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Bevacizumab Reduces Codon-Specific Influences of Trifluridine/Tipiracil on Treatment Efficacy in Metastatic Colorectal Cancer

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ABSTRACT

The advent of biomarker-guided treatments has transformed therapeutic approaches in metastatic colorectal cancer (mCRC). Lately, KRAS G12 alterations, the predominant RAS variants in mCRC, have emerged as potential indicators of reduced response to trifluridine/tipiracil (FTD/TPI) alone. It remains unclear if this potential resistance persists when FTD/TPI is administered alongside bevacizumab. This investigation sought to evaluate the effectiveness of FTD/TPI combined with bevacizumab across different RAS mutation profiles in a clinical practice setting. Individuals with mCRC treated with FTD/TPI plus bevacizumab across any therapy stage at five Austrian oncology facilities, with documented genomic profiling, were included. Information was gathered retrospectively via medical record review. Differences in survival outcomes were assessed with log-rank testing. Adjusted Cox proportional hazards models incorporated multiple known prognostic factors. The analysis encompassed 123 cases of mCRC. Overall survival (OS) medians were nearly identical between RAS wild-type (WT) cases [9.63 months (95% CI 8.055–13.775)] and RAS-mutated cases [8.78 months (95% CI 8.055–11.014)], a finding upheld in multivariable analysis accounting for confounders; hazard ratio (HR) 1.05 (95% CI 0.618–1.785; P = 0.857). Furthermore, KRAS G12 mutation status showed no impact on outcomes. Specifically, OS reached 8.88 months (95% CI 7.332–12.921) among those with KRAS G12 alterations versus 9.47 months (95% CI 8.088–11.375) in RAS WT or non-KRAS G12 cases [HR 0.822 (95% CI 0.527–1.282; P = 0.387)]. Evidence from this clinical practice cohort suggests that FTD/TPI combined with bevacizumab delivers comparable benefits regardless of RAS mutation profile, implying that bevacizumab could counteract the possible diminished activity of FTD/TPI alone in KRAS G12-altered tumors.

Keywords: mCRC, FTD/TPI, Bevacizumab, KRAS G12, Clinical practice data

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Introduction

Biomarker-driven strategies in managing metastatic colorectal cancer (mCRC), incorporating markers like microsatellite instability (MSI), RAS, HER2neu, BRAF V600E, and tumor sidedness, have profoundly altered patient care [1-4].

Mutations in (K)RAS, occurring in around 40% of mCRC patients, were instrumental in advancing targeted therapy, establishing that anti-EGFR antibodies plus chemotherapy benefit only RAS wild-type individuals [5].

To date, precision approaches primarily guide selection of targeted agents, monoclonal antibodies, or immune therapies. Conventional chemotherapy remains the backbone of mCRC regimens and is generally viewed as non-specific, without reliable biologic markers [4].

Trifluridine/tipiracil (FTD/TPI), an oral agent combining trifluridine (a thymidine-based cytotoxic) with tipiracil (a thymidine phosphorylase blocker), is an established later-line option, supported by findings from the RECOURSE study. It represents one of the latest chemotherapeutic innovations for mCRC [6-8].

Interest has grown regarding FTD/TPI (also known as TAS-102) performance in (K)RAS-mutated subsets. Post-hoc reviews of RECOURSE and European clinical practice series indicate that KRAS exon 2 codon 12 variants—

the most common changes, affecting roughly one-third of mCRC patients—may confer lesser advantage from FTD/TPI than seen in KRAS wild-type or non-codon 12 cases [9].

Results from the SUNLIGHT study, revealing superior outcomes with bevacizumab added to FTD/TPI versus FTD/TPI alone, have introduced a novel standard for advanced-line therapy [10]. An important unresolved issue is whether bevacizumab co-administration can overcome the apparently lower responsiveness to standalone FTD/TPI in KRAS G12-mutated disease [11].

This multicenter clinical practice evaluation of FTD/TPI plus bevacizumab in mCRC aims to offer valuable real-world perspectives on this question, enriching current efforts to refine precision-based treatment strategies.

Materials and Methods

Study population

Data were gathered retrospectively from 123 individuals diagnosed with metastatic colorectal cancer (mCRC) who underwent treatment with trifluridine/tipiracil (FTD/TPI) in routine clinical practice from 2016 to 2023 across five university hospitals or specialized teaching facilities in Austria. Inclusion criteria encompassed adults over 18 years old with histologically verified colorectal cancer (CRC), who were administered FTD/TPI combined with bevacizumab at any stage of metastatic disease, and for whom molecular profiling data were accessible. Assessment of tumor mutations (minimally covering KRAS, NRAS, and BRAF statuses) followed institutional guidelines. Exclusion applied to cases lacking RAS mutation information, with inadequate documentation, or those previously treated with FTD/TPI alone or paired with antiangiogenic therapies other than bevacizumab.

The treatment protocol involved oral FTD/TPI at 35 mg/m² body surface area, given twice daily on days 1–5 and 8–12 of each 28-day cycle, alongside intravenous bevacizumab at 5 mg/kg body weight every two weeks within the same cycle. Adjustments to dosing were managed based on the judgment of the attending clinicians.

The data lock occurred in July 2023. Ethical approval was granted by the Ethics Committee of Kepler University Linz (reference 1205/2023), and the investigation adhered to the principles outlined in the Declaration of Helsinki (fourth revision). Patients had previously consented in writing to genomic tumor analysis as part of standard care. Additional specific consent for this retrospective review of clinical data was waived.

Endpoints

The main goal was to investigate the relationship between KRAS G12 mutational status and overall survival (OS), with secondary aims examining links to progression-free survival (PFS) and tumor response rates. These relationships were evaluated in the full patient group and in subgroups stratified by RAS/RAF alterations. In this observational real-world study, all outcomes were measured starting from the initiation of FTD/TPI treatment and followed according to standard practices at the participating sites. Reported survival figures from analyses represent median durations.

Statistical approach

Kaplan-Meier methodology was employed to estimate median OS and PFS. Follow-up duration was assessed via the reverse Kaplan-Meier technique. Comparisons of survival curves utilized the log-rank test. Categorical baseline features and response proportions were compared with Fisher's exact test. A two-sided p-value threshold of 0.05 was applied for these exploratory analyses. Verification of the proportional hazards assumption relied on Schoenfeld residuals ($p = 0.05$ cutoff). Univariate Cox proportional hazards models were performed without adjustment, reporting hazard ratios (HR) alongside 95% confidence intervals (CI). Multivariate Cox models incorporated 16 predefined covariates, drawn from variables highlighted in the RECOURSE and SUNLIGHT studies as well as from the work of van de Haar *et al*. [6, 10, 11]. These covariates were: age (<65 vs. ≥65 years); gender; tumor primary location (left- vs. right-sided); history of curative-intent surgery (yes/no); count of prior metastatic therapies (0–1, 2, or ≥3); refractoriness to fluoropyrimidine in the immediate prior regimen (yes/no); previous use of bevacizumab or alternative VEGF-targeted agents (yes/no); interval from metastatic diagnosis to start of FTD/TPI + bevacizumab (<18 vs. ≥18 months); ECOG performance status (0–1 vs. 2); metastatic site count (1–2 vs. ≥3); presence of peritoneal involvement at treatment start (yes/no); exclusive lung metastases (yes/no); locoregional interventions post-treatment initiation (yes/no); subsequent systemic treatments after progression (yes/no); prior irinotecan exposure (yes/no); and prior oxaliplatin exposure (yes/no). Analyses were conducted with STATA software, version 18.0 (StataCorp, College Station, TX, USA).

Results and Discussion

Baseline patient features

The cohort comprised 123 patients **(Table 1).** Median age was 65.2 years (95% CI 59.48–69.33). Most individuals (87.8%) presented with an ECOG performance status of 0 or 1. Curative-intent surgery had been performed previously in 59.3% of cases. Tumors originated from the left side in 74% of patients. For 79.7%, the combination of FTD/TPI and bevacizumab was administered as third- or fourth-line therapy. The median duration of follow-up reached 20.45 months (95% CI 14.827–23.836).

Table 1. Characteristics of Patients Enrolled in the Study

Characteristic	RAS Mutant n=76 (61.8%)	RAS Wild-Type n=47 (38.2%)	KRAS G13 Mutant n=8 (6.5%)	KRAS G12 Mutant n=51 (41.5%)	Other RAS Mutants n=25 (20.3%)	Overall Cohort n=123 (100.0%)	P-value KRAS WT vs. KRAS Mutant	P-value Overall: G12 vs. Non-G12	P-value RAS Mutant: G12 vs. Non-G12	P-value KRAS Exon 2: G12 vs. Non-G12
Age, years Median [95% CI]	65.5 [62.64–68.64]	64.3 [60.49–68.92]	64.8 [58.78–72.31]	66.1 [59.45–71.08]	64.8 [59.48–69.33]	65.2 [62.73–68.05]	0.909	0.796	0.807	0.959
Age <65 years	38 (50.0%)	24 (51.1%)	4 (50.0%)	25 (49.0%)	13 (52.0%)	59 (50.4%)				
Age ≥65 years	38 (50.0%)	23 (48.9%)	4 (50.0%)	26 (51.0%)	12 (48.0%)	58 (49.6%)				
Sex, male	45 (59.2%)	30 (63.8%)	6 (75.0%)	28 (54.9%)	17 (68.0%)	71 (60.7%)	0.610	0.245	0.275	0.285
Sex, female	31 (40.8%)	17 (36.2%)	2 (25.0%)	23 (45.1%)	8 (32.0%)	46 (39.3%)				
Left-sided primary tumor	55 (72.4%)	36 (76.6%)	5 (62.5%)	37 (72.5%)	18 (72.0%)	91 (74.0%)	0.604	0.760	0.960	0.560
Prior curative-intent surgery	43 (56.6%)	30 (63.8%)	1 (12.5%)	32 (62.7%)	11 (44.0%)	73 (59.3%)	0.426	0.519	0.121	0.008

Lung-only metastases	Peritoneal metastases	Metastatic sites: 1–2	ECOG performance status 0–1	Time from metastasis diagnosis <18 months	Previous bevacizumab exposure	Refractory to fluoropyrimidine	Previous treatment lines: ≥3	Previous treatment lines: 2	Previous treatment lines: 0–1
8 (10.5%)	21 (27.6%)	51 (67.1%)	68 (89.5%)	35 (46.1%)	68 (89.5%)	45 (59.2%)	14 (18.4%)	42 (55.3%)	20 (26.3%)
4 (8.5%)	11 (23.4%)	38 (80.9%)	40 (85.1%)	17 (36.2%)	34 (72.3%)	25 (53.2%)	18 (38.3%)	24 (51.1%)	5 (10.6%)
1 (12.5%)	4 (50.0%)	4 (50.0%)	7 (87.5%)	4 (50.0%)	8 (100.0%)	5 (62.5%)	0 (0.0%)	6 (75.0%)	2 (25.0%)
7 (13.7%)	11 (21.6%)	33 (64.7%)	47 (92.2%)	22 (43.1%)	47 (92.2%)	31 (60.8%)	9 (17.6%)	28 (54.9%)	14 (27.5%)
1 (4.0%)	10 (40.0%)	18 (72.0%)	21 (84.0%)	13 (52.0%)	21 (84.0%)	14 (56.0%)	5 (20.0%)	14 (56.0%)	6 (24.0%)
12 (9.8%)	32 (26.0%)	89 (72.4%)	108 (87.8%)	52 (42.3%)	102 (82.9%)	70 (56.9%)	32 (26.0%)	66 (53.7%)	25 (20.3%)
0.714	0.604	0.098	0.472	0.281	0.014	0.512	0.015	0.650	0.036
0.212	0.344	0.110	0.214	0.871	0.022	0.465	0.075	0.816	0.098
0.194	0.091	0.525	0.276	0.466	0.276	0.690	0.804	0.928	0.748
0.925	0.086	0.424	0.660	0.716	0.412	0.926	0.197	0.285	0.885

Best response: Not assessable	Best response: Progressive disease (PD)	Disease control rate (CR+PR+SD)	Best response: Stable disease (SD)	Best response: Partial response (PR)	Best response: Complete response (CR)	Prior oxaliplatin exposure	Prior irinotecan exposure	Subsequent systemic therapy	Locoregional treatment after start
6 (7.9%)	37 (52.9%)	33 (47.1%)	28 (40%)	5 (7.1%)	0 (0%)	58 (76.3%)	59 (77.6%)	30 (39.5%)	9 (11.8%)
3 (6.4%)	26 (59.1%)	18 (40.9%)	16 (36.4%)	2 (4.5%)	0 (0%)	44 (93.6%)	43 (91.5%)	18 (38.3%)	10 (21.3%)
0 (0%)	5 (62.5%)	3 (37.5%)	3 (37.5%)	0 (0%)	0 (0%)	6 (75.0%)	6 (75.0%)	2 (25.0%)	0 (0.0%)
4 (7.8%)	26 (55.3%)	21 (44.7%)	18 (38.3%)	3 (6.4%)	0 (0%)	40 (78.4%)	40 (78.4%)	22 (43.1%)	4 (7.8%)
2 (8%)	11 (47.8%)	12 (52.2%)	10 (43.5%)	2 (8.7%)	0 (0%)	18 (72.0%)	19 (76.0%)	8 (32.0%)	5 (20.0%)
9 (7.3%)	63 (55.3%)	51 (44.7%)	44 (38.6%)	7 (6.1%)	0 (0%)	102 (82.9%)	102 (82.9%)	48 (39.0%)	19 (15.4%)
					0.515	0.013	0.047	0.897	0.159
					0.990	0.265	0.265	0.431	0.050
					0.851	0.536	0.811	0.351	0.123
					0.990	0.828	0.828	0.332	0.412

Abbreviations: 5-FU, 5-fluorouracil; CR, complete response; DCR, disease control rate (complete response + partial response + stable disease); ECOG, Eastern Cooperative Oncology Group; PD, progressive disease; PR, partial response; SD, stable disease; WT, wild-type; MT, mutant. Time from metastasis diagnosis refers to the interval between diagnosis of first distant metastases and initiation of treatment.

The majority of patients carried a RAS mutation (61.8%). Within the mutated cases, KRAS exon 2 codon 12 variants were the most common, accounting for 41.5% of the entire study population (or 67.1% of all RAS-mutant cases). The remaining RAS mutations consisted of nine NRAS alterations, eight KRAS exon 2 codon 13 mutations, and eight uncommon KRAS variants (including A146T, Q61L, or K117N).

The key molecular subgroups (RAS wild-type, RAS mutant, KRAS G12, KRAS G13, and other KRAS mutations) showed good balance across the primary baseline features listed in **Table 1**. A significantly higher proportion of RAS-mutant patients received the FTD/TPI + bevacizumab combination as first- or second-line palliative therapy compared with RAS wild-type patients (26.3% vs. 10.6%; P = 0.036). Conversely, the regimen was more frequently administered as fourth-line or later treatment in RAS wild-type patients than in RAS-mutant patients (38.3% vs. 18.4 percent; P = 0.014). Further details are available in **Table 1.**

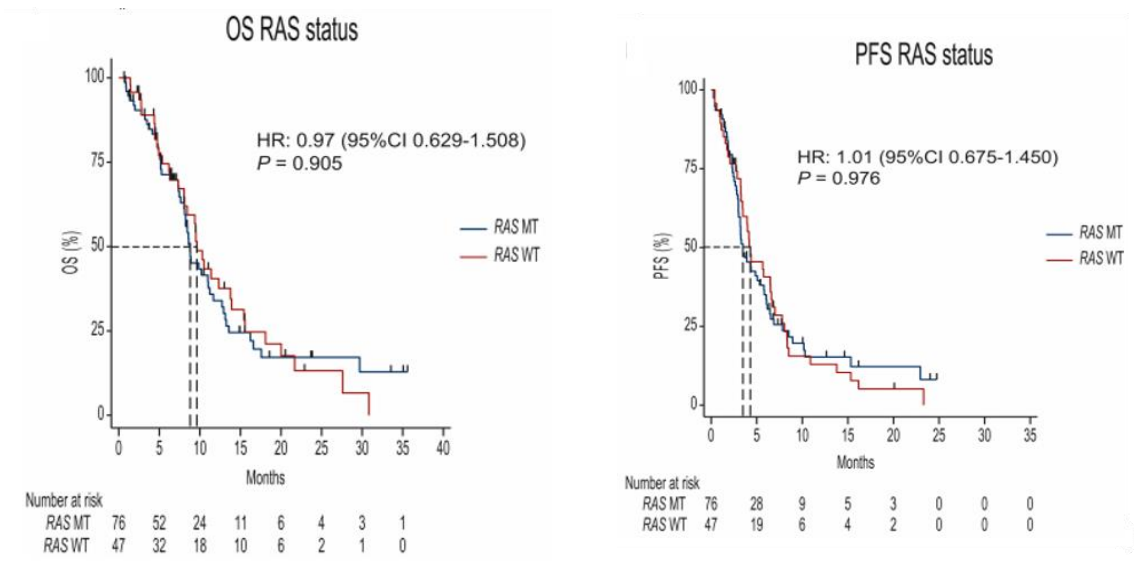
Treatment outcomes in the full cohort

The disease control rate (DCR) across all patients was 44.7%, including partial response as the best imaging outcome in 6.1% of cases. Median progression-free survival (PFS) reached 3.95 months (95 percent CI 3.255–5.326 months), while median overall survival (OS) was 9.37 months (95 percent CI 8.252–11.014 months).

Efficacy according to RAS mutation status

Disease control rates were similar between the RAS wild-type and RAS-mutant groups (40.9% vs. 47.1%; P = 0.515). Objective response rates were numerically slightly higher in the RAS-mutant subgroup (4.5% vs. 7.1 percent; P = 0.707) **(Table 1).**

No significant differences in PFS or OS were detected based on RAS mutation status. In the RAS wild-type group, median PFS was 4.31 months (95 percent CI 3.288–6.608 months) compared with 3.49 months (95 percent CI 2.992–5.326 months) in the RAS-mutant group. Unadjusted univariate analysis yielded a hazard ratio of 1.01 (95% CI 0.675–1.450; P = 0.976). Multivariable adjustment for potential confounding factors produced comparable findings (HR 0.91; 95% CI 0.560–1.468; P = 0.690) **(Figure 1b).**



a) b)

Figure 1.

Kaplan-Meier curves illustrating overall survival (OS; panel a, left) and progression-free survival (PFS; panel b, right) for patients with RAS wild-type versus RAS mutant tumors are shown in **Figure 1.**

Abbreviations: CI, confidence interval; HR, hazard ratio; MT, mutant; OS, overall survival; PFS, progression-free survival; WT, wild-type.

Median OS was 9.63 months (95 percent CI 8.055–13.775 months) in the RAS wild-type group compared with 8.78 months (95 percent CI 8.055–11.014 months) in the RAS mutant group. This corresponded to a hazard ratio

of 0.97 (95 percent CI 0.629–1.508; P = 0.905) in univariate analysis and 1.05 (95% CI 0.618–1.785; P = 0.857) after multivariable adjustment **(Figure 1a).**

To evaluate a possible interaction between RAS mutation status and prior bevacizumab exposure with respect to OS, an interaction term was added to the multivariate model. No significant interaction was identified (P = 0.243).

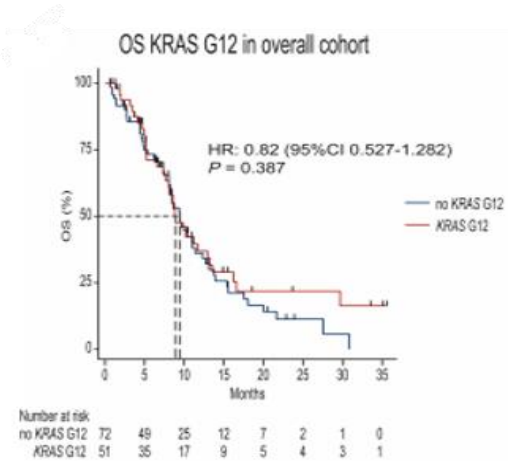
Outcomes according to KRAS codon 12 mutation status

Subsequent analyses explored potential codon-specific effects of (K)RAS mutations on survival, beginning with comparisons based on the presence or absence of KRAS G12 alterations.

In patients harboring KRAS G12 mutations, median OS was 8.88 months (95 percent CI 7.332–12.921 months) versus 9.47 months (95 percent CI 8.088–11.375 months) in the remaining patients (RAS wild-type plus non-G12 RAS mutations). Unadjusted univariate analysis yielded a hazard ratio of 0.82 (95 percent CI 0.527–1.282; P = 0.387), while multivariable analysis showed a hazard ratio of 0.87 (95% CI 0.488–1.537; P = 0.624) **(Figure 2a).**

In the largest homogeneous subgroup of patients treated strictly in the third-line setting (n = 66), median OS was 8.09 months (95 percent CI 4.932–9.501 months) for those with KRAS G12 mutations compared with 8.05 months (95 percent CI 5.162–11.671 months) for those without, resulting in a hazard ratio of 1.25 (95 percent CI 0.575–2.705; P = 0.58).

No significant prognostic effect of KRAS G12 status was observed in the smaller subgroups receiving the combination as first- or second-line therapy (n = 25; HR 0.21, 95 percent CI 0.011–3.789; P = 0.29) or as fourth-line or later treatment (n = 32; HR 0.25, 95 percent CI 0.024–2.505; P = 0.24).



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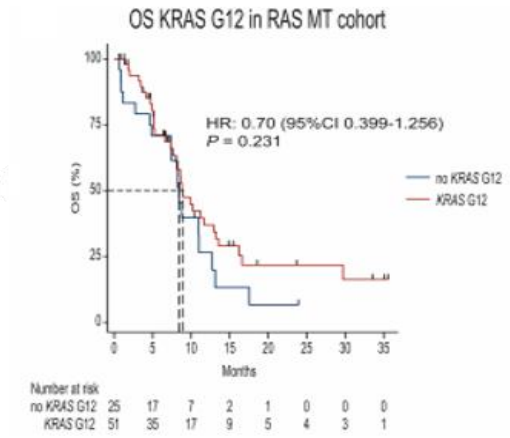

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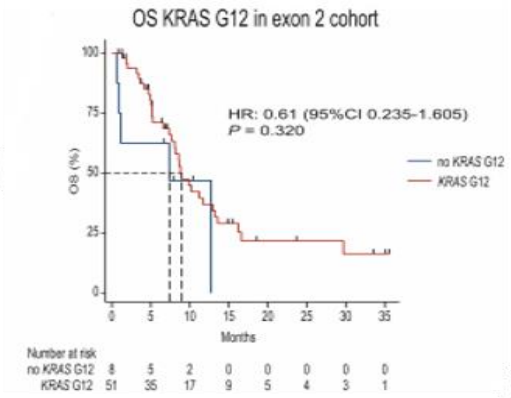

c)

Figure 2.

Kaplan-Meier estimates of overall survival (OS) are presented in **Figure 2**, comparing the cohort with KRAS G12 mutations versus RAS wild-type plus non-KRAS G12 mutated cases (panel a, left), KRAS G12 mutated versus

all non-KRAS G12 cases (panel b, middle), and KRAS G12 mutated versus KRAS G13 mutated tumors (panel c, right).

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival; MT, mutant; WT, wild-type.

Progression-free survival (PFS) showed close similarity between the KRAS G12 group and the combined RAS wild-type/non-KRAS G12 group: median PFS of 3.32 months (95 percent CI 2.762–5.063 months) in KRAS G12 patients versus 4.18 months (95 percent CI 3.255–6.477 months) in the comparator group. Univariate analysis produced a hazard ratio of 1.03 (95% CI 0.691–1.545; P = 0.874), and multivariable analysis yielded a hazard ratio of 1.21 (95% CI 0.730–2.00; P = 0.461).

Outcomes for KRAS codon 12 status versus other RAS mutations

Within the 76 patients with RAS-mutated tumors, median OS in the non-KRAS G12 subgroup was 8.45 months (95 percent CI 4.833–11.014 months). Comparison to the KRAS G12 group gave a hazard ratio of 0.699 (95 percent CI 0.399–1.256; P = 0.231) in univariate analysis and 0.681 (95% CI 0.290–1.599; P = 0.378) after multivariable adjustment **(Figure 2b).**

Median PFS in the non-KRAS G12 subgroup was 3.91 months (95 percent CI 2.926–6.871 months). Hazard ratios indicated no significant difference: 1.104 (95% CI 0.635–1.918; P = 0.726) univariately and 1.384 (95% CI 0.658–2.912; P = 0.392) multivariately.

Among patients with KRAS exon 2 mutations, outcomes were comparable between KRAS G12 and KRAS G13 variants. Median OS for KRAS G13 cases was 7.364 months (95 percent CI 0.690 months–not reached), and median PFS was 2.992 months (95 percent CI 0.263 months–not reached) **(Figure 2c).**

Hazard ratios relative to KRAS G12 showed no significance for OS [univariate HR 0.614 (95 percent CI 0.235–1.605; P = 0.320); multivariate HR 0.632 (95 percent CI 0.188–2.126; P = 0.459)] or PFS [univariate HR 1.096 (95 percent CI 0.429–2.80; P = 0.848); multivariate HR 1.232 (95 percent CI 0.401–3.783; P = 0.716)].

Prognostic factors for survival

In a multivariable model incorporating RAS mutation status, only Eastern Cooperative Oncology Group (ECOG) performance status (2 versus 0/1) [HR 3.88 (95 percent CI 1.901–7.938; P < 0.0001)] and number of metastatic sites at baseline (≥3 versus ≤2) [HR 2.34 (95 percent CI 1.317–4.153; P = 0.004)] were independently associated with overall survival during FTD/TPI + bevacizumab therapy.

Trends toward significance were observed for female sex (versus male) [HR 1.650 (95 percent CI 1–2.721; P = 0.05)], receipt of subsequent systemic therapy after progression (yes versus no) [HR 0.601 (95 percent CI 0.356–1.013; P = 0.056)], and longer interval from metastatic diagnosis to treatment start (≥18 versus <18 months) [HR 0.613 (95 percent CI 0.353–1.063; P = 0.081)] **(Figure 3).**

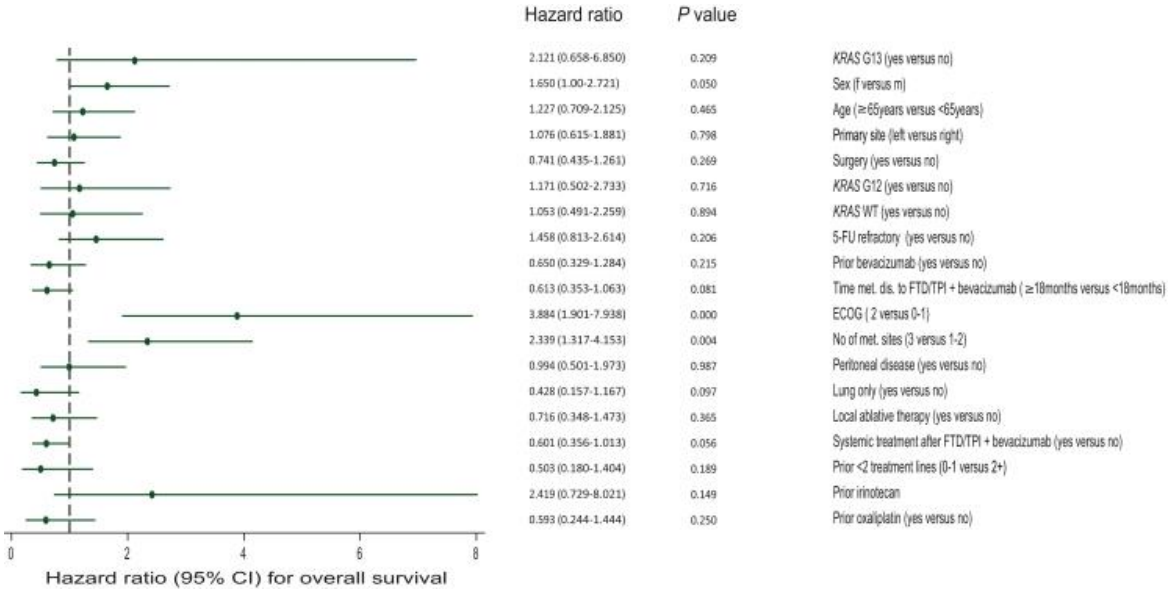

Figure 3.

A multivariable Cox proportional hazards model was constructed, incorporating (K)RAS mutational subgroups alongside 16 additional covariates **(Figure 3).** No independent predictive or prognostic effect was identified for KRAS wild-type, KRAS G12, or KRAS G13 status.
Abbreviations: 5-FU, 5-fluorouracil; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FTD, trifluridine; MT, mutant; TPI, tipiracil; WT, wild-type.

RAS mutation status showed no association with outcome in this adjusted model. Hazard ratios were as follows: KRAS G13 (present versus absent) HR 2.12 (95% CI 0.658–6.850; P = 0.209); KRAS wild-type (present versus absent) HR 1.05 (95% CI 0.491–2.259; P = 0.894); KRAS G12 (present versus absent) HR 1.171 (95% CI 0.502–2.733; P = 0.716).
This investigation is clinically relevant for oncologists managing patients in everyday practice for two main reasons: (i) it constitutes the largest published real-world series of metastatic colorectal cancer (mCRC) patients receiving FTD/TPI combined with bevacizumab in a Western population [12–15], and (ii) it provides detailed evaluation of outcomes across specific molecular subgroups.
Early in the year, the gastrointestinal oncology field saw debate sparked by retrospective real-world evaluations of FTD/TPI monotherapy [9]. These reports, together with a post-hoc analysis of the phase III RECOURSE trial, raised the possibility that tumors harboring KRAS G12 mutations might derive limited benefit from single-agent FTD/TPI. Given the high prevalence of KRAS G12 alterations in mCRC, such a finding would have major practical consequences, potentially requiring repeat molecular testing (e.g., via liquid biopsy or tissue re-biopsy) prior to initiating FTD/TPI and possibly favoring alternative agents such as multikinase inhibitors over standard chemotherapy-based options in later lines.
The phase III SUNLIGHT trial, however, introduced a new benchmark for late-line mCRC management by demonstrating that adding bevacizumab to FTD/TPI conferred a clinically meaningful 3.3-month improvement in overall survival compared with FTD/TPI monotherapy [10].
In the present cohort, median OS was approximately 1 month shorter (9.37 months) than the 10.8 months reported in SUNLIGHT. This difference is largely explained by the inclusion of patients with poorer prognostic features: 12.2% had an ECOG performance status of 2, nearly half (49.6%) were aged ≥65 years (versus 40.7% in SUNLIGHT), and 26% received the regimen in fourth-line or later settings. Despite these baseline differences, survival outcomes were consistent with other published real-world experiences [12].
No heterogeneity in treatment effect according to RAS status (wild-type versus mutant) was observed in the SUNLIGHT trial, a finding supported by a smaller phase II study conducted in Asian patients [16]. The current results are in agreement with these prior observations.
A distinctive strength of our analysis lies in its dedicated examination of the KRAS G12-mutated subgroup, which represented 41.5% of patients—a proportion aligned with established epidemiological data. Comparisons were performed against three reference groups: the combined RAS wild-type/non-KRAS G12 cohort, the broader RAS-mutant population, and the KRAS exon 2-mutated subset. No meaningful differences emerged in objective response rates, progression-free survival, or overall survival. These data indicate that the efficacy of FTD/TPI plus bevacizumab is preserved across molecular subgroups. Notably, the addition of bevacizumab may mitigate any potential resistance associated with KRAS G12 mutations under FTD/TPI monotherapy. Preclinical evidence suggesting heightened vulnerability of KRAS-mutant tumors to VEGF pathway blockade provides a plausible biological rationale for this clinical observation [17–19].

Limitations
As a retrospective study, inherent biases cannot be fully excluded. The cohort was not restricted to a pure third-line population as in the SUNLIGHT trial. Additionally, the size of the non-KRAS G12 subgroup limited statistical power for definitive conclusions regarding rarer (K)RAS variants. Finally, confirmatory mechanistic insights from in vitro or organoid models are currently unavailable.

Conclusion

This real-world retrospective analysis adds important evidence to the ongoing discussion about the relevance of RAS mutational profiling—particularly the common KRAS G12 alterations—when selecting later-line therapy with FTD/TPI-based regimens in mCRC. Our findings support that the SUNLIGHT-defined standard of FTD/TPI

combined with bevacizumab retains consistent activity irrespective of RAS status, with tumors harboring KRAS G12 mutations appearing equally responsive compared with KRAS wild-type or other RAS-mutated subgroups.

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