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Trifluridine/tipiracil (FTD/TPI) in metastatic colorectal cancer treatment

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Abstract

Metastatic colorectal cancer (mCRC) remains a formidable health challenge that needs novel therapeutic approaches. Trifluridine/tipiracil (FTD/TPI), an oral cytostatic antimetabolite drug, has emerged as a promising option in mCRC management. Trifluridine/tipiracil's mechanism involves incorporating trifluridine into DNA, impeding cell proliferation, and inhibiting thymidine synthase. Clinical investigations underscore its efficacy as both monotherapy and polytherapy. Phase II trials in Japan and a significant multicenter phase III trial (RECOURSE) globally established FTD/TPI's superiority in terms of overall survival (OS) and progression-free survival (PFS) compared to placebo in heavily pretreated mCRC patients. White blood cells, platelet count, lactate dehydrogenase, alkaline phosphatase, carcinoembryonic antigen, chemotherapy-induced neutropenia, and multiple metastatic sites were determined as potential prognostic factors in FTD/TPI treatment. Intriguingly, recent studies demonstrated that specific KRAS mutations (G12 *vs.* G13) may potentially guide personalized treatment strategies for achieving better therapeutic outcomes and decreasing drug toxicity. Thanks to clinical trials and real-world studies, the role of FTD/TPI in personalized treatment approaches continues to evolve, with ongoing research poised to unlock further its therapeutic potential.

Keywords: trifluridine, tipiracil, FTD/TPI, TAS-102, metastatic colorectal cancer, real-life data

Introduction

Colorectal cancer (CRC) is the third most common cancer in men and second in women in Poland [1]. Approximately 15–30% of diagnosed patients already have metastases while 20–50% of patients with initially localized disease develop them in the future. In disseminated metastatic colorectal cancer (mCRC), 5-fluorouracil (5-FU) is the mainstay of treatment. Other drugs recommended in palliative treatment include oxaliplatin, irinotecan, an anti-vascular endothelial growth factor (VEGF), and, in the case of RAS wild type tumors, anti-epidermal growth factor receptor (EGFR) therapy [2]. According to the European Society of Medical Oncology (ESMO), the treatment options for patients with mCRC depend on HER-2, BRAF, and RAS mutation status. Trifluridine/tipiracil (FTD/TPI) is one of oral drugs recommended in monotherapy for previously treated adult mCRC patients as a third-line therapy [2, 3]. The molecular mechanism of action of FTD/TPI is presented in Figure 1. This review aims to present the FTD/TPI clinical data and show future directions in mCRC treatment.

Trifluridine/tipiracil belongs to a family of cytostatic antimetabolite drugs. After uptake by tumor cells, trifluridine (FTD) is phosphorylated by thymidine kinase (TK) to the monophosphate form (FTD-MP), then metabolized in cells to the triphosphate form (FTD-TP) and incorporated directly into DNA, which prevents cell proliferation. In addition, FTD-MP reversibly inhibits thymidine synthase (TS), which leads to an imbalance between deoxythymidine triphosphate (dTTP) and thymidine monophosphate

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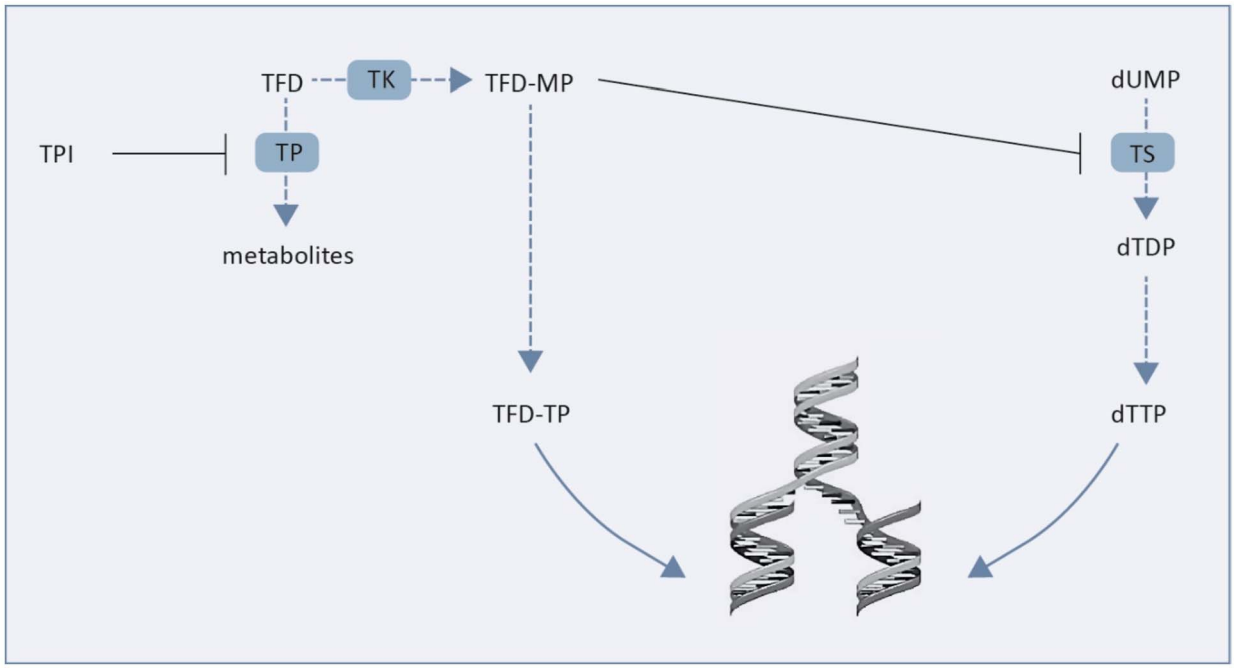

Figure 1. Molecular mechanism of action of trifluridine/tipiracil (FTD/TPI); dTDP — deoxythymidine diphosphate; dTTP — deoxythymidine triphosphate; dUMP — deoxyuridine monophosphate; FTD-MP — monophosphate form of FTD; FTD-TP — triphosphate form of FTD; TK — thymidine kinase; TP — thymidine phosphorylase; TS — thymidine synthase

(dUMP) in favor of dUMP, resulting in the interruption of DNA structure [4]. As the antitumor potential of trifluridine is affected by thymidine phosphorylase (TP), the combination medicine also contains its inhibitor — tipiracil (TPI) [5].

Results of studies with FTD/TPI in monotherapy

Phase I studies of oral FTD/TPI in patients with refractory mCRC evaluated the safety and determined the dose and schedule of FTD/TPI in Japanese and Western populations of patients. The studies showed that adverse events were acceptable and recommended the 35 mg/m^2 dose for further studies [6].

The next randomized phase II trial was also performed in Japan. The primary endpoint was overall survival (OS) in the intention-to-treat population of CRC patients previously treated with two or more standard chemotherapy regimens, including fluoropyrimidine, irinotecan, and oxaliplatin. Eligible patients were stratified into FTD/TPI or placebo groups. The study showed that median OS was higher in the study group [9 months (mo.); 95% confidence interval (CI) 7.3–11.3] than in the control or placebo groups (6.6 mo.; 95% CI 4.9–8.0; p = 0.0011) [7].

The RECOURSE trial (NCT01607957) was a phase III multicenter randomized double-blind placebo-controlled study that compared the FTD/TPI efficacy *vs.* placebo in 800 patients in the USA, Europe, and Japan. Patients were stratified according to their geographical location, age, time from the first diagnosis of metastases, and KRAS status. Patients eligible for the study had biopsy-proven adenocarcinoma of the colon or rectum. Patients previously had been treated with two or more standard chemotherapy regimens for metastatic disease. The primary outcome measure was OS, and the secondary were progression-free survival (PFS) and the percentage of participants with adverse events (AEs). Results of the study showed that median OS (mOS) was higher in the study group (7.1 mo.) than in the placebo group [5.3 mo.; hazard ratio (HR) = 0.68; 95% CI 0.58–0.81; p < 0.001]. The most common AEs were neutropenia (38%) and leukopenia (21%) [8]. The results from the RECOURSE trial were consistent with those observed earlier in the phase II Japanese population study [9].

Although the survival benefit in the RECOURSE trial was relatively small, a population of patients in the study group achieved a durable response (up to 78 mo.), suggesting a need for a biomarker to stratify the patients. The survival benefit was observed in the RECOURSE trial regardless of KRAS status, geographical region, sex, age, the Eastern Cooperative Oncology Group (ECOG) performance status scale, or primary tumor site. A recently published study discovered that codon-specific KRAS mutations predict OS in mCRC patients treated with FTD/TPI. The RAS codon G12 (KRAS^{G12}) mutation was not associated with better survival *versus*

placebo in the patients treated in the RECOURSE trial. On the contrary, patients with $KRAS^{G13}$ had better OS. $KRAS^{G12}$ mutation was detected in 28% and $KRAS^{G13}$ in 8% of studied mCRC patients. It was also discovered that patients with $KRAS^{G12}$ mutations were observed more frequently in the right-sided primary tumor group and were more recently diagnosed with metastatic disease. Compared to the $KRAS^{G12}$ population, $KRAS^{G13}$ patients showed a distinct mOS benefit in the FTD/TPI arm *vs.* the placebo arm (HR = 0.34; 95% CI 0.17–0.67; p = 0.0018). Reduced responsiveness to FTD/TPI therapy of the $KRAS^{G12}$ population was also confirmed *in vitro* with SW48 and Colo320 models. However, sensitivity to 5-FU in $KRAS^{G12}$ cells was not significantly reduced, and overall results showed that resistance to FTD caused by $KRAS^{G12}$ mutation was caused by DNA damage induced by FTD. These preclinical and clinical data on $KRAS^{G12}$ mutant mCRC patients show that this population of patients is unlikely to benefit from FTD/TPI treatment, so it is important to avoid unnecessary exposure to toxicity in this group of patients and rationalize use of resources in healthcare systems by selecting patients for FTD/TPI therapy in the future [10].

In the same year that FTD/TPI was approved, it was observed that patients who experienced chemotherapy-induced neutropenia (CIN) in an arbitrarily chosen month (CIN-1-month) as cutoff benefited from a delay in administering the next dose [11]. In the Kasi et al. [12] study, patients with CIN-1-month had significantly higher mOS (14.0 *vs.* 5.6 mo.; p < 0.0001) and median PFS (mPFS) (3.0 *vs.* 2.4 mo.; p = 0.0096). Chemotherapy-induced neutropenia -1-month was indicated to be an independent predictor of OS [12].

A Japanese retrospective study confirmed a significantly better disease control rate in patients with Common Toxicity Criteria (CTC) grade 3–4 neutropenia compared to CTC 1–2. Grade ≥ 3 neutropenia, which occurred during the first cycle of FTD/TPI, was a significant predictive factor for PFS, but not for OS; nevertheless, analysis showed a trend toward longer survival in patients who developed neutropenia. These data conclude that escalation of FTD/TPI doses according to neutropenia grade during the first cycle may benefit mCRC patients [13]. Other small retrospective analyses demonstrated that grade ≥ 3 neutropenia at the first treatment cycle showed a statistically positive impact on OS (p = 0.046) [14].

Another study, a single-arm phase II Japanese study, determined the efficacy of FTD/TPI in a geriatric population of patients aged 65 to 81 years (median age: 73 years; 21 men, 9 women) with advanced colorectal cancer. In this study, patients with a higher G8 score (geriatric assessment scale) had longer PFS than those with a lower G8 score (median 4.6 *vs.* 2.0 mo.; p = 0.047). Treatment-related AEs grade ≥ 3 were observed in 80% of all patients, with neutropenia (47%) and anemia (17%) being the most common. The study confirmed that FTD/TPI could be a well-tolerated and effective therapy option for elderly patients with advanced colorectal cancer [15].

Another retrospective study included 160 mCRC patients treated with FTD/TPI in the third or higher line therapy in Spain. The authors created valuable tools to prognosticate OS, which consists of ECOG 2 (1 point), multiple metastatic sites and carcinoembryonic antigen (CEA) > 10 ng/mL (2 points), platelet count > 350,000/μL, and alkaline phosphatase > 500 IU/L: 3 points. The mOS rates were as follows: ≤ 3 points (8.43; 95% CI 7.64–9.22), 3–6 (5.05; 95% CI 3.77–6.33), > 6 (1.90; 95% CI 0.95–2.86). The mOS rate in the total population was 7.64 mo. (95% CI 6.15–9.13) and mPFS was 2.75 mo. (95% CI 2.57–2.94 mo.). A comparison between clinical practice and RECOURSE showed similar mPFS (2.75 *vs.* 2.0 mo.) and mOS (7.64 *vs.* 7.1 mo.). The differences between real-life-study and RECOURSE were response rates (0.6% *vs.* 1.65% in RECOURSE) and disease control rate (DCR) (11.9% *vs.* 16.0% in RECOURSE). The safety profile was better in clinical analysis than in clinical trials [AEs: neutropenia (48.1% *vs.* 67%), anemia (41.9% *vs.* 77%), diarrhea (13.8% *vs.* 32%), thrombocytopenia (6.3% *vs.* 42%), except asthenia (48.1% in this study *vs.* 18% in RECOURSE)]. Also, the incidence of neutropenia was lower in this study (respectively 48.1% *vs.* 67% in RECOURSE and 23.12% *vs.* 38% in RECOURSE) (Tab. 1) [16].

Fernández Montes et al. [17] compared the results of the clinical trials with real-world analysis in mCRC patients treated with FTD/TPI. These data showed a slight biphasic pattern with an initial protective effect weakening if the next FTD/TPI dose was delayed. Besides, the authors achieved results comparable to RECOURSE endpoints such as (respectively) 8.1 mo. (95% CI 6.7–9.5 mo.) *vs.* 7.1 mo. mOS and 2.7 mo. (95% CI 2.6–2.9 mo.) *vs.* 2.0 mo. mPFS [17].

In various studies, primary tumor location (PTL) was indicated as an important prognostic and predictive factor in the first-line mCRC treatment. A phase II retrospective study, carried out in Japan by Nakajima et al., analyzed the clinical impact of PTL in 550 mCRC patients treated in later lines with regorafenib (REG, n = 223) or FTD/TPI (FTD/TPI, n = 327), who met the requirement of ECOG 0–2, were refractory/intolerant to fluoropyrimidines, oxaliplatin, irinotecan, angiogenesis inhibitors, anti-EGFR therapy and did not used REG or FTD/TPI earlier. If PTL was right-sided, mPFS tended to be longer in the FTD/TPI group than in the REG group (unadjusted

Table 1. Summary of the results of studies with trifluridine/tipiracil (FTD/TPI) in metastatic colorectal cancer patients

Name of the study	Phase	NCT	Study arm	Control arm	Number of enrolled patients	mOS study arm	mOS control arm	mPFS study arm	mPFS control arm	AE 3/4 study arm	AE 3/4 control arm
RECOURCE [9]	III	NCT01607957	FTD/TPI	Placebo with BSC	800	7.1 mo.	5.3 mo.	2.0 mo.	1.7 mo.	Neutropenia (38%), leukopenia (21%) Anemia (18%), thrombocytopenia (8%)	Anemia (3%), thrombocytopenia (< 1%)
SOLSTICE [24]	III	NCT03869892	FTD/TPI plus bevacizumab	Capecitabine plus bevacizumab	856	–	–	9.4 mo.	9.3 mo.	Neutropenia (66.4%)	Hand-foot syndrome (14.5%), neutropenia (2.3%)
SUNLIGHT [25]	III	NCT04737187	FTD/TPI plus bevacizumab	FTD/TPI	492	10.8 mo.	7.5 mo.	5.6 mo.	2.4 mo.	Neutropenia (43%), Anemia (6%), Asthenia (4%), Nausea (2%), Fatigue (1%), Diarrhea (1%), Decreased appetite (1%)	Neutropenia (32%), anemia (11%), asthenia (4%) fatigue (4%), nausea (2%), diarrhea (2%), decreased appetite (1%)
Signorelli C et al. [37]	IV	–	FTD/TPI to regorafenib	Regorafenib to FTD/TPI	49	20 mo.	27 mo.	8 mo.	9 mo.	Neutropenia (21.1%), Fatigue (9.6%), Anemia (5.7%), Leucopenia (1.9%),	Fatigue (15.3%), hand-foot skin reaction (11.5%), neutropenia (9.6%), anemia (3.8%), leucopenia (1.9%)
TALLISUR [35]	IV	EudraCT: 2017-000292-83	FTD/TPI	BSC	185	6.9 mo.	–	2.5 mo.	–	Neutropenia (18.4%), Leukopenia (8.1%), Anemia (7.0%), Diarrhea (4.3%)	–
Kwakman JJM et al. [32]	RL	–	FTD/TPI	–	136	5.4 mo.	–	2.1 mo.	–	Neutropenia (44.32%), Leukopenia (8.6%), Anemia (7.5%), Fatigue (7.5%)	–
Fernandez Montes A et al. [34]	RL	–	FTD/TPI	–	160	7.94 mo.	–	2.75 mo.	–	Neutropenia (23.1%), Asthenia (6.9%), Anemia (6.3%), Diarrhea (2.5%)	–
Jalali A et al. [33]	RL	–	FTD/TPI	–	107	7.1 mo	–	3.3 mo.	–	Neutropenia (12%), Febrile neutropenia (2.3%), Anemia (1.2%)	–

→

Table 1 cont. Summary of the results of studies with trifluridine/tipiracil (FTD/TPI) in metastatic colorectal cancer patients

Name of the study	Phase	NCT	Study arm	Control arm	Number of enrolled patients	mOS study arm	mOS control arm	mPFS study arm	mPFS control arm	AE 3/4 study arm	AE 3/4 control arm
Vitale P et al. [36]	RL	–	FTD/TPI to regorafenib	Regorafenib to FTD/TPI	140	mOS1: 7.6 mo. (FTD/TPI group) mOS2: 5.1 mo. (FTD/TPI group after switching to regorafenib)	mOS1 6.8 mo. (regorafenib group) mOS2: 4.5 mo. (regorafenib group after switching to FTD/TPI)	mPFS1: 3.0 mo. (FTD/TPI group) mPFS2: 2.0 mo. (FTD/TPI group after switching to regorafenib)	mPFS1: 2.5 mo. (regorafenib group) mPFS2: 2.6 mo. (regorafenib group after switching to FTD/TPI)	Neutropenia (16%), anemia (6%), fatigue (6%), febrile neutropenia (5%)	Hand-foot syndrome (27%), fatigue (16%), neutropenia (2%)

AE — adverse event; mo. — months; mOS — medias overall survival; mPFS — median progression-free survival; NCT — National Clinical Trials

HR = 0.71; 95% CI 0.48–1.05; p = 0.086) while in the case of left-sided PTL, results were similar between the two groups (unadjusted HR = 1.05; 95% CI 0.85–1.29; p = 0.64) [18].

Results of studies with FTD/TPI in polytherapy

The confirmed activity of FTD/TPI in monotherapy and positive preclinical studies with FTD/TPI in polytherapy support findings of the clinical trials that assess the combination of FTD/TPI with targeted therapy like bevacizumab (anti-VEGF monoclonal antibody), nivolumab (anti-PD-1) or trametinib [19–29].

The C-TASK FORCE phase I/II trial, which determined the dose of FTD/TPI in combination with bevacizumab, showed the activity and manageable safety profile in heavily pretreated mCRC patients [19]. The promising results of the C-TASK FORCE study supported those of the phase II randomized trial, which assessed the activity of FTD/TPI alone (n = 47) or with bevacizumab (n = 46) in this group of mCRC patients. The study showed that mPFS was 2.6 mo. (95% CI 1.6–3.5) in monotherapy *vs.* 4.6 mo. (95% CI 3.5–6.5) in the polytherapy arm (HR = 0.45; 95% CI 0.29–0.72; p = 0.0015). The mOS rate was 6.7 mo. in the FTD/TPI arm (95% CI 4.9–7.6) *vs.* 9.4 mo. (95% CI 7.6–10.7) in the FTD/TPI plus bevacizumab arm (HR = 0.55; 95% CI 0.32–0.94; p = 0.028). Analysis of the safety profile showed that grade 3 (G3) and grade 4 (G4) neutropenia occurred more frequently in the polytherapy group (G3 — 41%, G4 — 26%) than in monotherapy (G3 — 23%, G4 — 15%) [20].

TAS-CC3 was a phase II, single-arm study that assessed the activity of FTD/TPI (35 mg/m^2 on days 1–5 and 8–12 every 4 weeks) with bevacizumab (5 mg/kg every 2 weeks) in the third line of CRC therapy. The eligible patients had been previously pretreated with fluoropyrimidine, irinotecan, and oxaliplatin in first- and second-line therapy. The mPFS and mOS rates were 4.5 mo. and 9.3 mo. respectively. The most common AEs grade $\geq$ 3 were neutropenia (47%) and thrombocytopenia (12.5%) [21]. A similar phase II single-arm study was initiated to test the alternative regimen (FTD/TPI at a dose of 35 mg/m^2 twice daily on days 1–5 and 15–19 of every 28-day cycle plus bevacizumab 5.0 mg/kg on days 1 and 15), which aimed to reduce the hematological AEs. The mPFS and mOS rates were comparable to the previous study; however, the incidence of AEs was lower. The most common CTC grade 3 AEs were neutropenia (15.9%), hypertension (13.6%), fatigue (6.8%), and anemia (4.5%) [22].

TASCO 1 (NCT02743221), a phase II randomized open-label study, compared the efficacy and safety of FTD/TPI plus bevacizumab (TT-B arm, n = 77) *vs.* capecitabine plus bevacizumab (C-B arm, n = 76) in the population of patients with untreated unresectable mCRC who were ineligible for standard doublet regimens with oxaliplatin or irinotecan due to age, performance status, or comorbidities. The primary outcome measure was PFS, and the secondary were overall response rate (ORR), duration of response (DR), disease control rate (DCR), and OS. mPFS was 9.2 mo. (95% CI 7.6–11.6) in the TT-B group and 7.8 mo. (95% CI 5.5–10.1) in the C-B group. Median OS was 18 mo. (95% CI 15.2–N/A) and 16.2 mo. (95% CI 12.5–N/A). The DCR was higher in the TT-B group — 86% compared to 78% in the C-B group. The C-B groups). Frequencies of other hematological grade 3 AEs, respectively, in the TT-B and C-B groups, were: decreased neutrophil count, 18% *vs.* 1%, decreased white blood cell count (10% *vs.* 3%), anemia (10% *vs.* 0%), and febrile neutropenia (5% *vs.* 4%). There were also other $\geq$ 3 grade AEs in both TT-B and C-B groups, such as hypertension (13% *vs.* 5%, respectively), hand-foot syndrome (0% *vs.* 12%), diarrhea (1% *vs.* 8%), vomiting (5% *vs.* 1%), and nausea (3% *vs.* 0%). Additionally, there were two intestinal perforation deaths were considered to be related to bevacizumab (TT-B therapy), one renal failure related to capecitabine (C-B therapy), and one Stevens-Johnson syndrome-related death related to both drugs. The ORR for the TT-B and C-B groups was similar (34% *vs.* 30%). The Quality of Life Questionnaire core 29 (QLQ-CR29) and Quality of Life Questionnaire core 30 (QLQ-CR30) showed that patients' mental health did not change significantly during the study. Overall, this study showed that TT-B treatment may be a promising treatment option in first-line unresectable mCRC patients who were ineligible for intensive therapy, especially since the safety profile was specified as acceptable [23].

SOLSTICE (NCT03869892) was a phase III randomized open-label study based on the TASCO 1 trial, which compared TT-B and CC-B therapy in first-line treatment of mCRC patients who were not candidates for intensive therapy. In total, 856 patients with mCRC were stratified in terms of ECOG (0 *vs.* 1 *vs.* 2), primary tumor location (right *vs.* left), and non-eligibility for intensive therapy (due to clinical *vs.* non-clinical reasons). Patients were assigned to two main groups: one treated with FTD/TPI with bevacizumab (TT-B group, n = 426 patients) and the second group treated with capecitabine and bevacizumab (C-B group, n = 430 patients). The study's primary endpoint was PFS. The key secondary endpoint was OS. Median PFS was similar in both groups — 9.4 mo. (95% CI 9.1–10.9) for the TT-B group and 9.3 mo. (95% CI 8.9–9.8) for the C-B group. The HR for PFS was specified as 0.87 (95% CI 0.75–1.02;

p = 0.09). Both TT-B and C-B groups had grade ≥ 3 AEs such as neutropenia in 66.4% to 2.3% cases, respectively, and hand-foot syndrome in up to 14.5% of cases. Subgroup analysis showed better TT-B therapy outcomes in three subsets: RAS wild-type tumor patients, male patients, and patients with a neutrophil--lymphocyte ratio < 5. TT-B treatment was not superior to C-B in the studied population regarding PFS [20, 24].

In the SUNLIGHT phase III study, FTD/TPI plus bevacizumab demonstrated a notable advance in treating mCRC. The trial involved heavily pretreated patients and showed a significant extension in OS, with median OS of 10.8 in the polytherapy arm *vs.* 7.5 mo. for FTD/TPI alone (HR = 0.61; 95% CI 0.49–0.77; p < 0.001). Moreover, PFS was significantly improved, 5.6 *vs.* 2.4 mo. (HR = 0.44; 95% CI 0.36–0.54; p < 0.001), without a notable increase in grade ≥ 3 AEs. This study underscores the efficacy and manageable safety of FTD/TPI plus bevacizumab in refractory mCRC, offering a promising therapeutic option [25].

The studied FTD/TPI polytherapy regimens, which did not show clinical benefit in mCRC patients, included FTD/TPI + nivolumab (microsatellite-stable) [26] or trametinib (RAS- mutated, PIK3CA/PTEN wild-type) [27]. The multikinase inhibitor-regorafenib was studied in a phase I trial (n = 12) in combination with FTD/TPI. mPFS was 3.81 mo. (95% CI 1.51–5.29), and mOS was 11.1 mo. (95% CI 2.3–18.2). [28] In China, a patient treated with FTD/TPI and anlotinib (multitarget tyrosine kinase inhibitor) in the third line of treatment (RAS/BRAF wild-type, pMMR/non-MSI-H) achieved PFS of 20 mo. [29].

The FIRE-8 study (NCT05007132) is an ongoing prospective randomized open-label multicenter phase II trial that evaluates the efficacy of FTD/TPI in combination with panitumumab or bevacizumab in first-line treatment of patients with RAS wild-type mCRC. The primary outcome measure is the ORR defined according to response evaluation criteria in solid tumors 1.1 (RECIST 1.1). The secondary outcome measures are OS and PFS, depth of response (DpR), and early tumor shrinkage (ETS). It is planned to assess the patient's quality of life (QoL) with the EQ-5D-5L questionnaires [30].

Phase IV and real-life data

Several real-life studies in different countries also examined the drug's efficacy. One of the biggest analyses (n = 717) was done in Canada. The authors assessed the relationships between the duration of treatment and the reason for treatment discontinuation. In the study population, only 28% of patients required dose reduction. Age, sex, RAS mutation status, or prior therapies did not affect therapy duration. Interestingly, patients pretreated with oxaliplatin-based chemotherapy were more likely to discontinue treatment [31].

Also, data from the Netherlands confirmed that FTD/TPI treatment is feasible and safe in daily clinical practice. The authors reviewed the medical records of 136 patients from 17 cancer centers treated with FTD/TPI according to RECOURSE eligibility criteria. Forty-three patients (32%) did not meet the RECOURSE eligibility criteria due to the ECOG scale (9% of patients were ECOG 2) or treatment history. Median PFS was 2.1 mo. (95% CI 1.8–2.3), and median OS was 5.4 mo. (95% CI 4.0–6.9). According to the RECOURSE results neutropenia was the most frequent AE; however, fewer grade ≥ 3 events (69% *vs.* 44%) and serious events (30% *vs.* 4%) were reported. A greater proportion of patients (14% *vs.* 23%) had dose reductions, while discontinuation due to AEs was the same (4%). The favorable prognostic factors for OS in multivariate analysis were ECOG 0–1, KRAS wild-type tumor, lower count of serum white blood cells (WBC), lower levels of lactate dehydrogenase (LDH), and alkaline phosphatase (ALP) [32].

Moreover, data from an Australian population of patients (n = 107) were consistent with the RECOURSE trial. Median PFS was 3.3 mo. *vs.* 2 mo. (RECOURSE). Median OS was 7.1 mo. in both trials. The authors suggested that the better PFS results might have been caused by less frequent imaging and not too rigorous application of RECIST criteria [33].

A similar analysis was performed in Spain. That retrospective study included mCRC 160 patients treated with FTD/TPI who had been previously treated or had not been considered candidates for treatment with other available therapies. In the study, median PFS was 2.75 mo. (95% CI 2.57–2.94), and median OS was 7.64 mo. (95% CI 6.15–9.13). Patients with ECOG 2 had worse mOS (4.0 mo.) than patients with ECOG 0-1 (8.2 mo.; p < 0.001). Patients with pulmonary metastases in a unique location had longer mOS *vs.* compared to patients with multifocal cancers (11.7 mo. *vs.* 6.8 mo.; p = 0.015), neutropenia as an AE (10.5 mo. *vs.* 5.0 mo.; p < 0.001), those who received dose reduction (10.5 mo. *vs.* 6.2 mo. without dose reduction; p = 0.002), and those with the neutrophil to lymphocyte ratio (NLR) < 5 (7.9 mo. for NLR < 5 *vs.* 5.5 mo. for NLR ≥ 5; p = 0.045). In that study, the most frequently reported CTC grade ≥3 AE was neutropenia (38 %). According to the multivariate analysis, multiple metastatic sites, platelet count > 350,000/μL, and CEA levels > 10 ng/mL were indicated as additional worse prognostic factors in relation to the data from the Dutch study [34].

TALLISUR was a prospective phase IV study in which patients underwent FTD/TPI therapy (n = 185) or best supportive care (BSC, n = 9), depending on

patient choice. Median OS in patients treated with FTD/TPI was 6.9 mo. (95% CI 6.1–8.2), and mPFS was 2.5 mo. (95% CI 2.1–2.9). As in previous studies, the most common AEs were neutropenia (27.6%) and anemia (22.7%). That study assessed the health-related quality of life (HRQoL) with the QLQ-C30 Version 3.0 questionnaire designed by the European Organization for Research and Treatment of Cancer (EORTC). Considering the extended time to complete the questionnaires, 67.0% (95% CI 57.3–75.7%) of patients reported a stabilized or improved HRQoL score [35].

Another study, a phase IV retrospective multi-institutional cohort real-life study, carried out between 2018 and 2020, compared the efficacy of treatment and safety in chemo-refractory mCRC patients treated with FTD/TPI (n = 76) or regorafenib (n = 64). After progression, 37% of regorafenib-treated patients switched to FTD/TPI treatment, 6% continued treatment, 11% switched to other therapies, and 45% switched to BSC. On the other hand, 45% of patients treated with FTD/TPI switched to secondary treatment with regorafenib, 8% continued treatment, 9% switched to other therapies, and 38% switched to BSC. Disease control was achieved in 22.4% of patients in the FTD/TPI group (n = 17) and 12.5% in the regorafenib group (n = 8). In terms of efficacy, PFS and OS rates were similar in both treatment groups for primary and secondary treatments with a slight advantage of the FTD/TPI group in all cases, except higher PFS after switching to FTD/TPI, when regorafenib was used first. Median PFS was longer in patients with RAS wild-type tumors than in patients with RAS mutants. The results of this trial seem to be a solid base for similar future studies and provide initial information about the use of FTD/TPI and regorafenib in patients with specified mCRC types necessary to provide the best possible treatment [36].

Signorelli et al. [37], in a phase IV study, presented outcomes for 49 patients who were treated with regorafenib-FTD/TPI or FTD/TPI-regorafenib sequence of treatment. mOS in patients in the FTD/TPI-regorafenib arm was 20 mo. (95% CI 16.7–23.3) while in the reversed sequence arm it was 27 mo. (95% CI 17.8–36.2). In the FTD/TPI-to-regorafenib arm, mPFS was 8 mo. (95% CI 6–10), and in the regorafenib-to-FTD/TPI arm, it was 9 mo. (95% CI 7.2–10.8). After 2 years of treatment with FTD/TPI-to-regorafenib, 43.6% of patients were still alive, contrary to 54.5% in the arm with the regorafenib-to-FTD/TPI treatment sequence. In the study group, mPFS was higher in patients > 70 years (11 *vs.* 8 mo.) and with ECOG 0 or 1 (9 *vs.* 7 mo.). In RAS wild-type or mutant mCRC patients, mPFS was higher in the regorafenib-to-FTD/TPI treatment sequence (9 *vs.* 7 mo.). Median PFS depended on the primary location of the tumor (rectum — 11 mo., left colon — 9 mo., right colon — 8mo.). The ORR was 6.9% in the FTD/TPI-to-regorafenib sequence and 5.0% in the regorafenib-to-FTD/TPI treatment sequence. The DCR was, respectively, 24.1% and 45.0% in those groups. The whole study showed possible benefits of using each sequence depending on patients' mCRC type, disease advancement, and tumor's primary location [37].

Conclusions

Clinical trials and real-life studies confirmed the efficacy of FTD/TPI in mCRC patients in terms of OS, PFS, and HRQoL [31–37]. Several real-life studies confirmed the activity of the drug and assessed the potential prognostic factors in patients treated with FTD/TPI. It was shown that the WBC, platelet count, LDH, ALP, CEA, chemotherapy-induced neutropenia, and multiple metastatic sites were additional prognostic factors in the population of patients treated with FTD/TPI [32, 34]. Recently, $KRAS^{G12}$ mutation was associated with decreased FTD/TPI therapy benefits [37]. Also, the localization of primary tumors may be a prognostic factor for FTD/TPI treatment. PFS tended to be longer in patients with right-sided tumors treated with FTD/TPI compared to regorafenib [18]. Malik et al. [38] also showed that sarcopenia is a negative prognostic factor in mCRC patients treated with FTD/TPI. Data on prognostic and predictive factors like KRAS mutation status or primary tumor location come mainly from retrospective analyses. It is crucial to emphasize that while these factors may hold significance and suggest certain trends, they do not present sufficient data for altering established clinical practice guidelines.

In addition, FTD/TPI is also an effective drug in the population of geriatric patients [15]. A study by Cicero et al. [39] showed that FTD/TPI was well tolerated and safe in mCRC patients > 70 years. Trifluridine/tipiracil may represent an important therapeutic alternative with manageable and relatively limited toxicity in heavily treated elderly patients [39]. One possible option to increase the FTD/TPI activity is to combine it with anti-EGFR, antiangiogenic drugs, chemotherapy (e.g., oxaliplatin), or other drugs. In mouse models, a phase II study recently showed the promising activity of fruquintinib, a kinase inhibitor of vascular endothelial growth factor receptor 1–3 [40]. Trifluridine and tipiracil combined with Yttrium-90 (^{90}Y) radioembolization (NCT02602327) have an activity in liver-dominant mCRC [41].

Despite the promising effects of mCRC treatment, there is a need for new therapies. One of the possible pathways to improve mCRC patient outcomes is precision genomics-based chemotherapy, which recently proved its importance in the selection process of FTD/TPI patients [10].

Article Information and Declarations

Author contributions

P.S.M., M.J.: concept and design, literature review, manuscript preparation, preparation of figures; D.S., T.K.: critical revision of the manuscript, supervision.

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Conflict of interest

Authors declares no conflict of interest.

Supplementary material

None.

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