Am J Cancer Res 2025;15(7):3142-3149
www.ajcr.us /ISSN:2156-6976/ajcr0166474

Original Article

Combination of anti-epidermal growth factor receptor antibodies plus trifluridine-tipiracil as rechallenge strategy improves treatment outcomes in patients with RAS/BRAF wild-type refractory metastatic colorectal cancer

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Received May 30, 2025; Accepted July 14, 2025; Epub July 15, 2025; Published July 30, 2025

Abstract: Trifluridine/tipiracil (FTD-TPI) plus bevacizumab is an established option for refractory metastatic colorectal cancer (mCRC). Rechallenging RAS/BRAF-wild-type tumours with an anti-EGFR antibody in combination with FTD-TPI is emerging, yet the two strategies have not been directly compared. We retrospectively identified consecutive RAS/BRAF-wild-type, chemotherapy-refractory mCRC patients treated at National Taiwan University Hospital between December 2018 and March 2023. All had received first-line anti-EGFR therapy; subsequent treatment comprised FTD-TPI with either anti-EGFR rechallenge (n = 20) or an anti-VEGF agent (n = 10). Anti-EGFR rechallenge yielded a higher objective response rate (30% vs 0%; P = 0.074) and disease-control rate (70% vs 30%; P = 0.440), plus numerically longer median progression-free (3.4 vs 2.3 months; P = 0.524) and overall survival (12.7 vs 9.9 months; P = 0.644). After adjustment for age, sex, tumour sidedness and time from metastatic diagnosis to FTD-TPI, anti-EGFR therapy remained the only independent predictor of response (posterior OR ≈ 7; 95% credible interval 1.1-66). These data suggest that FTD-TPI plus anti-EGFR rechallenge provides greater tumour shrinkage and at least comparable survival versus FTD-TPI plus anti-VEGF in heavily pre-treated, wild-type mCRC, supporting further prospective evaluation.

Keywords: Trifluridine/tipiracil, TAS-102, anti-EGFR rechallenge, real-world evidence, refractory mCRC, chemotherapy combination

Introduction

Refractory metastatic colorectal cancer (mCRC) remains one of the most challenging malignancies to treat [1]. Generally, refractory mCRC is defined by the failure of standard chemotherapies, oxaliplatin, irinotecan, and fluoropyrimidines, as well as the failure of targeted therapies, including anti-vascular endothelial growth factor (anti-VEGF) monoclonal antibodies and, in patients with RAS wild-type tumors, anti-epidermal growth factor receptor (anti-EGFR) monoclonal antibodies [2-5]. Overall, the treatment efficacy beyond the third lines remains unsatisfactory [6]. Monotherapies such as regorafenib, fruquintinib, and trifluridine-tipiracil (FTD-TPI) have demonstrated survival benefits in refractory settings but exhibit limited anti-tumor activity, with objective response rates (ORRs) of less than 2% [7-10]. Consequently, combination strategies are being actively explored to enhance treatment efficacy.

FTD-TPI is an orally administered compound composed of a thymidine-based nucleoside analog (trifluridine) and a thymidine phosphorylase inhibitor (tipiracil). It has demonstrated anti-tumor activity in patients with refractory mCRC following failure of fluoropyrimidine-based therapies [8]. Given its chemotherapeu-

https://doi.org/10.62347/MHBC7658

tic nature, FTD-TPI is a suitable candidate for combination with targeted therapies. Several phase 2 studies have shown its potential when combined with bevacizumab [11, 12]. In a recent global phase 3 SUNLIGHT trial, this combination exhibited superior ORR and progression-free survival (PFS) over FTD-TPI monotherapy [13]. Current guidelines suggest that the SUNLIGHT regimen is the most favorable regimen for refractory mCRC, especially for bevacizumab-naïve patients.

Simultaneously, anti-EGFR rechallenge in RAS wild-type refractory mCRC has long been recognized, especially for patients who were initially responsive to first-line anti-EGFR combination therapy [14]. Although the ORRs of most anti-EGFR monoclonal antibody rechallenge studies were promising, the PFSs were not durable [15]. In order to enhance anti-tumor activity, several anti-EGFR combinations have been developed for clinical trials, including targeted therapy, immunotherapy, and chemotherapy combinations. Two phase 2 studies have reported the promising efficacy of anti-EGFR rechallenge in combination with FTD-TPI for refractory mCRC patients with initial RAS/BRAF wild-type disease [16, 17]. However, the two strategies of FTD-TPI - in combination with anti-VEGF agents or anti-EGFR rechallenge - in the setting of refractory mCRC have not yet been directly compared. Therefore, this study aims to explore the optimal targeted therapeutic partner for FTD-TPI in the treatment of refractory mCRC.

Materials and methods

Patient enrollment

In this single-center retrospective study, we reviewed the medical records of patients with refractory mCRC who received concurrent FTD-TPI plus anti-EGFR rechallenge or anti-VEGF agents at the National Taiwan University Hospital (NTUH). The patients had to fulfill all of the following criteria: (1) wild-type RAS and BRAF mCRC; (2) a best response of partial response (PR), complete response (CR) or stable disease (SD) to the first-line treatment, which consisted of a combination of anti-EGFR monoclonal antibody and chemotherapy; (3) refractory mCRC, defined as progression or intolerance to both anti-EGFR and anti-VEGF targeted therapies, as well as all available chemotherapies, including irinotecan, oxaliplatin, and infusional 5-fluorouracil or oral fluoropyrimidine analogues (regorafenib was permitted but not required); (4) receipt of FTD-TPI in combination with either anti-EGFR rechallenge or anti-VEGF treatment during the study interval from December 1, 2018, to March 31, 2023; (5) age ≥ 18 years; and (6) comprehensive medical records available at NTUH.

Patients were excluded if they (1) received the FTD-TPI combination for less than 4 weeks, (2) received FTD-TPI monotherapy, or (3) received anti-EGFR rechallenge and anti-VEGF treatment simultaneously. Concurrent use of either oxaliplatin or irinotecan along with the FTD-TPI combination was allowed. If a patient received FTD-TPI combination multiple times, only the first combination was included. Anti-EGFR monoclonal antibodies included cetuximab and panitumumab, whereas anti-VEGF agents included bevacizumab, ramucirumab, and regorafenib.

Data collection

The following clinical data were collected from medical records: (1) age at enrollment, (2) sex, (3) pathology reports for RAS/BRAF and mismatch repair status, (4) location of the primary CRC, (5) date of the initiation of FTD-TPI combination, (6) date of progression, and (7) date of death or date of last follow-up (censored on July 31, 2024).

The right-sided colon was defined as the cecum, ascending colon, hepatic flexure, and transverse colon, whereas the left-sided colon was defined as the splenic flexure, descending colon, sigmoid colon, and rectum. A small proportion of patients underwent next-generation sequencing (NGS) of the circulating tumor DNA (ctDNA), also known as “liquid biopsy”, using Guardant360® - except for patient no.5 who underwent liquid biopsy using FoundationOne® Liquid CDX. This study was approved by the Institutional Review Board of NTUH (IRB No. NTUH #202108112RINC). This study adhered to the Declaration of Helsinki.

Statistical analysis

Chi-square test or Fisher’s exact test (when indicated) was used to compare nominal variables. A logistic regression model was utilized

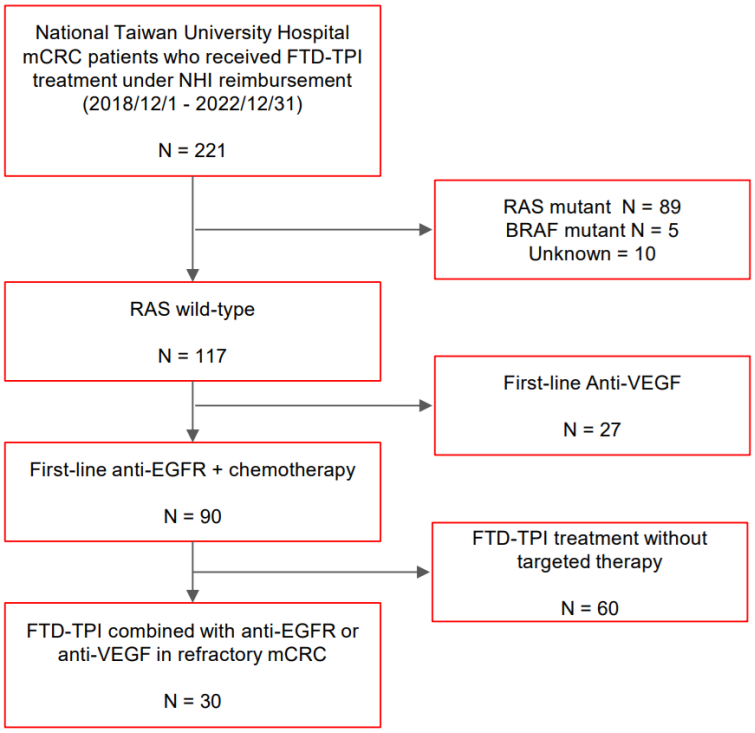

Figure 1. Patient enrollment and exclusion. FTD-TPI, trifluridine-tipiracil; mCRC, metastatic colorectal cancer.

Table 1. Patient characteristics

Variables	Combination (N, %)		*p*
	Anti-VEGF agents	Anti-EGFR	
Total number	10 (100)	20 (100)	
Age > 65 years	3 (30.0)	9 (45.0)	0.694
Male sex	7 (70.0)	10 (50.0)	0.440
Primary diagnosis			0.078
Colon cancer	5 (50.0)	17 (85.0)	
Rectal cancer	5 (50.0)	3 (15.0)	
Location of primary tumor			1.000
Right side	1 (10.0)	3 (15.0)	
Left side	9 (90.0)	17 (85.0)	
Diagnosis to FTD-TPI treatment			0.251
< 18 months	2 (20.0)	1 (5.0)	
≥ 18 months	8 (80.0)	19 (95.0)	
RAS status			
Mutated	0 (0)	0 (0)	
Wild type	10 (100)	20 (100)	
BRAF status			
Mutated	0 (0)	0 (0)	
Wild type	10 (100)	20 (100)	
Combined chemotherapy			0.690
Yes	6 (60.0)	14 (70.0)	
No	4 (40.0)	6 (30.0)	

FTD-TPI: trifluridine-tipiracil.

for multivariate analyses of binary endpoints. The PFS and overall survival (OS) of patient who received the FTD-TPI combinations were estimated using the Kaplan-Meier method and compared using a log-rank test. The data were locked on September 14, 2023. Statistical analyses were performed using R version 4.4.0 (R Core Team, Vienna, Austria). For cases of perfect separation encountered in logistic regression models, Firth's penalized likelihood approach was applied. A weakly informative normal (0, 1.5) prior was applied in the Bayesian logistic model to gently shrink implausible extremes while allowing the data to drive the estimates. In all statistical tests, a two-sided *p* value < 0.05 was considered statistically significant.

Results

Patient clinicopathological factors

A total of 215 patients with refractory mCRC who received FTD-TPI treatment at the NTUH were reviewed, with 114 having wild-type RAS/BRAF disease. Among them, 30 patients (26.3%) fulfilled inclusion criteria and were enrolled for analysis (**Figure 1**). Detailed patient characteristics were listed in **Table 1**: Two-thirds of the patients received FTD-TPI in combination with anti-EGFR rechallenge (n = 20, 66.7%), the other received FTD-TPI in combination with anti-VEGF agents (n = 10, 33.3%). Patients had a median age of 63.6 years, approximately half (n = 17, 56.7%) were men, and with a predominant left sided disease (n = 26, 86.7%). The median time from metastatic diagnosis

Table 2. Multivariate analysis for predictive factors of objective response

Variable	Odds ratio	95% CI	*p*
Age > 65 years	0.33	0.05-1.85	0.220
Male	1.51	0.28-8.84	0.640
Left-sided tumor	1.25	0.13-10.20	0.840
Metastatic status to FTD-TPI > 18 months	1.66	0.15-16.7	0.680
Anti-EGFR (compared to anti-VEGF agents)	7.00	1.06-66.2	0.043

FTD-TPI: trifluridine-tipiracil.

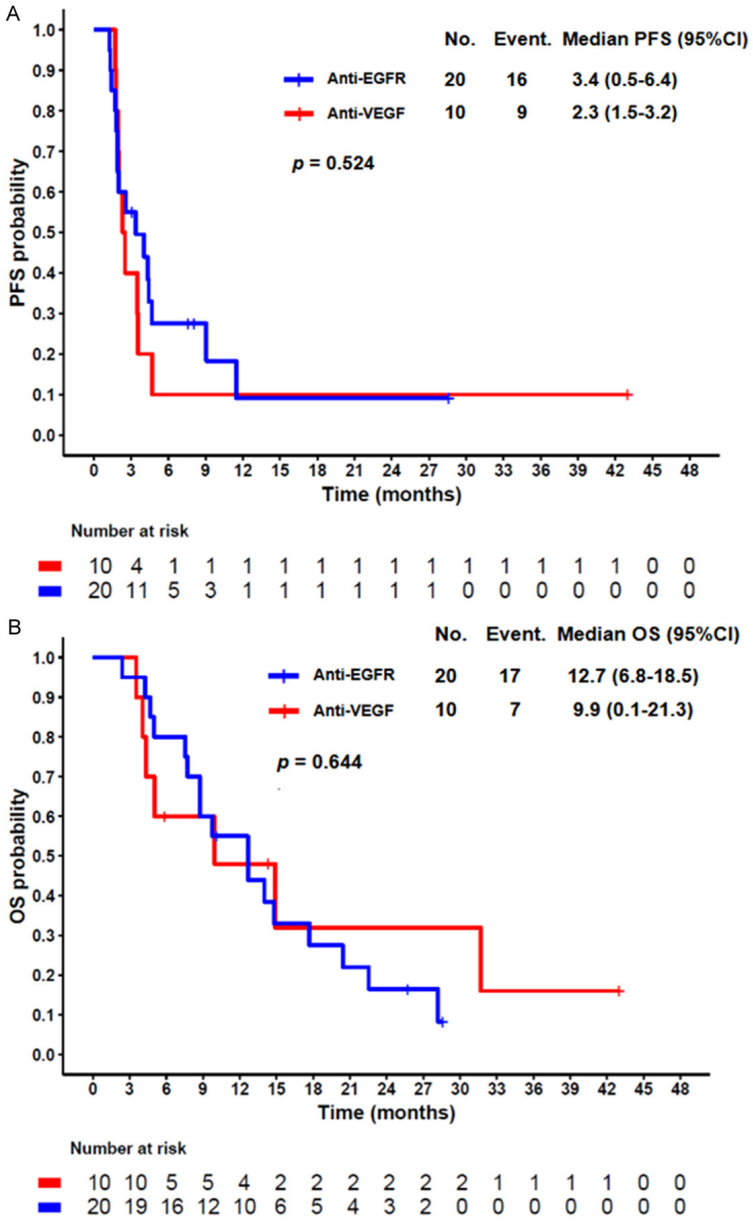

Figure 2. (A) Progression-free survival (PFS) and (B) overall survival (OS) of patients receiving trifluridine-tipiracil (FTD-TPI) combination therapy. CI, confidence interval; EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor.

to FTD-TPI combination treatment was 32.8 months (range: 15.6 to 103.1 months).

Treatment strategy and outcomes

The median number of treatment lines before the FTD-TPI combination treatment was 4 (range: 2-10), with 10% of patients receiving FTD-TPI combination treatment at the third line setting. A total of 66.6% of patients received concurrent chemotherapy (irinotecan or oxaliplatin) along with the FTD-TPI combination. The median dose intensity of FTD-TPI was 71.4%.

The anti-EGFR rechallenge group exhibited numerically higher ORR (30% vs 0%, P = 0.074) as well as a higher disease control rate (50% vs 30%, P = 0.440) compared to the anti-VEGF group. After adjusting for age, sex, tumor sidedness, and time from metastatic diagnosis to FTD-TPI treatment, combination therapy with anti-EGFR rechallenge remained an independent predictor of response, as detailed in **Table 2**.

The median time to treatment discontinuation (TTD) was 2.7 (95% CI: 1.6 to 3.7) months. The median PFS and median OS were 2.6 (95% CI 1.1 to 4.1) months and 12.7 (95% CI 7.8 to 17.5) months, respectively. The anti-EGFR rechallenge group exhibited numerically longer PFS (3.4 months vs 2.3 months, P = 0.524, **Figure 2A**) and OS (12.7 months vs 9.9 months, P = 0.644, **Figure 2B**), compared to the anti-VEGF group. FTD-TPI combination TTD was 3.37 months vs 2.23 months for ant-EGFR group and anti-VEGF group, respectively (*P* = 0.930).

Table 3. Next generation sequence analysis results and treatment efficacy of FTD-TPI combination

No.	Pre-treatment genetic alterations (VAF, %)	Sidedness	Targeted therapy	Combined chemotherapy	Best ORR	PFS (months)	OS (months)
1	TP53 R337fs (2.0) MAP2K1 E102_103 Del (0.3) APC A1325fs (1.7)	Left	Anti-EGFR	Irinotecan	PR	11.6	14.0
2	NRAS Q61H (0.6) NRAS Q61K (0.5) NRAS Q61R (0.09) BRAF V600E (0.3)	Left	Anti-VEGF	Irinotecan	PD	2.53	14.9
3	NRAS Q61L (0.05) TP53 splice site SNV (16.8) NOTCH1 A1635Fs (0.2) BRAF amplification EGFR amplification APC S1346fs (18.2) APC I1417fs (4)	Left	Anti-EGFR	Irinotecan	PD	1.9	12.7
4	BRAF amplification CDK12 spice site SNV (0.4) FGFR1 N546K (0.2) EGFR amplification TP53 R249M (49.9) TP53 P128fs (0.08) RB1 R698S (0.1) APC T1556fs (54.6)	Right	Anti-EGFR	Oxaliplatin	PR	4.4	17.7
5	KRAS G12V (0.25) KRAS Q61H (0.25) NRAS Q61R (0.23) MEK1 K57T (1.2) MEK1 K57N (1.2) ARID1A L511fs*108 (30.3) EGFR G465R (0.54) EGFR V441G (0.57) EGFR I491K (0.24) FGFR4 N495K (0.31)	Left	Anti-EGFR	Oxaliplatin	PR	4.3	7.7

FTD-TPI, trifluridine-tipiracil; PR, partial response; PD, progressive disease; VAF, variant allele frequency.

Next generation sequencing results

A total of five patients (16.7%) underwent liquid biopsy with NGS analysis before FTD-TPI combination treatment. The genetic alterations of these patients, along with their corresponding treatment patterns and efficacy, are listed in **Table 3**. Four of five (80%) patients exhibited sub-clonal RAS/BRAF alterations at the time of liquid biopsy. In these patients, anti-EGFR rechallenge still yielded responses, albeit with relatively short PFS. In contrast, the patient who did not develop RAS/BRAF alterations exhibited a relatively long PFS of 11.6 months with FTD-TPI plus anti-EGFR rechallenge. In contrast, the presence of sub-clonal RAS/BRAF alterations did not predict the response to anti-VEGF agents plus FTD-TPI.

Discussion

Principal findings

Global phase 3 studies have consistently reported ORRs below 10% for third-line treatment of refractory mCRC, highlighting the treatment challenge in this patient population [7-9]. SUNLIGHT study established that combination of FTD-TPI with anti-VEGF is a promising strategy in this setting that improved survival of these patients [13]. In the present study, we demonstrated that the combination of FTD-TPI with anti-EGFR rechallenge led to a relatively higher ORR of 30% and comparable survival outcomes compared to combination with anti-VEGF. No responder was observed in the anti-VEGF group in this study partially reflects the

heavily pretreated nature of the study population.

Comparison with previous studies

Although anti-EGFR therapy combined with chemotherapy has been established as the cornerstone of first-line treatment for patients with left-sided, wild-type RAS/BRAF mCRC, the role of anti-EGFR rechallenge in refractory mCRC remains uncertain. Several studies have shown that anti-EGFR rechallenge with irinotecan exhibits substantial anti-tumor activity, supporting the rationale for combining FTD-TPI with anti-EGFR rechallenge in refractory mCRC [14]. Notably, two previous studies have demonstrated the efficacy of this combination [16, 17].

To further enhance anti-tumor activity, combining FTD-TPI with additional chemotherapies, including irinotecan or oxaliplatin, is a reasonable strategy and has been commonly applied in clinical practice. A phase II trial combining FTD-TPI with irinotecan and bevacizumab yielded good ORR around 26%, highlighting the potential of FTD-TPI combination in this setting [18]. However, the combination of anti-EGFR monoclonal antibodies with FTD-TPI and other chemotherapies has been less studied. Since most of our patients (14 of 20 patients, 70%) in the anti-EGFR group received FTD-TPI plus chemotherapy and anti-EGFR rechallenge, our results support the feasibility and efficacy of this kind of novel combination.

Biomarker insights

Withdrawal of the initial anti-EGFR antibody allows the RAS-mutant subclones that mediated resistance to drift down, restoring EGFR dependency; rechallenge therefore targets a re-emerging wild-type population with promising ORRs, as demonstrated in single-armed phase 2 studies such as CRICKET and CHRONOUS trial [15, 19]. In prospective setting, the CITRIC trial allocated wild-type refractory mCRC patients to anti-EGFR rechallenge combination or investigator's choice, and anti-EGFR rechallenge group exhibited better ORR [20]. In another VELO trial, FTD-TPI combined with panitumumab demonstrated not only superior ORR, but also longer PFS and OS compared to FTD-TPI monotherapy [17]. Our study results not only are consistent with the evidence above, but also directly compare EGFR vs VEGF strategies. As NGS is not fully reimbursed in Taiwan, only one-sixth of our patients underwent liquid biopsies before FTD-TPI combination therapy. Combination strategy with anti-EGFR rechallenges still demonstrated a better ORR despite this limitation.

Limitations

This study has some limitations. First, the small sample size limited statistical power, reducing the likelihood of detecting a significant impact of anti-EGFR rechallenge on survival and response differences. Additionally, NGS testing was not reimbursed, and targeted therapies, including both anti-EGFR and anti-VEGF agents, were not reimbursed when used in combination with FTD-TPI in Taiwan. Nevertheless, a trend toward superior efficacy with anti-EGFR rechallenge was still observed despite the small sample size. Second, the retrospective nature of this study led to inherent biases and intergroup heterogeneity, which we sought to address through multivariate analysis for response prediction to minimize biases. Third, the median number of treatment lines before the FTD-TPI combination regimen was four, indicating a heavily pre-treated study population. This may have restricted the observed treatment potential of the combination strategy and applicability of this study result.

In summary, anti-EGFR rechallenge plus FTD-TPI achieved a higher ORR than the anti-VEGF combination, yet no significant difference in PFS and OS between these two strategies. Given the retrospective, small-cohort nature of this study, prospective ctDNA-guided trials are needed to confirm the clinical benefit in RAS/BRAF-wild-type refractory mCRC.

Acknowledgements

We thank all the patients and their families for their support in this study. This study was supported by the Ministry of Health and Welfare of Taiwan (grant number: MOHW113-TDU-B-221-134010).

Disclosure of conflict of interest

None.

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