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ORIGINAL ARTICLE

Effectiveness of FTD/TPI plus bevacizumab and impact of prior bevacizumab exposure in patients with mCRC: the Italian FLOWER study

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Background: The SUNLIGHT trial established trifluridine/tipiracil (FTD/TPI) plus bevacizumab as a new later-line standard in metastatic colorectal cancer (mCRC). However, evidence in real-world populations—often older and more heterogeneous—remains limited. This study evaluated the effectiveness and safety of FTD/TPI plus bevacizumab in a large, unselected real-world mCRC population and aimed to identify potential predictive factors associated with response to this treatment.

Patients and methods: We conducted a retrospective, multicenter analysis of patients with refractory mCRC treated with FTD/TPI plus bevacizumab across 15 Italian centers. The primary endpoint was overall survival (OS). Secondary endpoints included progression-free survival (PFS), overall response rate (ORR), and safety.

Results: 297 patients were included. Median age was 61.8 years, and 79.1% had $\geq$2 metastatic sites. Most patients (89.9%) had prior bevacizumab exposure, and 35.4% had received $\geq$3 treatment lines. ORR was 7.4%, and the disease control rate was 54.2%. Median PFS was 5.3 months [95% confidence interval (CI) 4.5-6.5 months], and median OS was 11.9 months (95% CI 10.5-14.3 months). Eastern Cooperative Oncology Group performance status, tumor sidedness, metastatic burden, and time from metastatic diagnosis to treatment initiation results were statistically associated with OS. Any grade adverse events occurred in 243 (81.8%) patients, and grade 3-4 events in 152 (52.2%); grade 3-4 neutropenia was the most frequent and emerged in 35.4% of patients, while non-hematologic toxicities were mostly low grade.

Conclusions: In this unselected real-world population, FTD/TPI plus bevacizumab demonstrated clinically meaningful activity and a tolerable safety profile. Outcomes were consistent with the SUNLIGHT trial, supporting the routine use of this combination in later-line option in mCRC.

Key words: colorectal cancer, trifluridine—tipiracil, bevacizumab, real-world

INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy and the second leading cause of cancer-related mortality worldwide.[1] Approximately 20% of patients present with metastatic stage at diagnosis, and $\leq$50% will eventually develop metastases during the course of their disease.[2] Despite substantial improvements in systemic treatment, including the introduction of fluoropyrimidines, oxaliplatin, irinotecan, anti-vascular endothelial growth factor (VEGF) and anti-EGF receptor monoclonal antibodies, and immune checkpoint inhibitors in selected subgroups, long-term survival in metastatic CRC (mCRC) remains limited.[3,4]

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In later treatment lines, therapeutic options are particularly restricted, and patient management must balance efficacy with tolerability in heavily pretreated populations.[5] Trifluridine/tipiracil (FTD/TPI) is an oral nucleoside analogue approved for refractory mCRC that demonstrated a significant improvement in overall survival (OS) compared with best supportive care in the phase III RECOURSE trial[6]; however, its activity as a monotherapy remains modest.[6,7]

Bevacizumab, a monoclonal antibody targeting VEGF, has been an established component of mCRC treatment of nearly 2 decades.[8] The rationale for combining bevacizumab with FTD/TPI arises from preclinical evidence suggesting synergistic antitumor activity through the modulation of tumor angiogenesis and enhancement of cytotoxic effects.[9,10] In the SUNLIGHT study,[11] a randomized phase III clinical trial, the combination of FTD/TPI and bevacizumab showed improved progression-free survival (PFS) [5.6 versus 2.4 months, hazard ratio (HR) 0.44, 95% confidence interval (CI) 0.36-0.54] and improved OS (10.8 versus 7.5 months, HR 0.61, 95% CI 0.49-0.77) than FTD/TPI monotherapy.

Nevertheless, clinical trial populations are often highly selected and may not adequately represent patients encountered in daily practice, who are frequently older, frailer, and burdened by comorbidities or poor performance status (PS).[12,13]

The present study aimed to evaluate the real-world effectiveness and safety of FTD/TPI combined with bevacizumab in patients with mCRC previously treated with standard therapies, and to explore potential clinical, molecular, and pathological factors associated with treatment response.

METHODS

Data from patients with pretreated metastatic colorectal adenocarcinoma who received the combination of FTD/TPI and bevacizumab were retrospectively collected across 15 Italian centers (Supplementary Table S1, available at https://doi.org/10.1016/j.esmogo.2026.100317). The treatment regimen was: FTD/TPI administered at a starting dose of 35 mg/m^2 by mouth twice a day (on day 1-5 and 8-12 of 28-days cycles) and bevacizumab administered at a dose of 5 mg/kg intravenously every 14 days. All patients enrolled received at least one dose of the treatment and had at least one disease reassessment after treatment start (or had clinical disease progression or death before radiological assessment). The following clinical, pathological and molecular characteristics were collected: age, sex, Eastern Cooperative Oncology Group (ECOG) PS, tumor sidedness, primary tumor resection, time to metastatic disease, number and sites of metastases, prior systemic treatments, *RAS* and *BRAF* mutational status, mismatch repair (MMR) system status [proficient (p) or deficient (d)] or microsatellite instability (MSI). MMR status was assessed by immunohistochemistry staining; MSI status by PCR; *RAS* and *BRAF* status by PCR, pyrosequencing or next-generation sequencing techniques, as per each center's current clinical practice. The study was conducted in accordance with the Declaration of Helsinki and received approval from the ethics committees of the Fondazione Policlinico Universitario Agostino Gemelli—IRCCS (No. 7242-2025).

The primary endpoint of the study was OS, defined as the time from the date of FTD/TPI and bevacizumab's start to the date of death from any cause (living patients were censored at last follow-up when the patient was known to be alive). Given the descriptive and retrospective nature of the study, no formal hypothesis-driven sample size calculation was carried out. The study population was defined by the enrollment capacity of the participating centers during the predefined study period, and all consecutive eligible patients were included. Based on feasibility, ∼300 patients were expected. Assuming a 1-year OS rate of 43% as reported in the SUNLIGHT trial, a sample size of 300 patients would allow an estimation of this proportion with a standard error of a∼3%, corresponding to a 95% CI of ±6%. With an expected median OS of ∼11 months (as reported in the SUNLIGHT trial) and an event rate exceeding 50%, this sample size would also allow an estimation of the median survival with an approximate 95% CI width of ±2 months.

Secondary endpoints included PFS, defined as the time from the start of the treatment to first evidence of disease progression or death from any cause, whichever occurred first (alive patients not experiencing disease progression were censored at the last visit), investigator-assessed overall response rate (ORR) according to RECIST criteria v1.1[14], and adverse events (AEs), reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.[15] Qualitative variables were evaluated using χ^2 test or Fisher's exact test and continuous variables using Mann—Whitney test when appropriate to compare clinical and molecular baseline characteristics among treatment groups. Survival curves were estimated by the Kaplan—Meier method and compared with the log-rank test. HRs with 95% CIs were estimated with Cox proportional hazards model.

All statistical analyses were carried out using R software (version 4.2.1) and Jamovi (version 2.3.28).

RESULTS

Patients

A total of 297 patients were included in the analysis (Table 1). The median age was 61.8 years (range 17-89 years), with 122 patients (41.1%) aged ≥65 years. Men represented 52.2% ($n = 155$) of the cohort. Most patients exhibited an ECOG PS of 0 ($n = 159$, 53.5%) or 1 ($n = 120$, 40.4%), whereas 18 patients (6.1%) had an ECOG PS of 2.

Regarding the primary tumor site, 134 patients (45.1%) had left-sided tumors, 82 (27.6%) had right-sided tumors, and 81 (27.3%) had rectal cancer. MMR status was predominantly proficient: 291 patients (98.0%) had pMMR tumors, whereas dMMR was identified in 6 patients (2.0%). *BRAF* mutations were detected in 13 patients (4.4%), and

Table 1. Table summarizing characteristics of enrolled patients and tumors

Characteristics	Patients $N = 297$ (%)
Age	
Median, years (range)	61.8 (17.8-89.1)
≥65 years	122 (41.1%)
<65 years	175 (58.9%)
Sex	
Female	142 (47.8%)
Male	155 (52.2%)
ECOG PS	
0	159 (53.5%)
1	120 (40.4%)
2	18 (6.1%)
Primary tumor location	
Left-sided	134 (45.1%)
Right-sided	82 (27.6%)
Rectum	81 (27.3%)
MMR status	
pMMR	291 (98.0%)
dMMR	6 (2.0%)
BRAF status	
Wild-type	284 (95.6%)
Mutated	13 (4.4%)
KRAS/NRAS status	
Wild-type	122 (41.1%)
Mutated	175 (58.9%)
Timing of metastatic disease	
Synchronous	198 (66.7%)
Metachronous	99 (33.3%)
Number of metastatic sites	
Single	62 (20.9%)
Multiple	235 (79.1%)
Sites of metastases	
Liver	187 (62.9%)
Lung	156 (52.5%)
Peritoneum	101 (34.0%)
Non-locoregional lymph nodes	78 (26.3%)
Bone	19 (6.4%)
CNS	2 (0.6%)
Other	17 (5.7%)
Previous treatments	
Median (range)	2 (1-7)
≤2	192 (64.6%)
>2	105 (35.4%)
Previous treatments for metastatic disease	
Fluoropyrimidine	296 (99.6%)
Irinotecan	275 (92.6%)
Oxaliplatin	267 (89.9%)
Bevacizumab	267 (89.9%)
Anti-EGFR	106 (35.7%)
Time from diagnosis of metastatic disease to FTD/TPI plus bevacizumab	
>18 months	206 (69.4%)
≤18 months	91 (30.6%)
Cumulative bevacizumab exposure	
>12 months	142 (53.2%)
≤12 months	125 (46.8%)
First-line regimen with bevacizumab	
Yes	184 (62.0%)
No	113 (38.0%)
Second-line regimen with bevacizumab	
Yes	201 (75.8%)
No	64 (24.2%)
Bevacizumab-free interval (BFI)	
≤6 months	162 (54.5%)
>6 months	85 (28.6%)
No bevacizumab exposure	30 (10.1%)
Missing data	20 (6.7%)

CNS, central nervous system; dMMR, deficient mismatch repair; ECOG PS, Eastern Cooperative Oncology Group performance status; FTD/TPI, trifluridine/tipiracil; MMR, mismatch repair; pMMR, proficient mismatch repair.

KRAS/NRAS mutations were present in 175 patients (58.9%).

Metastatic disease was synchronous (<6 months from diagnosis) in 198 patients (66.7%) and metachronous in 99 (33.3%). Most patients ($n = 235$, 79.1%) presented with multiple metastatic sites, whereas 62 patients (20.9%) had a single metastatic site. The most common metastatic locations were liver ($n = 187$ patients, 62.9%) and lung ($n = 156$ patients, 52.5%).

Patients had received a median of two previous systemic treatments (range 1-7); 105 (35.4%) had received ≥3 lines. Prior exposure to bevacizumab was documented in 267 patients (89.9%); 184 patients (62.0%) received bevacizumab in a first-line setting and 201 patients (75.8%) as part of a second-line regimen.

Cumulative bevacizumab exposure exceeded 12 months in 142 patients (53.2%), whereas 125 patients (46.8%) had ≤12 months of exposure. Eighty-five patients (28.6%) had >6 months between their last bevacizumab infusion and FTD/TPI plus bevacizumab start (bevacizumab-free interval, BFI), whereas 162 patients (54.5%) had <6 months.

Activity and effectiveness

Twenty-two patients (7.4%) achieved a partial response, and 139 (46.8%) experienced a stable disease, resulting in a disease control rate of 54.2%. After a median follow-up of 11.0 months (95% CI 9.7-18.0 months), 224 of 297 patients (75.4%) had experienced disease progression. The median PFS (mPFS) in the overall population was 5.3 months (95% CI 4.5-6.5 months), Figure 1A. Several patients' and tumors' characteristics showed prognostic relevance. ECOG PS 0 was associated with a mPFS of 6.5 months versus 4.5 months for patients with ECOG PS ≥1 ($P = 0.023$). Patients with right-sided primary tumors had significantly shorter PFS (4.6 months) compared with left-sided tumors (6.3 months; $P = 0.011$). dMMR status was also associated with poorer mPFS (3.2 months versus 5.4 months; $P = 0.047$). Having received more than two previous treatment lines corresponded to a mPFS of 6.8 months versus 4.6 months in patients who received ≤2 lines of therapy ($P = 0.047$). Longer bevacizumab exposure (>12 months versus ≤12 months; 6.5 months versus 4.4 months; $P = 0.010$) and longer first-line PFS (>12 months versus ≤12 months; 6.6 months versus 4.4 months; $P = 0.005$) showed improved mPFS. Patients who started FTD/TPI plus bevacizumab <18 months from metastatic disease diagnosis had a worse mPFS than patients who started treatment >18 months from diagnosis (3.5 months versus 6.5 months; $P < 0.001$). Bevacizumab in first-line treatment ($P = 0.207$), bevacizumab as part of second-line treatment ($P = 0.941$) and BFI before FTD/TPI plus bevacizumab start ($P = 0.084$) were not statistically associated with treatment PFS. At multivariate analysis, only ECOG PS (0 versus ≥1; HR 0.65, 95% CI 0.49-0.86, $P = 0.003$) and time from metastatic disease to treatment start (>18 months versus ≤18 months; HR 1.61, 95% CI 1.08-2.40, $P = 0.019$) remained statistically associated with PFS (Table 2, Figure 1B-C).

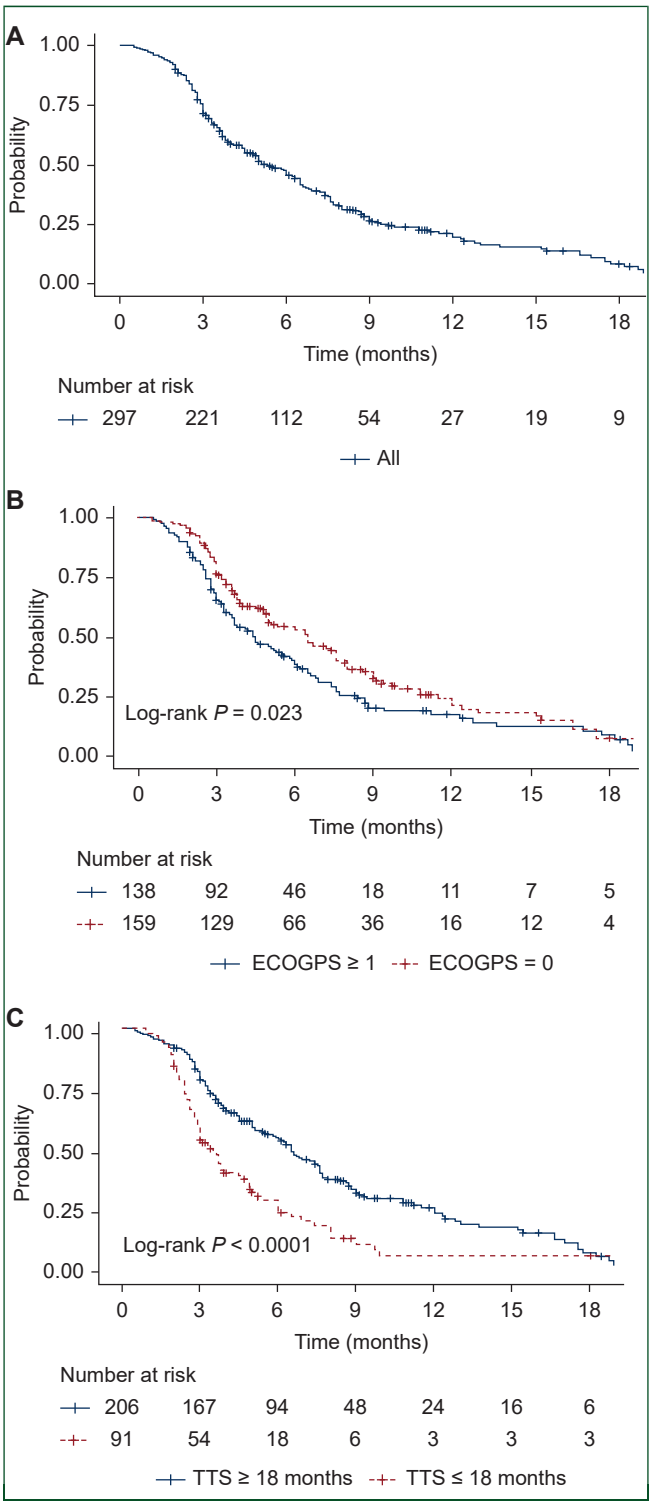

Figure 1. Progression-free survival analyses. Progression-free survival in the overall population (A), and subgroup analyses according to (B) Eastern Cooperative Oncology Group performance status (ECOG PS) (0 versus ≥1) and (C) time to treatment start (TTS) from metastatic disease diagnosis (>18 months versus ≤18 months).

After a median follow-up of 13.1 months (95% CI 11.0-15.9 months), 154/297 (51.9%) deaths were observed. Median OS (mOS) was 11.9 months (95% CI 10.5-14.3 months) (Figure 2A). Multiple patients' characteristics were associated with survival: patients with ECOG PS 0 had a longer mOS than those with ECOG PS ≥1 (14.3 versus 9.0 months; $P < 0.001$). Right-sided tumors were associated with inferior mOS compared with left-sided cancers (8.8 versus 13.3 months; $P < 0.001$). Patients with ≥2 metastatic sites had a shorter mOS than those with a single metastatic site (11.5 versus 16.0 months; $P = 0.026$). Prior exposure to more than two treatment lines corresponded with a mOS of 14.0 versus 10.8 months in patients who received ≤2 lines of therapy ($P = 0.012$). Patients with a shorter bevacizumab exposure (≤12 months) had a poorer mOS compared with those with longer exposure (9.5 versus 14.5 months; $P = 0.002$). Patients with first-line PFS >12 months had improved mOS compared with those with earlier progression (15.2 versus 10.0 months; $P = 0.003$). A time from metastatic disease diagnosis to FTD/TPI plus bevacizumab start <18 months was associated to a shorter mOS (7.7 versus 13.6 months; $P = 0.00013$).

Bevacizumab in first-line treatment ($P = 0.124$), bevacizumab as part of second-line treatment ($P = 0.375$) and BFI before FTD/TPI plus bevacizumab start ($P = 0.156$) were not statistically associated with treatment mOS.

At multivariate analysis, ECOG PS (0 versus ≤1; HR 0.56, 95% CI 0.40-0.80, $P = 0.001$), primary tumor sidedness (left versus right; HR 1.58, 95% CI 1.11-2.25, $P = 0.012$), time from metastatic diagnosis to FTD/TPI plus bevacizumab start (>18 versus ≤12 months; HR, 1.67, 95% CI 1.15-2.41, $P = 0.007$) and number of metastatic sites (1 versus ≥2; HR 1.65, 95% CI 1.05-2.60, $P = 0.030$) remained associated with OS (Table 2, Figure 2B-E).

Safety

Treatment was generally manageable, with AEs occurring in 243 (81.8%) patients, and grade 3-4 events in 152 (52.2%) patients. All AEs are reported in Table 3. The most common hematologic toxicity was neutropenia, reported in 172/297 (57.9%) patients, including 105 (35.4%) with grade 3-4 toxicity. Anemia (43.8%; grade 3-4 4.0%) and thrombocytopenia (23.2%; grade 3-4 2.7%) were also frequent but predominantly low grade. Among non-hematologic AEs, asthenia/fatigue was the most common (51.2%; grade 3-4 4.0%), followed by nausea (29.3%; grade 3-4 2.7%) and diarrhea (17.2%; grade 3-4 1.7%). Bleeding and thromboembolic events were rare (3.4% and 2.7%) and predominantly low grade (grade 3-4 0% and 1.7%, respectively). Data regarding the use of granulocyte colony-stimulating factors (G-CSF) were available for 237/297 patients; 88/237 (37.1%) patients received G-CSF.

DISCUSSION

In this large, multicenter real-world cohort of heavily pretreated patients with mCRC, the combination of FTD/TPI and bevacizumab demonstrated clinically meaningful activity and a manageable safety profile. The mOS of 11.9 months and mPFS of 5.3 months observed in our cohort are broadly consistent with the outcomes reported in the phase III SUNLIGHT trial (mOS 10.8 months, 95% CI 9.4-11.8 months; mPFS 5.6 months, 95% CI 4.5-5.9 months), which established FTD/TPI plus bevacizumab as a new third-line

Table 2. Univariate and multivariate analyses of progression-free survival and overall survival

	Progression-free survival			Overall survival		
	Median in months (95% CI)	HR Univariate (95% CI)	HR Multivariate (95% CI)	Median in months (95% CI)	HR Univariate (95% CI)	HR Multivariate (95% CI)
Age						
≤65 years	5.0 (3.8-6.5)	0.75 (0.56-1.00) $P = 0.052$	–	11.8 (10.0-13.3)	0.75 (0.54-1.05) $P = 0.091$	–
>65 years	6.0 (4.9-7.6)			15.2 (10.5-21.9)		
Sex						
Female	4.6 (3.8-6.5)	0.86 (0.66-1.12) $P = 0.269$	–	11.7 (9.9-15.0)	0.99 (0.72-1.35) $P = 0.931$	–
Male	5.8 (5.0-7.6)			13.2 (10.0-15.5)		
ECOG PS						
0	6.5 (5.0-7.7)	0.69 (0.52-0.91) $P = 0.023$	0.66 (0.50-0.88) $P = 0.004$	14.3 (12.0-17.2)	0.52 (0.37-0.72) $P < 0.001$	0.56 (0.40-0.80) $P = 0.001$
≥1	4.5 (3.7-5.9)			9.0 (7.5-11.7)		
Primary tumor						
Left	6.3 (4.9-7.6)	1.47 (1.09-1.98) $P = 0.011$	1.23 (0.90-1.69) $P = 0.195$	13.3 (11.8-16.0)	1.82 (1.29-2.56) $P < 0.001$	1.58 (1.11-2.25) $P = 0.012$
Right	4.6 (3.5-5.9)			8.8 (7.3-11.9)		
MMR						
Proficient	5.4 (4.6-6.5)	0.40 (0.17-0.99) $P = 0.047$	0.42 (0.17-1.06) $P = 0.066$	12.0 (10.5-14.5)	0.58 (0.22-1.58) $P = 0.290$	–
Deficient	3.2 (2.1-NR)			8.5 (4.2-NR)		
RAS						
Wild-type	5.6 (4.5-7.7)	0.86 (0.66-1.12) $P = 0.267$	–	13.2 (10.7-15.5)	0.94 (0.68-1.30) $P = 0.713$	–
Mutated	5.0 (4.1-6.5)			11.5 (9.1-14.5)		
BRAF						
Wild-type	5.2 (4.5-6.5)	0.89 (0.48-1.63) $P = 0.706$	–	11.9 (10.5-14.9)	0.74 (0.38-1.46) $P = 0.385$	–
Mutated	6.2 (3.7-NR)			10.5 (7.5-NR)		
Timing of metastatic disease						
Metachronous	5.3 (4.5-7.5)	1.10 (0.83-1.45) $P = 0.516$	–	14.3 (10.7-17.0)	1.20 (0.85-1.69) $P = 0.308$	–
Synchronous	5.4 (4.2-6.5)			11.5 (9.1-13.6)		
Number of metastatic sites						
1	7.4 (6.0-8.7)	1.29 (0.93-1.78) $P = 0.131$	–	16.0 (12.0-NR)	1.64 (1.05-2.54) $P = 0.026$	1.65 (1.05-2.60) $P = 0.030$
≥2	5.0 (4.0-6.0)			11.5 (9.9-13.6)		
Number of previous lines						
>2	6.8 (5.4-7.7)	1.34 (1.01-1.78) $P = 0.047$	1.18 (0.87-1.60) $P = 0.298$	14.0 (11.8-20.0)	1.55 (1.10-2.18) $P = 0.012$	1.22 (0.83-1.81) $P = 0.309$
≤2	4.6 (3.8-6.0)			10.8 (9.0-13.3)		
Previous bevacizumab						
No	6.2 (3.6-NR)	1.25 (0.78-2.0) $P = 0.353$	–	15.0 (9.9-NR)	1.42 (0.78-2.55) $P = 0.248$	–
Yes	5.2 (4.5-6.5)			11.9 (10.3-13.8)		
Bevacizumab exposure						
>12 months	6.5 (5.1-7.6)	1.44 (1.09-1.89) $P = 0.010$	1.28 (0.93-1.76) $P = 0.133$	14.5 (11.9-19.6)	1.68 (1.20-2.34) $P = 0.002$	1.36 (0.88-2.10) $P = 0.168$
≤12 months	4.4 (3.3-5.3)			9.5 (8.0-11.8)		
First-line progression-free survival						
>12 months	6.6 (5.5-8.7)	0.67 (0.50-0.88) $P = 0.005$	0.96 (0.68-1.37) $P = 0.840$	15.2 (12.2-20.0)	0.60 (0.43-0.84) $P = 0.003$	0.93 (0.62-1.41) $P = 0.746$
≤12 months	4.4 (3.5-5.8)			10.0 (8.7-11.9)		
Time from diagnosis of metastatic disease to FTD/TPI plus bevacizumab						
>18 months	6.5 (5.6-7.6)	1.84 (1.38-2.44) $P < 0.001$	1.60 (1.08-2.38) $P = 0.020$	13.6 (11.8-17.0)	1.90 (1.36-2.65) $P < 0.001$	1.67 (1.15-2.41) $P = 0.007$
≤18 months	3.5 (2.9-4.8)			7.7 (6.0-11.9)		
First-line regimen with bevacizumab						
Yes	5.0 (4.4-6.5)	0.84 (0.64-1.10) $P = 0.207$	–	10.8 (9.1-13.2)	0.77 (0.55-1.07) $P = 0.124$	–
No	6.1 (4.4-8.0)			14.0 (12.0-16.0)		

Continued

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Table 2. Continued

	Progression-free survival			Overall survival		
	Median in months (95% CI)	HR Univariate (95% CI)	HR Multivariate (95% CI)	Median in months (95% CI)	HR Univariate (95% CI)	HR Multivariate (95% CI)
Second-line regimen with bevacizumab						
Yes	6.0 (4.9-6.9)	1.01 (0.73-1.40) $P = 0.941$	–	13.0 (10.5-15.1)	1.18 (0.82-1.72) $P = 0.375$	–
No	5.0 (3.8-7.7)			10.7 (9.0-17.2)		
Bevacizumab-free interval (BFI)						
≤6 months	6.7 (5.0-7.7)	1.30 (0.97-1.76) $P = 0.084$	–	12.3 (10.4-19.9)	1.30 (0.91-1.86) $P = 0.156$	–
>6 months	4.8 (3.7-6.0)			11.5 (9.1-13.8)		

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; FTD/TPI, trifluridine/tipiracil; HR, hazard ratio; MMR, mismatch repair.

standard of care in mCRC.[11] Importantly, our study provides complementary evidence by including a broader and less selected patient population than that typically enrolled in randomized clinical trials. A substantial proportion of patients in our cohort presented with adverse prognostic features, including a markedly higher burden of metastatic disease: 79.1% had metastases involving at least two organ sites, whereas in the SUNLIGHT trial only 38.2% of patients had multiple organ involvement. Moreover, only 52.5% of patients received the combination as third-line therapy, whereas 105 patients (35.4%) had undergone ≥3 prior treatment lines (versus 2.4% in SUNLIGHT). In addition, our cohort included patients with ECOG PS 2 (6.1%), who were excluded from the SUNLIGHT trial. Despite these adverse baseline characteristics, the consistent benefit observed across subgroups reinforces the robustness and generalizability of this combination therapy in heterogeneous real-world clinical settings.

Several clinical factors emerged as prognostic in our analysis. ECOG PS remained one of the strongest predictors of outcome, confirming prior evidence that PS is a critical determinant of benefit from later-line therapies.[16,17] An exploratory objective of this study was to descriptively evaluate whether prior exposure to bevacizumab was associated with differences in outcomes in patients receiving FTD/TPI plus bevacizumab. This question has important clinical relevance, given that most patients with mCRC receive bevacizumab in earlier treatment lines and concerns have been raised regarding the potential attenuation of VEGF pathway inhibition due to prolonged or repeated drug exposure. In our cohort, prior bevacizumab use—whether administered in first-line or second-line treatment—or a prolonged BFI did not correlate with PFS or OS of FTD/TPI plus bevacizumab.

This finding is biologically plausible. Resistance to bevacizumab-based regimens is often driven by adaptive or intrinsic mechanisms (e.g. upregulation of alternative angiogenic pathways, stromal remodeling, or immunomodulatory changes) rather than by the emergence of mutations within the VEGF pathway itself.[18] As such, escape from bevacizumab-containing treatment does not necessarily indicate a loss of targetability of VEGF signaling. Preclinical studies also suggest that bevacizumab may potentiate the cytotoxic effect of FTD/TPI by normalizing tumor vasculature and enhancing drug delivery, mechanisms that may remain operative regardless of earlier exposure.[19] A descriptive association was observed between the duration of prior bevacizumab exposure and treatment outcomes. Patients who had received bevacizumab for >12 months experienced longer PFS and OS compared with those with shorter exposure, although this association did not retain statistical significance in the multivariable analysis. This pattern likely reflects underlying disease biology: prolonged bevacizumab exposure may act as a surrogate for more indolent disease and a longer therapeutic window,

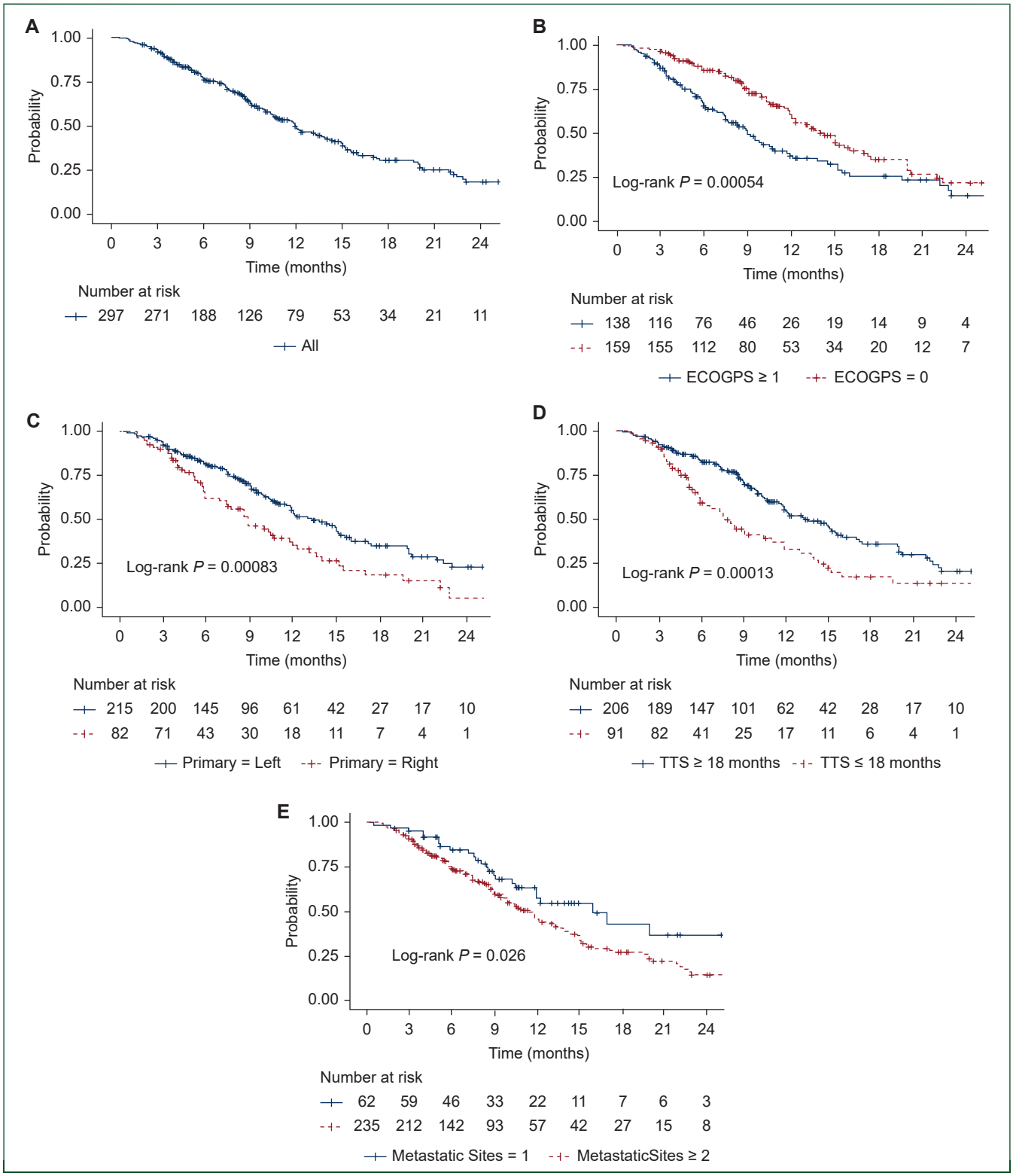

Figure 2. Overall survival analyses. Overall survival in the overall population (A), and subgroup analyses according to (B) Eastern Cooperative Oncology Group performance status (ECOG PS) (0 versus ≥1), (C) primary tumor sidedness (left versus right), (D) time to treatment start (TTS) from metastatic disease diagnosis (>18 months versus ≤18 months), and (E) number of metastatic sites (1 versus ≥2).

consistent with our observation that the interval between metastatic diagnosis and initiation of FTD/TPI plus bevacizumab was among the strongest predictors of improved survival. In line with the SUNLIGHT trial, where prior anti-VEGF therapy did not appear to diminish the benefit of adding bevacizumab to FTD/TPI,[20] our data do not suggest a clear detrimental association between previous bevacizumab exposure and outcomes. Together, these findings

Table 3. Adverse events and their frequencies

Adverse events	Any grade, *n* (%)	Grade 3-4, *n* (%)
Any adverse event	243 (81.8%)	152 (52.2%)
Neutropenia	172 (57.9%)	105 (35.4%)
Asthenia/fatigue	152 (51.2%)	12 (4.0%)
Anemia	130 (43.8%)	12 (4.0%)
Nausea	87 (29.3%)	8 (2.7%)
Thrombocytopenia	69 (23.2%)	8 (2.7%)
Diarrhea	51 (17.2%)	5 (1.7%)
Hypertension	46 (15.5%)	7 (2.4%)
Elevated AST/ALT	35 (11.8%)	1 (0.3%)
Proteinuria	16 (5.4%)	2 (0.7%)
Bleeding	10 (3.4%)	0 (0.0%)
Thromboembolism	8 (2.7%)	5 (1.7%)
Alopecia	7 (2.4%)	2 (0.7%)

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

support the concept that VEGF pathway inhibition retains antitumor activity even after prior bevacizumab exposure, consistent with the rationale for VEGF blockade beyond progression or rechallenge in later treatment lines.[21,22]

In our analysis, the clinical activity of FTD/TPI plus bevacizumab did not differ according to *KRAS* mutational status, indicating that the combination appears similarly effective in both *KRAS*-mutant and *KRAS*-wild-type tumors within a real-world setting. This observation is consistent with—and further supported by—the recent *post hoc* analysis of the SUNLIGHT trial by Tabernero et al.,[23,24] which demonstrated that *KRAS* G12 mutations were neither prognostic nor predictive of reduced benefit from the combination. They also found that the survival advantage of FTD/TPI plus bevacizumab over FTD/TPI monotherapy was maintained irrespective of *KRAS* G12 status. Taken together, these results support the notion that FTD/TPI plus bevacizumab maintains clinical activity across *KRAS* molecular subgroups—an observation of particular relevance in light of the emerging therapeutic strategies targeting *KRAS*.

The safety profile observed in our study was consistent with that reported in randomized trials. Myelotoxicity—particularly neutropenia—was the most common AE and aligned with the known toxicity spectrum of FTD/TPI.[25–27] The incidence of grade 3-4 neutropenia (35.4%) was comparable with that reported in the SUNLIGHT trial (38%).[11] The use of G-CSF in 37.1% of patients was in line with contemporary clinical practice and real-world experience, contributing to manageable hematologic toxicity without excessive treatment discontinuation.[28] Nonhematologic toxicities, including fatigue, nausea, and diarrhea, were mostly low grade and did not adversely impact treatment exposure.

The strengths of our study include its large, multicenter cohort and the comprehensive clinical and molecular characterization of 297 consecutive patients treated with FTD/TPI plus bevacizumab in routine practice. Other real-world analyses[29] have included larger populations and have carried out comparative evaluations between FTD/TPI plus bevacizumab and other later-line treatments. However, our study provides detailed outcome and prognostic data within a homogeneous cohort treated with FTD/TPI plus bevacizumab, allowing an in-depth assessment of survival estimates and associated clinical factors in this setting.

Nonetheless, limitations inherent to retrospective studies must be recognized, including potential selection bias, differences in patient management across centers, and, importantly, the absence of a comparator arm, which precludes direct comparative effectiveness conclusions. In addition, although most patients were pretreated with anti-VEGF therapy, the relatively small number of bevacizumab-naïve patients limited robust subgroup analyses. Within these constraints, our findings offer descriptive real-world effectiveness data that are consistent with the outcomes observed in pivotal clinical trials. The identification of prognostic factors may assist clinicians in contextualizing expected outcomes in everyday practice. Overall, our results support the activity and tolerability of FTD/TPI plus bevacizumab in a broad, unselected mCRC population and complement existing real-world and randomized evidence in this therapeutic setting.

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DISCLOSURE

MS reports consulting or advisory role for Bristol Myers Squibb (BMS), AstraZeneca, Servier, Merck, Amgen, Daiichi Sankyo, Merck Sharp and Dohme (MSD). MAC reports consulting or advisory role for Amgen, Bayer, Merck, Pierre Fabre, SERVIER, Takeda. GA reports advisory role for Amgen. FM reports honoraria from Incyte and Pierre Fabre; travel grants from Pierre Fabre, Amgen, and Daiichi Sankyo; and an institutional research grant from Incyte. FB reports personal honoraria as invited speaker from Eli Lilly, MSD, Bayer, BMS, Pierre Fabre, AstraZeneca, and Merck; and participation on advisory boards for AAA Novartis, Teysuno, and Takeda. GT reports funds from the Ministero della Salute (Ricerca Corrente 2022), the AIRC (Investigator Grant number IG26330), Ministero dell'Università e della Ricerca (PRIN 2022 PNRR Prot P2022LN3KS and PRIN 2022 Prot 2022P79F9N), and Agenzia Italiana del Farmaco, Ministero della Salute (J38D19000690001) FIMP; and consulting or advisory roles for BMS, AstraZeneca, MSD, Merck, and Servier. LS reports consulting or advisory roles for Pierre Fabre, AstraZeneca, Bayer, SERVIER, Merck, Amgen, GlaxoSmithKline, Incyte, LEO Pharma, MSD, and Takeda. All other authors declare no competing interests.

DATA SHARING

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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