Quality of Life and Survival of Metastatic Colorectal Cancer Patients Treated With Trifluridine-Tipiracil (QUALITAS)

Patricia A.H. Hamers,[1,2] Geraldine R. Vink,[1,3] Marloes A.G. Elferink,[3] Rebecca K. Stellato,[2] Willemieke P.M. Dijksterhuis,[3,4] Cornelis J.A. Punt,[2] Miriam Koopman,[1] Anne M. May[2], on behalf of the QUALITAS study group*

Abstract

Introduction: The RECOURSE trial demonstrated a modest benefit in overall survival (OS) for trifluridine/tipiracil (FTD/TPI) versus placebo in pretreated metastatic colorectal cancer (mCRC) patients. Unfortunately, quality of life (QoL) was not assessed. We evaluated QoL and survival of patients treated with FTD/TPI in daily practice. **Patients and Methods:** QUALITAS is a substudy of the Prospective Dutch CRC cohort (PLCRC). From 150 mCRC patients treated with FTD/TPI, QoL (EORTC QLQ-C30 and QLQ-CR29) was assessed monthly from study entry, and linked to clinical data of the Netherlands Cancer Registry. Joint models were constructed combining mixed effects models with Cox PH models. Primary endpoint was difference in QoL over time (which was deemed clinically relevant if $\geq$10 points). Secondary endpoints were progression-free survival (PFS), time to treatment failure (TTF), and OS. We analyzed the association between QLQ-C30 Summary Score (QoL-SS) at FTD/TPI initiation (baseline) and survival. **Results:** There was no clinically relevant change in QoL-SS from baseline to 10 months post-baseline (i.e. the cut-off point after which 90% of patients had discontinued FTD/TPI treatment): -5.3 [95% CI -8.7;-1.5]. Patients who were treated with FTD/TPI for $\geq$ 3 months (n = 85) reported 6.3 [1.6;11.1] points higher baseline QoL, compared to patients treated < 3 months (n = 65, "poor responders"). In the latter, time to a clinically relevant QoL deterioration was < 2 months. Median PFS, TTF and OS were 2.9 [2.7;3.1], 3.1 [2.9;3.2] and 7.7 [6.6;8.8] months, respectively. Worse baseline QoL-SS was independently associated with shorter OS (HR 0.45 [0.32;0.63]), PFS (0.63 [0.48;0.83]), and TTF (0.64 [0.47;0.86]). **Conclusion:** The maintenance of QoL during FTD/TPI treatment in daily practice supports its use. The QoL deterioration in "poor responders" is likely due to disease progression. The strong association between worse baseline QoL and shorter survival suggests that clinicians should take QoL into account when determining prognosis and treatment strategy for individual patients.

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Introduction

In metastatic colorectal cancer (mCRC), the main aim of treatment is to prolong overall survival (OS), and to maintain or improve quality of life (QoL). QoL is of particular importance in the management of patients in late-line treatment of mCRC given their limited life expectancy, and the delicate balance between benefits and harms of treatment.[1] The phase III RECOURSE trial demonstrated a statistically significant but modest survival benefit for trifluridine/tipiracil (FTD/TPI) over placebo in pretreated mCRC patients with a median OS of 7.1 months versus 5.3 months, respectively.[2] Toxicity was acceptable and the median time to worsening performance status (PS) was longer in the intervention group. Subsequently, FTD/TPI has been incorporated as a third-line treatment option in international guidelines.[3] In the Netherlands, FTD/TPI can be prescribed in daily practice since 2017 to patients with mCRC who have been progressive or intolerant to fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab, and - in RAS wild-type patients - to EGFR antibodies.[3] Although

Abbreviations: OS, overall survival; FTD/TPI, trifluridine/tipiracil; mCRC, metastatic colorectal cancer; QoL, quality of life; PLCRC, Prospective Dutch CRC cohort; PH, proportional hazards; PFS, progression-free survival; QoL-SS, QLQ-C30 Summary Score; PS, performance status; PROs, patient-reported outcomes; AEs, adverse events; NCR, Netherlands Cancer Registry; ICD-O-3, International Classification of Diseases for Oncology; PROFILES, Patient Reported Outcomes Following Initial Treatment and Long-term Evaluation of Survivorship; GHS, Global Health Status; HRs, hazard ratios; CI, confidence interval; TCI, threshold for clinical importance; CUP, compassionate use program.

[1]Department of Medical Oncology, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands
[2]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands
[3]Netherlands Comprehensive Cancer Organisation, Department of Research and Development, Utrecht, the Netherlands
[4]Department of Medical Oncology, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, the Netherlands

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Address for correspondence: Anne M. May, PhD, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Internal mail no: STR 7.112, P.O. Box 85060, 3508 AB Utrecht, the Netherlands
E-mail contact: A.M.May@umcutrecht.nl

* Members of the QUALITAS study group.

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FTD/TPI treatment was well tolerated in the RECOURSE trial based on physician-reported toxicity, no patient-reported outcomes (PROs) were collected. PROs may detect symptoms missed by clinicians, and as a result complement the physician-based description of adverse events (AEs).[1,4] In this study, we directly measured symptoms and QoL (PROs) during FTD/TPI treatment using validated questionnaires. The aim was to evaluate the course of QoL over time as well as time to treatment failure (TTF) and survival of patients treated with FTD/TPI in daily clinical practice.

Methods

Study Design and Population

QUALITAS is a prospective cohort study and a substudy of the Prospective Dutch CRC cohort (PLCRC).[5] PLCRC is linked to the population-based Netherlands Cancer Registry (NCR), which collects clinical data on all patients with cancer in the Netherlands. Patients were recruited via medical oncologists from Dutch hospitals participating in PLCRC. Adult (≥ 18 years) mCRC patients who were about to start or had started FTD/TPI treatment, and who provided written informed consent for the collection of clinical data and questionnaires in PLCRC, were eligible for inclusion. Patients were included in data analysis if they completed at least 1 questionnaire anytime in the period between 30 days before the start of FTD/TPI and 30 days after discontinuation of FTD/TPI.

Data Collection

Clinical Characteristics. Trained registrars collected patient, tumor, and treatment characteristics from medical records. Topography and morphology were coded according to the International Classification of Diseases for Oncology (ICD-O-3). Data on vital status were obtained by annual linkage to the Dutch Personal Records Database and updated until February 1, 2020.

Quality of Life. Collection of QoL data was performed within PROFILES (Patient Reported Outcomes Following Initial Treatment and Long-term Evaluation of Survivorship).[6] QoL was assessed monthly from study entry using the validated EORTC QLQ-C30[7] and QLQ-CR29[8,9] questionnaires until FTD/TPI was permanently discontinued. Questionnaires could be completed on paper or online, depending on patient preference. The questionnaire completion rate was defined as the proportion of questionnaires sent to participants that was returned. The general QLQ-C30 questionnaire contains 5 functional scales, 9 symptom scales/items, and the Global Health Status (GHS) scale. We calculated the QLQ-C30 Summary Score (QoL-SS), which encompasses all functional and symptom scales except for financial difficulties.[10] The tumor-specific QLQ-CR29 questionnaire incorporates 4 functional scales and 17 symptom scales. Scales and single-item scores range from 0 to 100.[11] Differences in scores over time were deemed clinically relevant if ≥ 10 points.[12,13]

Statistical Analysis

Quality of Life. Joint models[14,15] were constructed combining longitudinal (QoL) and time-to-event (time to treatment failure; TTF) data to appropriately account for nonignorable nonresponse in the longitudinal QoL-SS (ie patients who stopped completing questionnaires because of treatment failure were likely to have lower QoL than patients who completed questionnaires). In the mixed effects part of the joint models, the time interval between start of FTD/TPI and questionnaire completion date was the fixed effect, a random intercept and random "slope" for time (using natural cubic splines) were included. QoL at FTD/TPI initiation (baseline) and the course of QoL during FTD/TPI treatment were analyzed for the total study population, and separately for 2 groups based on treatment duration: (1) patients who were treated for at least the median treatment duration (≥ 3 months; the "good responders"), and (2) patients who were treated for less than the median treatment duration (< 3 months; the "poor responders"). For this purpose, we added an interaction between treatment duration and time between start of FTD/TPI and questionnaire completion date. For the time-to-event part of the joint model, a Cox proportional hazards (PH) regression model was used with TTF as the time-to-event; no covariates were included. Since patients were allowed to enter the study after FTD/TPI treatment had started, we also used this joint model to estimate baseline QoL-SS for use in subsequent analyses. All reported QoL scores are estimates stemming from joint models and are presented from the start of FTD/TPI until the time at which approximately 90% of patients had discontinued FTD/TPI treatment.

Time to Treatment Failure and Survival. Progression-free survival (PFS), TTF and OS were defined as the time interval between the start of FTD/TPI and progression of disease, discontinuation of FTD/TPI for any reason, and death,[16] respectively. Response evaluation took place according to daily practice. For OS, surviving patients were censored at January 31, 2020. In Suppl Table 1 , definitions regarding baseline characteristics, prior treatments and PFS are listed. Median TTF, PFS and OS were estimated using the Kaplan-Meier method. We investigated whether baseline QoL-SS was associated with PFS/TTF/OS using multivariable Cox PH regression models. The following potential prognostic variables were selected based on literature[2,17-19] and entered in the Cox PH model: number of metastatic sites at start of FTD/TPI, time between diagnosis mCRC and start of FTD/TPI, age at start of FTD/TPI, sidedness primary tumor, stage at diagnosis CRC, liver metastasis at start of FTD/TPI, liver-only metastasis at start of FTD/TPI, peritoneal metastasis at start of FTD/TPI, prior exposure to all standard treatments (fluoropyrimidine, irinotecan, oxaliplatin, and bevacizumab), and primary tumor resection. As the PH assumption did not hold for the association between baseline QoL-SS and OS based on the Schoenfeld residuals, an interaction between baseline QoL-SS and time was added to the model.[20] Hazard ratios (HRs) with 95% confidence intervals (CI) were obtained from the Cox PH models. For illustrative purposes, OS was predicted for varying baseline Summary Scores from an adjusted Cox PH model with mean values entered for the remaining prognostic variables.

P values < .05 were considered statistically significant and all tests were 2-sided. Analyses were carried out using SPSS version 25.0, R version 3.5.1.[21] and GraphPad Prism 8.3.

Table 1 Baseline Characteristics

Total study population	150 (100%)
Male sex	102 (68.0%)
Age in y at diagnosis CRC	
- Mean (±SD)	61.8 (±9.3)
- Range	32-82
Age at start of FTD/TPI, mean (±SD)	65.0 (±9.1)
Level of education[a]	
- Low	48 (32.2%)
- Medium	45 (30.0%)
- High	56 (37.3%)
- Missing	1 (0.7%)
Cohabitants	
- Living alone	21 (14.0%)
- With partner	95 (63.3%)
- With partner and children	22 (14.7%)
- Otherwise	10 (6.7%)
- Missing	2 (1.3%)
Y of diagnosis first metastasis CRC	
2009-2013	11 (7.3%)
2014	17 (11.3%)
2015	27 (18.0%)
2016	47 (31.3%)
2017	27 (18.0%)
2018	9 (6.0%)
Missing	12 (8.0%)
Y in which FTD/TPI was started	
2016	3 (2.0%)
2017	31 (20.7%)
2018	85 (56.7%)
2019	31 (20.7%)
Primary tumor site	
- Right-sided colon	44 (29.3%)
- Left-sided colon	54 (36.0%)
- Rectal	52 (34.7%)
Primary tumor resection	113 (75.3%)
Synchronous mCRC (stage IV CRC at diagnosis)	98 (65.3%)
Metachronous mCRC	52 (34.7%)
> 1 Primary tumor	4 (2.7%)
Morphology	
- Adenocarcinoma	141 (94.0%)
- Mucinous adenocarcinoma	8 (5.3%)
- Signet ring cell carcinoma	1 (0.7%)
Molecular pathology[b]	
BRAF mutation	4 (2.7%)
BRAF wildtype	108 (72.0%)
BRAF status unavailable	38 (25.3%)
RAS mutation	67 (44.7%)

(*continued on next page*)

Table 1 (*continued*)

RAS wildtype	49 (32.7%)
RAS status unavailable	34 (22.7%)
MSI	2 (1.3%)
MSS	87 (58.0%)
MS status unavailable	61 (40.7%)
Number of metastatic sites at the start of FTD/TPI	
- No distant metastasis	1 (0.7%)
- 1 organ	20 (13.3%)
- 2 organs	57 (38.0%)
- 3 organs	48 (32.0%)
- ≥ 4 organs	24 (16.0%)
Localization of metastases at the start of FTD/TPI	
- Liver	115 (76.7%)
- Liver-only	10 (6.7%)
- Lung	102 (68.0%)
- Lung-only	6 (4.0%)
- Peritoneal	31 (20.7%)
- Peritoneal-only	4 (2.7%)
- Bone	28 (18.7%)
- Brain	3 (2.0%)
Number of prior systemic treatment regimens[c]	
0	1 (0.7%)
1	18 (12.0%)
2	76 (50.7%)
3	41 (27.3%)
4	14 (9.3%)
Exposure to prior systemic anticancer agents[d]	
- fluoropyrimidine	150 (100%)
- irinotecan	82 (54.7%)
- oxaliplatin	132 (88.0%)
- bevacizumab	95 (63.3%)
- anti–EGFR	47 (31.3%)
- regorafenib	0 (0%)
Exposure to all standard chemotherapy agents[d] (fluoropyrimidine,oxaliplatin, irinotecan)	75 (50%)
Exposure to all standard chemotherapy agents + bevacizumab[d]	55 (36.7%)
Bevacizumab received simultaneously with FTD/TPI[e]	2 (1.3%)
Time in mo between diagnosis mCRC and start FTD/TPI	
Median (IQR)	26.2 (16.8-40.8)
< 18 mo	43 (28.7%)
≥ 18 mo	107 (71.3%)

CRC = colorectal cancer; SD = standard deviation; IQR = interquartile range; FTD/TPI = trifluridine/tipiracil; mCRC = metastatic colorectal cancer.
[a] Education: low (no education, primary school, lower general secondary education); medium (higher general secondary education or secondary vocational training); high (higher vocational training, university)[40]
[b] We assumed that RAS and BRAF mutations are mutually exclusive.
[c] If a tumor recurred within 6 months after the last administration of adjuvant systemic therapy, this adjuvant systemic therapy was counted as a prior treatment regimen for metastatic disease.
[d] Adjuvant chemotherapy was counted as prior exposure to fluoropyrimidine/oxaliplatin regardless of the interval between last administration of adjuvant chemotherapy and recurrence.
[e] Most likely in the context of the TASCO1 study.

Table 2 Estimated EORTC QLQ-C30 HRQL Baseline Scores and Estimated Change in Score During FTD/TPI Use Per Month. A Change of ≥10 Points From Baseline is Considered to be Clinically Relevant[12,13]

Scale/item	Estimated baseline score			Estimated mean change in score per mo		
	Score	SE	95% CI	Score	SE	95% CI
Summary Score[a]	76.4	1.27	(73.9;78.9)	-0.53	0.16	(-0.84;-0.21)
Global Health Status[a]	63.2	1.56	(60.2;66.3)	-0.60	0.23	(-1.05;-0.15)
Functional scales[b]						
Physical functioning	75.3	1.77	(71.8;78.7)	-0.66	0.20	(-1.05;-0.26)
Role functioning	61.7	2.38	(57.0;66.4)	-1.08	0.31	(-1.70;-0.46)
Emotional functioning	75.1	1.64	(71.9;78.3)	-0.52	0.21	(-0.93;-0.12)
Cognitive functioning	84.6	1.57	(81.5;87.6)	-0.11	0.18	(-0.46;0.24)
Social functioning	75.5	1.85	(71.8;79.1)	-0.45	0.27	(-0.97;0.08)
Symptom scales/items[c]						
Fatigue	40.9	2.05	(36.9;44.9)	0.95	0.29	(0.38;1.52)
Nausea and vomiting	14.4	1.52	(11.4;17.4)	0.23	0.21	(-0.17;0.64)
Pain	23.3	2.28	(18.9;27.8)	0.77	0.30	(0.17;1.36)
Dyspnea	21.8	2.13	(17.6;26.0)	1.57	0.38	(0.83;2.30)
Insomnia	27.9	3.01	(22.0;33.8)	-0.32	0.62	(-1.54;0.89)
Appetite loss	24.4	2.47	(19.5;29.2)	0.83	0.31	(0.22;1.45)
Constipation	13.2	1.78	(9.8;16.7)	0.52	0.25	(0.03;1.00)
Diarrhea	17.2	1.13	(15.0;19.4)	-0.23	0.22	(-0.65;0.20)
Financial difficulties	11.2	1.80	(7.6;14.7)	-0.33	0.17	(-0.67;0.01)

HRQL: health-related quality of life, FTD/TPI: trifluridine/tipiracil, SE: standard error, 95% CI: 95% confidence interval.
All of the scales and single-items measures range in score from 0 to 100.
[a] A high score represents a high quality of life.
[b] A high score represents a high level of functioning.
[c] A high score represents a high level of symptomatology/problems.

Table 3 Estimated EORTC QLQ-C30 Summary Score[a] Baseline Score and Estimated Change in Score During FTD/TPI Use Per Month, Stratified by FTD/TPI Treatment Duration

	Estimated baseline score			Estimated mean change in score per mo		
	Score	SE	95% CI	Score	SE	95% CI
Overall	76.4	1.27	(73.9;78.9)	-0.53	0.16	(-0.84;-0.21)
FTD/TPI treatment duration:						
< 3 mo	73.6	1.84	(70.0;77.2)	-6.73	1.24	(-9.16;-4.30)
≥ 3 mo	79.9	1.60	(76.8-83.1)	-0.55	0.18	(-0.89;-0.20)

[a] A high score represents a high quality of life.

Results

Study Population

Between February 2017 and July 2019, 177 patients from 26 different hospitals in the Netherlands were included in the QUALITAS study. Cut-off for data analysis was May 12, 2020, when only 2 participants were still on FTD/TPI treatment and completing questionnaires. Patients were excluded if they did not start FTD/TPI treatment, withdrew their consent for questionnaires prior to the first questionnaire, or did not complete any questionnaire within the predefined timeframe (Figure 1). One hundred fifty patients were included for data analysis. Just over one-third of patients had been exposed to all 3 standard chemotherapy agents and bevacizumab prior to FTD/TPI initiation (Table 1 for baseline characteristics). The median time from mCRC diagnosis to start of FTD/TPI was 26.2 months (interquartile range 16.8-40.8).

Quality of Life

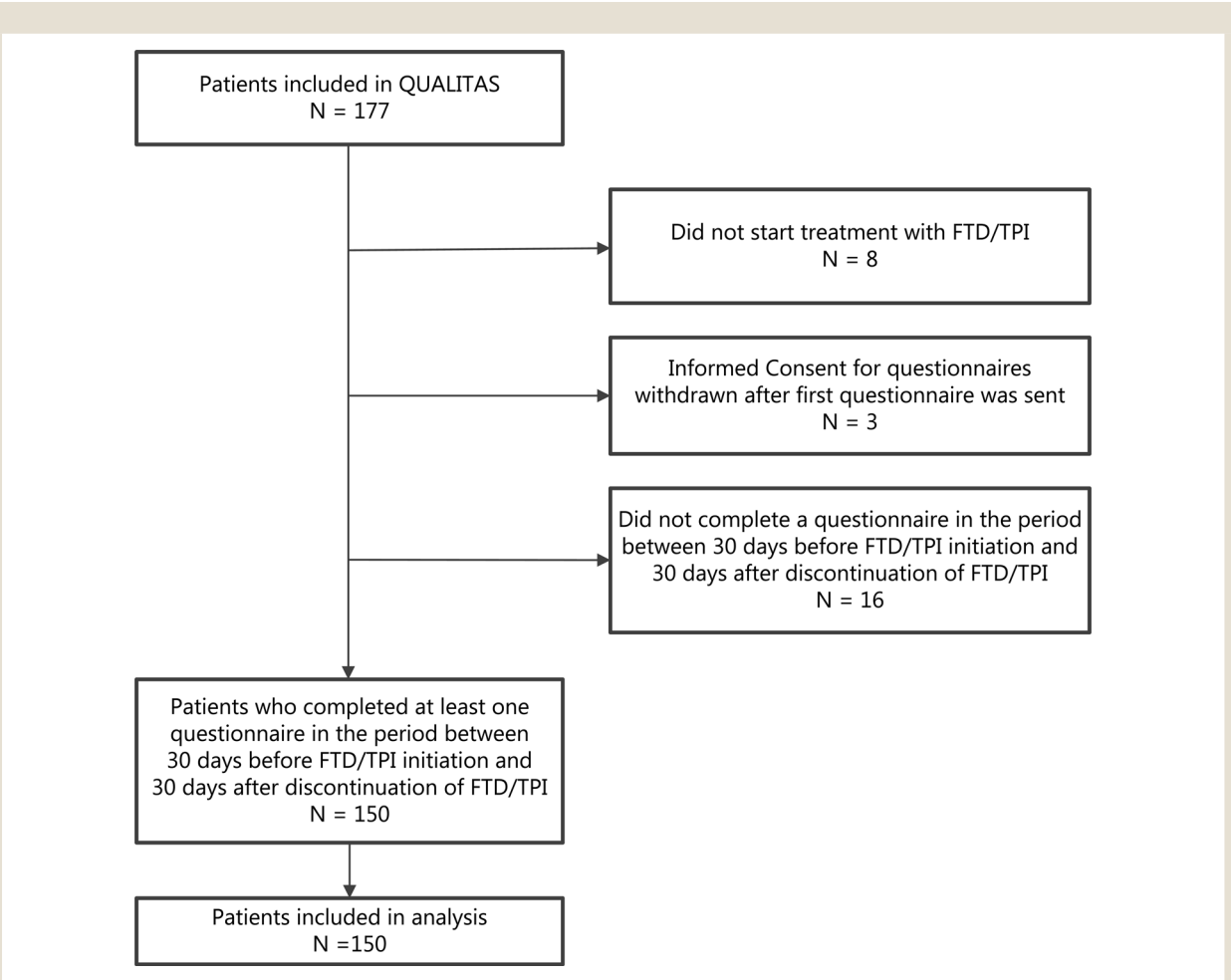
In total, 554 questionnaires were completed, on average 3.7 questionnaires per participant. The questionnaire completion rate was 85%. Sixty-two percent (93 of 150) of patients entered the study at start of FTD/TPI treatment. At FTD/TPI initiation, patients already experienced clinically important fatigue (threshold for clinical importance; TCI 39), nausea and vomiting (TCI 8), and dyspnea

Table 4 Multivariable Cox Proportional Hazards Regression Analysis for OS After Start of FTD/TPI

Prognostic factor	HR for death	95% CI	*P* value
Number of metastatic sites at start of FTD/TPI	1.20	0.96-1.49	.110
Time between diagnosis mCRC and start FTD/TPI (per mo increase)	0.98	0.97-1.00	.018[c]
Age at start of FTD/TPI (per 5-y increase)	0.93	0.84-1.04	.198
Sidedness primary tumor (left vs. right sided)[a]	0.71	0.46-1.10	.128
Stage at diagnosis CRC (stage IV vs. metachronous mCRC)	1.54	0.86-2.76	.147
Liver metastasis at start of FTD/TPI	0.81	0.47-1.40	.445
Liver-only metastasis at start of FTD/TPI	0.85	0.37-1.98	.710
Peritoneal metastasis at start of FTD/TPI	0.64	0.39-1.06	.084
Prior exposure to all standard treatments[b]	1.58	1.06-2.36	.025[c]
Primary tumor resection	1.06	0.63-1.79	.814
Baseline Summary Score EORTC QLQ-C30 (per 10-point increase)	0.45	0.32-0.63	.0000043[c]
- Interaction with time (in mo)	1.05	1.01-1.10	.011[c]
- After 10 mo of FTD/TPI treatment	0.45 x (1.05 ^ 10) = 0.73		

HR: hazard ratio, 95% CI: 95% confidence interval, mCRC: metastatic colorectal cancer.
[a] Left-sided colon and rectum versus right-sided colon.
[b] Fluoropyrimidine, irinotecan, oxaliplatin, and bevacizumab.
[c] $P < .05$.

Figure 1 Flowchart inclusions/exclusions QUALITAS study.



(TCI 17), as well as a clinically important impairment in physical functioning (TCI 83)[22] (Figure 2).

Change in QoL During FTD/TPI Treatment

As shown in Table 2, estimated mean change per month for the different QoL dimensions of the EORTC QLQ-C30 lies between -1.1 [95% CI -1.7;-0.5] (role functioning) and 1.6 (0.8;2.3) (dyspnea). Based on a 10-month cut-off point (after which approximately 90% of patients had discontinued FTD/TPI treatment), there were no clinically relevant changes from baseline in QoL-SS, GHS, functioning scales and symptom scales except for a deterioration in role functioning (change from baseline after 10 months -10.8 points [-4.3;-17.3]) and an increase in dyspnea (change from baseline after 7 months 11.0 points [5.2;16.8]) (Figure 2). Results are similar for the CRC-specific domains of the EORTC QLQ-CR29 (Suppl Table 2, Suppl Figure 1): no clinically relevant changes over time were found. As a sensitivity analysis, estimated mean change per month for the different QoL dimensions of the EORTC QLQ-C30 are provided separately for patients who completed a baseline questionnaire (n = 93) in Suppl Table 3. No consistent major differences were found when compared to the results of the whole study population.

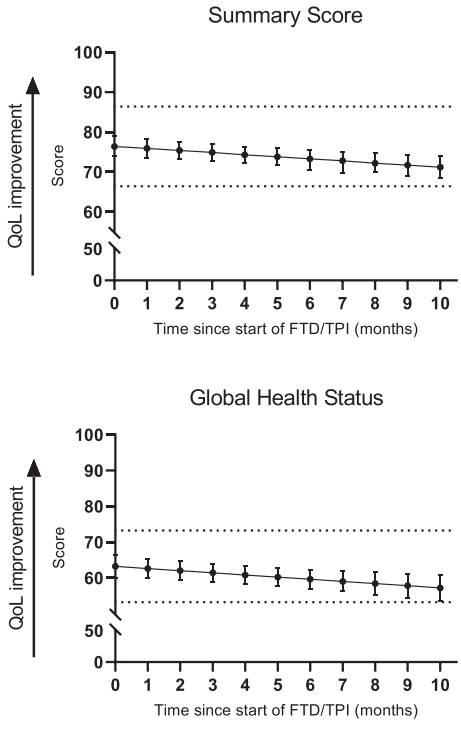
EORTC QLQ-C30 Summary Score Stratified by FTD/TPI Treatment Duration

Patients who were treated with FTD/TPI for ≥ 3 months (n = 85, "good responders") reported 6.3 [1.6;11.1] points higher baseline QoL, compared with patients who were treated for < 3 months (n = 65, "poor responders") (Table 3 and Figure 3). The QoL-SS of the good responders remained stable during FTD/TPI treatment, while the QoL-SS of the poor responders deteriorated. This is reflected by a statistically significant difference of 6.2 [3.7;8.6] points in the change of the score per month between the 2 groups: -0.6 [-0.9;-0.2] versus -6.7 [-9.2;-4.3]. Consequently, time to a clinically relevant deterioration in QoL was less than 2 months for the "poor responders".

Time to Treatment Failure and Survival

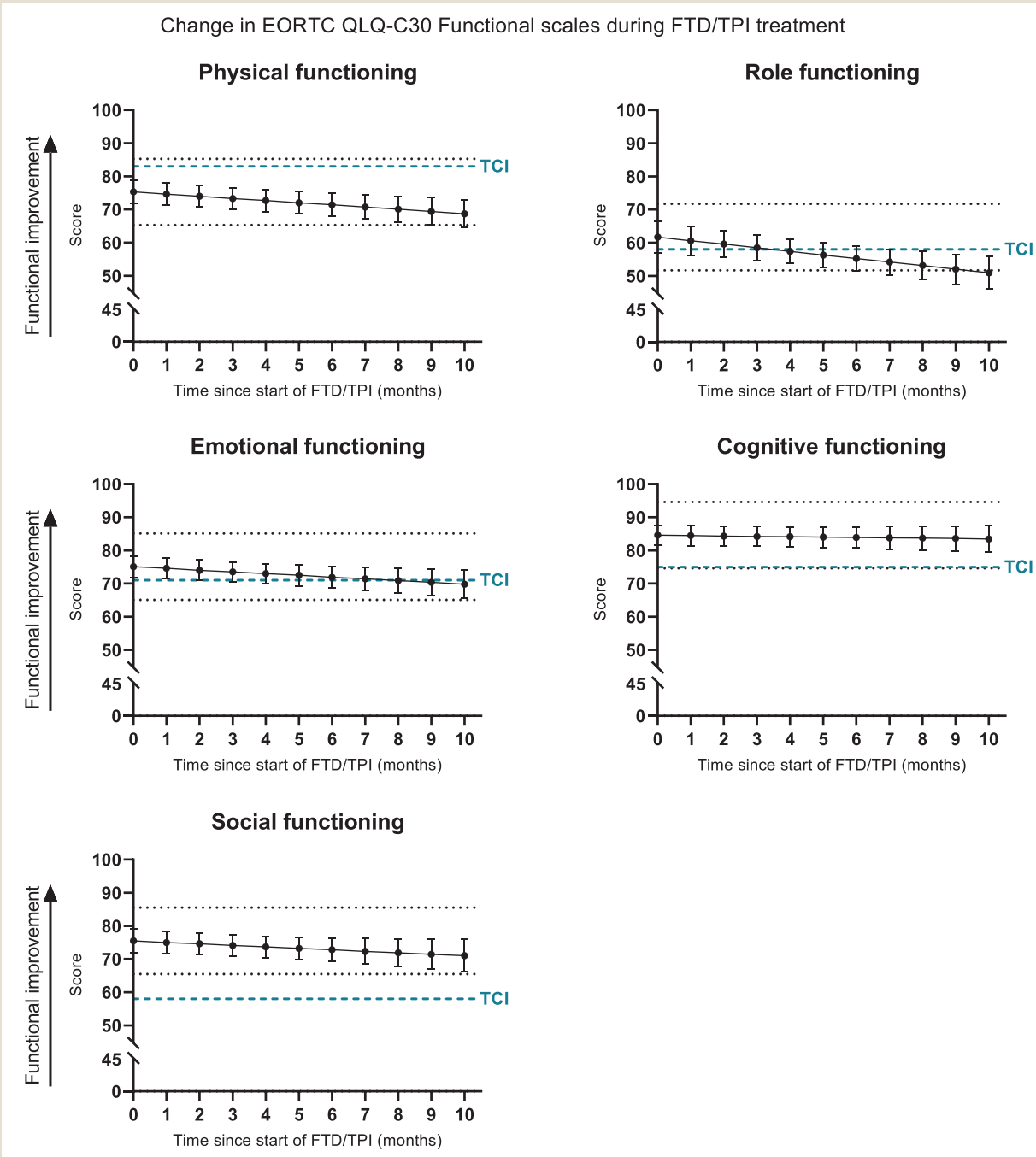
At end of follow up, 99% (n = 149) and 95% (n = 143) of participants had experienced treatment failure and progression of disease, respectively. By 31 January 2020, 82% of participants (n = 123) had died. Median PFS, TTF, and OS from FTD/TPI initiation were 2.9 [2.7;3.1], 3.1 [2.9;3.2], and 7.7 [6.6;8.8] months, respectively. Figure 4 shows Kaplan-Meier curves for PFS, TTF, and OS with the corresponding risk tables.

Figure 2 Change in EORTC QLQ-C30 scores during FTD/TPI treatment.



Error bars represent 95% CI
Grid lines represent a clinically relevant 10-point change from baseline score.

Figure 2 Continued

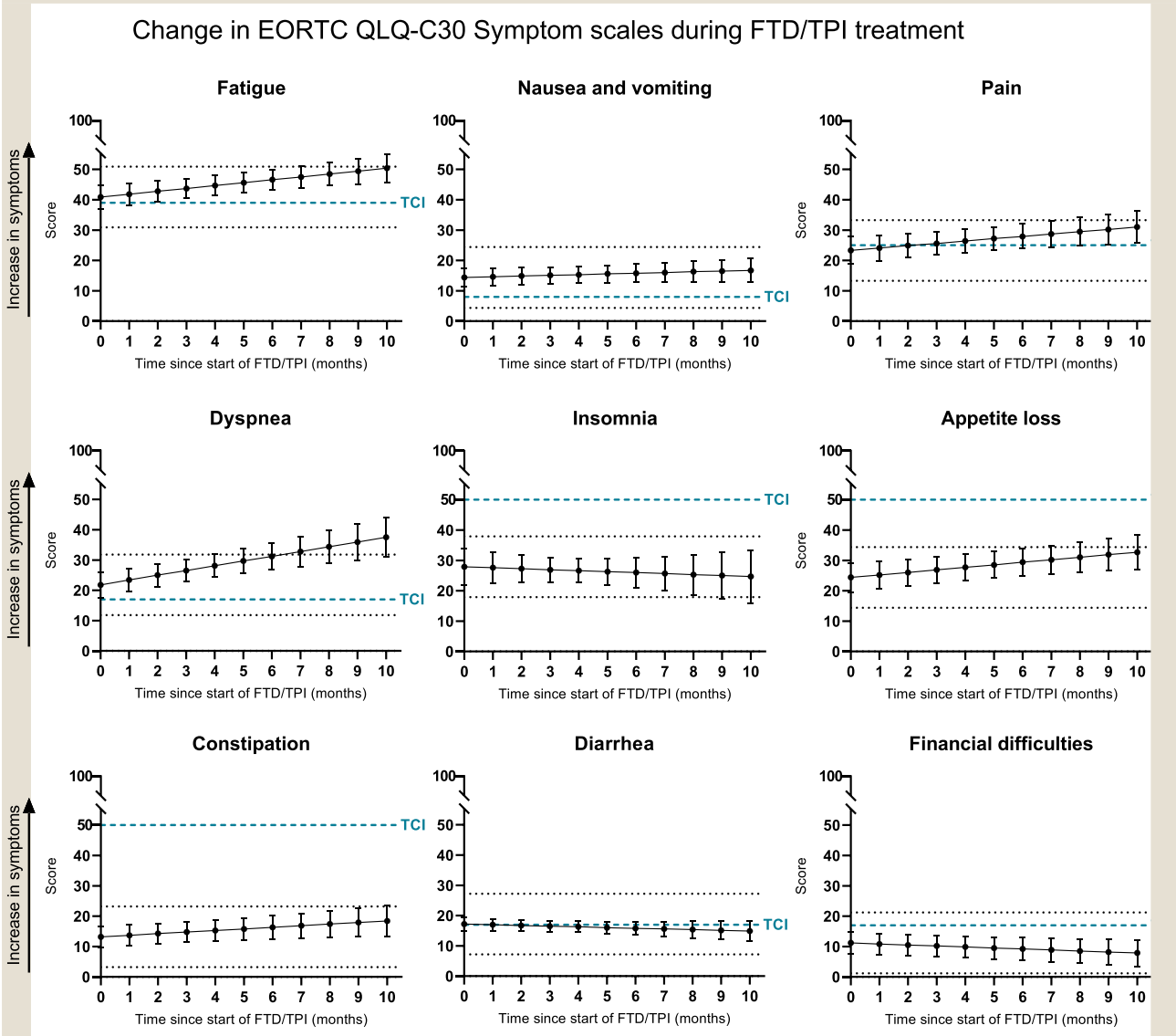


Error bars represent 95% CI
Black grid lines represent a clinically relevant 10-point change from baseline score.
Green grid lines represent threshold for clinical importance (TCI).

Prognostic Factors

Baseline QoL-SS was independently associated with OS (HR 0.45 [0.32;0.63] at baseline, HR 0.73 after 10 months), PFS (0.63 [0.48;0.83] at baseline, HR 0.77 after 10 months), and TTF (0.64 [0.47;0.86] at baseline, HR 0.71 after 10 months) (Table 4, Suppl Table 4, Suppl Table 5). The higher the baseline QoL-SS, the longer the PFS, TTF, and OS. In Figure 5, we illustrate the predicted OS for 5 fictional patients with varying baseline Summary Scores, adjusted for the other prespecified variables in a Cox PH model. Every 10-point increase in baseline QoL-SS is associated with an

Figure 2 Continued



Error bars represent 95% CI
Black grid lines represent a clinically relevant 10-point change from baseline score.
Green grid lines represent threshold for clinical importance (TCI).

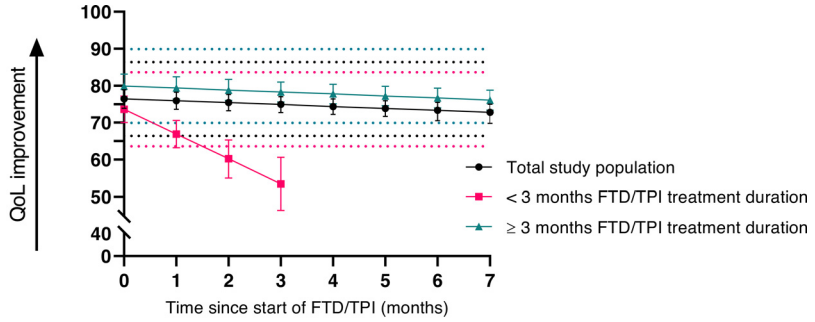
approximate 50% decrease in the hazard of dying (55% at baseline - 27% after 10 months).

Discussion

We assessed the course of QoL over time, TTF, and survival of mCRC patients treated with FTD/TPI in daily practice. QoL was maintained both in the overall study population, and in patients who were treated for ≥ 3 months ("good responders"). Only in "poor responders" (treatment duration < 3 months) time to a clinically relevant deterioration in QoL was <2 months, presumably due to disease progression since TTF corresponded to PFS. This concurs with previous research that has demonstrated that toxicity from FTD/TPI is limited and rarely leads to treatment discontinuation.[2,23–25]

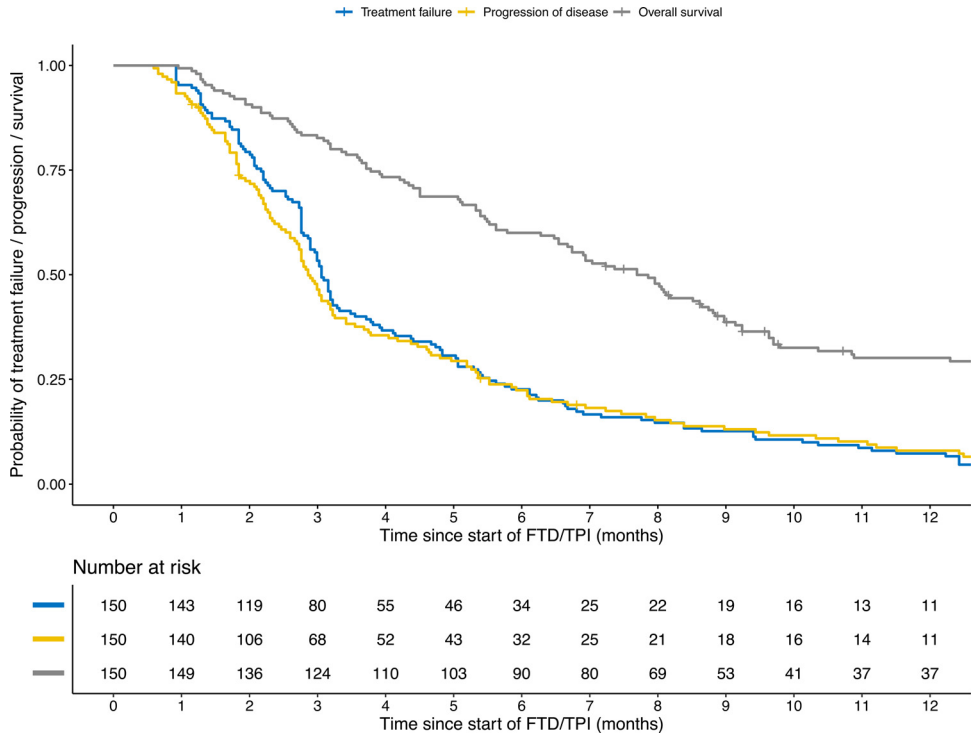
Efficacy of FTD/TPI in pretreated mCRC patients was demonstrated in the RECOURSE trial.[2]. Although QoL was not assessed in this RCT, the following AEs likely to affect QoL were reported more frequently in patients treated with FTD/TPI than placebo: nausea, vomiting, diarrhea, appetite loss, fatigue, and asthenia.[2,26] Patients in the current study did not report clinically relevant increases in these symptoms during FTD/TPI treatment. This might be explained by a difference between physician-reporting and

Figure 3 Change in EORTC QLQ-C30 summary score during FTD/TPI treatment, stratified by treatment duration.



Grid lines represent a clinically relevant 10-point change from baseline score.

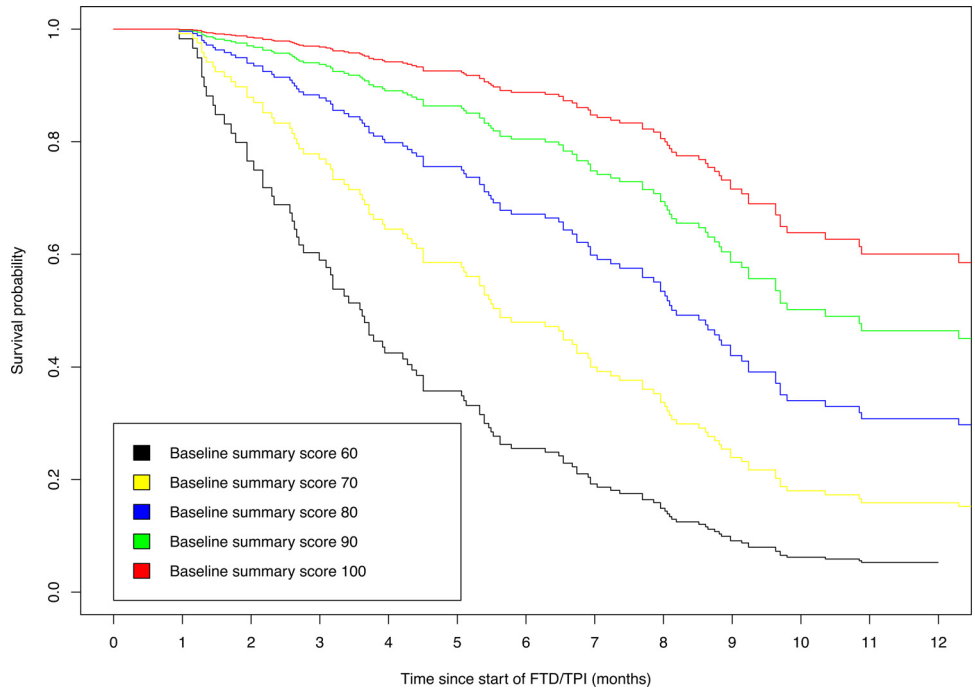
Figure 4 Kaplan-Meier curves for time to treatment failure, progression-free survival, and overall survival.



patient-reporting, although we expected underreporting instead of overreporting of symptoms by physicians in the RECOURSE trial.[4] The maintenance of QoL during FTD/TPI treatment in our study is consistent with 2 post hoc analyses of the RECOURSE data: (1) an analysis of AEs and ECOG PS suggesting that FTD/TPI treatment does not result in deterioration of QoL versus placebo,[26] and (2) a Quality-adjusted Time Without Symptoms of disease or Toxicity (QTWiST) analysis suggesting improved quality-adjusted survival in patients treated with FTD/TPI versus placebo.[27] Furthermore, our results confirm the results of the only previous study that measured QoL over time during FTD/TPI treatment in mCRC patients[18]; the PRECONNECT study, which found no clinically relevant change in QoL over time in 793 participants. Likewise, our results concur with the TAGS trial, which showed that QoL was maintained during FTD/TPI treatment in metastatic gastric patients.[28]

The OS of our cohort (7.7 months) is comparable with the OS of patients in the intervention arm of the RECOURSE[2] (7.1 months)

Figure 5 Predicted Overall Survival for 5 fictional patients with varying baseline Summary Score, adjusted for other prespecified variables.



and TERRA[29] (7.8 months) trials, and some cohort studies (7.4-8.3 months).[25,30,31] OS of patients in the Dutch[19] and Italian[24] compassionate use programs (CUP) was lower. This might be a consequence of selective participation,[32] and survivor bias due to late study entry in QUALITAS. Also, care must be taken when comparing results of trials, CUPs, and real-world studies such as QUALITAS, given the difference in study populations.[33] For example, the proportion of patients that was exposed to all standard anticancer agents prior to FTD/TPI initiation differed greatly between these studies: this was 100%, 69%, and 37%, for the RECOURSE, Dutch CUP, and QUALITAS study population, respectively. PFS and TTF in our cohort is similar to PFS and TTF found in the PRECONNECT study,[18] which is approximately 1 month longer than the PFS and TTF reported in the RECOURSE[2] and TERRA[29] trials. This might be due to the protocolized periodical (radiological) evaluations and strict stop criteria that apply to patients participating in trials, while response evaluation in our study took place according to daily practice. Also, only the first day of the last course of FTD/TPI was registered in the NCR. We defined the stop date of FTD/TPI as 28 days after the first day of the last prescribed course, which may have led to a minor overestimation of PFS, and TTF.

Baseline QoL was strongly and independently associated with OS, PFS, and TTF. At baseline, a 10-point higher QoL-SS is associated with a 55% decrease in the hazard of dying - although the strength of the association decreases over time. Several possible explanations for the relation between baseline QoL and outcome, which is in line with previous research,[34–36] have been described by Gotay et al.[36] First, baseline QoL-SS better reflects patient functioning and well-being than traditional prognostic (physician-reported) indicators. In fact, it was reported that PROs have superior prognostic value to physician-reported PS.[36,37] Second, PROs detect relevant lowered patient well-being earlier than other measures. Third, higher baseline QoL is linked with more positive behaviors that might affect survival.

The main strength of our study lies in the monthly measurement of patient-reported symptoms and QoL in mCRC patients who were treated in daily clinical practice in a large number of hospitals. Furthermore, contrary to other studies,[18,37] we used the recently developed QoL-SS, which has more prognostic value, better validity, and better responsiveness than the original, underlying QLQ-C30 scale scores.[10,35] Other strong points are the use of the CRC-specific EORTC QLQ-CR29 in addition to the generic EORTC QLQ-C30 questionnaire,[34] and the statistical analyses with joint modeling.

Several limitations of our study should be considered. First, due to the lack of a control group no inferences can be made on the effect of FTD/TPI on QoL or survival. Second, participation bias,[38] that is inherent to questionnaire studies, may have led to an overestimation of QoL in our study. Third, due to the high proportion of patients that entered the study after FTD/TPI treatment had started, baseline QoL could not be added to the mixed effects model as a fixed variable. This precluded the analysis of the association between baseline QoL and the course of QoL over time during FTD/TPI treatment. Finally, no data was available on other factors

that might impact QoL such as the quality of supportive care in the different hospitals.

This study has 2 main implications for clinical practice and future research. First, the use of FTD/TPI in daily practice is supported by the maintenance of QoL during FTD/TPI treatment in the overall study population. Second, the median PFS of 2.9 months implies that many patients do not benefit from FTD/TPI treatment. Adequate patient selection would avoid unnecessary exposure to toxicity and increase cost-effectiveness. The strong and independent association between worse QoL at the start of FTD/TPI and shorter survival suggests that baseline QoL should be integrated in prognostic scores. We recommend clinicians to take baseline QoL into account to achieve adequate prognostication, and to determine the optimal treatment strategy for individual patients. To make this possible, PROs need to be collected and reported more widely to complement traditional predictors and endpoints in oncology.[1,34,39]

In conclusion, we found that QoL is maintained during FTD/TPI treatment in the overall study population and in patients who were treated for at least 3 months, which supports its use in clinical practice. The strong and independent association between worse QoL at the start of FTD/TPI and shorter survival suggests that QoL should be incorporated in prognostication.

Clinical Practice Points

What is already known about this subject?

The RECOURSE trial demonstrated a modest benefit in OS for FTD/TPI versus placebo in pretreated mCRC patients.

What are the new findings?

In mCRC patients who were treated in daily practice, no clinically relevant change in QoL during FTD/TPI treatment was found. Median PFS, time to treatment failure (TTF), and OS were 2.9 (2.7;3.1), 3.1 (2.9;3.2) and 7.7 (6.6;8.8) months, respectively. Worse baseline QoL was independently associated with shorter OS, PFS, and TTF.

How might it impact on clinical practice in the forseeable future?

The maintenance of QoL during FTD/TPI treatment in daily practice supports its use. The short median PFS and the strong association between worse baseline QoL and shorter PFS/OS suggests that clinicians should take QoL into account when determining prognosis and treatment strategy for individual patients.

MicroAbstract Qualitas

Background

Efficacy of FTD/TPI was demonstrated in an RCT that did not assess QoL.

Patients and Methods

QoL was assessed in 150 mCRC patients that were treated with FTD/TPI in daily practice.

Results

No clinically relevant change in QoL during FTD/TPI treatment was found. Worse baseline QoL was independently associated with shorter survival.

Conclusion

The maintenance of QoL during FTD/TPI treatment supports its use. QoL should be incorporated in prognostication.

Author Contributions

Study design and supervision: Vink, Koopman, May. Funding acquisition: Vink, Koopman, May. Data collection: Hamers, Vink. Literature review: Hamers. Provided patients: QUALITAS study group. Data analysis: Hamers, Elferink, Stellato, Dijksterhuis, May. Manuscript preparation: Hamers. All authors contributed to the interpretation of the results, revised and critically reviewed the manuscript, and approved the submitted version.

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Ethics

The study was approved by the Privacy Review Board of the Netherlands Cancer Registry (NCR) and the scientific committee of the Dutch Colorectal Cancer Group. The Prospective Dutch CRC cohort (PLCRC) was approved by the Medical Research Ethics Committee (MREC) of Utrecht, the Netherlands (METC 12-510). Patients who participated in PLCRC provided written informed consent.

Data Availability

The data that support the findings of this study are available from the NCR and PLCRC. Restrictions apply to the availability of these data, which were used under license for this study.

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Disclosure

GRV reports research grants/funding paid to her institution by Servier, BMS, Bayer, Merck, PGDx, and Sirtex. GRV reports travel/accommodation fees from Servier. CJAP reports his advisory role for Nordic Pharma. MK reports personal travel/accommodation fees from Congress Care-Dutch oncology society (NVMO). MK reports research grants/funding paid to her institution by Amgen, Bayer, BMS, Merck-Serono, Nordic Pharma, Roche, Servier, Sirtex, and Sanofi-Aventis. MK reports honoraria paid to her institution by BMS, Nordic Pharma, and Servier. MK reports the following nonfinancial interests: an advisory role for ZON-MW, membership of the scientific board of the Dutch Cancer Society (KWF), chairmanship of the Dutch Colorectal Cancer Group (DCCG), principal investigator (PI) of the Prospective Dutch CRC Cohort (PLCRC), involvement in several clinical trials

as PI or co-investigator in colorectal cancer. AMM reports advisory fees from Novartis paid to her institution. JdV has served as a consultant for Amgen, AstraZeneca, MSD, Pierre Fabre, and Servier, and has received institutional research funding from Servier (all outside the submitted work). All remaining authors have declared no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clcc.2022.03.002.

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