IN VIVO *39*: 1505-1513 (2025)
doi: 10.21873/invivo.13950

Phase II Trial of Capecitabine Plus Bevacizumab for Elderly Patients With Metastatic Colorectal Cancer: OGSG 1102

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Abstract

Background/Aim: The combination of capecitabine and bevacizumab is a standard first-line chemotherapy regimen for vulnerable patients with unresectable colorectal cancer. However, the safety and efficacy of this regimen in Japanese patients have not been sufficiently investigated.

Patients and Methods: This phase II study included patients aged ≥76 years or those aged 65-75 years who were unsuitable for intensive chemotherapy. Capecitabine at 2000 mg/m^2/day (days 1-14) plus bevacizumab at 7.5 mg/kg (day 1) were administered every 3 weeks. The primary endpoint was progression-free survival. Secondary endpoints included overall survival, response rate, disease control rate, and toxicities.

Results: Thirty-six patients were enrolled between July 2011 and July 2014, of whom 33 were included in the analysis. The median patient age was 78 years (range=67-86 years). A total of 28 patients had a performance status of 0 or 1, and five of 2. The median progression-free and overall survival were 10.3 (95% confidence interval=9.2-15.4) and 27.9 (95% confidence interval=24.2-50.1) months, respectively. The response and disease control rates were 30.3%

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Received December 28, 2024 | Revised January 22, 2025 | Accepted January 24, 2025

and 91.0%, respectively. The major grade 3 or 4 toxicities were hypertension (n=12, 36%) and hand-foot syndrome (n=4, 12%). One patient experienced a grade 4 gastrointestinal perforation.
Conclusion: The combination of capecitabine and bevacizumab demonstrated favorable efficacy and tolerability in Japanese patients with metastatic colorectal cancer who were unsuitable for intensive chemotherapy.

Keywords: Colorectal cancer, elderly, capecitabine plus bevacizumab.

Introduction

Advanced metastatic colorectal cancer (mCRC) is the second most common cause of cancer-related deaths worldwide, after lung cancer (1). Treatment of mCRC has advanced significantly over the past 20 years, primarily through the introduction of novel active agents in clinical practice. The development of new cytotoxic drugs has increased the median overall survival (OS) of patients with mCRC from 8 months to approximately 30 months over the past two decades (2-6).

Frail and elderly populations often present with underlying health conditions and physical limitations. Consequently, meticulous selection of an optimal treatment plan is imperative for this demographic, especially when considering chemotherapy for mCRC. For vulnerable or elderly patients, it is important to modify chemotherapy regimens and schedules considering their overall health status and the impact on their quality of life. Such considerations are essential to improve the tolerability and efficacy of chemotherapy in vulnerable or elderly patients who are unsuitable for intensive chemotherapy (7-9).

Bevacizumab, a monoclonal antibody against vascular endothelial growth factor, extends the survival of patients with mCRC, particularly when combined with cytotoxic chemotherapy. Several studies have demonstrated the efficacy and safety of bevacizumab in combination with either oral or fluoropyrimidine infusions in patients with mCRC (8-12). Notably, the AVEX trial, which compared the efficacy of capecitabine with capecitabine plus bevacizumab for patients aged 70 years and older as first-line treatment, demonstrated a significant improvement in progression-free survival (PFS) with capecitabine plus bevacizumab compared to capecitabine alone [median of 9.1 (95% confidence interval (CI)=7.3-11.4) *vs.* 5.1 (95% CI=4.2-6.3) months; hazard ratio=0.53 (95% CI=0.41-0.69); $p<0.0001$] (7). Based on these results, capecitabine plus bevacizumab is considered standard first-line therapy for patients who are not eligible for intensive chemotherapy (10, 11). However, the efficacy and safety of capecitabine plus bevacizumab in Japanese patients have not been sufficiently investigated (12).

Therefore, we conducted a multicenter phase II study to investigate the efficacy and safety of capecitabine plus bevacizumab for patients aged ≥76 years or those 65-75 years who are ineligible for intensive chemotherapy.

Patients and Methods

Eligibility criteria. Eligible patients were those with mCRC aged ≥76 years, or aged ≥65 years who were considered ineligible for intensive chemotherapy by the treating investigator. Intensive chemotherapy was not considered appropriate for patients ≥65 years old due to the following reasons: i) History of radiation to the abdominal pelvis, ii) serum albumin level <3.5 g/dl, iii) considered by the physician to have difficulty psychologically accepting the high toxicity of chemotherapy or for other reasons. All patients had histologically or cytologically confirmed colon or rectal carcinomas. Eligibility criteria included evaluable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1), Eastern Cooperative Oncology Group performance status (PS) of 0-2, creatinine clearance of at least 30 mL/min, adequate organ function, and a life expectancy of 8 weeks or longer

at enrollment. Patients previously treated with adjuvant or neoadjuvant chemotherapy were eligible if the treatment had been completed more than 6 months before enrollment. Patients were excluded if they had serious complications such as gastrointestinal bleeding, symptomatic heart disease, uncontrolled diarrhea, symptomatic interstitial pneumonia, pulmonary fibrosis, cerebral infarction, or pulmonary embolism.

An independent data monitoring committee provided oversight of the study, and the protocol was approved by an independent ethics committee and all applicable institutional review boards. The study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients before enrollment. This study was registered in the UMIN Clinical Trial Registry (UMIN000005209), and an investigator initiated the trial.

Study treatment. The treatment regimen consisted of capecitabine at 2000 mg/m^2/day for 14 days plus bevacizumab at 7.5 mg/kg on day 1 every 3 weeks. The protocol specified that treatment should continue until disease progression, occurrence of intolerable toxic effects, or withdrawal of consent. Dose modification of capecitabine was permitted when creatinine clearance was below 50 mL/min at baseline. The capecitabine dose was also reduced after the occurrence of grade 2 hand-foot syndrome, grade 4 hematological toxicities, or grade 3 or 4 non-hematological toxicities. If toxicity necessitated a temporary or permanent interruption of bevacizumab, treatment with capecitabine alone continued. Disease response was mandatorily assessed every 8 weeks according to RECIST version 1. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Study endpoints and statistical considerations. This phase II study (OGSG 1102) aimed to assess the efficacy of capecitabine plus bevacizumab as a first-line treatment for patients with mCRC who were ineligible for intensive chemotherapy. The primary endpoint was PFS, defined as the time from enrollment to disease progression or death from any cause. Secondary endpoints included OS, defined as the time from enrollment to death from any cause; response rate, defined as the proportion of patients who achieved complete or partial response; disease control rate, defined as the proportion of patients who achieved complete response, partial response, or stable disease; and the incidence of grade 3/4 toxicities according to Common Terminology Criteria for Adverse Events version 4.0. Considering the results of the AVEX trial (7), which showed that PFS with capecitabine plus bevacizumab was 9.1 months and that with capecitabine alone was 5.1 months, the lowest margin of expected PFS in this study would be expected to exceed 5.1 months and the median PFS was expected to be >9 months. The null hypothesis postulated that PFS was 6.0 months, and the alternative hypothesis postulated that PFS was better than 9.0 months; this was assessed using an exact *p*-value of 0.10 and a power of 0.90 based on the Clopper-Pearson method. Thus, the required sample size was 32. The total sample size was set at 36 to account for any deviations. All statistical analyses were conducted at the Osaka Gastrointestinal Cancer Chemotherapy Study Group Data Centre.

Results

Patient characteristics. A total of 36 patients were enrolled from 11 institutions between July 2011 and July 2014. Three patients were excluded from the analysis; one was ineligible due to a creatinine clearance of <30 min/ml, and two were ineligible because they were younger than 65 years old. As a result, 33 patients were included in the analysis. The patient characteristics are shown in Table I. The median age was 78 years (range=67-86 years), with 25 (75.8%) patients aged ≥76 years. Twenty-eight (85%) patients had a PS of 0 or 1, and five (15%) had a PS of 2. A total of 13 patients (39.4%) had stage IV disease whereas 20 patients (60.6%) had recurrence. Twenty-seven (81.8%) patients underwent surgical resection of the primary tumor. Moreover, 13 patients (39.4%) had comorbidities at baseline, the most

Table I. *Patient characteristics (N=33).*

Characteristic	Subgroup	Value
Age, years	Median (range)	78 (67-86)
	<76 Years, n (%)	8 (24.2%)
	≥76 Years, n (%)	25 (75.8%)
Sex, n (%)	Male	17 (51.5%)
	Female	16 (48.5%)
Performance status, n (%)	0	14 (42.4%)
	1	14 (42.4%)
	2	5 (15.6%)
Histology, n (%)	Well-differentiated	9 (27.3%)
	Moderately differentiated	19 (57.5%)
	Poorly differentiated	2 (6.1%)
	Papillary	2 (6.1%)
	Unknown	1 (3.0%)
KRAS status, n (%)	Wild-type	15 (45.5%)
	Mutant	4 (12.1%)
	Unknown	14 (42.4%)
Tumor location, n (%)	Colon	20 (60.6%)
	Rectum	13 (39.4%)
	Stage IV	13 (39.4%)
	recurrence	20 (60.6%)
Surgical resection, n (%)	Yes	27 (81.8%)

KRAS: KRAS proto-oncogene, GTPase gene.

common of which were diabetes mellitus (n=6, 18.2%) and hypertension (n=5, 15.6%). In terms of medical history, one patient (3.0%) had cerebral infarction and congestive heart failure.

Treatment delivery. A total of 25 patients (75.8%) discontinued treatment because of disease progression. One patient (3.0%) underwent conversion surgery, and two patients (6.0%) discontinued treatment for other reasons. Treatment-related adverse events led to treatment discontinuation in five patients (15.2%). The adverse effects of two patients were related to capecitabine (hand-foot syndrome and diarrhea) and those of three patients were related to bevacizumab (thrombocytopenia, gastrointestinal perforation, and transient ischemic attack). Of the 33 patients, 16 (48.5%) received further therapy: seven patients received an oxaliplatin-containing regimen (21.2%), four received irinotecan or irinotecan plus bevacizumab (12.1%), three received an anti-epidermal growth factor receptor antibody-containing regimen (9.1%), and two received other therapy (6.1%).

Table II. *Best response to treatment with first-line capecitabine plus bevacizumab according to Response Evaluation Criteria for Solid Tumors version 1.1 (N=33).*

Response	Frequency (%)
Complete	0
Partial	10 (30.3)
Stable disease	20 (60.6)
Progressive disease	2 (6.1%)
Not evaluable	1 (3.0%)

Efficacy. The response rate stood at 30.3% (95% CI=15.6-48.7%), and the disease control rate reached 91.0% (95% CI=75.7-98.1%) (Table II). The median PFS was 10.3 (95% CI=9.2-15.4) months (Figure 1). The 6- and 12-month PFS rates were 87.5% (95% CI=76.8-99.7%) and 35.8% (95% CI=22.3-57.3%), respectively. The median OS was 27.9 months (95% CI=24.2-50.1) (Figure 2). The 12- and 24-month OS rates for the 33 patients included in the analysis were 93.8% (95% CI=85.7-100.0%) and 68.1% (95% CI=53.5-86.6%), respectively. The median time to treatment failure was 9.2 (95% CI=6.9-11.5) months.

Safety. The major grade 3 or 4 non-hematological toxicities were hypertension (n=12, 36%) and hand-foot syndrome (n=4, 12%) (Table III). One patient experienced a grade 4 gastrointestinal perforation. Two (6%) patients developed grade 3 proteinuria. Grade 3 hematological toxicities included neutropenia (n=1, 3%) and anemia (n=1, 3%). There was no treatment-related death.

Discussion

This study represents the first phase II trial assessing the efficacy of first-line capecitabine plus bevacizumab in Japanese patients with mCRC ineligible for intensive chemotherapy. Our findings revealed a favorable PFS of 10.3 (95% CI=9.2-15.4) months and OS of 27.9 (95% CI=24.2-50.1) months. The study met its primary

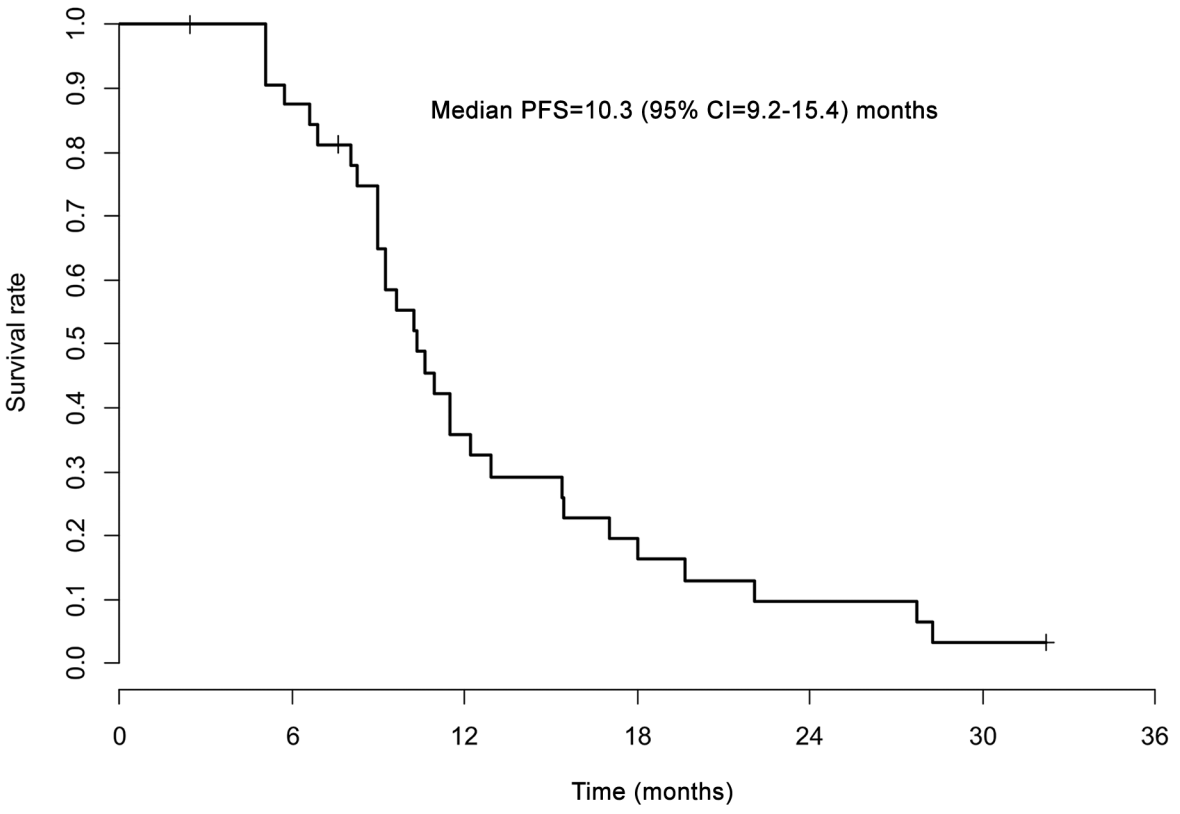

Figure 1. *Kaplan-Meier curve of progression-free survival (PFS) in elderly patients with colorectal cancer treated with first-line capecitabine plus bevacizumab (N=33). CI: Confidence interval.*

endpoint. These results underscore the safety and the efficacy of first-line capecitabine in combination with bevacizumab as a viable therapeutic option for vulnerable elderly Japanese patients deemed unsuitable for upfront oxaliplatin- or irinotecan-based combination regimens.

Elderly and vulnerable patients with mCRC typically exhibit lower OS rates than younger patients, attributable to various factors, including advanced disease stage at diagnosis, multiple comorbidities, and a higher frequency of suboptimal treatments (13). Two randomized phase III studies conducted on vulnerable or elderly populations aimed to determine whether combined treatment conferred benefits over fluoropyrimidine monotherapy. Prior to the development of bevacizumab, two randomized phase III trials were conducted on elderly populations to assess the potential benefits of combined treatment compared to fluoropyrimidine monotherapy. The FOCUS2 study enrolled 459 patients ineligible for intensive chemotherapy (14). Although the addition of oxaliplatin increased the response rate, it did not significantly impact PFS (5.8 *vs.* 4.5 months; p=0.07) or OS. Similarly, the FFCD 2001-02 trial, comparing folinic acid/fluorouracil/irinotecan (FOLFIRI) *versus* 5-fluorouracil/leucovorin administered in classic or simplified regimens, did not demonstrate any notable improvement in PFS or OS, with increased toxicity observed in the irinotecan arms (15). These trials collectively indicate that combination treatments failed to significantly enhance OS compared to fluoropyrimidine monotherapy in mCRC.

The AVEX study, as described earlier, investigated the efficacy of capecitabine with and without bevacizumab in mCRC patients aged ≥70 years ineligible for oxaliplatin- or irinotecan-based regimens. In that trial, the median PFS

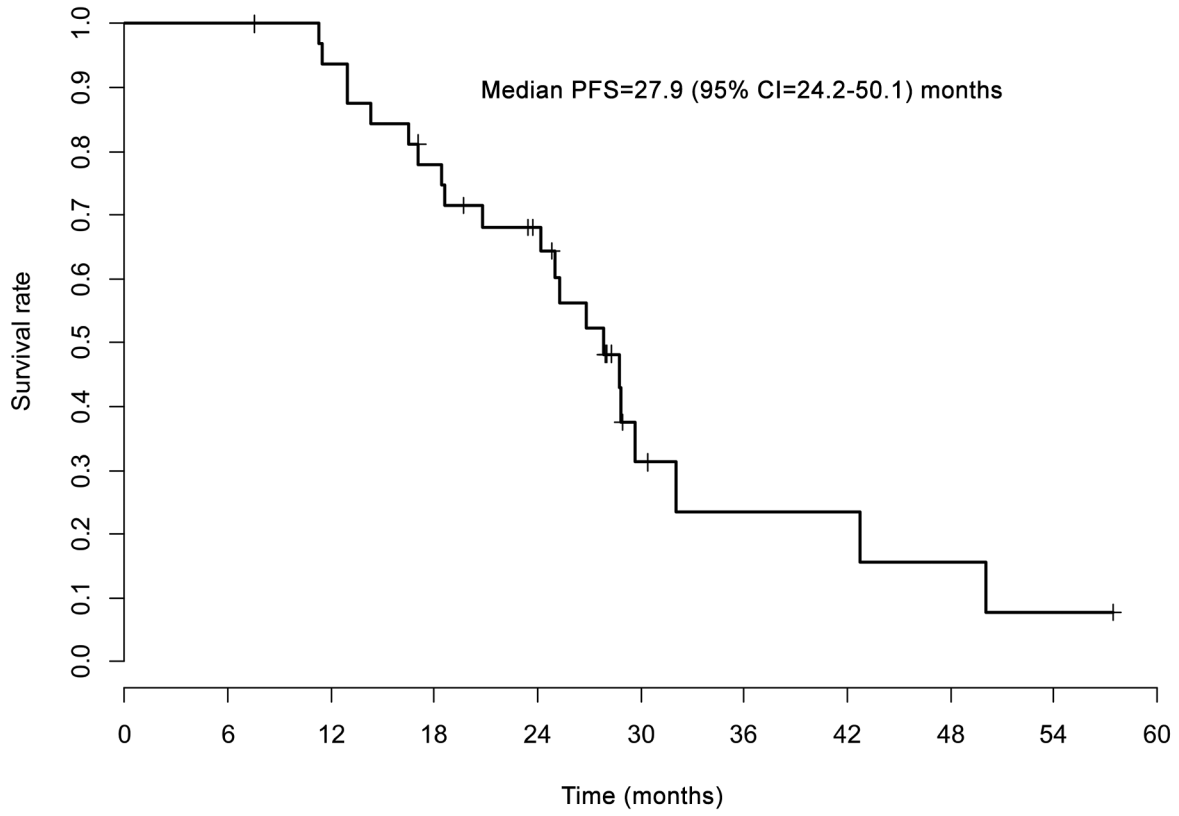

Figure 2. *Kaplan-Meier curve of overall survival (OS) in elderly patients with colorectal cancer treated with first-line capecitabine plus bevacizumab (N=33). CI: Confidence interval.*

was higher in the capecitabine and bevacizumab arm compared to treated with capecitabine alone, with a trend towards improved OS (20.7 *vs*. 16.8 months; *p*=0.18) and a higher response rate (19% *vs*. 10%; *p*=0.04). Furthermore, the JCOG1018 (RESPECT) study examined the benefit of adding oxaliplatin to fluoropyrimidine and bevacizumab treatment in patients aged ≥70 years with mCRC (16). In the oxaliplatin arm, the PFS was 9.4 months (compared to 10.0 months in the fluoropyrimidine and bevacizumab arm; *p*=0.086), the OS was 21.3 months (*versus* 19.7 months in the fluoropyrimidine and bevacizumab arm), and the response rate was 29.5% (compared to 47.7% in the fluoropyrimidine and bevacizumab arm), with no significant differences in the quality of life between the two arms. The authors did not recommend adding oxaliplatin to a combination of fluoropyrimidines and bevacizumab as first-line treatment for elderly patients.

Our data demonstrate the good antitumor activity of capecitabine plus bevacizumab as a first-line treatment for patients with mCRC, achieving an overall response rate of 30.3%, which is comparable to or even higher than that previously reported in clinical trials. The high antitumor efficacy of this combination also translates into prolonged survival, comparable to that reported in the AVEX and JCOG1018 trials. Furthermore, the most frequent grade 3 or 4 hematological toxicities during the initial treatment were neutropenia and anemia, with incidences of 3% each, which were comparable to those reported in previous studies of fluoropyrimidine plus bevacizumab. Severe bleeding and thromboembolism were not observed during treatment. In contrast, 36% of the

Table III. *Adverse events of treatment with first-line capecitabine plus bevacizumab in elderly patients with colorectal cancer (n=33) according to the Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.*

	Grade, n					
Toxicity	Any	1	2	3	4	3-4 (%)
Hematological						
Anemia	26	19	6	1	0	3
Neutropenia	13	10	2	1	0	3
Thrombocytopenia	11	10	1	0	0	0
Leukopenia	5	2	3	0	0	0
Non-hematological						
Hand-foot syndrome	27	4	19	4	0	12
Hypertension	21	3	6	12	0	36
Stomatitis	16	13	3	0	0	0
Urine protein	15	11	2	2	0	6
Elevated AST/ALT	15	15	0	0	0	0
Fatigue	13	6	6	1	0	3
Diarrhea	12	7	3	2	0	6
Hypokalemia	12	11	0	1	0	3
Nausea	11	10	1	0	0	0
Elevated creatinine	9	8	1	0	0	0
Vomiting	6	6	0	0	0	0
Gastrointestinal bleeding	2	1	1	0	0	0
Gastrointestinal perforation	1	0	0	0	1	3
Febrile neutropenia	1	0	0	1	0	3
Thromboembolism	1	1	0	0	0	0

ALT: Alanine aminotransferase; AST: aspartate aminotransferase.

patients developed grade 3 hypertension, while 12% developed grade 3 hand-foot syndrome. The incidence of adverse events of any grade was comparable to that observed in other clinical trials. One patient developed rectal perforation and underwent surgery; however, no treatment-related deaths occurred.

These findings suggest that combination therapy with capecitabine and bevacizumab may be well-tolerated and potentially effective in elderly and vulnerable Japanese patients with mCRC. The advantage of the capecitabine plus bevacizumab regimen is that it allows for treatment with fewer toxicities, such as peripheral neuropathy or severe bone marrow suppression, while maintaining the quality of life during treatment. Other factors, such as primary tumor sidedness and genetic mutation, could be considered, but the number of cases in this study was small and the analysis was insufficient. Prospective studies on the predictive role of primary tumor sidedness and also providing elucidation of the molecular background responsible for such effects are urgently needed (17-19).

This study had several limitations. Firstly, this was a single-arm, phase II study with a relatively small sample size. Secondly, neither quality of life nor geriatric investigations were conducted. We decided to include only patients aged ≥76 years or those ≥65 years who were not considered eligible for intensive chemotherapy, given that there was no established method for identifying frailty before the beginning of this clinical trial. Thirdly, biomarkers, such as *RAS* or *BRAF* mutation status, and sidedness information were not collected. At the beginning of the trial, tests for *RAS* and *BRAF* status were not approved in Japan. Fourthly, it was not possible to calculate the dose intensity because of a lack of detailed medication records. Fifthly, aged and vulnerable patients were not analyzed separately due to the small sample size. Finally, the duration of treatment-related adverse events was not recorded.

Conclusion

Our data suggest that the combination regimen of capecitabine plus bevacizumab offers an additional therapeutic option for elderly Japanese patients with mCRC, and those who are unsuitable for upfront oxaliplatin- or irinotecan-based combination regimens.

Funding

No funding source was involved in the study.

Conflicts of Interest

There are no conflicts of interest to declare.

Authors' Contributions

Conception and design: Toshifumi Y and Taroh S. Acquisition of data: All Authors. Analysis and interpretation

of data: All Authors. Drafting the manuscript or revising it critically for important intellectual content: Toshifumi Y, Taroh S, Toshio S and Hisato K. Final approval of the version to be published: All Authors. Agreement to be accountable for all aspects of the work: All Authors.

Acknowledgements

The Authors thank all patients and their families. The Authors thank Akemi Morita, Nami Yoshida, and Yoshiro Matsubara for their assistance with data management.

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