); M. Chikakiyo (Tokushima Prefecture Naruto Hospital); T. Fujita and S. Mori (JCHO Ritsurin Hospital); A. Soeda and M. Kobayashi (Tsukuba Memorial Hospital); J. Higashijima and T. Nakao (Tokushima University); M. Inukai and Y. Suzuki (Kagawa University); M. Goto (Ibaraki Prefectural Central Hospital and Cancer Center). This work is supported by the NPO Tsukuba Cancer Clinical Trial Group. We would like to thank Editage (www.editage.jp) for English language editing.

Compliance with ethical standards

Conflict of interest MS received a research funding from Chugai, Taiho, CSL Behring, MSD, Astellas, AbbVie, Eisai, Ono, TSUMURA, Coviklen Japan, Johnson&Johnson, Takeda, Novartis, Bayer Yakuhin, and Merck Serono; KA received research funding from Taiho, Hisamitsu, and MSD; AT received honoraria from Chugai and Taiho; TN received research funding from Taiho; IH received honoraria and research funding from Taiho and Chugai. All other authors declare no potential conflicts of interest.

References

1. Ferlay J, Soerjomataram I, Dikshit R et al (2015) Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 136(5):E359–E386. <https://www.ncbi.nlm.nih.gov/pubmed/25220842>
2. Matsuda A, Matsuda T, Shibata A et al (2013) Cancer incidence and incidence rates in Japan in 2007: a study of 21 population-based cancer registries for the Monitoring of Cancer Incidence in Japan (MCIJ) project. *Jpn J Clin Oncol* 43(3):328–336. <https://www.ncbi.nlm.nih.gov/pubmed/23296772>
3. Saltz LB, Clarke S, Diaz-Rubio E et al (2008) Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol* 26(12):2013–2019. <https://www.ncbi.nlm.nih.gov/pubmed/18421054>
4. Van Cutsem E, Kohne CH, Hitre E et al (2009) Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 360(14):1408–1417. <https://www.ncbi.nlm.nih.gov/pubmed/19339720>
5. Douillard JY, Siena S, Cassidy J et al (2010) Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic

- colorectal cancer: the PRIME study. *J Clin Oncol* 28(31):4697–4705. <https://www.ncbi.nlm.nih.gov/pubmed/20921465>
6. Kabbinar FF, Hambleton J, Mass RD et al (2005) Combined analysis of efficacy: the addition of bevacizumab to fluorouracil/leucovorin improves survival for patients with metastatic colorectal cancer. *J Clin Oncol* 23(16):3706–3712. <https://www.ncbi.nlm.nih.gov/pubmed/15867200>
 7. Cunningham D, Lang I, Marcuello E et al (2013) Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): an open-label, randomised phase 3 trial. *Lancet Oncol* 14(11):1077–1085. <https://www.ncbi.nlm.nih.gov/pubmed/24028813>
 8. Price TJ, Zannino D, Wilson K et al (2012) Bevacizumab is equally effective and no more toxic in elderly patients with advanced colorectal cancer: a subgroup analysis from the AGITG MAX trial: an international randomised controlled trial of Capecitabine, Bevacizumab and Mitomycin C. *Ann Oncol* 23(6):1531–1536. <https://www.ncbi.nlm.nih.gov/pubmed/22039086>
 9. Ohtsu A, Baba H, Sakata Y et al (2000) Phase II study of S-1, a novel oral fluoropyrimidine derivative, in patients with metastatic colorectal carcinoma. S-1 Cooperative Colorectal Carcinoma Study Group. *Br J Cancer* 83 2:141–145. <https://www.ncbi.nlm.nih.gov/pubmed/10901361>
 10. Shirao K, Ohtsu A, Takada H et al (2004) Phase II study of oral S-1 for treatment of metastatic colorectal carcinoma. *Cancer* 100(11):2355–2361. <https://www.ncbi.nlm.nih.gov/pubmed/15160338>
 11. Shirasaka T (2009) Development history and concept of an oral anticancer agent S-1 (TS-1): its clinical usefulness and future vistas. *Jpn J Clin Oncol* 39(1):2–15. <https://www.ncbi.nlm.nih.gov/pubmed/19052037>
 12. Cronkite EP, Bond VP, Flidner TM et al (1959) The use of tritiated thymidine in the study of DNS synthesis and cell turnover in hemopoietic tissues. *Lab Invest* 8(1):263–275; discussion 276–267. <https://www.ncbi.nlm.nih.gov/pubmed/13621625>
 13. Lipkin M, Sherlock P, Bell B (1963) Cell proliferation kinetics in the gastrointestinal tract of man. II. Cell renewal in stomach, ileum, colon, and rectum. *Gastroenterology* 45:721–729. <https://www.ncbi.nlm.nih.gov/pubmed/14134007>
 14. Clarkson B, Ota K, Ohkita T et al (1965) Kinetics of proliferation of cancer cells in neoplastic effusions in man. *Cancer* 18(10):1189–1213. <https://www.ncbi.nlm.nih.gov/pubmed/5890960>
 15. Arai W, Hosoya Y, Haruta H et al (2008) Comparison of alternate-day versus consecutive-day treatment with S-1: assessment of tumor growth inhibition and toxicity reduction in gastric cancer cell lines in vitro and in vivo. *Int J Clin Oncol* 13(6):515–520. <https://www.ncbi.nlm.nih.gov/pubmed/19093179>
 16. Arai W, Hosoya Y, Hyodo M et al (2004) Alternate-day oral therapy with TS-1 for advanced gastric cancer. *Int J Clin Oncol* 9(3):143–148. <https://www.ncbi.nlm.nih.gov/pubmed/15221596>
 17. Moriwaki T, Eto T, Tsuji A et al (2017) 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 \geq 75 years with metastatic colorectal cancer. *J Cancer Therapy* 08(11):1040–1048. https://file.scirp.org/Html/9-8902654_80659.htm
 18. Yoshino T, Muro K, Yamaguchi K et al (2015) Clinical validation of a multiplex kit for RAS mutations in colorectal cancer: results of the RASKET (RAS KEy Testing) prospective, multicenter study. *EBioMedicine* 2(4):317–323. <https://www.ncbi.nlm.nih.gov/pubmed/26137573>
 19. Alqahtani QM, Crowley A, Rapp S et al (2016) QIAGEN therascreen KRAS RGQ assay, QIAGEN KRAS pyro assay, and dideoxy sequencing for clinical laboratory analysis of KRAS mutations in tumor specimens. *Lab Med* 47(1):30–38. <https://www.ncbi.nlm.nih.gov/pubmed/26732779>
 20. Nishina T, Moriwaki T, Shimada M et al (2016) Uracil-tegafur and oral leucovorin combined with bevacizumab in elderly PATIENTS (Aged \geq 75 Years) with metastatic colorectal cancer: a multicenter, phase II trial (joint study of bevacizumab, oral leucovorin, and uracil-tegafur in elderly patients [J-BLUE] study). *Clin Colorectal Cancer* 15(3):236–242. <https://www.ncbi.nlm.nih.gov/pubmed/26778644>
 21. Mizushima T, Tamagawa H, Matsuda C et al (2015) Phase II study of oral tegafur/uracil and leucovorin plus bevacizumab as a first-line therapy for elderly patients with advanced or metastatic colorectal cancer. *Oncology* 89(3):152–158. <https://www.ncbi.nlm.nih.gov/pubmed/25967649>
 22. Yoshida M, Muro K, Tsuji A et al (2015) Combination chemotherapy with bevacizumab and S-1 for elderly patients with metastatic colorectal cancer (BASIC trial). *Eur J Cancer* 51(8):935–941. <https://www.ncbi.nlm.nih.gov/pubmed/25837882>
 23. Seymour MT, Thompson LC, Wasan HS et al (2011) Chemotherapy options in elderly and frail patients with metastatic colorectal cancer (MRC FOCUS2): an open-label, randomised factorial trial. *Lancet* 377(9779):1749–1759. <https://www.ncbi.nlm.nih.gov/pubmed/21570111>
 24. Tanaka H, Kanda M, Morita S et al (2017) Randomized phase II study of daily and alternate-day administration of S-1 for advanced gastric cancer (JFMC43-1003). *Int J Clin Oncol* 22(6):1052–1059. <https://www.ncbi.nlm.nih.gov/pubmed/28667408>
 25. Yamae H, Shimizu A, Hagiwara Y et al (2017) Multicenter, randomized, open-label Phase II study comparing S-1 alternate-day oral therapy with the standard daily regimen as a first-line treatment in patients with unresectable advanced pancreatic cancer. *Cancer Chemother Pharmacol* 79(4):813–823. <https://www.ncbi.nlm.nih.gov/pubmed/28251282>
 26. Naeim A, Ward PR, Wang HJ et al (2013) A phase II trial of front-line capecitabine and bevacizumab in poor performance status and/or elderly patients with metastatic colorectal cancer. *J Geriatr Oncol* 4(4):302–309. <https://www.ncbi.nlm.nih.gov/pubmed/24472472>
 27. Rosati G, Avallone A, Aprile G et al (2013) XELOX and bevacizumab followed by single-agent bevacizumab as maintenance therapy as first-line treatment in elderly patients with advanced colorectal cancer: the boxe study. *Cancer Chemother Pharmacol* 71(1):257–264. <https://www.ncbi.nlm.nih.gov/pubmed/23100174>
 28. Feliu J, Salud A, Safont MJ et al (2014) First-line bevacizumab and capecitabine-oxaliplatin in elderly patients with mCRC: GEMCAD phase II BECOX study. *Br J Cancer* 111(2):241–248. <https://www.ncbi.nlm.nih.gov/pubmed/24946000>
 29. Munemoto Y, Kanda M, Ishibashi K et al (2015) Capecitabine and oxaliplatin combined with bevacizumab are feasible for treating selected Japanese patients at least 75 years of age with metastatic colorectal cancer. *BMC Cancer* 15:786. <https://www.ncbi.nlm.nih.gov/pubmed/26497654>
 30. Vamvakas L, Matikas A, Karampeazis A et al (2014) Capecitabine in combination with oxaliplatin and bevacizumab (AXELOX) as 1st line treatment for fit and vulnerable elderly patients (aged $>$ 70 years) with metastatic colorectal cancer (mCRC): a multicenter phase II study of the Hellenic Oncology Research Group (HORG). *BMC Cancer* 14:277. <https://www.ncbi.nlm.nih.gov/pubmed/24755296>
 31. Price TJ, Hardingham JE, Lee CK et al (2011) Impact of KRAS and BRAF gene mutation status on outcomes from the phase III AGITG MAX trial of capecitabine alone or in combination with bevacizumab and mitomycin in advanced colorectal cancer. *J Clin Oncol* 29(19):2675–2682. <https://www.ncbi.nlm.nih.gov/pubmed/21646616>

32. Sastre J, Gravalos C, Rivera F et al (2012) First-line cetuximab plus capecitabine in elderly patients with advanced colorectal cancer: clinical outcome and subgroup analysis according to KRAS status from a Spanish TTD Group Study. *Oncologist* 17(3):339–345. <https://www.ncbi.nlm.nih.gov/pubmed/22363067>
33. Sastre J, Massuti B, Pulido G et al (2015) First-line single-agent panitumumab in frail elderly patients with wild-type KRAS metastatic colorectal cancer and poor prognostic factors: a phase II study of the Spanish Cooperative Group for the Treatment of Digestive Tumours. *Eur J Cancer* 51(11):1371–1380. <https://www.ncbi.nlm.nih.gov/pubmed/25963019>
34. Pietrantonio F, Cremolini C, Aprile G et al (2015) Single-agent panitumumab in frail elderly patients with advanced RAS and BRAF wild-type colorectal cancer: challenging drug label to light up new hope. *Oncologist* 20(11):1261–1265. <https://www.ncbi.nlm.nih.gov/pubmed/26446234>
35. Extermann M, Hurria A (2007) Comprehensive geriatric assessment for older patients with cancer. *J Clin Oncol* 25(14):1824–1831. <https://www.ncbi.nlm.nih.gov/pubmed/17488980>
36. Li D, Soto-Perez-de-Celis E, Hurria A (2017) Geriatric assessment and tools for predicting treatment toxicity in older adults with cancer. *Cancer J* 23(4):206–210. <https://www.ncbi.nlm.nih.gov/pubmed/28731942>
37. Seal BS, Anderson S, Shermock KM (2016) Factors associated with adherence rates for oral and intravenous anticancer therapy in commercially insured patients with metastatic colon cancer. *J Manag Care Spec Pharm* 22(3):227–235. <https://www.ncbi.nlm.nih.gov/pubmed/27003552>

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations

Affiliations

Toshikazu Moriwaki¹  · Yoshinori Sakai² · Hiroyasu Ishida³ · Yoshiyuki Yamamoto¹ · Shinji Endo⁴ · Hideaki Kuramochi⁵ · Mikio Sato⁶ · Yukimasa Hatachi⁷ · Yoshiaki Bando⁸ · Takashi Maeba⁹ · Kazuto Ikezawa¹⁰ · Mitsuo Shimada¹¹ · Kenji Amagai¹² · Masamitsu Morimoto¹³ · Kazuma Kobayashi¹⁴ · Akihito Tsuji¹⁵ · Tomohiro Nishina¹⁶ · Ichinosuke Hyodo¹

¹ Division of Gastroenterology, Faculty of Medicine, University of Tsukuba, 1-1-1, Tennodai, Tsukuba 305-8575, Ibaraki, Japan

² Department of Gastroenterology, Tsuchiura Kyodo General Hospital, Tsuchiura City, Ibaraki, Japan

³ Department of Gastroenterology, National Hospital Organization Mito Medical Center, Higashi Ibaraki-Gun, Ibaraki, Japan

⁴ Division of Gastroenterology and Hepatology, Shinmatsudo Central General Hospital, Matsudo City, Chiba, Japan

⁵ Department of Chemotherapy, Yachiyo Medical Center, Tokyo Women's University, Yachiyo City, Chiba, Japan

⁶ Department of Gastroenterology and Hepatology, Ryugasaki Saiseikai Hospital, Ryugasaki City, Ibaraki, Japan

⁷ Department of Medical Oncology, Kobe City Medical Center General Hospital, Kobe City, Hyogo, Japan

⁸ Department of Surgery, Tokushima Prefecture Naruto Hospital, Naruto City, Tokushima, Japan

⁹ Department of Surgery, Japan Community Health Care Organization Ritsurin Hospital, Takamatsu City, Kagawa, Japan

¹⁰ Division of Gastroenterology, Department of Internal Medicine, Tsukuba Memorial Hospital, Tsukuba City, Ibaraki, Japan

¹¹ Department of Surgery, Tokushima University, Tokushima City, Tokushima, Japan

¹² Division of Gastroenterology and G.I. Oncology, Ibaraki Prefectural Central Hospital and Cancer Center, Kasama City, Ibaraki, Japan

¹³ Department of Surgery, Ehime Medical Center, Toon City, Ehime, Japan

¹⁴ Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki City, Nagasaki, Japan

¹⁵ Department of Clinical Oncology, Faculty of Medicine, Kagawa University, Kita-gun, Kagawa, Japan

¹⁶ Department of Gastrointestinal Medical Oncology, National Hospital Organization Shikoku Cancer Center, Matsuyama City, Ehime, Japan