Original Study

WJOG13219G: The Efficacy and Safety of FOLFOXIRI or Doublet plus Anti-VEGF Therapy in Previously Untreated *BRAF*^{V600E} Mutant Metastatic Colorectal Cancer: A Multi-Institutional Registry-Based Study (BRACELET Study)

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Abstract

The survival benefit of FOLFOXIRI plus anti-VEGF therapy (triplet) over doublet chemotherapy is unclear for *BRAF*^{V600E} mutant mCRC. This was a multicenter, retrospective study, including 79 and 91 patients in the triplet and doublet groups, respectively. No survival benefit of the triplet therapy over the doublet therapy was observed in the overall cohort or specific subgroups of real-world patients with *BRAF*^{V600E} mutant mCRC.

Background: The real-world survival benefit of FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin, and irinotecan) plus anti-VEGF therapy (Triplet) over doublet chemotherapy (Doublet) remains controversial in patients with *BRAF*^{V600E} mutant metastatic colorectal cancer (mCRC). **Patients and Methods:** WJOG13219G was a multicenter, retrospective, registry-based study of patients with *BRAF*^{V600E} mutant mCRC who received first-line triplet or doublet chemotherapy from January 2014 to December 2019 in Japan. Inverse probability of treatment weighting (IPTW) was used to adjust for patient background. **Results:** The analysis included 79 and 91 patients in the Triplet and Doublet groups, respectively. The Triplet group was significantly younger and had better performance status. No statistical difference was noted in progression-free survival (PFS; HR, 0.82; 95% CI, 0.60–1.13; $P = .22$) and overall survival (OS; HR, 0.88; 95% CI, 0.62–1.25; $P = .48$) between both groups. IPTW analysis also showed no difference between the 2 groups in PFS (HR,

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0.86; 95% CI, 0.69–1.08; $P = .20$) and OS (HR, 0.93; 95% CI, 0.73–1.20; $P = .59$). The Triplet and Doublet groups had an objective response rate of 53% and 41%, respectively ($P = .10$). At least one grade 3 or 4 adverse event was seen in 51 (65%) and 43 (47%) patients in the Triplet and Doublet groups, respectively, with the incidence of neutropenia being significantly higher in the former. **Conclusion:** Triplet therapy had no survival benefit versus doublet therapy in the overall and IPTW cohorts or specific subgroups for real-world patients with *BRAF*^{V600E} mutant mCRC.

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Introduction

Therapeutic options for individuals with metastatic colorectal cancer (mCRC) have dramatically improved in recent decades, resulting in a survival time of more than 30 months.[1,2] The first-line treatment of mCRC includes doublet cytotoxic regimens plus molecular-targeting agents such as anti-epidermal growth factor receptor (EGFR) antibodies and anti-vascular endothelial growth factor (VEGF) antibodies.[1-6] The TRIBE study, which compared the efficacy of FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin, and irinotecan) plus bevacizumab to FOLFIRI plus bevacizumab, demonstrated improvement in progression-free survival (PFS) (hazard ratio [HR], 0.77; 95% confidence interval [CI] 0.65–0.93; $P = .006$) and overall survival (OS) (HR, 0.80; 95% CI, 0.65–0.98; $P = .030$).[7,8] Triplet therapy has become an attractive treatment option for patients with good general condition but with rapid disease progression or a possibility of conversion surgery.[8]

BRAF^{V600E} mutations occur in 8% to 15%[9-11] mCRC patients; these are tumors with a mucinous histology, right-sided primary tumors, peritoneal or nodal metastases, or microsatellite instability-high (MSI-H).[12-14] *BRAF*^{V600E} mutant mCRC has markedly poor prognosis compared to *BRAF*-wild mCRC.[11] The TRIBE study, which suggested the potential benefit of the triplet chemotherapy, also observed the same finding among patients with *BRAF*^{V600E} mutant mCRC. Favorable trends of FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab in terms of objective response rate (ORR) (56% vs. 42%), PFS (HR, 0.57; 95% CI, 0.26–1.18), and OS (HR, 0.55; 95% CI, 0.24–1.23) were shown in the subgroup analysis of 28 patients.[8] Thus, FOLFOXIRI plus bevacizumab has been recognized as one of the initial standards of care for the first-line treatment of *BRAF*^{V600E} mutant mCRC in clinical practice.[15,16]

However, the TRIBE2 study, which aimed to verify the efficacy of the upfront exposure to FOLFOXIRI plus bevacizumab versus the sequential strategy of doublets, did not show consistent evidence of increased benefit from the intensified approach over the sequential strategy for patients with *BRAF*^{V600E} mutant mCRC (n = 66 in total) in PFS (HR, 1.02; 95% CI, 0.61–1.71) or OS (HR, 1.35; 95% CI, 0.79–2.30).[17] Recently, an individual patient data meta-analysis of FOLFOXIRI plus bevacizumab versus doublet plus bevacizumab revealed only a minimal benefit of the triplet regimen for patients with *BRAF*^{V600E} mutant mCRC (n = 115) in terms of PFS (HR, 0.84; 95% CI, 0.56–1.25) and OS (HR, 1.14; 95% CI, 0.75–1.73).[18] It should be noted that these post-hoc subgroup analyses were based on relatively a small sample size and patient background was not adjusted by known prognostic factors between the two groups. Thus, the evidence regarding triplet chemotherapy for *BRAF*^{V600E} mutant mCRC remains controversial. This multi-institutional registry-based study aimed to evaluate the efficacy of FOLFOXIRI plus anti-VEGF therapy versus doublet plus anti-VEGF therapy for the treatment of *BRAF*^{V600E} mutant mCRC, as well as to identify patient subgroups that could benefit from the triplet chemotherapy using real-world data with a large cohort.

Patients and Methods

Study design

The West Japan Oncology Group (WJOG) 13219G was a multicenter, retrospective, registry-based study wherein patients with *BRAF*^{V600E} mutant mCRC were recruited from 33 hospitals in Japan (Supplementary Table 1). The key eligibility criteria were as follows: (1) histologically confirmed colorectal adenocarcinoma, (2) diagnosed as unresectable or recurrent CRC and initiated first-line chemotherapy (ie, at least 2 of the following: fluoropyrimidines, irinotecan, and oxaliplatin) between April 2014 and December 2019, and (3) *BRAF*^{V600E} mutation in tumor tissue confirmed via real-time polymerase chain reaction (RT-PCR) or next gene sequencing analysis. If the disease recurred during or within 6 months after completion of platinum-containing adjuvant or neoadjuvant chemotherapy, then chemotherapy was regarded as first-line palliative chemotherapy in this study. The main exclusion criteria were as follows: (1) has received previous palliative chemotherapy or biological therapy for metastatic disease and (2) had received adjuvant treatment with fluoropyrimidine monotherapy during or within 6 months before recurrence. We reviewed the medical records and collected data on baseline characteristics, clinical outcomes, and treatment-related adverse events (AEs) of grade 3 or greater according to the Common Terminology Criteria for Adverse Events version 4.0. This study was approved by the WJOG Protocol Review Committee and the institutional review board of each participating institution with the provisions of the Declaration of Helsinki and Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan (UMIN000041098). Consent for participation was obtained via an opt-out form on the website.

Statistical analysis

The overall population included patients who were eligible for the study. The efficacy and safety analyses included patients who had received FOLFOXIRI plus anti-VEGF therapy (defined as the Triplet group) or doublet (ie, fluoropyrimidine plus oxaliplatin or irinotecan) plus anti-VEGF therapy (the Doublet group). To

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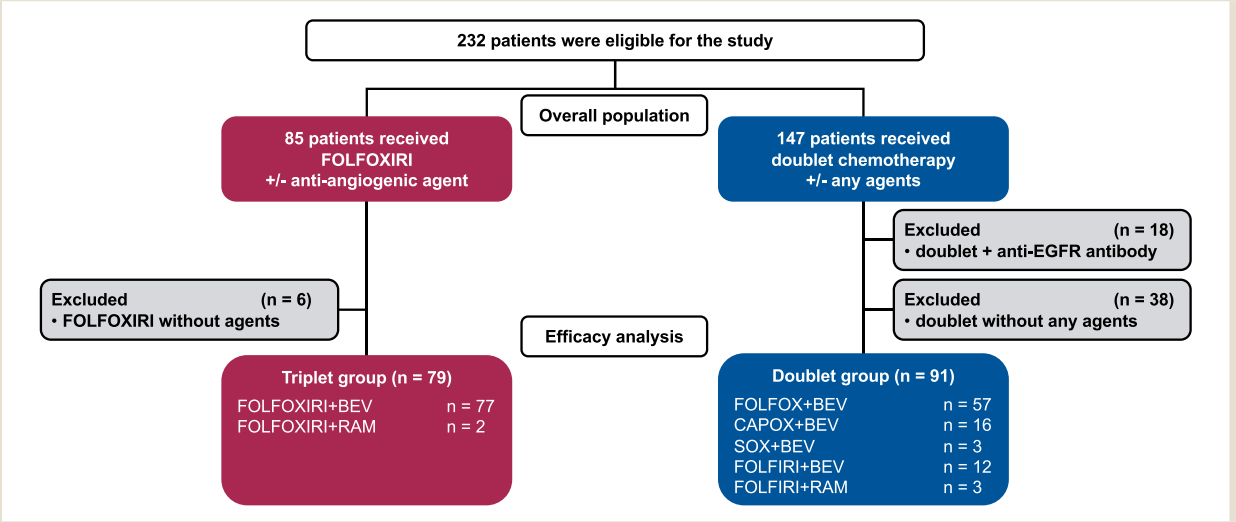
Figure 1 Patient flow diagram. BEV = bevacizumab; RAM = ramucirumab.



evaluate patient characteristics, summary statistics were constructed by employing frequencies and proportions for categorical data and means and standard deviations for continuous variables. We compared patient characteristics using Fisher's exact test for categorical variables and t-tests for continuous variables, as appropriate.

OS was evaluated from the initiation of the treatment to the day of death from any cause. For subjects lost to follow-up or those who were alive at the cutoff date, data will be censored at the time the subject was last confirmed to be alive. PFS was evaluated from the initiation of the treatment to the day of disease progression or death from any cause. For survivors without disease progression, data will be censored on the day of last evaluable imaging. The time-to-event outcomes were assessed via the Kaplan-Meier method. The HR was estimated using the Cox proportional hazards model. For sensitivity analysis, the propensity score was calculated, and then the adjusted HR and 95% CI were estimated using the inverse probability of treatment weighting (IPTW) method based on propensity scores calculated via logistic regression analysis with prespecified variables (ie, age, the Eastern Cooperative Oncology Group performance status [PS], and disease status [metastatic and/or recurrent]). All *P* values were based on a 2-sided hypothesis, and *P* values less than .05 were considered statistically significant. We performed all statistical analyses using the SAS version 9.4 and the JMP version 14.2.0 software (SAS Institute, Cary, NC, USA).

Results

Patient characteristics for the overall population

A total of 232 patients were eligible for this study (Figure 1). The details of the patient's demographic and clinical characteristics for the overall population are described in Supplementary Table 2. The entire patient cohort had a median OS of 17.2 months (95% CI, 14.0–19.1) and median PFS of 7.8 months (95% CI, 7.1–8.5). The PFS and OS of patients who received triplet (n = 85) and doublet chemotherapy (n = 147) are shown in Supplementary Figure 1.

Patient characteristics for Triplet and Doublet groups

A total of 170 patients had received triplet plus anti-VEGF therapy (Triplet group, n = 79) or doublet plus anti-VEGF therapy (Doublet group, n = 91). Eighteen patients who were treated with anti-EGFR antibody-containing regimens and 44 who were treated without any targeted agents were excluded from the primary analysis evaluating Triplet and Doublet chemotherapy (Figure 1). Patients divided according to the time of initiating first-line chemotherapy (ie, 2014–2015, 2016–2017, and 2018–2019) were described in Supplementary Figure 2.

Patients had a median age of 61 years (range, 19–83), and 51% were male. An ECOG PS of 0, 1, and ≥2 were seen in 63%, 32%, and 5% of patients. The initial diagnosis was metastasis in 74% of patients and recurrence in 26%. Within our cohort, 68% and 32% had right- and left-sided primary tumors, respectively. Distant metastasis was seen in the lymph nodes (61%), liver (49%), peritoneum (47%), and lungs (18%). Of 138 patients who were evaluated for the microsatellite instability or mismatch repair status, 14 (8%) were confirmed as MSI-H and/or deficient mismatch repair (dMMR).

The Triplet group was significantly younger than the Doublet group (median: 59 vs. 65 years old, $P = .002$). Furthermore, patients in the Triplet group had statistically better PS (0/1/≥2) than the Doublet group (72%/27%/1% vs. 55%/36%/9%, $P = .02$). The other variables were not significantly different between the groups (Table 1).

A total of 36 patients (21%) received a reduced dose of chemotherapy at the initial cycle of the first-line treatment (Supplementary Table 3). The number of patients who received dose reduction of either oxaliplatin and/or irinotecan was significantly

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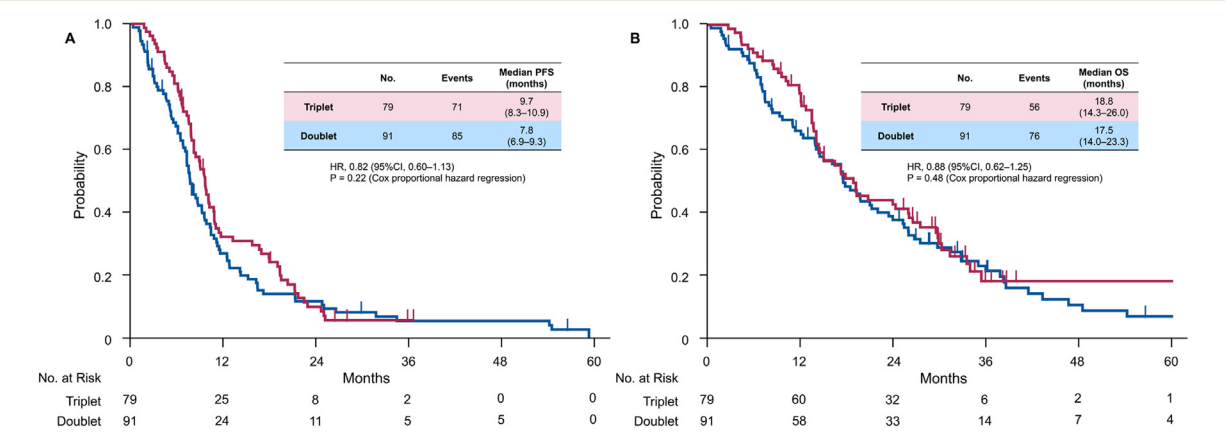
Table 1 Baseline Patient and Tumor Characteristics

Characteristics		Total (N = 170)	Triplet group (n = 79)	Doublet group (n = 91)	*P* value
Age, median (range)		61 (19–83)	59 (19–75)	65 (27–83)	0.0022*
Sex, male		87 (51%)	45 (57%)	42 (46%)	0.15
ECOG PS	0	107 (63%)	57 (72%)	50 (55%)	0.02*
	1	54 (32%)	21 (27%)	33 (36%)	
	≥2	9 (5%)	1	8 (9%)	
Primary tumor site	Right	116 (68%)	54 (68%)	62 (69%)	0.97
	Left	54 (32%)	25 (32%)	29 (32%)	
Disease status	Recurrent	44 (26%)	17 (22%)	27 (30%)	0.22
	Metastatic/unresectable	126 (74%)	62 (78%)	64 (70%)	
Surgery on primary tumor	Yes	75 (44%)	42 (53%)	53 (58%)	0.506
	No	95 (56%)	37 (47%)	38 (42%)	
Metastatic site	Lymph node	104 (61%)	45 (57%)	59 (65%)	0.29
	Liver	84 (49%)	43 (54%)	41 (45%)	0.22
	Liver-only	16 (9%)	11 (14%)	5 (5%)	0.059
	Peritoneum	80 (47%)	33 (42%)	47 (52%)	0.19
	Lung	31 (18%)	12 (15%)	19 (21%)	0.33
No. of metastatic sites	0–1	61 (36%)	31 (39%)	30 (33%)	0.39
	≥2	109 (64%)	48 (61%)	61 (67%)	
MSI and MMR status	dMMR and/or MSI-H	14 (8%)	5 (6%)	9 (10%)	0.17
	pMMR and/or MSI-L/MSS	124 (73%)	63 (80%)	61 (67%)	
	Missing	32 (19%)	11 (14%)	21 (23%)	

Abbreviations: dMMR = deficient MMR; ECOG = Eastern Cooperative Oncology Group; MMR = mismatch repair; MSI-H = microsatellite instability-high; MSS = microsatellite stable; PS = performance status; pMMR = proficient MMR.

Figure 2 Kaplan-Meier curve of progression-free survival (A) and overall survival (B) in the Triplet (n = 79) and Doublet groups (n = 91). HR = hazard ratio; OS = overall survival; PFS = progression-free survival.



higher in the Triplet group (n = 24; 30%) than that in the Doublet group (n = 6; 7%) ($P < .0001$).

Efficacy

At a median follow-up of 36.5 months with 132 deaths, the Triplet and Doublet groups, respectively, had a median PFS of 9.7 and 7.8 months (HR, 0.82; 95% CI, 0.60–1.13; $P = .02$) (Figure 2A) and a median OS of 18.8 and 17.5 months (HR, 0.88; 95% CI, 0.62–1.25; $P = .48$) (Figure 2B). The ORR was 53% in the Triplet group and 41% in Doublet group ($P = .10$), whereas the disease control rate was 91% and 86%, respectively (Supplementary Table 4).

IPTW analysis for PFS and OS

On IPTW analysis, the Triplet group did demonstrate superiority over the Doublet group in terms of PFS (median, 9.9 vs. 8.0

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Figure 3 Kaplan-Meier curve of progression-free survival (A) and overall survival (B) in the Triplet and Doublet groups adjusted by via inverse probability of treatment weighting. HR = hazard ratio; OS = overall survival; PFS = progression-free survival.

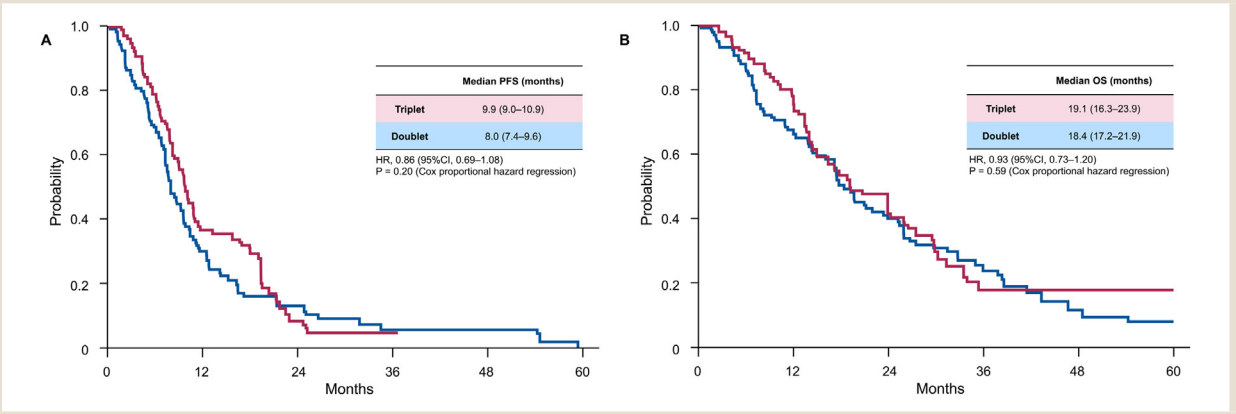
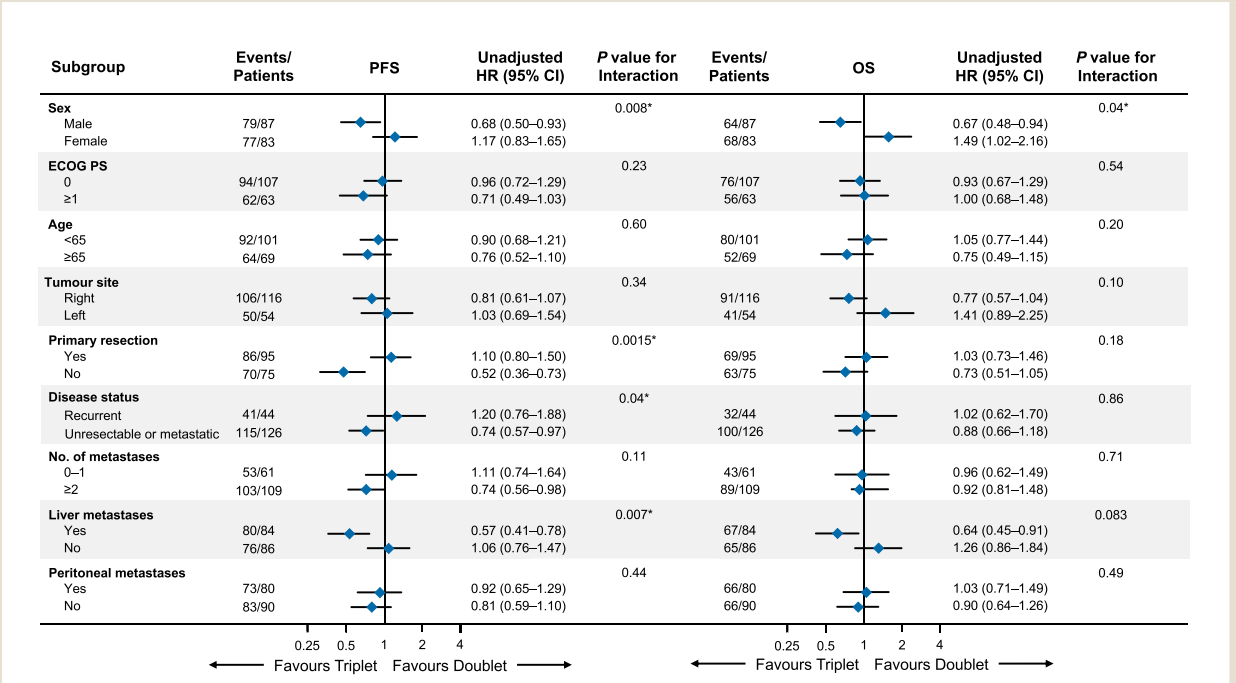


Figure 4 Subgroup analysis of progression-free survival and overall survival in groups stratified according to each variable. HR = hazard ratio; OS = overall survival; PFS = progression-free survival.



months; HR, 0.86; 95% CI, 0.69–1.08; $P = .20$) (Figure 3A) and OS (19.1 vs. 18.4 months; HR, 0.93; 95% CI, 0.73–1.20; $P = .59$) (Figure 3B).

Subgroup analyses for PFS and OS were performed to examine the interaction effect of treatment. Although a noticeable interaction effect of treatment with sex, primary resection, and liver metastases was seen in PFS, the trend for OS was consistent only in sex (Figure 4).

Safety

At least one grade ≥3 adverse event was seen in 51 and 43 patients in the Triplet and Doublet groups, respectively (Table 2). The most commonly reported grade ≥3 AEs were neutropenia (51%), thrombocytopenia (5%), diarrhea (5%), and hypertension (5%) in the Triplet group and neutropenia (24%) and hypertension (7%) in the Doublet group. None of the deaths in either group was related to therapy.

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Table 2 Grade ≥ 3 all-Cause Adverse Events Occurring During First-Line Therapy

Any event	Triplet group (n = 79) 51 (65%)	Doublet group (n = 91) 43 (47%)
Hematologic adverse events		
Neutropenia	40 (51%)	22 (24%)
Thrombocytopenia	4 (5%)	1 (1%)
Anemia	3 (4%)	1 (1%)
Nonhematologic adverse events		
Hypertension	4 (5%)	6 (7%)
Diarrhea	4 (5%)	0
Febrile neutropenia	3 (4%)	2 (2%)
Nausea/vomiting	2 (3%)	4 (4%)
Appetite loss	2 (3%)	2 (2%)
Peripheral sensory neuropathy	1 (1%)	2 (2%)
Proteinuria	1 (1%)	3 (3%)
Thrombosis	0	2 (2%)
Perforation	0	2 (2%)
Others	6 (8%)	12 (13%)

Treatment discontinuation and subsequent treatment

Ninety-two percent of the patients in the Triplet group and 98% of the patients in the Doublet group discontinued the first-line treatment. The main reason for treatment discontinuation was disease progression (75% in the Triplet group and 80% in the Doublet group). Only 3% and 5% of the patients in the Triplet and Doublet groups, respectively, discontinued the first-line chemotherapy due to toxicity. The details of the reasons for the termination of the first-line treatment are described in Supplementary Table 5.

The proportion of patients who underwent curative-intent surgery after first-line chemotherapy was higher in the Triplet group than in the Doublet group (13% vs. 3%; $P = .022$). In the Triplet group, the median PFS and OS were 17.3 months (95% CI, 6.4–not reached [NR]) and NR (95% CI, 17.8–NR), respectively, while in the Doublet group, the median PFS and OS were 11.2 months (95% CI, 8.7–12.8) and 42.4 months (95% CI, 38.2–46.5), respectively.

In the Triplet group, 52 (66%) patients received subsequent chemotherapy after discontinuation of the first-line treatment, whereas in the Doublet group, this was 73 (80%) patients (Supplementary Table 6). In the Triplet and Doublet groups, respectively, 13 (25%) and 43 (59%) patients received irinotecan-based chemotherapy, 16 (31%) and 6 (8%) patients received BRAF inhibitor-containing treatment, and 2 (4%) and 6 (8%) patients diagnosed as MSI-H/dMMR received immune checkpoint blockade.

Discussion

To the best of our knowledge, WJOG13219G is the first study to evaluate the efficacy and safety of FOLFOXIRI or doublet chemotherapy with anti-VEGF therapy for *BRAF*^{V600E} mutant mCRC with a significant number of real-world patients in Japan. In this study, FOLFOXIRI plus anti-VEGF therapy did not improve PFS or OS compared to doublet chemotherapy plus anti-VEGF therapy, even after adjusting for variables via IPTW. These results were consistent with a subgroup analysis previously conducted by Cremolini et al.[18] Patients with *BRAF*^{V600E} mutant mCRC in our study had lower PS (63% with PS 0) than those who had participated in TRIBE (90%) and TRIBE2 (85%) trials,[8,17] implying that real-world patients with *BRAF*^{V600E} mutant mCRC seem to be less eligible to receive the intensive chemotherapy.

FOLFOXIRI plus anti-VEGF therapy should not be routinely initiated in patients with *BRAF*^{V600E} mutant mCRC, because toxicity, particularly in the form of hematologic AEs, undoubtedly increases during triplet chemotherapy, as proven in previous trials and in real-world patients.[7] *BRAF*^{V600E} mutant mCRC is frequently associated with poor prognosis, but these cases have molecular heterogeneity that results in distinct clinicopathological features and prognostic impacts in each tumor.[10,11,19,20] Thus, the heterogeneity of *BRAF*^{V600E} mutant mCRC may account for some apparent differences in the efficacy of cytotoxic chemotherapy. Thus, further investigation is warranted to fully characterize *BRAF*^{V600E} mutant mCRC by correlating different variables such as clinicopathological features, gene expression profiles, and metagenomic analysis.[10,20,21]

Our study showed that patients who are potential candidates for conversion surgery might be considered for triplet chemotherapy. In the TRIBE2 trial, 17% and 12% of the FOLFOXIRI and doublet chemotherapy groups, respectively, underwent R0 resection for metastasis.[17] Unfortunately, not all patients with *BRAF*^{V600E} mutant mCRC undergo conversion surgery because they often have multi-organ metastases. In our study, the efficacy of FOLFOXIRI plus anti-VEGF therapy for these patients is inconclusive, due the small number of patients who underwent conversion surgery. Nevertheless, intensive chemotherapy for *BRAF*^{V600E} mutant mCRC can improve the possibility of surgical resection of metastases.

Subgroup analysis suggested an interaction according to sex. Dose modification or withdrawal more frequently occurred in females,

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possibly because of serious AEs. The pooled analysis of the TRIBE and TRIBE2 trials showed that females had a significantly higher risk of experiencing grade ≥3 AEs than males, independent of regimens (triplet or doublet chemotherapy), whereas improvements in the efficacy of triplet chemotherapy over doublet chemotherapy were observed independent of sex.[22] Although no data have been reported on the efficacy and safety of triplet chemotherapy compared with doublet chemotherapy in patients with *BRAF*^{V600E} mutant mCRC particularly, the incidence of serious AEs might have influenced the results in our cohort. In addition, the heterogeneity of *BRAF*^{V600E} mutant mCRC might explain in some part the obvious difference in the efficacy of chemotherapy.[10,11,20] Furthermore, FOLFOXIRI plus anti-VEGF therapy had more favorable PFS versus doublet chemotherapy among patients with metastasis at diagnosis, those with liver metastases, and those not undergoing resection of the primary tumor. Thus, patients with a high tumor burden might benefit from intensive chemotherapy. However, OS was not significantly different in these populations; hence, the clinical benefit of FOLFOXIRI plus anti-VEGF therapy remains debatable.

Notably, more than 70% of patients received second-line chemotherapy in our cohort. Generally, patients with *BRAF*^{V600E} mutant mCRC with aggressive disease conditions had less opportunity to receive second-line or later treatment.[23] Recently, BRAF inhibitor (encorafenib) plus anti-EGFR antibody (cetuximab) with or without MEK inhibitor (binimetinib) showed significantly longer OS and a higher response in phase III trial than those shown by the standard chemotherapy as the second-line treatment. Thus, a combination of BRAF inhibitor plus anti-EGFR antibody with or without MEK inhibitor is the new standard of care for the second-line treatment for patients with *BRAF*^{V600E} mutant mCRC.[24] Similarly, patients with MSI-H/dMMR tumors, which harbor approximately 30% of *BRAF*^{V600E} mutant mCRC, could also undergo immunotherapy.[25] The availability of these options for second-line treatment might have contributed to the high incidence of transition to subsequent treatment in our cohort. Further development of these therapeutic options may help prolong survival in this population.

This study has several limitations. First, it was a non-randomized retrospective study, and thus, the regimen for first-line treatment depended on the physician's judgment. This caused some patient characteristics to differ between groups. Furthermore, the small sample size due to the rarity of *BRAF*^{V600E} mutant mCRC might have influenced the power of evaluating the efficacy of triplet and doublet chemotherapy regimens and restricted any conclusive evidence from our study. To reduce bias, we adopted the IPTW method based on propensity scores for balancing covariates between treatment groups, contributing to yield correct estimations of treatment efficacy with preserving sample size. Second, some outcomes could have been affected by subsequent treatments such as immunotherapy or BRAF-targeted treatment. This disparity in treatment period between the two groups could partially explain why patients in the Triplet group received BRAF inhibitor-containing regimen more often than those in the Doublet group.

Conclusion

In conclusion, FOLFOXIRI plus anti-VEGF therapy showed no survival benefit versus doublet plus anti-VEGF antibody in the overall and IPTW cohorts or subgroups of real-world patients with *BRAF*^{V600E} mutant mCRC.

Clinical Practice Points

- Whether FOLFOXIRI plus anti-VEGF therapy (triplet) could confer a survival benefit over doublet plus anti-VEGF therapy (doublet) in real-world patients with *BRAF*^{V600E} mutant metastatic colorectal cancer remains unclear.
- This real-world retrospective study revealed that the triplet chemotherapy was not superior to the doublet chemotherapy in terms of OS (HR, 0.88; 95% CI, 0.62–1.25; $P = .48$) and PFS (HR, 0.82; 95% CI, 0.60–1.13; $P = .22$). Furthermore, IPTW analysis revealed no difference in PFS and OS between the 2 groups. No specific subgroups were found to benefit from the triplet chemotherapy. Grade 3 and 4 adverse events were frequently observed in the triplet group.
- The results help determine the optimal therapeutic strategy of first-line chemotherapy for patients with *BRAF*^{V600E} mutant metastatic colorectal cancer.

Disclosure

Yosuke Kito: Honoraria–Taiho Pharmaceutical; Daiichi Sankyo; Merck BioPharma; Takeda. Toshihiko Matsumoto: Honoraria–Lilly Japan; Ono Pharmaceutical; Bristol-Myers Squibb; Taiho Pharmaceutical. Takeshi Kawakami: Honoraria–Taiho Pharmaceutical; Bristol-Myers Squibb; Ono Pharmaceutical. Masato Komoda: Honoraria–Eisai Co., Ltd; Lilly Japan; Ono Pharmaceutical; Bristol-Myers Squibb; Daiichi Sankyo; Taiho Pharmaceutical. Kengo Nagashima: Consulting fees–Fujimoto Pharmaceutical Corporation; SENJU Pharmaceutical Co., Ltd.; Toray Industries, Inc. Lecture fee–Pfizer R&D Japan G.K. Yasunori Sato: Honoraria–Eisai Co., Ltd; Kowa Company, Ltd. Kentaro Yamazaki: Honoraria–Bayer; Bristol-Myers Squibb; Chugai Pharma; Daiichi Sankyo; Lilly Japan; Merck Biopharma; MSD; Ono Pharmaceutical; Sanofi; Taiho Pharmaceutical; Takeda; Yakult Honsha. Research Funding–Taiho Pharmaceutical. Shuichi Hironaka: Consulting fees–Ono Pharmaceutical; Bristol-Myers Squibb; Daiichi Sankyo. Honoraria–Ono Pharmaceutical; Bristol-Myers Squibb; Daiichi Sankyo; Taiho Pharmaceutical; Lilly Japan, Chugai Pharma; Nihonkayaku; Thumura & Co.; Sanofi; Merck; AstraZeneca; Yakult Honsha; Takeda

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clcc.2022.08.002.

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