

ORIGINAL ARTICLE

Real-world outcomes and prognostic factors of trifluridine/tipiracil plus bevacizumab in metastatic colorectal cancer: a multicenter study in Spain

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Background: Trifluridine/tipiracil plus bevacizumab (FTD/TPI+BEV) has demonstrated survival benefit in patients with metastatic colorectal cancer (mCRC) after failure of at least two prior treatment regimens in the phase III SUNLIGHT trial (NCT04737187), which compared FTD/TPI+BEV with FTD/TPI monotherapy; however, real-world evidence remains limited. The BeTAS real-world study evaluated the real-world effectiveness and safety of FTD/TPI+BEV in Spanish routine clinical practice.

Patients and methods: This ambispective, multicenter observational study included 549 patients with mCRC treated with FTD/TPI+BEV across 19 Spanish university hospitals [retrospectively (2019–2023) and prospectively (from 2024 onward)]. Outcomes included overall survival (OS), progression-free survival (PFS), and tumor response according to RECIST version 1.1. Safety was assessed using Common Terminology Criteria for Adverse Events version 5.0. Univariate and multivariate analyses evaluated baseline and treatment-emergent prognostic factors.

Results: Median OS was 10.8 months and median PFS was 5.0 months. The objective response rate was 9.6% and the disease control rate was 51.9%. Treatment efficacy was independent of sex, RAS/BRAF mutational status, and prior anti-vascular endothelial growth factor exposure. Improved survival outcomes were observed in patients with lower metastatic burden, longer time from metastatic diagnosis, Eastern Cooperative Oncology Group performance status 0–1, left-sided primary tumors, and favorable baseline prognostic classification. Development of grade 3–4 neutropenia and primary prophylactic granulocyte colony-stimulating factor (G-CSF) use were independently associated with prolonged OS and PFS; however, these findings should be interpreted cautiously given the observational design. Neutropenia was the most frequent grade ≥3 adverse event. Two treatment-related deaths were reported.

Conclusions: FTD/TPI+BEV is effective and well tolerated in Spanish real-world clinical practice, consistent with SUNLIGHT. Baseline prognostic classification, performance status, metastatic burden, and treatment-emergent factors were associated with clinical outcomes. The observed associations for grade 3–4 neutropenia and primary prophylactic G-CSF use should be considered exploratory and hypothesis-generating.

Key words: bevacizumab, metastatic colorectal cancer, neutropenia, trifluridine/tipiracil

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INTRODUCTION

Colorectal cancer (CRC) remains one of the leading causes of cancer-related morbidity and mortality worldwide. In 2020, >1.9 million new cases and >930 000 deaths were reported globally, placing CRC among the most frequently diagnosed and lethal malignancies.¹ In Europe, it represents the second leading cause of cancer-related death.² According to current European Society for Medical Oncology Guidelines, ~15%-30% of patients present with metastatic disease at diagnosis and up to half of those initially diagnosed with localized tumors will eventually develop metastases.³ In Spain, CRC is the most frequently diagnosed malignancy, with ~44 500 new cases estimated for 2025, accounting for nearly 16% of all cancer diagnoses nationwide.⁴

Over the past two decades, the therapeutic landscape of metastatic CRC (mCRC) has evolved substantially through the incorporation of combination chemotherapy regimens and targeted therapies.⁵ Standard first- and second-line strategies based on fluoropyrimidines combined with oxaliplatin or irinotecan, together with monoclonal antibodies targeting vascular endothelial growth factor (VEGF) or epidermal growth factor receptor (EGFR) in RAS wild-type tumors^{3,6} have translated into meaningful improvements in response rates and overall survival (OS), allowing median survival to exceed 30 months in selected populations.⁷ Nevertheless, most patients ultimately experience disease progression, and therapeutic options beyond second-line strategies remain limited, with modest survival gains in the refractory setting.⁸

Trifluridine/tipiracil (FTD/TPI) is an oral nucleoside analog that has demonstrated antitumor activity in patients with mCRC refractory to standard therapies.^{9,10} Trifluridine acts as the active cytotoxic component, whereas tipiracil, a thymidine phosphorylase inhibitor, prevents its rapid degradation, thereby increasing systemic exposure. In the pivotal phase III RECURSE trial (NCT01607957), FTD/TPI demonstrated a clinically modest improvement in OS and progression-free survival (PFS) compared with placebo with a predictable safety profile predominantly characterized by hematologic toxicity.¹¹ Nevertheless, the magnitude of benefit with FTD/TPI monotherapy remains limited, highlighting the need to optimize patient selection and explore more effective combination strategies in this setting. These limitations provided the rationale for investigating combination strategies aimed at enhancing treatment efficacy.

Post hoc analyses of the RECURSE trial provided important insights into prognostic stratification in this setting. The Tabernero classification, based on baseline clinical characteristics including the number of metastatic sites, the presence of liver metastases, and the time from diagnosis of metastatic disease, identified distinct risk groups with markedly different survival outcomes among patients treated with FTD/TPI.¹² Additionally, treatment-emergent neutropenia was identified as a relevant prognostic marker, suggesting its potential role as a pharmacodynamic indicator of adequate drug exposure rather than a causal determinant of efficacy and was subsequently

explored as a practical tool for prognostic stratification in clinical practice.¹³ Together, these findings underscored the importance of both baseline and treatment-related factors in refining prognostic assessment in later-line mCRC.

Given the limited efficacy of FTD/TPI monotherapy, combination approaches were explored to enhance antitumor activity. Bevacizumab (BEV), a monoclonal antibody targeting VEGF, has demonstrated consistent clinical benefit when combined with cytotoxic chemotherapy across multiple treatment lines.¹⁴⁻¹⁶ Preclinical models showed a synergistic antitumor effect when BEV was combined with FTD/TPI (FTD/TPI+BEV),¹⁷ providing a strong biological rationale for the clinical development of the combination. Early-phase studies, including the Japanese phase I/II C-TASK FORCE trial¹⁸, study evaluating FTD/TPI+BEV in refractory mCRC, and a randomized Danish phase II study,¹⁹ subsequently reported encouraging clinical activity with acceptable safety.

The clinical benefit of FTD/TPI+BEV was confirmed in the phase III SUNLIGHT trial (NCT04737187), a randomized study comparing FTD/TPI+BEV with FTD/TPI monotherapy, in which the combination improved OS, PFS, and disease control rate (DCR) without a clinically meaningful increase in severe toxicity.²⁰ This study currently represents a key therapeutic standard in the later-line treatment of mCRC. SUNLIGHT, however, was conducted under controlled trial conditions with strict eligibility criteria, including the exclusion of patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 2, and provided limited information regarding outcomes across prognostic subgroups or the role of treatment-emergent factors such as neutropenia. Consequently, the generalizability of these findings to routine clinical practice remains unclear.

In this context, real-world evidence has become essential to complement randomized clinical trials by capturing the heterogeneity of routine oncology practice.²¹ The BeTAS real-world study of FTD/TPI+BEV was therefore designed as a multicenter, ambispective, real-world observational study to evaluate the effectiveness and safety of FTD/TPI+BEV in Spanish clinical practice and to explore the prognostic value of baseline clinical classifications and treatment-emergent factors on survival outcomes in patients with pretreated mCRC.

MATERIALS AND METHODS

Study design and setting

This was an ambispective, observational, multicenter real-world study conducted across 19 Spanish university hospitals. Clinical data were collected retrospectively for patients treated between January 2019 and December 2023 and prospectively from January 2024 onward using a unified study protocol. The study was designed and reported in accordance with methodological recommendations for real-world evidence studies in oncology.

Patient population

Eligible patients were adults (≥ 18 years) with histologically confirmed mCRC who had received FTD/TPI+BEV after failure or intolerance to two or more prior systemic regimens including fluoropyrimidines, irinotecan, and oxaliplatin, with or without anti-VEGF or anti-EGFR therapy (for *RAS/BRAF* wild-type tumors). Patients were included regardless of microsatellite instability (MSI) status.

Treatment decisions were made by the treating physicians according to routine clinical practice and institutional standards. Patients receiving concurrent investigational drugs or other anticancer therapy during FTD/TPI+BEV treatment were excluded. No additional exclusion criteria beyond those applied in routine clinical care were imposed.

Treatment exposure

FTD/TPI was administered orally at a dose of 35 mg/m² twice daily on days 1-5 and 8-12 of each 28-day treatment cycle, according to standard clinical practice. BEV was administered intravenously at a dose of 5 mg/kg on days 1 and 15 of each 28-day cycle, according to institutional protocols. Treatment could be initiated at full or reduced doses at the investigator's discretion. Dose delays, dose reductions, treatment interruptions, and supportive care interventions including granulocyte colony-stimulating factor (G-CSF), were permitted and managed according to routine clinical practice. Primary and/or secondary prophylactic G-CSF use was allowed according to routine clinical practice at each participating center including the use of short-acting (filgrastim) or long-acting (pegfilgrastim) formulations.

Endpoints and variables

The primary endpoint was OS, defined as the time from treatment initiation with FTD/TPI+BEV to death from any cause or last follow-up. Secondary endpoints included PFS (time from treatment initiation to disease progression, death from any cause, or last follow-up), objective response rate (ORR including complete and partial response), and DCR (including complete and partial response plus stable disease) assessed by RECIST version 1.1, as well as safety according to Common Terminology Criteria for Adverse Events version 5.0.

Exploratory analyses evaluated baseline and treatment-emergent prognostic variables including sex, ECOG PS, primary tumor location and resection, histologic grade, *RAS/BRAF* mutational status, presence of liver metastases, number of metastatic sites, time from metastatic diagnosis, initial FTD/TPI dose, primary prophylactic G-CSF use, development of grade 3-4 neutropenia, and baseline prognostic classification.

Baseline prognostic stratification was carried out using the Tabernero classification.¹² Patients with one to two metastatic sites and ≥ 18 months from diagnosis of metastatic disease were classified as having good prognostic characteristics (GPCs). Among these, patients without liver metastases were categorized as having best prognostic characteristics (BPCs). Patients with three or more metastatic sites and/or

< 18 months from metastatic diagnosis were classified as having poor prognostic characteristics (PPCs).

Data collection

Demographic, clinical, pathological, molecular, treatment, and outcome data were extracted from electronic medical records and recorded in a standardized electronic database. Data were anonymized and centrally reviewed to ensure consistency and completeness before statistical analysis.

Statistical analysis

Continuous variables were summarized as medians and ranges and categorical variables were summarized as absolute and relative frequencies. OS and PFS were estimated by the Kaplan–Meier method and compared using the log-rank test.

Univariate Cox proportional hazards regression analyses were carried out to evaluate associations between individual variables and survival outcomes. Variables with a *P* value < 0.10 in univariate analysis, together with clinically relevant factors predefined by the investigators, were included in multivariate Cox regression models to identify independent prognostic factors. The multivariable analysis for primary G-CSF prophylaxis included the time from diagnosis ≤ 18 or > 18 months. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were reported.

Missing data were handled by complete-case analysis. The proportional hazards assumption was assessed graphically and through Schoenfeld residuals. All statistical analyses were conducted using SPSS software (IBM Corp., Armonk, NY) and statistical significance was defined as a two-sided *P* value < 0.05 .

RESULTS

Patient population and baseline characteristics

A total of 549 patients with mCRC treated with FTD/TPI+BEV were included across 19 Spanish university hospitals. All patients received at least one treatment cycle and were assessable for safety.

Baseline characteristics are summarized in Table 1. The median age at treatment initiation was 67.6 years (range 26-92 years) and 64.3% of patients were male. Most patients had an ECOG PS of 0-1 (89.6%), whereas 10.4% presented with ECOG PS 2 at baseline.

Primary tumors were left-sided in 63.6% of patients (Table 1). Prior primary tumor resection was observed in 72.3% of patients. *RAS* mutations were identified in 57.7% and *BRAF* mutations in 3.6%, whereas 37.3% were *RAS/BRAF* wild-type. Deficient mismatch repair/MSI-high (MMR/MSI) status was identified in three patients (0.5%), and HER2 positivity was identified in six patients (1.1%). HE2 status were available only in a limited subset of patients.

Liver metastases were present in 76.1% of cases and 70.7% had fewer than three metastatic sites at treatment initiation. The time from diagnosis of metastatic disease

Table 1. Baseline characteristics of the study population (N = 549)

Characteristics	Values
Age (years), median (range)	67.6 (26-92)
Sex, n (%)	
Male	353 (64.3)
Female	196 (35.7)
ECOG performance status, n (%)	
0-1	492 (89.6)
2	57 (10.4)
Tumor location, n (%)	
Right-sided	194 (35.3)
Left-sided	349 (63.6)
Unknown	6 (1.1)
Primary tumor resection, n (%)	
Yes	397 (72.3)
No	152 (27.7)
Tumor presentation, n (%)	
Synchronous	305 (55.6)
Metachronous	244 (44.4)
Histologic grade, n (%)	
Low grade (G1-G2)	419 (76.3)
High grade (G3-G4)	38 (6.9)
Unknown	92 (16.8)
RAS/BRAF status, n (%)	
RAS/BRAFwt	205 (37.3)
RASmt	317 (57.7)
BRAFmt	20 (3.6)
RASmt and BRAFmt	4 (0.7)
Unknown	3 (0.5)
MMR/MSI status, n (%)	
dMMR/MSI-H	3 (0.5)
pMMR/MSS	525 (95.6)
Missing	21 (3.8)
HER2 status, n (%)	
Positive	6 (1.1)
Negative	210 (38.3)
Missing	333 (60.7)
Presence of liver metastases, n (%)	
No	131 (23.9)
Yes	418 (76.1)
No. of metastatic sites	
<3	388 (70.7)
≥3	161 (29.3)
Time from metastatic diagnosis, n (%)	
≥18 months	382 (69.6)
<18 months	167 (30.4)
Baseline prognostic group (Tabernero classification), n = 548 (%)	
Best (BPC)	82 (15.1)
Good (GPC)	185 (33.7)
Poor (PPC)	281 (51.2)
Line of use FTD/TPI+BEV, n (%)	
2	33 (6.0)
3	364 (66.3)
4 or later	152 (27.7)
Prior anti-VEGF use, n (%)	497 (90.5)

Data on the Tabernero classification were missing for one patient.

BEV, bevacizumab; BPC, best prognostic characteristic; dMMR, deficient mismatch repair; ECOG, Eastern Cooperative Oncology Group; FTD/TPI, trifluridine/tipiracil; GPC, good prognostic characteristic; HER2, human epidermal growth factor receptor 2; MMR, mismatch repair; MSI, microsatellite instability; MSI-H, microsatellite instability-high; MSS, microsatellite stable; mt, mutant; pMMR, proficient mismatch repair; PPC, poor prognostic characteristic; VEGF, vascular endothelial growth factor; wt, wild-type.

was ≥18 months in 69.6% of patients. According to the Tabernero prognostic classification, 15.1% of patients were classified as having BPCs, 33.7% as having GPCs, and 51.2% as having PPCs (Table 1). This distribution appears broadly consistent with that described in the original Tabernero analysis.

Table 2. Treatment exposure and efficacy outcomes (N = 549)

Variable	Values
Treatment exposure, n (%)	
Reduced initial dose FTD/TPI	49 (8.9)
Primary prophylactic G-CSF	142 (25.9)
No. of treatment cycles, median (range)	4 (1-31)
Tumor response (RECIST version 1.1), n (%)	
Assessable patients	491 (89.4)
Not assessable patients	58 (10.6)
Best overall response among assessable patients (n = 491), n (%)	
CR	3 (0.6)
PR	44 (9.0)
SD	208 (42.4)
PD	236 (48.1)
Response rates among assessable patients (n = 491), n (%)	
Objective response rate (CR + PR)	47 (9.6)
Disease control rate (CR + PR + SD)	255 (51.9)
Survival outcomes	
Progression-free survival (months), median (95% CI)	5.0 (4.4-5.7)
Overall survival (months), median (95% CI)	10.8 (9.6-12.0)

CI, confidence interval; CR, complete response; FTD/TPI, trifluridine/tipiracil; G-CSF, granulocyte colony-stimulating factor; PD, progressive disease; PR, partial response; SD, stable disease.

FTD/TPI+BEV was administered predominantly as third-line treatment (66.3%), and prior exposure to anti-VEGF therapy was documented in 90.5% of cases.

Treatment exposure

All patients received FTD/TPI+BEV as part of standard clinical practice. Most patients initiated FTD/TPI at the standard recommended dose (91.1%), whereas 8.9% started treatment with a reduced dose (Table 2). The median number of administered treatment cycles was 4 (range 1-31). Primary prophylactic G-CSF was used in 25.9% of patients (Table 2).

Efficacy outcomes

Radiological response according to RECIST version 1.1 was assessable in 491 patients; 58 patients (10.6%) were not assessable owing to lack of postbaseline radiological assessment or early treatment discontinuation.

Among assessable patients, the ORR was 9.6% including complete responses in 0.6% and partial responses in 9.0% (Table 2). Stable disease was observed in 42.4% of patients, resulting in a DCR of 51.9%, whereas 48.1% experienced progressive disease as best response.

After a median follow-up of 19.5 months, 410 deaths had occurred. Median OS was 10.8 months (95% CI 9.6-12.0) and median PFS was 5.0 months (95% CI 4.4-5.7). Kaplan–Meier survival curves are presented in Figure 1A and B.

Safety

Treatment-related adverse events are summarized in Table 3. The most frequent adverse event was neutropenia, reported in 64.8% of patients with grade 3-4 neutropenia

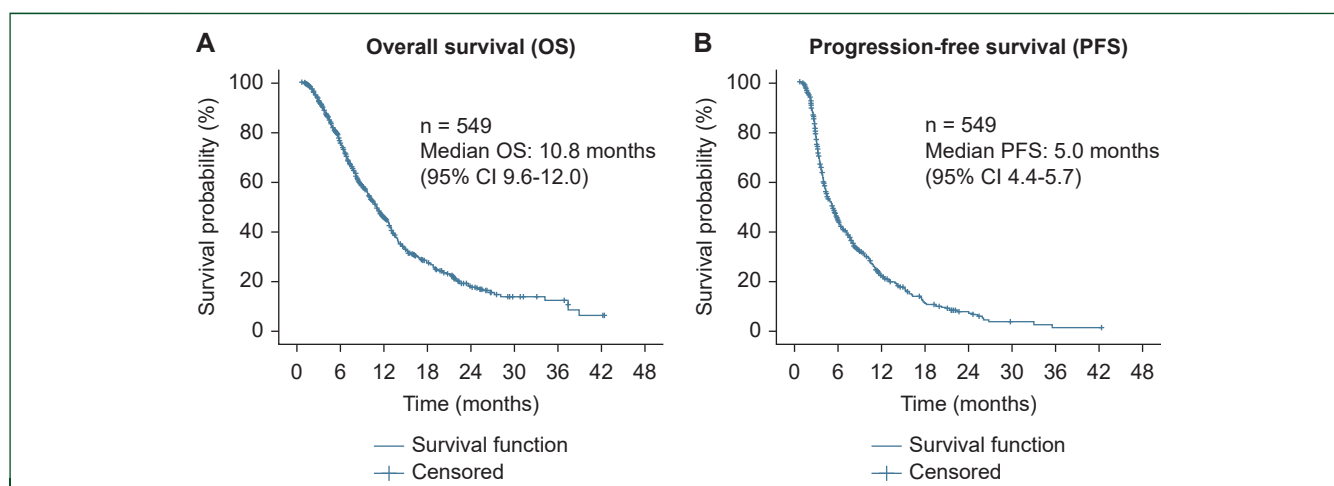


Figure 1. Kaplan–Meier curves for OS (A) and PFS (B) in the overall population ($N = 549$). Median OS was 10.8 months (95% CI 9.6–12.0) and median PFS was 5.0 months (95% CI 4.4–5.7).

CI, confidence interval; OS, overall survival; PFS, progression-free survival.

occurring in 34.8%. Febrile neutropenia was reported in 1.8% of patients.

Other grade 3–4 adverse events included anemia (4.6%), asthenia (4.4%), diarrhea (2.2%), perforation (2.2%), and thrombocytopenia (1.7%) (Table 3).

BEV-related adverse events included hypertension (17.3%), proteinuria (8.2%), bleeding events (20.6%; grade ≥ 3 in 1.6%), gastrointestinal perforation (2.2%), fistula formation (1.3%), and thromboembolic events (1.5%) (Table 3).

Dose reductions of FTD/TPI were required in 30.6% of patients. Treatment discontinuation owing to toxicity occurred in 13.1% for FTD/TPI and 17.1% for BEV. Twenty-nine hospital admissions related to treatment toxicity (5.3%) were recorded. Two treatment-related deaths occurred during the study period: one due to necrotizing fasciitis and one due to cerebral hemorrhage (Table 3). No unexpected safety signals were identified. Neutropenia management included FTD/TPI dose reductions in 34 patients (6.2%), G-CSF administration in 157 patients (28.6%),

and combined use of both interventions in 59 patients (10.7%).

Prognostic analyses

Several baseline clinical characteristics and treatment-emergent variables were associated with survival outcomes following treatment with FTD/TPI+BEV.

Baseline ECOG PS had a major impact on prognosis. Patients with an ECOG PS 0–1 experienced markedly longer OS than those with ECOG PS 2 (13.5 versus 6.2 months; $P < 0.001$). This association remained robust in multivariate analysis, where ECOG PS 2 independently predicted inferior OS (HR 1.77, 95% CI 1.30–2.43, $P < 0.001$). A similar numerical trend was observed for PFS, although this did not reach statistical significance (Tables 4 and 5).

Primary tumor location was also prognostically relevant. Patients with left-sided tumors achieved longer OS than those with right-sided primaries (12.5 versus 8.8 months; $P < 0.001$), with right-sided location independently associated with increased mortality risk (HR 1.34, 95% CI 1.05–1.71, $P = 0.018$). A consistent, although less pronounced, effect was observed for PFS (Tables 4 and 5).

Metastatic burden and pattern strongly influenced outcomes. Patients with fewer than three metastatic sites demonstrated significantly prolonged OS (12.8 versus 7.4 months; $P < 0.001$) and PFS (8.1 versus 5.8 months; $P < 0.001$) compared with those with a higher metastatic burden. Likewise, a longer interval from diagnosis of metastatic disease (≥ 18 months) was associated with improved survival outcomes. The presence of liver metastases remained consistently associated with inferior prognosis across survival endpoints (Tables 4 and 5).

Primary tumor resection was similarly associated with improved outcomes with a longer median OS (11.5 versus 7.8 months; $P < 0.001$) and PFS (8.3 versus 6.2 months; $P = 0.001$). Nonresected patients presented a significantly higher risk of death (HR 1.44, 95% CI 1.14–1.81, $P = 0.002$) and an increased risk of progression (HR 1.36, 95% CI 1.09–

Table 3. Adverse events during the study period ($N = 549$)

Adverse event	All grades, n (%)	Grade ≥ 3 , n (%)
Neutropenia	356 (64.8)	191 (34.8)
Febrile neutropenia	10 (1.8)	10 (1.8)
Anemia	299 (54.5)	25 (4.6)
Asthenia	376 (68.5)	24 (4.4)
Nausea	193 (35.2)	0 (0.0)
Diarrhea	153 (27.9)	12 (2.2)
Thrombocytopenia	133 (24.2)	9 (1.7)
Hepatic toxicity (elevated AST/ALT)	78 (14.2)	7 (1.3)
Mucositis	39 (7.1)	3 (0.5)
Hypertension	95 (17.3)	5 (0.9)
Proteinuria	45 (8.2)	1 (0.2)
Bleeding	113 (20.6)	9 (1.6)
Perforation	—	12 (2.2)
Fistula	—	7 (1.3)
Thromboembolic events	—	8 (1.5)

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 4. Univariate analysis of OS and PFS

Variable	Median OS (months)	P (log-rank)	Median PFS (months)	P (log-rank)
Sex (female versus male)	11.2 versus 10.7	0.146	7.3 versus 7.0	0.736
ECOG PS (0-1 versus 2)	13.5 versus 6.2	<0.001	9.2 versus 5.4	0.106
Tumor location (left versus right)	12.5 versus 8.8	<0.001	5.5 versus 4.2	0.024
Primary tumor resection (yes versus no)	11.5 versus 7.8	<0.001	8.3 versus 6.2	0.001
Histologic grade (G1-G2 versus G3)	11.3 versus 8.9	0.039	7.3 versus 6.9	0.836
RAS/BRAF status (wild-type versus mutant)	10.9 versus 10.6	0.915	7.6 versus 7.3	0.757
Number of metastatic sites (<3 versus ≥3)	12.8 versus 7.4	<0.001	8.1 versus 5.8	<0.001
Time from metastatic diagnosis (≥18 versus <18 months)	13.9 versus 8.4	<0.001	8.8 versus 6.6	0.010
Liver metastases (no versus yes)	13.7 versus 7.6	<0.001	8.4 versus 6.2	<0.001
Baseline prognostic group (BPC/GPC versus PPC)	13.6 versus 8.1	<0.001	8.5 versus 6.1	<0.001
Initial FTD/TPI dose (100% versus reduced)	10.9 versus 10.9	0.978	7.5 versus 7.5	0.971
Primary prophylactic G-CSF (yes versus no)	13.4 versus 9.7	0.001	8.6 versus 6.4	0.001
Grade 3-4 neutropenia (yes versus no)	15.7 versus 8.5	<0.001	9.5 versus 6.0	<0.001

Bold values indicate statistically significant results ($P < 0.05$).

BPC, best prognostic characteristic; ECOG, Eastern Cooperative Oncology Group; FTD/TPI, trifluridine/tipiracil; G-CSF, granulocyte colony-stimulating factor; PFS, progression-free survival; GPC, good prognostic characteristic; OS, overall survival; PPC, poor prognostic characteristic; PS, performance status.

1.69, $P = 0.007$) (Tables 4 and 5). Patients with G1-G2 tumors had a longer median OS than those with G3 tumors (11.3 versus 8.9 months; $P = 0.039$), although the corresponding HR did not reach significance. No effect was observed for PFS (Tables 4 and 5).

Baseline prognostic stratification according to the Taberner classification showed a pronounced and clinically meaningful impact on treatment outcomes. As outcomes were similar between patients with BPCs and GPCs, these categories were pooled for survival analyses. Patients with BPCs/GPCs achieved significantly longer OS (13.6 versus 8.1 months; $P < 0.001$) and PFS (8.5 versus 6.1 months; $P < 0.001$) compared with those with PPCs. In multivariate models, PPCs remained independently associated with inferior OS (HR 1.89, 95% CI 1.52-2.34, $P < 0.001$) and PFS (HR 1.44, 95% CI 1.18-1.75, $P < 0.001$) (Tables 4 and 5; Figure 2A and B).

Among treatment-emergent factors, development of grade 3-4 neutropenia was strongly associated with improved clinical outcomes. Patients experiencing grade 3-4 neutropenia achieved substantially longer OS (15.7 versus 8.5 months; $P < 0.001$) and PFS (9.5 versus 6.0 months; $P < 0.001$). Absence of grade 3-4 neutropenia remained an independent adverse prognostic factor in multivariate analysis with increased risks of death (HR 1.86, 95% CI 1.47-2.35, $P < 0.001$) and disease progression (HR

1.74, 95% CI 1.41-2.14, $P < 0.001$) (Tables 4 and 5; Figure 2C and D).

Similarly, the use of primary prophylactic G-CSF was associated with improved survival outcomes with a longer OS (13.4 versus 9.7 months; $P = 0.001$) and PFS (8.6 versus 6.4 months; $P = 0.001$). In multivariate analysis, absence of primary prophylactic G-CSF remained independently associated with inferior OS (HR 1.51, 95% CI 1.16-1.95, $P = 0.002$) and PFS (HR 1.42, 95% CI 1.13-1.78, $P = 0.003$) (Tables 4 and 5; Figure 2E and F).

No significant associations with survival outcomes were observed for sex, RAS or BRAF mutational status, or initial FTD/TPI dose (Tables 4 and 5).

DISCUSSION

In this large multicenter real-world study, treatment with FTD/TPI+BEV in routine Spanish clinical practice demonstrated clinically meaningful activity and a manageable safety profile in patients with pretreated mCRC. The survival outcomes observed in this unselected population support the external validity of randomized clinical trial evidence and reinforce the role of this combination as a standard later-line option in mCRC.

FTD/TPI+BEV improved survival outcomes in patients with mCRC in the international, open-label, randomized phase III SUNLIGHT trial.²⁰ Randomized studies, however,

Table 5. Multivariate Cox analysis for OS and PFS

Variable	HR (95% CI) OS	P (log-rank)	HR (95% CI) PFS	P value
ECOG PS (2 versus 0-1)	1.77 (1.30-2.43)	<0.001	1.20 (0.88-1.63)	0.252
Tumor location (right versus left)	1.34 (1.05-1.71)	0.018	1.15 (0.92-1.44)	0.234
Primary tumor resection (no versus yes)	1.44 (1.14-1.81)	0.002	1.36 (1.09-1.69)	0.007
Histologic grade (G3 versus G1-G2) ^a	1.33 (0.90-1.97)	0.157	1.03 (0.66-1.44)	0.883
Baseline prognostic classification (PPC versus BPC/GPC)	1.89 (1.52-2.34)	<0.001	1.44 (1.18-1.75)	<0.001
Grade 3-4 neutropenia (no versus yes)	1.86 (1.47-2.35)	<0.001	1.74 (1.41-2.14)	<0.001
Primary prophylactic G-CSF (no versus yes)	1.51 (1.16-1.95)	0.002	1.42 (1.13-1.78)	0.003

Bold values indicate statistically significant results ($P < 0.05$).

BPC, best prognostic characteristic; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; G-CSF, granulocyte colony-stimulating factor; GPC, good prognostic characteristic; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PPC, poor prognostic characteristic; PS, performance status.

^aIncluded for completeness, not significant in multivariate analysis.

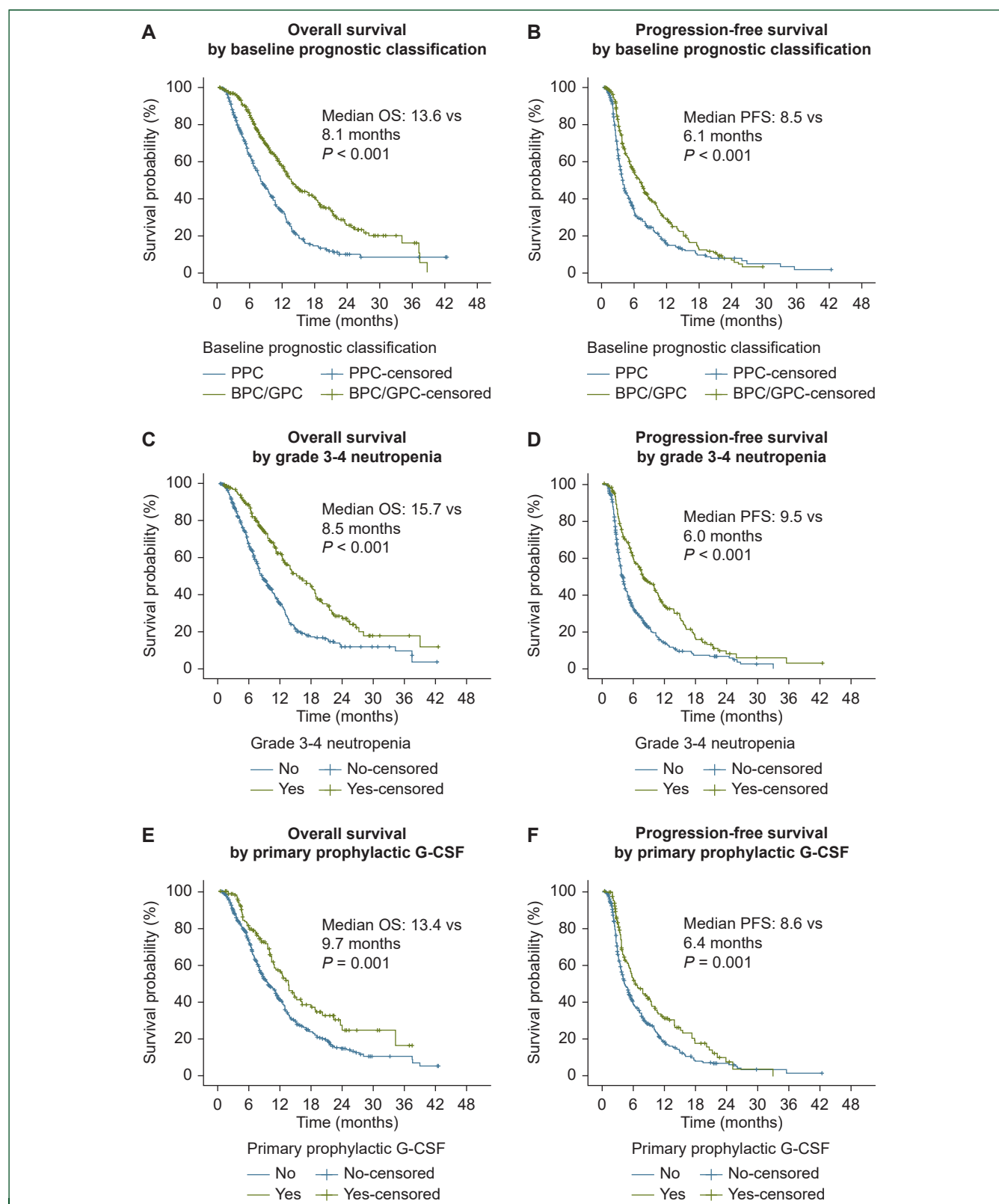


Figure 2. Kaplan–Meier curves for OS (A, C, E) and PFS (B, D, F) according to baseline prognostic classification, development of grade 3-4 neutropenia, and use of primary prophylactic G-CSF. Baseline prognostic classification is shown according to the Tabernero criteria (BPC/GPC versus PPC). Median survival times and P values are displayed for each comparison.

BPC, best prognostic characteristic; GPC, good prognostic characteristic; OS, overall survival; G-CSF, granulocyte colony-stimulating factor; PFS, progression-free survival; PPC, poor prognostic characteristic.

may not fully capture the heterogeneity of clinical practice, creating a gap between trial efficacy and real-world effectiveness. Variability in clinical practice across Europe may further limit the generalizability of trial results. Hence, real-world evidence provides complementary information to randomized studies, particularly in later-line settings characterized by substantial clinical heterogeneity. Accordingly, the present study was designed to evaluate the effectiveness and safety of FTD/TPI+BEV in routine Spanish clinical practice and to explore prognostic determinants of treatment outcomes beyond the constraints of clinical trials.

The effectiveness observed in our cohort is consistent with that reported in the SUNLIGHT trial and previous real-world findings. Across studies, the antitumor activity of FTD/TPI+BEV has been characterized by a relatively low ORR accompanied by durable disease stabilization, a pattern that was also evident in our series.^{18,22} Indeed, ORR was low, and DCR accounted for most of the therapeutic benefit. These findings emphasize that the clinical benefit of this regimen relies primarily on sustained disease control rather than tumor shrinkage, underscoring the importance of treatment continuity and adequate cumulative exposure over time. In our cohort, treatment with FTD/TPI+BEV achieved a median OS of 10.8 months and a median PFS of 5.0 months. Similar benefits have been reported in Japanese,^{23,24} USA Black adult,²⁵ and Korean²⁶ retrospective cohorts, demonstrating that the clinical activity of FTD/TPI+BEV is consistent across different geographic regions and patient populations. Treatment efficacy was independent of *RAS* and *BRAF* mutational status and prior exposure to anti-VEGF therapy, supporting the broad applicability of this regimen in refractory disease.^{18,20,27} These findings are consistent with recent real-world data specifically evaluating patients with *BRAF* V600E—mutated mCRC treated with FTD/TPI, in which clinically meaningful activity was observed despite the known adverse prognosis of this subgroup,²⁸ although these observations should be interpreted in the context of limited sample sizes.²⁸

Baseline disease characteristics were associated with treatment outcomes. Patients with lower metastatic burden and longer intervals from metastatic diagnosis experienced superior survival, emphasizing the relevance of tumor burden and disease tempo in later-line treatment efficacy. In the RECURSE trial, the absence of liver metastases was one of the strongest favorable prognostic factors, associated with improved OS and PFS.¹¹ In our cohort, ~10% of patients presented with ECOG PS 2 and demonstrated inferior OS compared with those with ECOG PS 0-1. This observation is particularly relevant given that such patients were excluded from the SUNLIGHT trial, highlighting the added value of real-world studies in characterizing outcomes among populations underrepresented in randomized trials. Tumor sidedness and prior primary tumor resection were also associated with improved survival, although their prognostic impact was more modest and not consistently retained in multivariate analyses. Tumor histologic grade showed limited prognostic value,

reflecting its known variability and weaker predictive capacity in advanced disease.

Baseline prognostic classification emerged as one of the strongest predictors of survival in this study. Patients classified as having BPCs or GPCs achieved markedly superior outcomes compared with those with PPCs with an 89% higher risk of death and a 44% higher risk of disease progression, which is consistent with a post hoc analysis of RECURSE.¹² Similar observations have been reported in Portuguese real-world studies evaluating both FTD/TPI monotherapy and FTD/TPI+BEV.^{29,30} Collectively, these data support the clinical utility of the Taberero prognostic classification as a practical and reproducible tool to identify patients most likely to benefit from FTD/TPI-based therapy. These findings reinforce the relevance of baseline clinical stratification in optimizing patient selection for later-line treatment.

Among treatment-emergent factors, the development of grade 3-4 neutropenia was associated with prolonged OS and PFS. Consistent with these findings, *post hoc* analyses of both SUNLIGHT²⁰ and RECURSE³¹⁻³³ trials demonstrated that severe neutropenia or marked neutrophil count reduction—particularly during early treatment cycles—correlated with improved clinical outcomes.^{34,35} Importantly, prior real-world data from our group have shown that neutropenia associated with FTD/TPI+BEV tends to occur early, predominantly within the first treatment cycles, supporting its role as an early pharmacodynamic marker of adequate drug exposure.³⁶ These observations support the hypothesis that chemotherapy-induced neutropenia may reflect sufficient systemic exposure to FTD/TPI rather than acting as a direct causal determinant of efficacy.

Similarly, the use of primary prophylactic G-CSF was associated with improved survival outcomes in our cohort; however, this finding should be interpreted with caution. Given the observational design, residual confounding, selection bias, and immortal-time bias cannot be excluded, particularly as patients must remain on treatment long enough to receive G-CSF or to develop treatment-emergent neutropenia. Therefore, the observed association between G-CSF use and survival should be considered hypothesis-generating rather than indicative of a causal relationship.

G-CSF promotes neutrophil recovery and may contribute to maintaining planned dose intensity.³⁷ Given the schedule- and exposure-dependent mechanism of action of FTD/TPI, maintaining adequate treatment exposure may be clinically relevant for optimizing therapeutic outcomes. The present data, however, do not allow definitive conclusions regarding the impact of these mechanisms on survival outcomes. Prospective studies incorporating time-dependent analyses, dose-intensity metrics, and pharmacokinetic data are warranted to further elucidate the role of G-CSF in this setting.

This study has certain limitations, mainly related to its ambispective design. Nevertheless, the large sample size, multicenter participation, and consistency of findings across univariate and multivariate analyses strengthen the

robustness of the conclusions. The safety profile was comparable with that reported in randomized trials, confirming the regimen's overall tolerability in routine practice.³⁸ The two treatment-related deaths should be interpreted in the context of advanced disease, extensive prior treatment exposure, and the known risks of cytotoxic chemotherapy and antiangiogenic therapy. In addition, the absence of centralized radiological review may have introduced variability in response assessment.

In summary, this large multicenter real-world study confirms the effectiveness and manageable safety profile of FTD/TPI+BEV in patients with pretreated mCRC treated in Spanish routine clinical practice. Baseline prognostic classification, PS, metastatic burden, tumor sidedness, development of grade 3-4 neutropenia, and use of primary prophylactic G-CSF were associated with clinical outcomes. The observed associations for treatment-emergent factors should be interpreted cautiously and considered exploratory. Integration of these baseline and treatment-emergent factors may facilitate refined patient selection and support more individualized and clinically informed therapeutic strategies in later-line mCRC.

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ETHICAL APPROVAL

The study was approved by the Research Ethics Committee of Galicia (CEIm-G 2021/071) and conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and current data protection regulations (EU Regulation 2016/679).

INFORMED CONSENT

Written or oral informed consent was obtained from all participants. Data from deceased patients were included when no prior objection had been documented.

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