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Real-world use of trifluridine/tipiracil for patients with metastatic colorectal cancer in Canada

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ABSTRACT

Background Outcomes for patients with metastatic colorectal cancer (mCRC) are improving with the introduction of new treatments. Treatment for patients who are still fit after failure of all available therapies represents a significant unmet need. In the present study, we analyzed real-world treatment patterns for patients enrolled in Health Canada's trifluridine/tipiracil (FTD/TPI) Special Access Program (SAP) and Taiho Pharma Canada's Patient Support Program (PSP).

Methods Demographic information and clinical treatment data were collected from adults with mCRC who were previously treated with, or were not candidates for, available therapies and who were enrolled in the SAP and PSP. For all patients, FTD/TPI treatment status, discontinuation reasons, and prior therapies were examined.

Results The analysis included 717 Canadian patients enrolled in the FTD/TPI SAP and PSP from September 2017 to October 2018. In that cohort, 59.7% were men, median age was 65 years, and median duration of therapy was 77 days (25%–75% interquartile range: 43–106 days). Of treated patients, 67.1% maintained the same dose for the duration of therapy; 28.0% had a dose reduction.

On multivariable analysis, duration of therapy was not influenced by sex, age, province, *RAS* mutation status, or prior therapies. However, prior oxaliplatin-based chemotherapy (CAPOX or FOLFOX) appeared to be associated with higher rates of discontinuation because of death or disease progression.

Conclusions In advanced mCRC, FTD/TPI is a well-tolerated therapy. The large number of patients enrolled in the access programs within a short period of time is reflective of major clinical need in this area, with many patients being eligible and interested in pursuing treatment in the refractory setting.

Key Words Colorectal cancer, compassionate use programs, compassionate access, patient support programs, SAP programs, Canada, trifluridine/tipiracil, FTD/TPI, TAS-102

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BACKGROUND

Colorectal cancer is the 2nd most common cancer in Canada, with approximately 26,800 new cases being diagnosed and 9400 deaths occurring in 2017, per estimates from the Canadian Cancer Society[1]. Treatment for patients with metastatic colorectal cancer (mCRC) is generally palliative and consists of systemic therapies that include chemotherapeutic drugs such as fluoropyrimidines[2–4], irinotecan[5,6], and oxaliplatin[7]; angiogenesis inhibitors such as bevacizumab[8–10]; and for select patients, monoclonal antibodies such as cetuximab[8] or panitumumab[11]. Regorafenib, a small-molecule multi-kinase inhibitor, has shown efficacy in patients with refractory disease[12], but it is not publicly funded in Canada.

Although the optimal treatment combinations and sequencing of the foregoing drugs are still being determined,

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the new agents available in Canada have significantly improved outcomes for patients with mCRC to more than 33 months[13]. But despite the optimism, treatment for patients who are still fit after standard lines of therapy have failed represents a significant unmet need in the clinical management of mCRC. Treatment options in that setting are limited, and no large real-world studies are assessing outcomes of newer agents in clinical practice.

Trifluridine/tipiracil (FTD/TPI) is a novel oral combination chemotherapeutic agent that was recently introduced to the armamentarium in Canada for the treatment of refractory mCRC after existing chemotherapeutics and targeted therapeutics have failed. It combines two pharmaceutical components, specifically FTD, a nucleoside analog, and TPI, a thymidine phosphorylase inhibitor. Incorporation of FTD into DNA results in DNA dysfunction, and prevention by TPI of the rapid metabolism of FTD increases FTD bioavailability[14].

The efficacy and safety of FTD/TPI was demonstrated in the phase III RECOURSE study, which assessed the combination in a global population, randomizing 800 patients in a 2:1 ratio to receive FTD/TPI or placebo[15]. The primary endpoint of RECOURSE—an improvement in overall survival—was met, reaching 7.2 months with FTD/TPI [95% confidence interval (CI): 6.6 months to 7.8 months] compared with 5.2 months with placebo (95% CI: 4.6 months to 5.9 months; hazard ratio: 0.7; 95% CI: 0.6 to 0.8; $p < 0.001$)[16]. Adverse events associated with FTD/TPI were acceptable and manageable with dose delays and dose reductions. A subgroup analysis of the RECOURSE trial demonstrated that FTD/TPI was effective in all subgroups, regardless of age, geographic origin, or *KRAS* status[17]. As a result of RECOURSE, FTD/TPI is now registered in more than 50 countries (including the United States, Japan, and many in the European Union) for the treatment of patients with mCRC who have progressed on standard therapies. The efficacy and safety of FTD/TPI has been confirmed in real-world patients who have accessed the treatment through expanded access, compassionate access, and patient support programs in other countries. However, because the drug was approved in Canada only in 2018, a similar evaluation in Canada has not yet been conducted[18–27].

Quebec is the first and only province to have made FTD/TPI accessible with reimbursement under the Régie de l'assurance maladie du Québec. Despite significant positive clinical recommendations, the pan-Canadian Oncology Drug Review in July 2019 issued a negative initial recommendation for Lonsurf (FTD/TPI from Taiho Pharmaceutical, Princeton, NJ, U.S.A.). The drug is therefore not accessible with reimbursement in any other province in the country. It was available through Health Canada's Special Access Program (SAP) from 1 September 2017 to 6 March 2018, and since Health Canada's approval of FTD/TPI on 6 March 2018, it has been available through the Taiho Pharma Canada (TCAN) patient support program (PSP). To date, more than 700 Canadian patients have applied for the drug through that program over a 12-month period, many of whom have accessed it for the treatment of their mCRC. In this real-world evidence study, we retrospectively evaluated treatment patterns and characteristics for Canadian mCRC patients who progressed on prior systemic chemotherapy and targeted therapy regimens for metastatic disease and who enrolled in the Canadian FTD/TPI SAP and TCAN PSP.

The goals of the study were to characterize the current treatment landscape, define the applicability of emerging trial outcomes to Canadian practice, identify local evidence and treatment gaps, and define areas of unmet clinical need to inform optimal patient care.

METHODS

SAP/PSP Enrolment and FTD/TPI Treatment

Patients in this analysis include those who were enrolled to receive FTD/TPI through Health Canada's SAP from 1 September 2017 to 6 March 2018 or through the TCAN PSP (called Conexus) from 6 March 2018 to 30 September 2018. The patients were adults with refractory mCRC who had progressed on, or were not candidates for, available therapies (fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, biologic agents targeting the vascular endothelial growth factor, and if *RAS* wild-type, agents targeting the epidermal growth factor receptor[28]. Extended *RAS* testing is standard at most centres in Canada, and so testing was conducted per centre protocol. Patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 were permitted to receive the drug through the SAP; those who enrolled in the PSP had to have an ECOG PS of 0 or 1.

Notably, the TCAN PSP included patients who accessed treatment through the Health Canada SAP and other programs, including compassionate access, bridging, and private and public funding. The definitions of "compassionate use" or "expanded access" differ by jurisdiction, and so this article refers to those programs using their chosen nomenclature.

The treating physician initiated the FTD/TPI treatment process by referring the patient using an enrolment form faxed to the PSP. As part of program enrolment, patients signed a consent form agreeing to their de-identified data being used for research purposes. Once a patient was successfully enrolled, the PSP shipped the FTD/TPI directly to the patient's residence. For each treatment, dosing was based on body surface area, and patients received FTD/TPI at a starting dose of 35 mg/m^2 (twice daily) per the treating physician's discretion[15,28]. The medication was administered orally 1 hour after the morning and evening meals, on days 1–5 and days 8–12 of each 28-day cycle. A complete blood cell count was obtained before initiation of therapy and as needed for monitoring, but at a minimum, before each treatment cycle. The treatment cycle was repeated every 4 weeks as long as benefit was observed or until unacceptable toxicity occurred.

The start of each treatment cycle was interrupted or delayed if the patient's absolute neutrophil count was less than 1.5×10^9/L or platelet count was less than 75×10^9/L, or if a grade 3 or 4 nonhematologic toxicity from prior therapy or a prior FTD/TPI cycle remained unresolved. Dose reductions occurred in 5 mg/m^2 per-dose decrements, according to the dose interruption, resumption, and reduction criteria specified in the product monograph[28]. A maximum of 3 dose reductions were permitted to a minimum dose of

20 mg/m^2 twice daily. Dose escalation was not permitted after the dose had been reduced.

Study Oversight and Data Collection

The authors (HHS, CBM, WYC) initiated this study by discussing study details in-person with TCAN personnel and subsequently sending a formal request to TCAN to make use of the SAP and Conexus PSP data. Approval was obtained from both TCAN and the University of Calgary Research Ethics Board. The study complies with the ethics standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Study outcomes of interest included the duration of FTD/TPI treatment in Canadian mCRC patients, reasons for treatment discontinuation (if available), and all prior mCRC therapies.

Bayshore HealthCare provided relevant data points that were collected as part of patient enrolment, including demographic and clinical treatment data. The data included all de-identified patients enrolled in the SAP and the PSP up to and including 30 September 2018; the date for data cut-off (where clinical treatment data would have been collected) was 31 October 2018. Demographic data included sex, age, province, extended *RAS* status, funding mechanisms or reimbursement, and prior lines of mCRC therapy. Clinical treatment data included FTD/TPI treatment status, dates of referral, PSP enrolment and first treatment, reasons for FTD/TPI discontinuation, and FTD/TPI dose reductions. Options for FTD/TPI treatment status consisted of discontinued, on treatment, never received treatment, or pending treatment. Reasons for treatment discontinuation consisted of toxicity, death, disease progression, treating physician's decision, withdrawal of patient consent, and other.

Data Analysis Plan

Exploratory retrospective analyses were conducted to delineate the relationships between treatment patterns and various patient and disease characteristics. Baseline characteristics are summarized using descriptive statistics. Continuous variables are presented as medians with 25%–75% interquartile range (IQR) or means with standard deviation; categorical variables are expressed as frequencies and percentages. In addition, patient characteristics were compared by province using the Mann–Whitney *U*-test for continuous variables and the chi-square or Fisher exact test for categorical variables, as appropriate. Finally, multivariate logistic regression analyses were conducted to explore the relationships of treatment duration and reason for treatment discontinuation with various clinical characteristics, while controlling for potentially confounding covariates, including age and sex.

The "referral to therapy time" is the interval between the date that the physician faxed the patient enrolment form and the date of therapy initiation. The "days to start therapy" is the interval between the date that the patient was enrolled in the PSP and the date that the patient initiated therapy. Because at least 2 cycles are required to calculate a dose difference, dose increase and decrease data were collected only for patients who received at least 2 cycles of FTD/TPI.

Role of the Funding Source

This real-world treatment study was supported by TCAN, who also contributed to study design, data collection, and data interpretation. The authors had full access to all of the data in the study, and all authors had responsibility for the final decision to submit the work for publication.

RESULTS

Patient and Disease Characteristics

The analysis included 717 Canadian patients: 88 who were enrolled in the Health Canada SAP from 1 September 2017 to 6 March 2018, and 629 who were enrolled in the SAP or the PSP between 6 March 2018 and 30 September 2018. Table I shows the sociodemographic, clinical, and treatment characteristics of those patients at the time of analysis. In this cohort, 59.7% of the patients (n = 428) were men, median age was 65 years, and 49.2% were 64 years of age or younger (n = 353).

Patients were distributed nationwide as follows: 15.3% of patients were from British Columbia; 14.8%, from Alberta, Saskatchewan, or Manitoba; 30.0%, from Ontario; 31.2%, from Quebec; 8.7%, from New Brunswick, Newfoundland and Labrador, Nova Scotia, or Prince Edward Island; and more than 1% each from the Yukon Territory and the Northwest Territories. Patients in the Prairie provinces (Alberta, Saskatchewan, Manitoba) and the Maritime provinces (New Brunswick, Newfoundland and Labrador, Nova Scotia, Prince Edward Island) were grouped based on sample size and geography. The very small sample sizes in the Yukon Territory and Northwest Territories led to the exclusion of those patients from all further analyses.

Extended *RAS* mutation status was captured for 98.6% of the patients, with 60.0% of the patients overall (n = 430) being classified as *RAS* mutant; 38.6% (n = 277), as *RAS* wild-type; and 1.4% (n = 10), as *RAS* status unknown. The high rate of *RAS* mutation testing is clinically meaningful and conforms to the published recommendations by expert Canadian groups[29–31].

Therapy reimbursement for each patient was described. Currently, FTD/TPI is publicly reimbursed only in Quebec; it is not accessible with public reimbursement in any other province in the country. Slightly more than one third of the patients (n = 249, 34.7%) received the drug through a compassionate access program paid for by TCAN, and another 30.1% (n = 216) were on a bridging program, in which TCAN paid for the drug while the patient's own insurance or the Régie de l'assurance maladie du Québec confirmed eligibility. Private insurance paid for the drug for 17.7% of the patients (n = 127), and in Quebec only, the drug was covered completely by the Régie de l'assurance maladie du Québec [15.5% of the patients (n = 111) received the drug through that mechanism]. The reimbursement method was undocumented for a small proportion of patients (2%, n = 14).

Most patients received a fluorouracil-based chemotherapy regimen, including FOLFIRI [leucovorin–fluorouracil–irinotecan (82.8%, n = 594)], FOLFOX [leucovorin–fluorouracil–oxaliplatin (80.6%, n = 578)], fluorouracil alone (3.5%, n = 25), FOLFOXIRI [leucovorin–fluorouracil–oxaliplatin–irinotecan (0.7%, n = 5)], capecitabine (11%,

n = 81), or CAPOX [capecitabine–oxaliplatin (7.7%, *n* = 55)]. Two thirds of patients were treated with an vascular endothelial growth factor inhibitor: either bevacizumab (66.4%, *n* = 476) or aflibercept (0.1%, *n* = 1). Almost one third received an epidermal growth factor receptor inhibitor: either panitumumab (25.5%, *n* = 183) or cetuximab (5.9%, *n* = 42). A very small proportion of patients had been pretreated with regorafenib (13.7%, *n* = 98) or irinotecan alone (10.7%, *n* = 77).

Therapy with FTD/TPI

Patients were classified by their treatment status at 30 September 2018 (Table I, Figure 1). Of the 717 patients analyzed, a small number (10.2%, *n* = 73) never received FTD/TPI, despite enrolment. At the time of analysis, treatment was pending for 6.6% of the patients (*n* = 47), and 32.8% (*n* = 235) were still on treatment. The main reasons for discontinuation in the 362 patients who had discontinued treatment were disease progression (51.9%, *n* = 188), treating physician decision (19.3%, *n* = 70), or death (13.0%, *n* = 47). Only 4.4% of the patients (*n* = 16) discontinued treatment because of toxicity. An additional 4.4% of the patients (*n* = 16) discontinued treatment because of withdrawal of consent; 6.9% (*n* = 25) discontinued treatment for other reasons that were not described.

Median duration of FTD/TPI therapy was 77 days (IQR: 43–106 days); the mean duration was 80 ± 48.7 days. That analysis includes the 341 patients with available therapy start and stop dates; it does not include the 235 patients who were still on therapy at data cut-off. The time to therapy start was short, being a median of 10 days (IQR: 5–15 days) from PSP enrolment to first treatment. Most patients who enrolled in the PSP received the drug within 3 weeks of applying to the program. The duration from referral to receiving the drug was 14 days (IQR: 7–21 days).

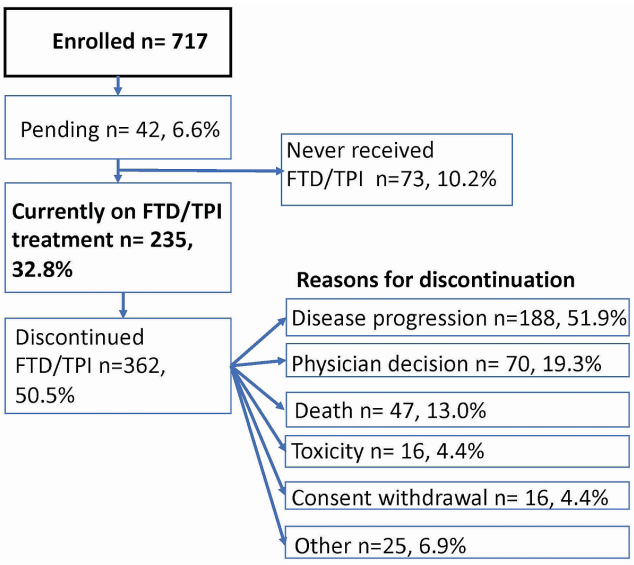

FIGURE 1 Patient flow diagram. Includes all 717 patients who received trifluridine/tipiracil (FTD/TPI) through the Heath Canada Special Access Program or Taiho Pharma Canada's Conexus Patient Support Program as of September 2018.

Median initial FTD/TPI dose was 60 mg twice daily (IQR: 55–70 mg), which was determined for 385 of the 422 patients who received at least 2 cycles with a reported first dose. Although most patients analyzed (283 of 422, 67.1%) maintained the same dose for the entire duration of therapy, a small proportion of the patients (118 of 422, 28.0%) had a dose reduction, with a mean percentage drop in the dose of 18.2% (IQR: 10.0%–25.0%). Dose delays were observed in 17.0% of patients (*n* = 106).

Predictors for FTD/TPI Duration and Discontinuation

Table II shows the multivariable logistic regression analyses of factors predicting duration of therapy (<2 months vs. ≥2 months). The analysis included 338 patients who discontinued therapy for any reason and for whom therapy start and stop dates were available. None of the factors analyzed—including sex, age, province, *RAS* mutation status, or prior therapies—were associated with duration of therapy.

Table III shows the multivariable logistic regression analysis of factors predicting discontinuation of FTD/TPI, which includes the 360 patients who had been taking FTD/TPI and discontinued therapy for any reason. The only factor that was significant in predicting discontinuation of FTD/TPI because of death or disease progression was prior receipt of oxaliplatin-based chemotherapy, either CAPOX (odds ratio: 3.1; 95% CI: 1.2 to 12.2; $p = 0.03$) or FOLFOX (odds ratio: 3.1; 95% CI: 1.1 to 8.6; $p = 0.03$). Table III omits FOLFOXIRI and ziv-aflibercept because only a few patients received those regimens.

Differences Between Canadian Provinces

Associations between provinces and other factors were analyzed to describe how the patterns of practice in mCRC differ by province (Table IV). Some statistically significant differences in patient status and prior therapies were evident between the provinces, but patient time on FTD/TPI (2–3 months) did not differ significantly between provinces, nor did *RAS* status or reasons for discontinuation.

As Table IV shows, significant differences in patient status were evident between the provinces, including variations in prior treatments received and differences in the proportion of patients who continued to receive FTD/TPI at the time of analysis compared with patients who discontinued the medication or who never received treatment. In addition, patients in the various provinces received prior therapies in significantly different proportions. Notable trends included receipt of FOLFOX and FOLFIRI by a higher proportion of patients in Quebec, Ontario, and the Maritime provinces than of those in British Columbia and the Prairie provinces. Meanwhile, CAPOX and irinotecan were received by a higher proportion of patients in British Columbia and the Prairie provinces than of those in Quebec, Ontario, and the Maritime provinces. Higher proportions of patients in Quebec than in other provinces received prior bevacizumab and regorafenib; the use of regorafenib was particularly notable, with patients in Quebec receiving regorafenib at 4 times the rate of patients in British Columbia and the Prairie provinces. Finally, patients in the Prairie provinces received fluorouracil alone in highest proportion; no patients in the Maritime provinces received that drug alone.

TABLE 1 Demographic and clinical characteristics of 717 patients enrolled in Health Canada's Special Access Program and Taiho Pharma Canada's Patient Support Program for trifluridine/tipiracil (FTD/TPI) at the time of the study analysis

Variable	Value	
	(*n*)	(%)
Demographics		
Sex		
Women	289	40.3
Men	428	59.7
Age group		
≤64 Years	353	49.2
≥65 years	364	50.8
Geographic location		
Prairie provinces[a]	106	14.8
British Columbia	109	15.2
Maritime provinces[b]	62	8.7
Ontario	214	29.9
Quebec	223	31.1
Yukon Territory	1	0.1
Northwest Territories	2	0.3
Extended *RAS* status		
Mutant	430	60.0
Wild-type	277	38.6
Unknown	10	1.4
Reimbursement type		
Compassionate	249	34.7
Bridging	216	30.1
Private	127	17.7
Public	111	15.5
Unknown	14	2.0
Prior lines of therapy[c]		
FOLFIRI	628	87.6
FOLFOX	606	84.5
Fluorouracil alone	27	3.8
FOLFOXIRI	6	0.8
Bevacizumab	501	69.9
EGFR inhibitor	240	33.5
Panitumumab	195	27.2
Cetuximab	45	6.3
Capecitabine	88	12.3
CAPOX	61	8.5
Irinotecan	85	11.9
Regorafenib	104	14.5
Ziv-aflibercept	1	0.1
FTP/TPI treatment status		
Discontinued	362	50.5
Receiving	235	32.8
Never received	73	10.2
Pending	47	6.6
Reasons for ...		
Never having received FTP/TPI[d]		
Death	25	34.2
Declining health	15	20.6
Physician decision	13	17.8
Withdrawal of patient consent	12	16.4
Lost to follow up	8	11.0
Treatment discontinuation[e]		
Toxicity	16	4.4
Death	47	13.0
Disease progression	188	51.9
Treating physician's decision	70	19.3
Withdrawal of patient consent	16	4.4
Other	25	6.9
FTD/TPI treatment data		
Therapy duration (days)[f]		
Median	77 (11 weeks)	
IQR	43–106	
Mean	80±48.7	
Time to therapy start (days)[g]		
Median	10	
IQR	5–15	
Time from referral to therapy (days)[g]		
Median	14	
IQR	7–21	
First dose (mg)[h]		
Median	60	
IQR	55–70	
Dose maintained for duration of therapy[i]	283	67.1
Dose reduction[i]	118	28.0
Drop in dose (%)[j]		
Median	18.2	
IQR	10–25	
Dose delay	106	17.0

[a] Alberta, Saskatchewan, Manitoba.
[b] New Brunswick, Newfoundland and Labrador, Nova Scotia, Prince Edward Island.
[c] Denominator includes all 717 patients.
[d] Includes 73 patients.
[e] Includes 362 patients.
[f] Includes 341 patients.
[g] Includes 586 patients.
[h] Includes 539 patients.
[i] Includes 422 patients.
[j] Includes 118 patients.

FOLFIRI = leucovorin–fluorouracil–irinotecan; FOLFOX = leucovorin–fluorouracil–oxaliplatin; FOLFOXIRI = leucovorin–fluorouracil–oxaliplatin–irinotecan; EGFR = epidermal growth factor receptor; CAPOX = capecitabine–oxaliplatin; IQR = interquartile range.

TABLE II Multivariable logistic regression, factors predicting a duration of trifluridine/tipiracil therapy of 2 months or more[a]

Factor	OR	95% CI	*p* Value
Age group			
≤64 Years	1		
≥65 Years	1.17	0.63 to 2.18	0.61
Sex			
Women	1		
Men	0.93	0.50 to 1.72	0.81
Geographic location			
Prairie provinces[b]	1		
British Columbia	0.46	0.15 to 1.40	0.17
Maritime provinces	0.49	0.12 to 2.03	0.32
Ontario	0.61	0.21 to 1.78	0.37
Quebec	0.71	0.25 to 2.00	0.52
KRAS status			
Mutant	1		
Wild-type	1.12	0.34 to 3.70	0.85
Fluorouracil–leucovorin			
No	1		
Yes	1.00	0.24 to 4.10	1.00
Bevacizumab			
No	1		
Yes	0.95	0.46 to 1.98	0.89
Capecitabine			
No	1		
Yes	0.54	0.22 to 1.33	0.18
CAPOX			
No	1		
Yes	2.70	0.63 to 11.56	0.18
Cetuximab			
No	1		
Yes	0.97	0.17 to 5.57	0.98
FOLFIRI			
No	1		
Yes	0.56	0.14 to 2.17	0.40
FOLFOX			
No	1		
Yes	3.02	0.92 to 9.87	0.07
Irinotecan			
No	1		
Yes	1.14	0.36 to 3.64	0.82
Panitumumab			
No	1		
Yes	0.88	0.26 to 3.02	0.84
Regorafenib			
No	1		
Yes	0.77	0.37 to 1.59	0.47

[a] Includes the 338 patients who discontinued therapy for any reason, who had available therapy start and stop dates, with non-missing covariate values.
[b] Alberta, Saskatchewan, Manitoba.
[c] New Brunswick, Newfoundland and Labrador, Nova Scotia, Prince Edward Island.
OR = odds ratio; CI =confidence interval; CAPOX = capecitabine–oxaliplatin; FOLFIRI = leucovorin–fluorouracil–irinotecan; FOLFOX = leucovorin–fluorouracil–oxaliplatin.

DISCUSSION

This retrospective analysis of real-world experience with FTD/TPI in refractory mCRC used pan-Canadian data from Health Canada's SAP and the TCAN PSP, which provided access to FTD/TPI while collecting data about the feasibility, use, and toxicity of the drug. The program enrolled 717 Canadian patients in a relatively short period, demonstrating that the clinical need for effective therapies among heavily pretreated mCRC patients is urgent and that many patients are eligible and interested in pursuing this new treatment once all other available lines of therapy are exhausted. A well-tolerated and feasible therapy, FTD/TPI is discontinued mainly for disease progression or death, and not for toxicity. In addition, our study showcased the important role of PSPs in facilitating public access to novel or non-funded therapies. Importantly, it also demonstrated that data from PSPs can be a useful platform for generating real-world evidence within a relatively short period. The Canadian population included in this real-world study was consistent with the populations in RECOURSE[15], other compassionate use programs (CUPS), and prior reports of Canadian patients with refractory mCRC[18–27] in terms of sex, age, *RAS* status, and high burden of previous therapies.

In the present study, median duration on treatment was 77 days (11 weeks), with a mean of 80 days. That duration was slightly longer than had been observed for patients receiving FTD/TPI in RECOURSE (median: 6.7 weeks; range: 0.1–78.0 weeks; mean: 12.7 ± 12.0 weeks), but consistent with other reports (2.8 months; range: 1–12.1 months[23]; 9.7 weeks[26]; and 2.5 cycles[21]). Although the duration-of-therapy data were not robust enough to draw any definitive conclusions about response or survival, they do represent real-world evidence of tolerability and feasibility of administration.

TABLE III Multivariable logistic regression, factors predicting discontinuation of trifluridine/tipiracil because of disease progression or death

Factor	OR	95% CI	*p* Value[b]
Age group			
≤64 Years	1		
≥65 Years	0.67	0.42 to 1.07	0.09
Sex			
Women	1		
Men	1.24	0.78 to 1.98	0.36
Geographic location			
Prairie provinces[c]	1		
British Columbia	0.71	0.31 to 1.64	0.43
Maritime provinces[d]	0.38	0.13 to 1.11	0.08
Ontario	1.03	0.47 to 2.25	0.94
Quebec	0.76	0.37 to 1.58	0.47
Extended *RAS* status			
Mutant	1		
Wild-type	1.29	0.52 to 3.19	0.58
Fluorouracil alone			
No	1		
Yes	0.54	0.18 to 1.59	0.26
Bevacizumab			
No	1		
Yes	1.24	0.73 to 2.11	0.43
Capecitabine			
No	1		
Yes	0.97	0.46 to 2.04	0.93
CAPOX			
No	1		
Yes	3.79	1.18 to 12.15	**0.03**
Cetuximab			
No	1		
Yes	0.56	0.15 to 2.06	0.38
FOLFIRI			
No	1		
Yes	0.67	0.24 to 1.91	0.45
FOLFOX			
No	1		
Yes	3.11	1.13 to 8.57	**0.03**
Irinotecan			
No	1		
Yes	0.74	0.30 to 1.82	0.51
Panitumumab			
No	1		
Yes	0.52	0.21 to 1.32	0.17
Regorafenib			
No	1		
Yes	0.68	0.39 to 1.19	0.18

[a] Includes the 360 patients who were previously receiving trifluridine/tipiracil and discontinued it for any reason, with non-missing covariate values.
[b] Values significant at α = 0.05 shown in boldface type.
[c] Alberta, Saskatchewan, Manitoba.
[d] New Brunswick, Newfoundland and Labrador, Nova Scotia, Prince Edward Island.

OR = odds ratio; CI =confidence interval; CAPOX = capecitabine–oxaliplatin; FOLFIRI = leucovorin–fluorouracil–irinotecan; FOLFOX = leucovorin–fluorouracil–oxaliplatin.

Only a small proportion of patients (4.4%) discontinued treatment because of toxicity—a rate very similar to that for discontinuations in RECOURSE (4.0%) and other CUPS (5.2%[18], 4.0%[26]), and lower than the discontinuation-for-toxicity rate in another report (17.2%[21]).

The dose data in our study appear to suggest fewer dose delays (17.0%) relative to dose reductions (28.0%)—the opposite of RECOURSE, in which dose delays were more frequent (50.0%), and dose reductions, less frequent (14.0%)[25]. Only patients with an ECOG PS of 0 or 1 were included in the PSP, but the SAP included some patients with an ECOG PS of 2, although the exact number was not captured as part of our study.

Most patients discontinued therapy because of disease progression and death, but a small proportion of patients (10.2%, n = 73) never received FTD/TPI despite program enrolment. Table I sets out the reasons (predominantly death and declining patient health), which are consistent with the experiences reported from other CUPS. In an international CUP that enrolled 2371 patients, 12.0% did not initiate therapy, primarily because of worsening patient condition[18]. In a Spanish CUP with 636 registered patients, 15.4% of enrolees did not receive FTD/TPI, largely because of cancellation of the drug request on account of worsening condition and progressive disease in the patient[20]. Nevertheless, programs showed high and successful uptake of FTD/TPI, with most Canadian patients receiving the treatment after enrolment in the program.

In the present study, none of the analyzed factors, including prior therapies, *RAS* status, geographic location, age, or sex predicted the duration of treatment with FTD/TPI. However, previous treatment with oxaliplatin-based chemotherapy (CAPOX or FOLFOX) appeared to predict discontinuation of FTD/TPI because of disease progression

or death. The reasons for that association are unclear and hypothesis-generating. One potential reason is that irinotecan-based chemotherapy is more heavily used in most of Canada, especially in the first-line setting, and no association was evident between that exposure and FTD/TPI discontinuation. Conversely, oxaliplatin-based chemotherapy is more frequently used in the second-line setting, indicating a more heavily pretreated group of patients.

Our study was retrospective and has several associated limitations. The key purpose of the Canadian PSP was to

TABLE IV Association of geographic location of patients receiving trifluridine/tipiracil (FTD/TPI) with other factors

Variable	Geographic location					*p* Value[c]
	Prairie provinces[a] (*n*=106)	British Columbia (*n*=109)	Maritime provinces[b] (*n*=62)	Ontario (*n*=214)	Quebec (*n*=2230)	
KRAS status [*n* (%)]						
Mutant	60 (56.6)	69 (63.3)	35 (56.5)	120 (56.1)	144 (64.6)	0.39
Wild-type	46 (43.4)	39 (35.8)	25 (40.3)	89 (41.6)	77 (34.5)	
Unknown	0 (0.0)	1 (0.9)	2 (3.2)	5 (2.3)	2 (0.9)	
Duration of FTD/TPI (months)						
Median	2	3	3	2	3	0.87
IQR	2–3	1–4	1.3–3	1–4	2–4	
Patient status [*n* (%)]						
Discontinued FTD/TPI	56 (52.8)	57 (52.3)	21 (33.9)	87 (40.7)	141 (63.2)	**<0.001**
Receiving FTD/TPI	31 (29.2)	26 (23.9)	25 (40.3)	90 (42.1)	63 (28.3)	
Never received FTD/TPI	14 (13.2)	18 (16.5)	7 (11.3)	18 (8.4)	14 (6.3)	
Pending	5 (4.7)	8 (7.3)	9 (14.5)	19 (8.9)	5 (2.2)	
Reason for discontinuation [*n* (%)]						
Toxicity	3 (5.4)	1 (1.8)	1 (4.8)	4 (4.6)	7 (5.0)	0.20
Death	4 (7.1)	6 (10.5)	4 (19.0)	9 (10.3)	24 (17.0)	
Disease progression	36 (64.3)	28 (49.1)	6 (28.6)	50 (57.5)	68 (48.2)	
Treating physician's decision	9 (16.1)	18 (31.6)	7 (33.3)	13 (14.9)	23 (16.3)	
Patient withdrawal of consent	1 (1.8)	3 (5.3)	2 (9.5)	4 (4.6)	6 (4.3)	
Other	3 (5.4)	1 (1.8)	1 (4.8)	7 (8.0)	13 (9.2)	
Prior treatments [*n* (%)]						
Fluorouracil alone	1 (0.9)	10 (9.2)	0 (0.0)	3 (1.4)	13 (5.8)	**0.001**
Bevacizumab	59 (55.7)	78 (71.6)	41 (66.1)	141 (65.9)	181 (81.2)	**<0.001**
Capecitabine	15 (14.2)	22 (20.2)	5 (8.1)	25 (11.7)	21 (9.4)	0.05
CAPOX	14 (13.2)	16 (14.7)	4 (6.5)	15 (7.0)	11 (4.9)	**0.01**
FOLFIRI	82 (77.4)	86 (78.9)	57 (91.9)	192 (89.7)	209 (93.7)	**<0.001**
FOLFOX	82 (77.4)	81 (74.3)	55 (88.7)	179 (83.6)	208 (93.3)	**<0.001**
FOLFOXIRI	1 (0.9)	1 (0.9)	0 (0.0)	2 (0.9)	2 (0.9)	1.00
Irinotecan	21 (19.8)	21 (19.3)	3 (4.8)	24 (11.2)	16 (7.2)	**0.001**
Panitumumab	34 (32.1)	30 (27.5)	21 (33.9)	54 (25.2)	55 (24.7)	0.43
Cetuximab	4 (3.8)	6 (5.5)	1 (1.6)	21 (9.8)	13 (5.8)	0.11
Regorafenib	7 (6.6)	7 (6.4)	7 (11.3)	28 (13.1)	55 (24.7)	**<0.001**

[a] Alberta, Saskatchewan, Manitoba.
[b] New Brunswick, Newfoundland and Labrador, Nova Scotia, Prince Edward Island.
[c] Values significant at $\alpha = 0.05$ shown in boldface type.
IQR = interquartile range; CAPOX = capecitabine–oxaliplatin; FOLFIRI = leucovorin–fluorouracil–irinotecan; FOLFOX = leucovorin–fluorouracil–oxaliplatin; FOLFOXIRI = leucovorin–fluorouracil–oxaliplatin–irinotecan.

provide access to therapy, and it therefore did not capture survival outcomes or safety signals in a quantitative way, nor did it record clinical benefit from or resistance to prior agents, sites and numbers of metastasis, and tumour sidedness. One inherent weakness of using PSP data is that we lacked access to more granular clinical information about prior lines of therapy, including sequencing, duration, and dose. Likewise, we were not permitted to link the PSP data with other data sources. Because of those data limitations, the exact reasons for the observed relationships are unclear and should be the focus of future prospective studies. We also did not capture prior therapies for individual patients, which made comparisons of treatment patterns with other jurisdictions difficult. However, those limitations should be weighed against the many strengths of the study, including the its ability to offer real-world insights into the need for and the use of FTD/TPI outside a clinical trial setting. In addition, it was encouraging to observe that patients enrolled in the Canadian PSP were able to start the drug within only 3 weeks of applying for the program, which indicates a rapid and successful process, with minimal delays. The study also highlights an opportunity for future manufacturers to design their programs such that robust data linkages are permitted, which would allow for more clinically meaningful analyses. Ongoing collection of real-world evidence should include response and survival data.

CONCLUSIONS

The present real-world evidence study captured treatment patterns in third- or subsequent-line treatment for patients with mCRC in the context of the Canadian health care system. The analysis demonstrates a need for effective therapies in advanced mCRC and the fact that FTD/TPI is a well-tolerated therapy in that setting. In Canada, FTD/TPI is currently approved but not funded; however, active steps are being undertaken to pursue public reimbursement of this agent. The information presented in our analysis should help to inform funding, regulatory, and health policy bodies about the urgent unmet clinical need for the growing number of patients with refractory mCRC. Finally, because the treatment of mCRC will continue to evolve, many future clinical trials evaluating the potential role of novel agents in the third- or later-line settings will be forthcoming. Characterization of the current treatment landscape will therefore be important in defining the applicability of emerging trial outcomes to Canadian practice, identifying local evidence and treatment gaps, and defining areas of unmet medical need that could inform and optimize patient care.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: AD is the Director, Medical, Taiho Pharma Canada, Inc.; WYC serves as an advisor to Taiho and has received research grants and honoraria from the company; CBM has served as a consultant for, and received honoraria from, Amgen, AstraZeneca, Eli Lilly, Novartis, Pfizer, Roche, Servier, and Taiho, and has received grants from Amgen, AstraZeneca, Eli Lilly, Novartis, Pfizer, and Roche. HHS and ARA have no conflicts of interest to disclose.

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