

Quality of life in a real-world study of patients with metastatic colorectal cancer treated with trifluridine/tipiracil

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ABSTRACT

Background Quality of life (QOL) is important for oncology patients, especially for those with late-stage disease. The present study was initiated to address the lack of published prospective data about the QOL benefits of trifluridine/tipiracil (FTD/TPI) compared with best supportive care (BSC) in patients with refractory metastatic colorectal cancer (mCRC).

Methods This prospective, cross-sectional, non-interventional study used multidimensional validated scales to evaluate patient-reported QOL in two study cohorts of patients and also to measure differences in mCRC-related symptoms and pain in a real-world clinical setting.

Results Our findings demonstrate that patients with refractory mCRC report better overall QOL when treated with FTD/TPI than with BSC alone. In that population, statistically significant differences in mean QOL measures favoured FTD/TPI over BSC for physical symptom distress, psychological distress, activity impairment, overall valuation of life, and symptomatology. The overall better QOL for patients receiving FTD/TPI implies that treatment was well tolerated and was associated with a lower symptom burden. No significant differences for pain were observed between the groups.

Conclusions This study suggests that FTD/TPI is a well-tolerated option for the treatment of patients with refractory mCRC, showcasing the value of capturing real-world QOL data in routine clinical practice.

Key Words TAS-102, refractory disease, QOL, symptoms, pain

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INTRODUCTION

Trifluridine/tipiracil (FTD/TPI) is an oral medication approved by Health Canada for the treatment of adult patients with refractory metastatic colorectal cancer (mCRC) who have previously been treated with, or who are not candidates for, available therapies¹. Approval in that setting was based on results of the phase III RECURSE trial, which demonstrated a statistically significant survival benefit of 7.1 months for FTD/TPI compared with 5.3 months for best supportive care (BSC). In RECURSE, the hazard ratio for death was 0.68, with a 95% confidence interval of 0.58 to 0.81, $p < 0.001$ ². Trifluridine/tipiracil was associated with few serious adverse events, neutropenia being the most frequently observed, occurring in 38% of patients treated

with FTD/TPI compared with 0% of patients treated with placebo. Based on the RECURSE study results, FTD/TPI is considered a potential new treatment option, and it is included in the treatment algorithm for colon cancer from the U.S. National Comprehensive Cancer Network³ and in the guidelines published by the European Society for Medical Oncology⁴ as a preferred third-line choice for cytoreduction and disease control in patients with *RAS*-mutated and *BRAF*-mutated mCRC, and as a third-line choice in patients with *RAS* wild-type mCRC⁴.

Despite Health Canada approval and the inclusion of FTD/TPI in international guidelines, reimbursement for FTD/TPI is inconsistent in Canada⁵. Quebec's Institut national d'excellence en santé et en services sociaux made a positive

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recommendation that FTD/TPI be included on the list of medications for the treatment of adult patients with mCRC for whom previous standard therapies have failed⁶. Since August 2019, FTD/TPI has been reimbursed for patients with mCRC in Quebec under the Régie de l'assurance maladie du Québec⁷; however, patients with mCRC living in the rest of Canada are not yet able to receive public reimbursement for the drug. In August 2019, the pan-Canadian Oncology Drug Review issued a final negative recommendation, stating that FTD/TPI had only “potentially modest [progression-free survival] and [overall survival] benefit, moderate toxicities and an uncertain quality of life”⁸. Patients with mCRC outside Quebec can currently access FTD/TPI only through private insurance or the Taiho Canada (TCAN) patient support program.

Patients with refractory mCRC have an unmet need and high demand for a tolerable therapy. A previous study reported that more than 700 Canadian patients applied for the drug through the TCAN patient support program over a 12-month period⁹. As of February 2020, the number of patients who have accessed FTD/TPI through the TCAN patient support program has increased by 1497, including 982 patients who received FTD/TPI in 2019, most with mCRC. The only other Health Canada–approved treatment option in this setting is regorafenib, which, compared with placebo, was associated with a difference in median overall survival of 1.4 months¹⁰. According to a systemic review and network meta-analysis, significantly more treatment toxicities are associated with regorafenib than FTD/TPI¹¹, affecting tolerability and patient quality of life (QOL). Regorafenib is not reimbursed in Canada.

Quality of life is important to cancer patients and can influence their well-being and survival¹². One study found that 55% of patients with advanced cancer valued QOL and length of life equally; an additional 27% valued QOL over survival¹³. Although chemotherapy can alleviate some CRC-related symptoms, it can introduce others, including nausea and vomiting, fatigue, and change or loss of taste^{14–16}. Measures of QOL are now recognized as being an important element for inclusion in clinical trials and are most typically captured through patient-reported outcomes^{17–19}.

To date, few prospective comparative data have been published about the QOL benefit of FTD/TPI compared with BSC. The internationally validated QOL tools used in the prospective PRECONNECT trial suggested that patients with mCRC treated with FTD/TPI can maintain their QOL; however, because the trial lacked a comparator arm, it did not demonstrate whether, relative to BSC, FTD/TPI is associated with improved QOL²⁰. Other FTD/TPI QOL studies were retrospective and did not use validated QOL tools^{21,22}.

In the present real-world study, we used a cross-sectional, non-interventional design to understand the difference in QOL for patients with refractory mCRC treated with either FTD/TPI or with BSC only. The study used 3 validated QOL instruments specifically selected for their relevance to the symptomatology, side effects, and clinical problems associated with mCRC, including the Rotterdam Symptom Checklist [RSC (University Medical Center Groningen, Research Institute SHARE, Groningen, Netherlands)]^{23,24}, the FACT Colorectal Cancer Symptom Index [FCSI (FACIT.org, Ponte Vedra, FL, U.S.A.)]²⁵, and a visual analogue scale (VAS) for pain^{26,27}.

METHODS

Study Design, Objectives, and Endpoints

This cross-sectional, non-interventional study compared patient-reported QOL, symptoms, and pain between two cohorts of patients. The primary objective was to quantify the difference in QOL between patients with mCRC who were treated with FTD/TPI or with BSC in a real-world setting. Secondary objectives were to quantify the differences in mCRC-related symptoms and pain between patients with mCRC who were treated with FTD/TPI or with BSC.

Study Oversight and Confidentiality

The study protocol was submitted to independent ethics committees or institutional review boards (or both) for review and written approval. The study was conducted in accordance with the principles of the Helsinki Declaration of 1975, as revised in 2008. In addition, the study was consistent with the International Conference on Harmonization Good Clinical Practice, the Good Epidemiology Practices, and applicable regulatory requirements. Patients undertook no risks in participating in the study.

Consent was obtained from all patients before they completed any questionnaires. All patients who entered the study were assigned a unique identification number before they completed the questionnaires; that number was used to ensure that all patient-reported outcome scales and all study documentation were related to an individual patient. All data collected were encrypted, and only authorized members of the study team had access to the patient identification list.

The study was conducted between 27 November 2018 and 29 January 2020. Patients were enrolled from across Canada, with participating sites in Quebec, Ontario, and Alberta.

Patient Eligibility and Recruitment

Patients were eligible for the study if they had received at least 2 prior lines of treatment for mCRC. Because the study was non-interventional, there was no requirement to assign patients to any specific treatment, and they were neither randomized nor stratified with respect to sex, Eastern Cooperative Oncology Group performance status (ECOG PS), or number of prior therapies. Patients who, as an outpatient at their oncology centre, had received at least 1 cycle of FTD/TPI per label²⁸ were assigned to one study group. Patients who had not received FTD/TPI because of patient refusal, clinical comorbidities, ECOG PS greater than 1, or a rapidly progressing tumour were assigned to the other study group. Patients were excluded if they had previously participated in a clinical trial.

Data Collection and QOL Tools

Patient demographics were captured by the treating oncologists on the subject eligibility form, including information about patient age, sex, number of prior lines of therapy for mCRC, *KRAS* status, and ECOG PS at the start of current treatment, medications concomitant with the current intervention, and current treatment details. The physician also confirmed the inclusion and exclusion criteria for participating patients.

Data collection was performed using a combination of validated QOL scales, including the RSCL, the FCSI, and the VAS for pain, described briefly below and included in the supplementary appendixes.

Rotterdam Symptom Checklist

The RSCL^{23,24} measures QOL in cancer patients specifically, covering the domains of physical symptom distress, psychological distress, activity level, and overall global life quality.

FACT Colorectal Cancer Symptom Index

The FACIT measurement system is a collection of questionnaires measuring health-related quality of life for people with chronic illnesses. Those questionnaires often serve as validation benchmarks for newer measures^{12,29}. The FCSI²⁵ is a CRC-specific scale designed to capture the clinically relevant problems associated with CRC.

Visual Analogue Scale

The VAS for pain^{26,27} uses a numerical rating scale that has been shown to be reliable and valid for subjective cancer pain measurement.

The patient (or a caregiver) completed the RSCL, FCSI, and VAS questionnaires in paper format at the time of the visit with the oncologist for a regular mCRC appointment. The set of questionnaires took approximately 15–20 minutes to complete. Validated French versions of the questionnaires were provided for francophone patients in Quebec. The questionnaire was anonymous, and no identifying information was collected. This was a one-time data collection, and patients were not contacted for follow-up.

After the questionnaires were completed by the patient or caregiver, the treating physician reviewed and indicated causality for each item making up the RSCL and FCSI scores for patients treated with FTD/TPI; the treating physician also commented whether the patient experienced worsening of pain as a result of treatment.

Data Analysis and Statistics

Patient-reported outcomes data were summarized descriptively by group for each scale, and mean scores were compared. The data are presented as frequencies and proportions, and as means with standard deviation and range.

Proportions were compared using the chi-square test. Continuous variables were compared using the Student *t*-test. Calculations were performed in the IBM SPSS Statistics software application (version 21: IBM, Armonk, NY, U.S.A.). Two-tailed *p* values less than 0.05 were considered statistically significant.

Data analysis focused on the differences in mean QOL scores between the FTD/TPI-treated cohort and the BSC-treated cohort. Endpoints were analyzed as follows:

- Differences between the study groups in overall QOL, including physical symptom distress, activity level, psychological distress, and overall valuation of life (measured using the RSCL)
- Difference between the study groups in CRC symptoms (measured using the FCSI)
- Difference between the study groups with respect to pain (measured using the VAS for pain)

RESULTS

Patient Enrolment and Demographics

The analysis included 105 patients: 50 in the FTD/TPI cohort and 55 in the BSC cohort. Table 1 shows baseline demographics for the cohorts. Patients in the FTD/TPI cohort were slightly younger (62 years vs. 68 years), slightly more likely to be female (44% vs. 31%), slightly more likely to have received 4 or more previous therapies (14% vs. 9%), and more likely to have a lower overall ECOG PS (ECOG PS 0–1: 98% vs. 35%). *KRAS* status was balanced between the cohorts (*KRAS*-mutated: 50% FTD/TPI vs. 53% BSC).

QOL in Four Domains and Symptomology from the RSCL

Patients treated with FTD/TPI reported significantly lower mean impairment across all domains: lower physical distress (*p* = 0.0042), lower psychological distress (*p* < 0.0001), lower activity impairment (*p* < 0.0001), and better overall valuation of life (*p* < 0.0001, Table II). Results of the RSCL were also calculated only for patients with an ECOG PS of 0–1, although the group included just 19 patients receiving BSC. Of patients with an ECOG PS of 0–1, significantly lower

TABLE I Baseline demographics of enrolled patients

Characteristic	Patient group		
	FTD/TPI	BSC	Overall
Patients (<i>n</i>)	50	55	105
Age (years)			
Median	62	68	64
Range	40–82	33–88	33–88
Sex [<i>n</i> (%)]			
Men	28 (56)	38 (69)	66 (63)
Women	22 (44)	17 (31)	39 (37)
Prior mCRC therapies [<i>n</i> (%)]			
2	21 (42)	21 (38)	42 (40)
3	22 (44)	29 (53)	51 (49)
4	6 (12)	5 (9)	11 (10)
5	1 (2)	—	1 (1)
<i>KRAS</i> status [<i>n</i> (%)]			
Mutated	25 (50)	29 (53)	54 (51)
Not mutated	25 (50)	25 (45)	50 (48)
Not tested	—	1 (2)	1 (1)
ECOG PS at start of current treatment [<i>n</i> (%)]			
0	6 (12)	1 (2)	7 (7)
1	43 (86)	18 (33)	61 (58)
2	—	31 (56)	31 (30)
3	1 (2)	5 (9)	6 (6)
Province of residence [<i>n</i> (%)]			
Quebec	32 (64)	23 (42)	55 (52)
Ontario	5 (10)	9 (16)	14 (13)
Alberta	13 (26)	23 (42)	36 (34)

FTD/TPI = trifluridine/tipiracil; BSC = best supportive care; mCRC = metastatic colorectal cancer; ECOG PS = Eastern Cooperative Oncology Group performance status.

TABLE II Standardized results of the Rotterdam Symptom Checklist^a in the study patients

Checklist item	All patients			Patients with ECOG PS 0–1		
	FTD/TPI (n=50)	BSC (n=55)	<i>p</i> Value	FTD/TPI (n=49)	BSC (n=19)	<i>p</i> Value
Physical distress			0.0042			0.1727
Mean	22±11	28±12		22±11	26±10	
Range	0–51	6–55		0–51	12–49	
Psychological distress			<0.0001			0.0047
Mean	24±21	41±17		24±21	39±12	
Range	0–67	5–76		0–67	14–67	
Activity level			<0.0001			0.0520
Mean	21±20	43±22		21±20	32±22	
Range	4–83	0–88		4–83	0–79	
Overall valuation of life			<0.0001			0.1389
Mean	33±21	54±19		33±21	41±16	
Range	0–83	17–83		0–83	17–67	

^a Scale of 0–100, where 0 implies no impairment and 100 implies the highest level of impairment. See the supplemental material for the calculation details.

FTD/TPI = trifluridine/tipiracil; BSC = best supportive care; ECOG PS = Eastern Cooperative Oncology Group performance status.

psychological distress was reported by those who were treated with FTD/TPI than by those who were treated with BSC ($p = 0.0047$). All other domains were also better for patients treated with FTD/TPI, but the differences were not statistically significant: physical distress, $p = 0.1727$; activity level, $p = 0.0520$; and overall valuation of life, $p = 0.1389$.

Table III shows the analysis of individual symptoms in the RSCL for the FTD/TPI and BSC groups. The RSCL contains 39 items, with most being graded on a 4-point Likert-type scale whose responses range from “not at all” to “very much.” Significantly fewer patients in the FTD/TPI cohort than in the BSC cohort reported experiencing 14 of the symptoms itemized in the RSCL, including lack of appetite, irritability, tiredness, worrying, depression, nervousness, despair, difficulty sleeping, headaches, dizziness, tension, anxiety, difficulty concentrating, and shortness of breath. Although fewer patients in the FTD/TPI cohort experienced lack of energy, low back pain, decreased sex interest, abdominal aches, constipation, acid indigestion, shivering, tingling hands or feet, sore mouth or pain with swallowing, hair loss, burning or sore eyes, and dry mouth, the differences were not statistically significant. A higher proportion of patients in the FTD/TPI cohort than in the BSC cohort experienced sore muscles, nausea, vomiting, and diarrhea, but those differences were not statistically significant.

In the analysis of overall QOL in the RSCL, 70% of patients treated with FTD/TPI rated their overall valuation of life as excellent, good, or moderately good; 27% of the patients receiving BSC gave such ratings ($p < 0.0001$, Table IV). No patient in either cohort rated their overall valuation of life as extremely poor.

Symptomology and Pain

Table V presents the results of the FCSI colorectal cancer-specific scale and the VAS for pain. The possible FCSI scores ranged from 0 to 36, where a higher score indicates less symptomology. Patients treated with FTD/TPI reported a higher mean score of 22.9 ± 6.0 (range: 11–34) compared with

the 20.3 ± 5.5 (range: 8–31) reported by patients treated with BSC ($p = 0.0197$). The reported VAS for pain was low in both groups, with no significant difference in the level of pain for patients receiving FTD/TPI (2.4 ± 2.6 ; range: 0–8.0) and for those receiving BSC (3.0 ± 2.4 ; range: 0–8.5; $p = 0.1421$).

DISCUSSION

This prospective, real-world, non-interventional study evaluated patient-reported QOL and measured differences in mCRC-related symptoms and pain in 105 patients. Results demonstrated that, compared with patients with refractory mCRC who received BSC, those who received FTD/TPI reported better overall QOL. Results were consistent across the 3 QOL instruments used. Patients receiving FTD/TPI reported better outcomes across all domains of the RSCL: less physical symptom distress, less psychological distress, lower activity level impairment, and better overall valuation of life. Those results are consistent with the FCSI, which indicated that, compared with patients receiving BSC, those receiving FTD/TPI reported fewer CRC symptoms. The parameters measured by those indices are important to patients with mCRC.

Patients in this real-world experience (RWE) study were neither stratified nor randomized—representing one reason why the cohorts were imbalanced with respect to sex (male vs. female), ECOG PS, and number of prior therapies. In this non-interventional study, most patients who received FTD/TPI had an ECOG PS of 0–1, reflecting the Canadian indication for that agent²⁸; patients who declined treatment or who had an ECOG PS of 2 received BSC. That difference might also confound the finding of a lower activity level in the BSC cohort; ECOG PS 2 is defined as “ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours”³⁰. To account for the large difference in ECOG PS between the patients in the two groups, patients who had an ECOG PS of 0–1 were analyzed separately, and self-reported QOL was directionally

TABLE III Dichotomized analysis of symptoms in the Rotterdam Symptom Checklist^a

Symptom	Pts experiencing the symptom (%)		p Value ^b
	FTD/TPI (n=50)	BSC (n=55)	
Lack of appetite	66	96	0.0001
Irritability	46	85	0.0001
Tiredness	86	98	0.0194
Worrying	60	85	0.0034
Sore muscles ^c	50	47	0.7811
Depressed	44	91	0.0001
Lack of energy	92	96	0.3383
Low back pain	42	45	0.7229
Nervousness	52	82	0.0012
Nausea ^c	54	51	0.7526
Despair	56	87	0.0004
Difficulty sleeping	60	82	0.0139
Headaches	24	44	0.0351
Vomiting ^c	28	27	0.9340
Dizziness	16	47	0.0007
Decreased sex interest	76	80	0.6223
Tension	48	71	0.0172
Abdominal aches	58	62	0.6914
Anxiety	56	87	0.0004
Constipation	50	53	0.7811
Acid indigestion	46	60	0.1529
Diarrhea ^c	50	42	0.4029
Shivering	16	29	0.1123
Tingling hands or feet	68	75	0.4605
Difficulty concentrating	64	96	<0.0001
Sore mouth or pain swallowing	24	33	0.3251
Loss of hair	34	40	0.5271
Burning or sore eyes	14	27	0.0967
Shortness of breath	32	56	0.0126
Dry mouth	42	51	0.3631

^a Scale of 0–100, where 0 implies no impairment and 100 implies the highest level of impairment. See the supplemental material for the calculation details.
^b Boldface type indicates statistical significance.
^c Better score in patients receiving FTD/TPI, but not significantly so. Pts = patients; FTD/TPI = trifluridine/tipiracil; BSC = best supportive care; ECOG PS = Eastern Cooperative Oncology Group performance status.

better, but not statistically different, in patients treated with FTD/TPI compared with those treated with BSC. Unfortunately, the numbers of patients in the groups were small, which made the analysis inaccurate.

TABLE IV Analysis of overall valuation of life in the Rotterdam Symptom Checklist^a

Rating for overall valuation of life	Patient group		p Value ^b
	FTD/TPI (n=50)	BSC (n=55)	
Excellent, good, or moderately good	35 (70)	15 (27)	<0.0001
Excellent	3 (6)	—	
Good	19 (38)	5 (9)	
Moderately good	13 (26)	10 (18)	
Neither good nor bad	9 (18)	12 (22)	—
Rather poor, poor, or extremely poor	6 (12)	28 (51)	—
Rather poor	3 (6)	22 (40)	
Poor	3 (6)	6 (11)	
Extremely poor	—	—	

^a Scale of 0–100, where 0 implies no impairment and 100 implies the highest level of impairment. See the supplemental material for the calculation details.
^b Boldface type indicates statistical significance. FTD/TPI = trifluridine/tipiracil; BSC = best supportive care.

TABLE V Results of the FACT Colorectal Cancer Symptom Index (FCSI)^a and visual analogue scale (VAS) for pain^b

Rating	Patient group		p Value ^c
	FTD/TPI (n=50)	BSC (n=55)	
FCSI			0.0197
Mean	22.9±6.0	20.3±5.5	
Range	11–34	8–31	
VAS for pain			0.2418
Mean	2.4±2.6	3.0±2.4	
Range	0–8.0	0–8.5	

^a FACIT.org, Ponte Vedra, FL, U.S.A. The range of possible scores is 0–36, where a higher score indicates less symptomatology.
^b The range of possible scores is 0–10, where 0 indicates no pain and 10 indicates the worst possible pain within the last 24 hours.
^c Boldface type indicates statistical significance. FTD/TPI = trifluridine/tipiracil; BSC = best supportive care.

Active treatments can have toxicities that can negatively affect QoL and make the active treatment poorly tolerated. Fatigue is commonly reported with the use of FTD/TPI, but it is a symptom that can also be attributed to the disease itself³¹. The RSCL results indicated that lower proportions of patients experienced tiredness and lack of energy when treated with FTD/TPI than with BSC, suggesting that any FTD/TPI-induced fatigue might have been offset by a reduction in disease-related fatigue. The only chemotherapy-related symptoms that were proportionally higher in the FTD/TPI cohort compared with the BSC cohort were sore muscles, nausea, vomiting, and diarrhea—differences that were not statistically significant. Those adverse events were as expected with other chemotherapeutic agents (for example, fluoropyrimidines), and in RECOURSE, they were reported more frequently in the FTD/TPI group than in the placebo group². However, as in RECOURSE, those adverse events were easily manageable in the real-world setting

with appropriate supportive treatment—a reassuring observation. Our study captured patient-reported symptoms and QOL only, and so levels of neutropenia experienced by patients were not documented because that side effect is benign and easy to manage with granulocyte colony-stimulating factor and likely did not affect QOL.

Although average pain levels were not significantly different between the groups, it is noteworthy that pain scores were low in both groups. We do not know if the pain scores were influenced by pain medications or pain management strategies because our study did not report concurrent medications. However, it is likely that patients in this late treatment setting have engaged with palliative care and that their pain is being well controlled by palliative care physicians and nurses.

Our results add to the established evidence supporting FTD/TPI as a tolerable treatment for patients with refractory mCRC, which includes the pivotal phase III RECURSE trial², the prospective PRECONNECT QOL study²⁰, and the Canadian retrospective RWE study of FTD/TPI in refractory mCRC⁹. The PRECONNECT and Canadian RWE studies both generated clinically relevant data, but they were single-arm noncomparative studies. Although prospective QOL data were not collected as part of RECURSE², the RECURSE and Canadian RWE⁹ studies both evaluated the maintenance or stabilization of a patient's baseline ECOG PS status, which is a clinically important parameter in routine practice. In addition, the results of the studies are consistent with real-world data from FTD/TPI compassionate use programs in Italy³², Spain³³, and Germany³⁴ (all of which are among the 11 countries of the Patented Medicine Prices Review Board); however, none of the compassionate use program studies specifically evaluated QOL.

The present study is the first to use validated QOL instruments to compare QOL and symptomatology in patients with mCRC treated with FTD/TPI or with BSC. The QOL questionnaires in our study were completed either by the patient or a caregiver directly. That approach is aligned with various studies showing that QOL and symptom reporting are most accurately captured by the patients themselves, because physicians underreport both the severity and the prevalence of toxicities and symptoms³⁵. Capturing QOL as part of patient-reported outcome measures is generally accepted as necessary, important, and beneficial³⁶.

A benefit of RWE studies is that they examine the generalizability of interventions in practice by capturing the experience of patients who are treated in a clinical environment. Such patients are often excluded from randomized clinical trials because of personal characteristics or comorbidities, and their treatment responses and symptoms are monitored less rigidly³⁷. Evidence demonstrates that capturing QOL and symptoms in a real-world context improves symptom control, patient satisfaction^{38,39}, and health-related quality of life⁴⁰; is associated with increased survival duration^{36,37,41–43}; and is becoming more common in real-world clinical settings^{44,45}. In recognition of those benefits, a group of Canadian experts and stakeholders, including the Colorectal Cancer Resource and Action Network, developed and published a position statement supporting the greater use of patient-reported outcomes in Canadian health care and research contexts⁴⁶.

The present study characterizes QOL in the real-world context. It had a comparative design, which showed higher QOL in patients with mCRC who were treated with FTD/TPI than in those treated with BSC. However, the study was based on one-time data capture and did not track change from baseline in patient-reported QOL. Likewise, it did not quantitatively capture survival outcomes or safety signals, nor did it capture prior therapies in a specific and sequenced way to permit comparison of treatment patterns with those in other jurisdictions.

A benefit of the one-time data capture was that it eliminated recall and response shift bias⁴⁷, and also ensured that the data were complete and that no patients were lost to follow-up, which are common problems with RWE studies³⁷. A distinguishing feature of the study was its use of tools specific to mCRC to capture patient QOL. Those tools included 3 validated QOL instruments selected for their relevance to the symptomology, side effects, and clinical problems associated with mCRC: the RSCL^{23,24}, the FCSI²⁵, and a VAS for pain^{26,27}. Importantly, our real-world evaluation of QOL for patients treated with FTD/TPI is reflective of the heavily pretreated mCRC population, and the results are applicable to other patients with mCRC who are treated with FTD/TPI.

CONCLUSIONS

The results of this real-world study demonstrated favourable outcomes for FTD/TPI compared with BSC for overall QOL in patients with refractory mCRC. They showcase the tremendous value of real-world QOL data in capturing the experience of patients with mCRC treated in a routine clinical setting. Because such data are complementary to data from randomized controlled trials, 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.

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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: WYC serves as an advisor to TCAN and has received research grants and honoraria from the company; PK has received educational and research grants from TCAN and participated on company-organized advisory boards; AD is Director, Medical, at TCAN.

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 data in the study, and all authors had responsibility for the final decision to submit the work for publication.

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REFERENCES

- Health Canada. Regulatory Decision Summary for Lonsurf [Web page]. Ottawa, ON: Health Canada; 2018. [Available at: <https://hpr-rps.hres.ca/reg-content/regulatory-decision-summary-detail.php?lang=en&linkID=RDS00325>; cited 4 February 2020]
- Mayer RJ, Van Cutsem E, Falcone A, *et al.* on behalf of the RECOURSE Study Group. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *N Engl J Med* 2015;372:1909–19.
- National Comprehensive Cancer Network (NCCN). *NCCN Clinical Practice Guidelines in Oncology: Colon Cancer*. Ver. 1.2020. Fort Washington, PA: NCCN; 2019. [Current version available online at: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf (free registration required); cited 31 January 2020]
- Van Cutsem E, Cervantes A, Adam R, *et al.* ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol* 2016;27:1386–422.
- Canada Health Act, RSC, 1985, c. C-6.
- Institut national d'excellence en santé et en services sociaux (INESSS). *Lonsurf – Cancer colorectal métastatique. Avis transmis au ministre en mai 2018*. Quebec, QC: INESSS; 2018.
- Régie de l'assurance maladie du Québec (RAMQ). Demande d'autorisation de paiement – Médicaments d'exception [Web page]. Quebec City, QC: RAMQ; n.d. [Available at: <http://www.ramq.gouv.qc.ca/fr/professionnels/pharmaciens/medicaments/medicaments-patient-exception/Pages/index-formulaires-mc.aspx>; cited 31 January 2020]
- Pan-Canadian Oncology Drug Review (pCODR). *pCODR Expert Review Committee (pERC) Final Recommendation* [re. trifluridine and tipiracil (Lonsurf)]. Ottawa, ON: pCODR; 2019.
- Samawi HH, Brezden-Masley C, Afzal AR, Cheung WY, Doley A. Real-world use of trifluridine/tipiracil for patients with metastatic colorectal cancer in Canada. *Curr Oncol* 2019;26:319–29.
- Grothey A, Van Cutsem E, Sobrero A, *et al.* on behalf of the CORRECT Study Group. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 2013;381:303–12.
- Abrahao ABK, Ko YJ, Berry S, Chan KKW. A comparison of regorafenib and TAS-102 for metastatic colorectal cancer: a systematic review and network meta-analysis. *Clin Colorectal Cancer* 2018;17:113–20.
- Sitlinger A, Zafar SY. Health-related quality of life: the impact on morbidity and mortality. *Surg Oncol Clin N Am* 2018;27:675–84.
- Meropol NJ, Egleston BL, Buzaglo JS, *et al.* on behalf of the CONNECT study research group. Cancer patient preferences for quality and length of life. *Cancer* 2008;113:3459–66.
- Sommariva S, Pongiglione B, Tarricone R. Impact of chemotherapy-induced nausea and vomiting on health-related quality of life and resource utilization: a systematic review. *Crit Rev Oncol Hematol* 2016;99:13–36.
- Vardy JL, Dhillon HM, Pond GR, *et al.* Fatigue in people with localized colorectal cancer who do and do not receive chemotherapy: a longitudinal prospective study. *Ann Oncol* 2016;27:1761–7.
- Murtaza B, Hichami A, Khan AS, Ghiringhelli F, Khan NA. Alteration in taste perception in cancer: causes and strategies of treatment. *Front Physiol* 2017;8:134.
- Calvert M, Kyte D, Mercieca-Bebber R, *et al.* Guidelines for inclusion of patient-reported outcomes in clinical trial protocols: the SPIRIT-PRO extension. *JAMA* 2018;319:483–94.
- Bottomley A, Reijneveld JC, Koller M, Flechtner H, Tomaszewski KA, Greimel E on behalf of the 5th EORTC Quality of Life in Cancer Clinical Trials Conference Faculty. Current state of quality of life and patient-reported outcomes research. *Eur J Cancer* 2019;121:55–63.
- Mercieca-Bebber R, King MT, Calvert MJ, Stockler MR, Friedlander M. The importance of patient-reported outcomes in clinical trials and strategies for future optimization. *Patient Relat Outcome Meas* 2018;9:353–67.
- Taieb J, Price TJ, Ciardiello F, *et al.* Health-related quality of life in the early-access phase IIIb study of trifluridine/tipiracil in pretreated metastatic colorectal cancer (mCRC): results from PRECONNECT study [abstract 638]. *J Clin Oncol* 2019;37:. [Available online at: https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.4_suppl.638; cited 5 September 2020]
- Van Cutsem E, Falcone A, Garcia-Carbonero R, *et al.* Proxies of quality of life in metastatic colorectal cancer: analyses in the RECOURSE trial. *ESMO Open* 2017;2:e000261.
- Taberero J, Van Cutsem E, Ohtsu A, *et al.* QTWIST analysis of the RECOURSE trial of trifluridine/tipiracil in metastatic colorectal cancer. *ESMO Open* 2017;2:e000284.
- de Haes JC, van Knippenberg FC, Neijt JP. Measuring psychological and physical distress in cancer patients: structure and application of the Rotterdam Symptom Checklist. *Br J Cancer* 1990;62:1034–8.
- de Haes JCJM, Olschewski M, Fayers P, *et al.* *Measuring the Quality of Life of Cancer Patients with the Rotterdam Symptom Checklist (RSCL): A Manual*. 2nd ed. Groningen, Netherlands: Noordelijk Centrum voor Gezondheidsvraagstukken [North-eastern Centre for Healthcare Research]; 2012.
- Colwell HH, Mathias SD, Turner MP, *et al.* Psychometric evaluation of the FACT Colorectal Cancer Symptom Index (FCSI-9): reliability, validity, responsiveness, and clinical meaningfulness. *Oncologist* 2010;15:308–16.
- Brunelli C, Zecca E, Martini C, *et al.* Comparison of numerical and verbal rating scales to measure pain exacerbations in patients with chronic cancer pain. *Health Qual Life Outcomes* 2010;8:42.
- Serlin RC, Mendoza TR, Nakamura Y, Edwards KR, Cleeland CS. When is cancer pain mild, moderate or severe? Grading pain severity by its interference with function. *Pain* 1995;61:277–84.
- Taiho Pharma Canada. *Lonsurf: Trifluridine and Tipiracil Tablet* [product monograph]. Oakville, ON: Taiho Pharma Canada; 2018.
- Webster K, Cella D, Yost K. The functional assessment of chronic illness therapy (FACIT) measurement system: properties, applications, and interpretation. *Health Qual Life Outcomes* 2003;1:79.
- Oken MM, Creech RH, Tormey DC, *et al.* Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5:649–55.
- Aapro M, Scotte F, Bouillet T, Currow D, Vigano A. A practical approach to fatigue management in colorectal cancer. *Clin Colorectal Cancer* 2017;16:275–85.
- Cremolini C, Rossini D, Martinelli E, *et al.* Trifluridine/tipiracil (TAS-102) in refractory metastatic colorectal cancer: a multicenter register in the frame of the Italian compassionate use program. *Oncologist* 2018;23:1178–87.
- Garcia-Alfonso P, Ruiz A, Carrato A, *et al.* Compassionate use program with FDT-TPI (trifluridine–tipiracil) in pre-treated metastatic colorectal cancer patients: Spanish real world data [abstract e15019]. *J Clin Oncol* 2017;35:. [Available online at: https://ascopubs.org/doi/10.1200/JCO.2017.35.15_suppl.e15019; cited 5 September 2020]
- Kasper S, Kisro J, Fuchs M, *et al.* Safety profile of trifluridine/tipiracil monotherapy in clinical practice: results of the German compassionate-use program for patients with metastatic colorectal cancer. *BMC Cancer* 2018;18:1124.
- Di Maio M, Basch E, Bryce J, Perrone F. Patient-reported

- outcomes in the evaluation of toxicity of anticancer treatments. *Nat Rev Clin Oncol* 2016;13:319–25.
36. Rivera SC, Kyte DG, Aiyegbusi OL, Slade AL, McMullan C, Calvert MJ. The impact of patient-reported outcome (PRO) data from clinical trials: a systematic review and critical analysis. *Health Qual Life Outcomes* 2019;17:156.
 37. Bartlett VL, Dhruva SS, Shah ND, Ryan P, Ross JS. Feasibility of using real-world data to replicate clinical trial evidence. *JAMA Netw Open* 2019;2:e1912869.
 38. Chen J, Ou L, Hollis SJ. A systematic review of the impact of routine collection of patient reported outcome measures on patients, providers and health organisations in an oncologic setting. *BMC Health Serv Res* 2013;13:211.
 39. Kotronoulas G, Kearney N, Maguire R, *et al.* What is the value of the routine use of patient-reported outcome measures toward improvement of patient outcomes, processes of care, and health service outcomes in cancer care? A systematic review of controlled trials. *J Clin Oncol* 2014;32:1480–501.
 40. Basch E. Patient-reported outcomes—harnessing patients' voices to improve clinical care. *N Engl J Med* 2017;376:105–8.
 41. Basch E, Deal AM, Dueck AC, *et al.* Overall survival results of a trial assessing patient-reported outcomes for symptom monitoring during routine cancer treatment. *JAMA* 2017;318:197–8.
 42. Olson RA, Howard F, Lapointe V, *et al.* Provincial development of a patient-reported outcome initiative to guide patient care, quality improvement, and research. *Health Manage Forum* 2018;31:13–17.
 43. Sperti E, Di Maio M. Outcomes research: integrating PROs into the clinic—overall survival benefit or not, it's worth the trouble. *Nat Rev Clin Oncol* 2017;14:529–30.
 44. Anatchkova M, Donelson SM, Skalicky AM, McHorney CA, Jagun D, Whiteley J. Exploring the implementation of patient-reported outcome measures in cancer care: need for more real-world evidence results in the peer reviewed literature. *J Patient Rep Outcomes* 2018;2:64.
 45. Gonçalves Bradley D, Gibbons C, Ricci-Cabello I, *et al.* Routine provision of information on patient-reported outcome measures to healthcare providers and patients in clinical practice. *Cochrane Database Syst Rev* 2015;4:CD011589.
 46. Ahmed S, Barbera L, Bartlett SJ, *et al.* A catalyst for transforming health systems and person-centered care: Canadian national position statement on patient reported outcomes (PROs). *Curr Oncol* 2020;27:90–9.
 47. Blome C, Augustin M. Measuring change in quality of life: bias in prospective and retrospective evaluation. *Value Health* 2015;18:110–15.