Safety, efficacy and patient-reported outcomes with trifluridine/tipiracil in pretreated metastatic colorectal cancer: results of the PRECONNECT study

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ABSTRACT

Background In RECOURSE (, trifluridine/tipiracil significantly improved overall survival and progression-free survival (PFS) versus placebo in patients with pretreated metastatic colorectal cancer (mCRC). PRECONNECT was designed to further characterise safety and clinical use of trifluridine/tipiracil.

Methods In this ongoing, international, multicentre, open-label trial, patients with pretreated mCRC received oral trifluridine/tipiracil 35 mg/m^2 twice daily on days 1–5 and 8–12 of each 28-day cycle. The primary endpoint was safety; secondary endpoints included PFS and quality of life (QoL).

Results 793 patients (median age 62 years) from 13 countries received trifluridine/tipiracil for a median of 2.84 months (IQR 2.64). Adverse events (AEs) were experienced by 96.7%; the most common (≥20% of patients) were neutropaenia, asthenia/fatigue, nausea, anaemia and diarrhoea. Grade ≥3 AEs occurred in 73.9% of patients, with the most common being neutropaenia (39.1% of patients), anaemia (9.8%) and asthenia/fatigue (5.0%). Median PFS was 2.8 months (95% CI 2.7 to 2.9). Median time to Eastern Cooperative Oncology Group performance status deterioration (≥2) was 8.9 months (range 0.03–14.72). There was no clinically relevant change from baseline in QoL.

Conclusions PRECONNECT showed consistent results with the previously demonstrated safety and efficacy profile of trifluridine/tipiracil, with no new safety concerns identified. QoL was maintained during treatment.

Trial registration number NCT03306394.

Key questions

What is already known about this subject?

► In the pivotal phase III RECOURSE study (NCT01607957), trifluridine/tipiracil significantly improved overall survival and progression-free survival versus placebo in patients with metastatic colorectal cancer who had progressed on standard therapies. However, quality of life is an important outcome in later-line therapy, and it was not assessed in the RECOURSE trial.

What does this study add?

► PRECONNECT was initiated to provide a large cohort of eligible adult patients with mCRC early access to trifluridine/tipiracil. It showed that trifluridine/tipiracil safety profile was acceptable and consistent with that reported in the randomised phase III RECOURSE trial. The efficacy of trifluridine/tipiracil was also confirmed. Lastly, quality of life was maintained while on trifluridine/tipiracil treatment.

How might this impact on clinical practice?

► The results of this study support the use of trifluridine/tipiracil as a monotherapy beyond second line of treatment of patients with mCRC.

INTRODUCTION

As a result of significant improvements in the treatment and management of patients with metastatic colorectal cancer (mCRC) in the past two decades, substantial gains in treatment outcomes have been observed, with median overall survival (OS) reaching approximately 30 months in randomised clinical trials.[1] First-line and second-line treatment includes chemotherapeutic drugs and targeted monoclonal antibodies. Many patients continue to have good performance status beyond second line, meaning that additional treatment options are needed. In third line, therapeutic options recommended by the European Society of Medical Oncology include agents such as trifluridine/tipiracil.[1 2]

Trifluridine/tipiracil (formerly known as TAS-102) is an oral cytotoxic chemotherapy consisting of the thymidine analogue trifluridine and the thymidine phosphorylase inhibitor tipiracil hydrochloride.[3 4] In the pivotal phase III RECOURSE trial (n=800), compared with placebo, trifluridine/tipiracil significantly improved median OS (7.2 vs 5.2 months; HR 0.69, p<0.0001)[5] and

progression-free survival (PFS; 2.0 vs 1.7 months; HR 0.48, p<0.001) and had an acceptable toxicity profile in patients with mCRC who had progressed on standard therapies.[6] These survival benefits were observed across several prognostic subgroups.[5]

Although the RECOURSE study did not include a formal assessment of quality of life (QoL),[6] an analysis of proxies of QoL such as Eastern Cooperative Oncology Group performance status (ECOG PS) and a quality-adjusted time without symptoms of disease or toxicity analysis showed clinically meaningful improvements in patients treated with trifluridine/tipiracil versus placebo in pretreated mCRC.[7 8]

PRECONNECT, an international, phase IIIb study, was initiated to provide a large cohort of eligible adult patients with mCRC early access to trifluridine/tipiracil, in order to further assess safety, efficacy and QoL as measured by patient-reported outcomes (PROs).

METHODS

Study design and patients

PRECONNECT is an ongoing, international, multicentre, open-label, single-arm, phase IIIb study of trifluridine/tipiracil in men or women (aged ≥18 years) with pretreated, histologically confirmed adenocarcinoma of the colon or rectum and metastatic lesions. The cut-off date for this analysis was 30 September 2018. Inclusion and exclusion criteria were the same as those in the RECOURSE trial.[6] In summary, eligible patients had received at least two prior regimens of standard chemotherapies (including fluoropyrimidines, irinotecan, oxaliplatin, an antivascular endothelial growth factor monoclonal antibody and at least one of epidermal growth factor receptor monoclonal antibodies for *RAS* wild-type tumours) for mCRC, had an ECOG PS of 0 or 1 during the screening period and had adequate renal, hepatic, cardiac and bone marrow function. Exclusion criteria included a serious illness or medical condition.

All patients gave written informed consent before participation. The trial was registered on ClinicalTrials.gov.

Treatment

Eligible patients received oral trifluridine/tipiracil 35 mg/m^2 twice daily (after morning and evening meals) on days 1–5 and 8–12 of each 28-day cycle. The starting dose of 35 mg/m^2 was maintained throughout the treatment period as long as the patient was receiving benefit from trifluridine/tipiracil and no adverse events leading to dose reduction occurred. Dose adjustments and dose delays were based on individual safety and tolerability (figure 1). Patients continued receiving treatment until one or more of the following criteria for treatment discontinuation were met: disease progression, unacceptable toxicity, withdrawal of consent, physician decision, pregnancy, major protocol deviation (defined as 'a deviation that interferes with the study evaluations and/or jeopardises patient's safety', mainly related to eligibility criteria or study drug management) or commercial availability of trifluridine/tipiracil.

Endpoints

The primary endpoint was safety, assessed from baseline through to the end-of-treatment visit, which was up to 28 days after the last study drug administration. Safety assessments included treatment-emergent adverse events (TEAEs), graded according to the National Institute of Health Common Terminology Criteria for Adverse Events version 4.03.[9]

Secondary endpoints included PFS and QoL. PFS was defined as the time from the first intake of trifluridine/tipiracil until the date of investigator-assessed disease progression or death from any cause. Tumour measurements were not formally planned in the protocol and were made according to the investigator's usual practice. The date of disease progression was collected with radiographic imaging if available. Deaths occurring up to 28 days after treatment were recorded. As there was no follow-up beyond that time, no OS data were available. Time to ECOG PS deterioration was defined as the time from the first intake of trifluridine/tipiracil until the first ECOG deterioration from 0 to 1 or missing at baseline to ≥2 postbaseline or death without previous ECOG ≥2 deterioration. ECOG PS was assessed at baseline, on day 1 of each treatment cycle (before treatment) and at the end-of-treatment visit.

QoL was assessed using the European Organization for Research and Treatment of Cancer Quality of Life (EORTC QLQ-C30) health questionnaire.[10 11] Patients were asked to complete the questionnaire at baseline, before the beginning of each treatment cycle, and then at the end of treatment. A questionnaire was considered non-evaluable when all EORTC QLQ-C30 scale scores were missing. Here, we considered all EORTC QLQ-C30 Global Health Status (GHS) scores, which were not set to missing (at least half of the items were completed). Results were considered valid only for cycles in which ≥10% of patients from the initial cohort had completed the questionnaire; after seven cycles of treatment, EORTC QLQ-C30 GHS analyses were not performed as fewer than 10% of the initial cohort of patients completed the questionnaire. Changes in QoL were considered to be clinically relevant if there was a ≥10-point change from baseline for the EORTC QLQ-C30 GHS score.[12] Only the EORTC QLQ-C30 GHS score will be detailed in this article.

A post hoc analysis was also undertaken to examine time to first tumour evaluation in the overall population and in patient subgroups defined by *RAS* status, primary tumour site, age, baseline ECOG PS and number of previous lines of therapy. This post hoc analysis was not planned and is exploratory.

Statistical analyses

Safety and efficacy variables were analysed in patients who received at least one dose of trifluridine/tipiracil. The

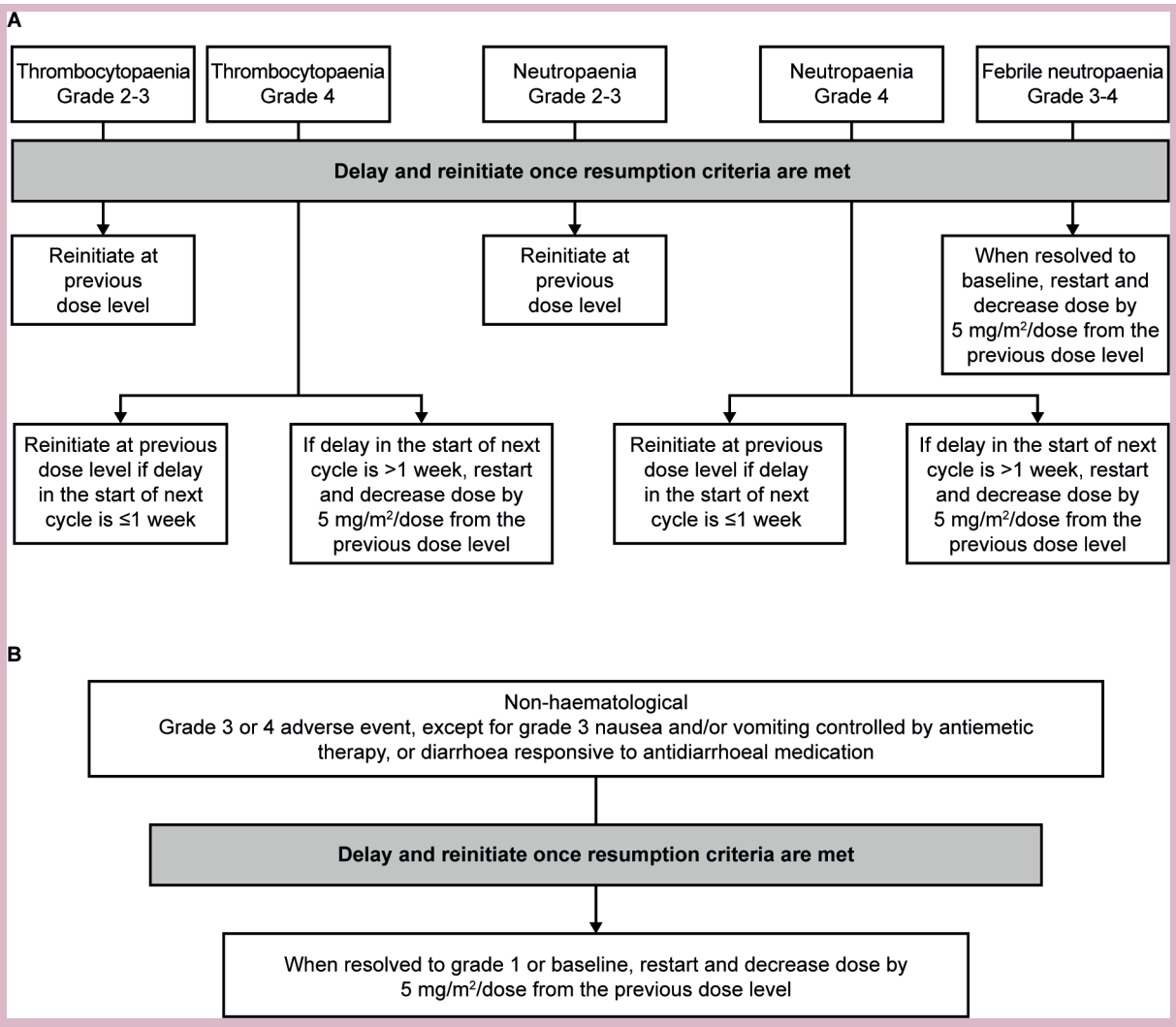

Figure 1 Management of (A) haematological and (B) non-haematological adverse events. §Resumption criteria are ≥1.5 × 10^9/L for neutrophils and ≥75 × 10^9/L for platelets. *Dose reductions are permitted to a minimum dose of 20 mg/m^2/dose twice daily; dose increase is not permitted after dose reduction.

aim of this study was to provide patients with treatment-refractory mCRC early access to trifluridine/tipiracil and to assess the efficacy and safety of trifluridine/tipiracil and health-related QoL using PROs in a setting similar to clinical practice, so there was no sample size calculation. Descriptive statistics (frequency and percentage for categorical variables, mean with SD and median with range or IQR for continuous variables) were used to summarise baseline demographics and clinical characteristics, TEAEs, ECOG PS and PROs. Median and 95% CIs were reported for survival analyses and were estimated using the Kaplan-Meier method. For PFS analysis, patients without disease progression or death before or at the last visit were censored at the date of the last evaluable tumour assessment. For time to ECOG PS deterioration analysis, patients not reaching an ECOG PS of ≥2 and not dead were censored at the last recorded ECOG PS assessment. For PROs, a mixed effects model was used to investigate the mean change from baseline in EORTC QLQ-C30 GHS score by cycle; in this model, the baseline EORTC QLQ-C30 GHS score was the fixed effect, no random effect was included and an unstructured covariance matrix was used for repeated measures. All statistical analyses were performed using SAS (V.9.2) software under the responsibility of the Centre of Excellence Methodology and Valorisation of Data of the sponsor (I.R.I.S).

RESULTS

Between 18 October 2016 and 31May 2018, 793 patients (59.9% male, median age 62 years) from 13 countries (Australia, Belgium, Bulgaria, Croatia, France, Ireland, Italy, Panama, Poland, Portugal, Slovakia, Slovenia and Turkey) were enrolled and treated (table 1). At the analysis cut-off date, the study was still ongoing. At the time of writing, recruitment was ended with 917 patients recruited in 16 countries, and some patients were still receiving treatment.

At baseline, 48.7% of patients had an ECOG PS of 0% and 52.6% had a mutant global *RAS* tumour status

Table 1 Patient baseline characteristics and demographics

Characteristic	n=793
Age, median (range), years	62 (24–87)
≤70	636 (80.2)
>70	157 (19.8)
Male	475 (59.9)
Race	
White	693 (87.4)
Black/African-American	4 (0.5)
Asian	12 (1.5)
Other/not reported	84 (10.6)
ECOG PS	
0	386 (48.7)
1	381 (48.0)
2	2 (0.3)
Data missing	24 (3.0)
Primary tumour site*	
Right colon	211 (26.6)
Left colon	496 (62.5)
Not specified/data missing	86 (10.8)
Time since first diagnosis of metastatic disease to first FTD/TPI intake	
Median (range), months	32.7 (0.0†–190.7)
<18 months	138 (17.4)
≥18 months	653 (82.3)
Data missing	2 (0.3)
Synchronous metastasis at diagnosis	416 (52.5)
Number of metastatic sites	
1	379 (47.8)
2	258 (32.5)
≥3	152 (19.2)
Data missing	4 (0.5)
Liver metastases at study entry	576 (72.6)
RAS status	
Wild type	227 (28.6)
Mutant	417 (52.6)
Not evaluable‡	149 (18.8)
BRAF status for *RAS* wild type§	
Wild type	154 (67.8)
Mutant	9 (4.0)
Not reported	64 (28.2)
Median time from last fluoropyrimidine intake, days (IQR)	88 (181)
Previous treatment¶	
Fluoropyrimidine	788 (99.8)
Oxaliplatin	776 (98.2)
Irinotecan	773 (97.9)
Oxaliplatin +irinotecan	762 (96.5)
Folinic acid agent	746 (94.4)
Anti-VEGF	655 (82.9)
Anti-EGFR	305 (38.6)
Regorafenib	264 (33.4)
No. of previous treatment lines**	
≤2	286 (36.1)
3	243 (30.6)
4	138 (17.4)
≥5	122 (15.4)
Data missing	4 (0.5)

All values presented as n (% patients) unless otherwise specified.
*Right colon includes transverse location, left colon includes rectum.
†Due to a transcription error, one patient had the date of first diagnosis of metastasis incorrectly reported as the same day as first FTD/TPI intake.
‡Global *RAS* status was measured according to both *KRAS* and *NRAS* status. If one patient was wild type for *KRAS* or *NRAS* and unknown for the other, he or she was considered as global *RAS* unknown.
§n=227 (patients with *RAS* wild type tumour status).
¶n=790 (data missing for three patients).
**A line of treatment is defined as a treatment that ends in progression of disease after first metastasis as stated by investigators.
ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; FTD/TPI, trifluridine/tipiracil; VEGF, vascular endothelial growth factor.

(table 1). The majority of patients (63.4%) had received at least three previous lines of treatment (table 1). Three patients were considered to have a major protocol deviation (one with brain metastasis and two with a baseline ECOG PS of 2); none of these patients were withdrawn because of this.

The median duration of treatment was 2.8 months (IQR 2.64), and the median number of cycles was 3 (range 1–16). Median relative dose intensity was 89.9% (table 2). At the analysis cut-off date, 789/793 patients (99.5%) had discontinued treatment; the reasons for discontinuation were progressive disease (n=633, 79.8%), commercial availability of trifluridine/tipiracil (n=82, 10.3%), TEAEs (n=40, 5.0%), non-medical reasons (n=17, 2.1% (including patient decision, n=11)), physician decision (n=15, 1.9%) and loss to follow-up (n=2, 0.3%). During the treatment period, 130 patients (16.4%) received at least one dose of granulocyte colony-stimulating factor.

Safety

TEAEs occurred in 96.7% of patients; at least one event was considered to be drug related in 78.7% of patients and at least one grade ≥3 TEAE occurred in 73.9% of patients (table 3). Serious TEAEs were experienced by 33.5% of

Table 2 Treatment exposure

	n=793
Duration of treatment, months	
Mean (SD)	3.5 (2.4)
Median (range)	2.8 (0.2–15.2)
Relative dose intensity,* median, %	89.9
Number of treatment cycles, months, mean (SD)	3.5 (2.3)
Number of treatment cycles, median (range)	3 (1–16)
≥3 cycles, n (%)	470 (59.3)
Patients with ≥1 day cycle delay (for any reason)	327 (41.2)
Cycles completed without interruption,† %	90.7

*n=789.
†Based on the total number of cycles.

patients and were considered related to trifluridine/tipiracil in 8.8% of patients. TEAEs led to dose reduction in 70 patients (8.8%); these events included neutropaenia in 27 patients (3.4%), anaemia and diarrhoea (each in eight patients, 1.0%). Drug-related AEs led to dose reduction in 61 patients (7.7%) and included neutropaenia (27 patients, 3.4%), diarrhoea (8 patients, 1.0%) and anaemia (7 patients, 0.9%). TEAEs led to treatment interruption/delay in 367 patients (46.3%), and these events were drug-related in 300 patients (37.8%); the most common of these events was neutropaenia (245 patients, 30.9%).

The most common TEAEs (occurring in >20% of patients) were neutropaenia (53.0% of patients), asthenia/fatigue (37.3%), nausea (29.9%), anaemia (29.6%) and diarrhoea (24.6%; table 3). Grade ≥3 drug-related TEAEs occurring in >5% of patients were neutropaenia (303 patients, 38.2%) and anaemia (52, 6.5%; table 3). One patient died at home due to diarrhoea/vomiting, which was reported as related to trifluridine/tipiracil.

Other TEAEs experienced by <10% of patients but of interest were thrombocytopaenia (9.5% of patients, 1.6% grade ≥3), fever (9.5%, 0.6% grade ≥3), increased aspartate aminotransferase (3.8%, 1.1% grade ≥3), increased alanine aminotransferase (3.4%, 0.5% grade ≥3), febrile neutropaenia (1.4%, 1.4% grade ≥3) and increased

Table 3 Treatment-emergent and drug-related treatment-emergent adverse events, with 95% CIs of incidence*

	TEAE		Drug related TEAE	
TEAE, n (%)	Any grade	Grade ≥3	Any grade	Grade ≥3
Any	767 (96.7)	586 (73.9)	624 (78.7)	394 (49.7)
95% CI	(95.2 to 97.9)	(70.7 to 76.9)	(75.7 to 81.5)	(46.2 to 53.2)
Haematological				
Neutropaenia	420 (53.0)	310 (39.1)	410 (51.7)	303 (38.2)
95% CI	(49.4 to 56.5)	(35.7 to 42.6)	(48.2 to 55.2)	(34.8 to 41.7)
Anaemia	235 (29.6)	78 (9.8)	163 (20.6)	52 (6.5)
95% CI	(26.5 to 33.0)	(7.9 to 12.1)	(17.8 to 23.5)	(4.9 to 8.5)
Non-haematological				
Asthenia/fatigue	296 (37.3)	40 (5.0)	214 (27.0)	25 (3.2)
95% CI	(34.0 to 40.8)	(3.6 to 6.8)	(23.9 to 30.2)	(2.1 to 4.6)
Nausea	237 (29.9)	10 (1.3)	211 (26.6)	9 (1.1)
95% CI	(26.7 to 33.2)	(0.6 to 2.3)	(23.6 to 29.8)	(0.5 to 2.1)
Diarrhoea	195 (24.6)	35 (4.4)	160 (20.2)	25 (3.2)
95% CI	(21.6 to 27.7)	(3.1 to 6.1)	(17.6 to 23.3)	(2.1 to 4.6)
Vomiting	141 (17.8)	14 (1.8)	100 (12.6)	10 (1.3)
95% CI	(15.2 to 20.6)	(1.0 to 2.9)	(10.4 to 15.1)	(0.6 to 2.3)
Decreased appetite	126 (15.9)	13 (1.6)	69 (8.7)	5 (0.6)
95% CI	(13.4 to 18.6)	(0.9 to 2.8)	(6.8 to 10.9)	(0.2 to 1.5)
Abdominal pain	96 (12.1)	22 (2.8)	34 (4.3)	6 (0.8)
95% CI	(9.9 to 14.6)	(1.8 to 4.2)	(3.1 to 6.1)	(0.3 to 1.6)
Constipation	80 (10.1)	2 (0.3)	27 (3.4)	0
95% CI	(8.1 to 12.4)	(0.0 to 0.9)	(2.3 to 4.9)	None

*Events listed are TEAEs that occurred in ≥10% of patients.
TEAE, treatment-emergent adverse event.

creatinine level (0.4%, 0.1% grade ≥3). Respective values for drug-related AEs (any grade, grade ≥3) were thrombocytopaenia (8.1%, 1.2%), fever (1.1%, 0.1%), increased aspartate aminotransferase levels (1.4%, 0.1%) and increased alanine aminotransferase levels (1.0%, 0). All 11 cases of febrile neutropaenia were considered drug related, whereas no increases in creatinine level were drug related.

When analysed by age, 98.1% of patients aged >70 years and 96.4% of those aged ≤70 years experienced at least one TEAE; these were drug related in 82.2% and 77.8% of patients, respectively. Grade ≥3 TEAEs occurred in 79.6% of patients aged >70 years and in 72.5% of those aged ≤70 years.

Efficacy

Trifluridine/tipiracil was associated with a median PFS of 2.8 months (95% CI 2.7 to 2.9; figure 2A), an objective response rate of 2.3% (95% CI 1.4 to 3.6; n=18) and a disease control rate of 34.4% (95% CI 31.1 to 37.9; n=273). The proportion of patients with PFS at 3 and 6 months were 45% (95% CI 41 to 49) and 18% (95% CI 15 to 21), respectively.

When analysed by baseline characteristic subgroups, median PFS was numerically higher in patients with a baseline ECOG PS 0 (3.2 months; 95% CI 3.0 to 3.4) than an ECOG PS 1 (2.3 months; 95% CI 2.1 to 2.6) and in those who had previously received ≤2 lines of treatment (3.1 months; 95% CI 2.8 to 3.5) compared with >2 lines (2.7 months; 95% CI 2.6 to 2.8). Median PFS did not appear to be impacted by *RAS* status (wild type: 2.8 months; 95% CI 2.3 to 3.3; mutant: 2.7 months; 95% CI 2.6 to 2.9; *RAS* not reported: 3.0 months; 95% CI 2.7 to 3.7), primary tumour site (right colon: 2.8 months; 95% CI 2.6 to 3.1; left colon: 2.8 months; 95% CI 2.6 to 3.0; not specified: 3.0 months; 95% CI 2.4 to 3.7) or age (≤70 years: 2.8; 95% CI 2.7 to 2.9; >70 years: 2.8; 95% CI 2.5 to 3.4). In patients with 1, 2 or ≥3 metastatic sites at baseline, median PFS was 2.9 months (95% CI 2.8 to 3.2), 2.8 months (95% CI 2.6 to 3.1) and 2.6 months (95% CI 2.1 to 2.8), respectively.

Overall median time to first tumour evaluation was 2.1 months (95% CI 2.0 to 2.2) and did not differ between patient subgroups except ECOG-PS subgroups for which ECOG-PS 0 was associated with a longer time to first evaluation than ECOG-PS 1 (2.4 (95% CI 2.3 to 2.6) vs 1.9 (95% CI 1.8 to 2.0) months; see supporting table 1).

The median time to ECOG deterioration (PS ≥2) was 8.9 months (range 0.03–14.7; figure 2B) and was longer in the 286 patients who had previously received ≤2 lines of treatment (14.3 months; range 0.03–14.3) than the 503 patients who had received >2 lines of treatment (8.5 months; range 0.03–14.7). Of the 722 patients with ECOG data available at treatment discontinuation, 79.8% had an ECOG PS of 0/1.

Quality of life

The EORTC QLQ-C30 GHS questionnaire completion rate, based on the number of patients still on treatment at each cycle, was at least 92% for each treatment cycle. At baseline, the mean±SD and the median EORTC QLQ-C30 GHS score (n=772) were 62.4±20.7 and 66.7 (IQR, 33.3), respectively. After seven cycles of treatment (cut-off), mean changes from baseline were not clinically relevant at any time point (figure 3). EORTC QLQ-C30 GHS score at baseline and at the time of study withdrawal were available for 374 patients; the mean±SD and the median EORTC QLQ-C30 GHS score were, respectively, 56.2±23.8 and 58.3 (IQR 25.0) at this time. For patients with baseline and end-of-treatment data available (n=363), the EORTC QLQ-C30 GHS score improved from baseline to end of treatment in 20.4% of patients, improved or did not deteriorate in 55.9% of patients and deteriorated from baseline to end of treatment in 44.1% of patients. The mixed effects model shows that there is no clinically meaningful deterioration in EORTC QLQ-C30 GHS score (see supporting table 2).

DISCUSSION

The multinational phase IIIb PRECONNECT study was initiated to allow a large group of patients with mCRC early access to trifluridine/tipiracil before it became commercially available. Trifluridine/tipiracil was generally well tolerated, and no new safety concerns were identified. Results from PRECONNECT confirm the efficacy of trifluridine/tipiracil and show that patients with pretreated mCRC can maintain their health-related QoL while on trifluridine/tipiracil treatment.

As an early-access study, data from PRECONNECT reflect daily clinical practice but are limited to those patients who fulfilled the eligibility criteria. Analysis of the baseline characteristics shows a population of pretreated patients with mCRC, who still require treatment. As the eligibility criteria were similar, it is unsurprising that the baseline characteristics in PRECONNECT were broadly comparable with those in other large trials in similar patients with mCRC (ECOG PS of 0 or 1; after having received ≥2 previous chemotherapies).[6 13 14] The proportion of patients with a baseline ECOG PS of 0 was slightly higher in RECOURSE than PRECONNECT (56.4% vs 50.2%).[6] RECOURSE also included patients from Japan, and thus 34% of the enrolled patients were Asian, compared with 1.5% in the current study.

Results from PRECONNECT confirm the acceptable safety profile of trifluridine/tipiracil previously observed in randomised, placebo-controlled trials.[6 15 16] As observed in previous trials,[6 15 16] haematological TEAEs (such as neutropaenia and anaemia) were relatively common in PRECONNECT, as were gastrointestinal TEAEs and asthenia/fatigue; any necessary dose adjustments were performed according to the European Medicines Agency prescribing recommendations.[17] Neutropaenia grade ≥3 and febrile neutropaenia were experienced by 39% and 1.4% of patients in PRECONNECT and 38% and 4% of patients in the RECOURSE treatment arm, respectively.[6] Although gastrointestinal adverse events were also

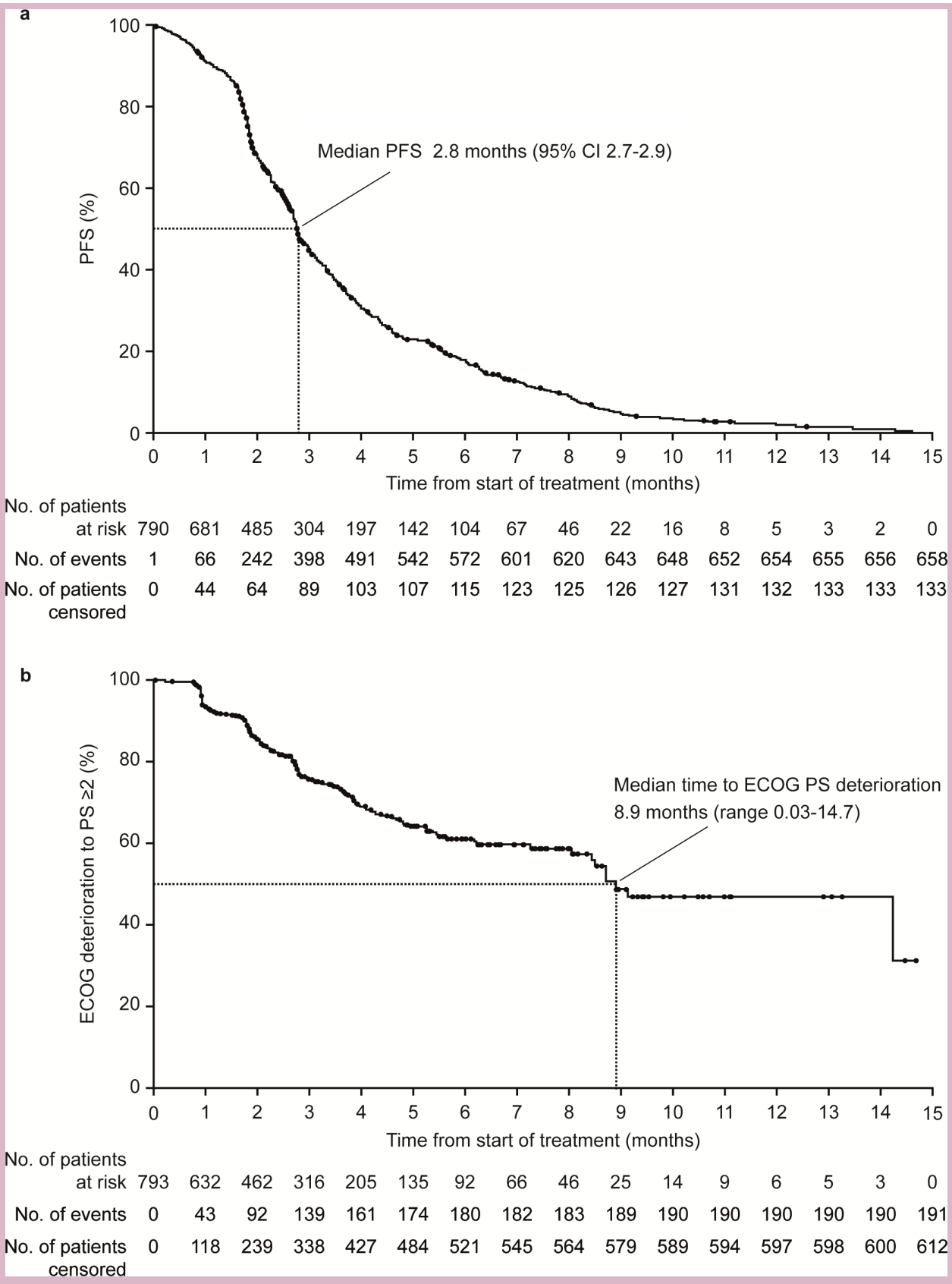

Figure 2 (A) PFS (n=793*) and (B) time to Eastern Cooperative Oncology Group performance status (ECOG PS) of 2 or higher (n=793†). *Two patients were censored from the analysis because they received another anticancer therapy after withdrawal from the study drug and no postbaseline efficacy evaluation was performed. †Although baseline ECOG PS data were not collected for 24 patients, data were collected at subsequent visits so these patients were included in the analysis. PFS, progression-free survival.

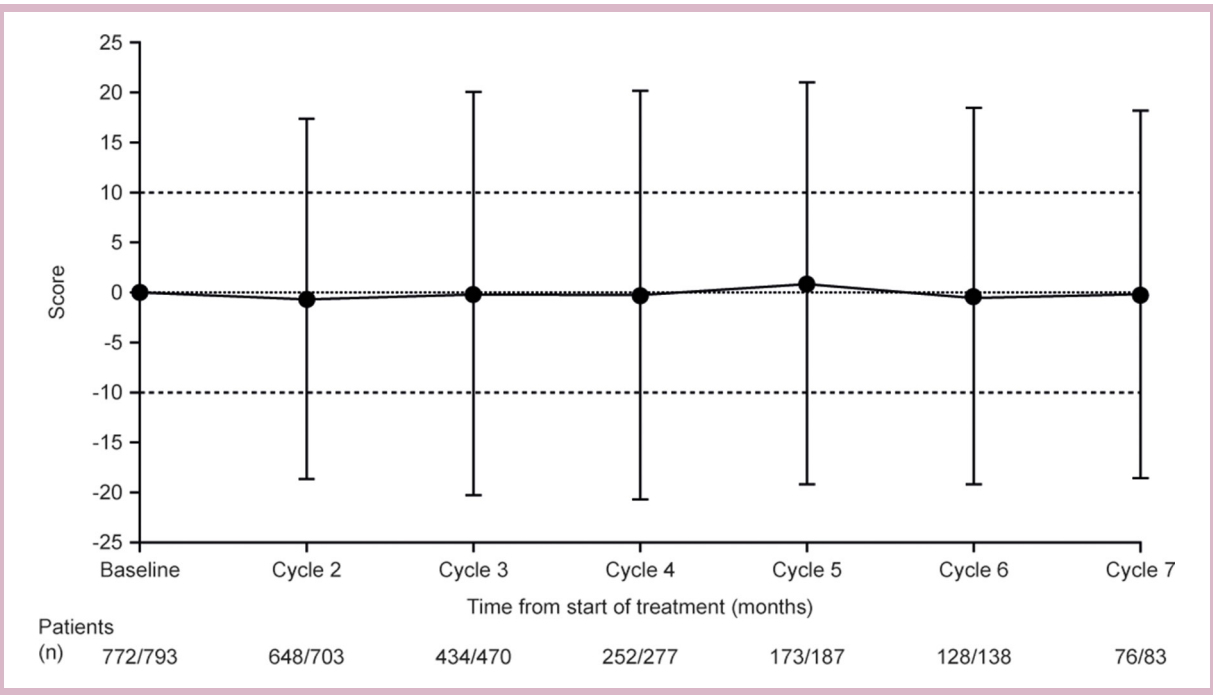

Figure 3 Change from baseline across cycles in the EORTC QLQ-C30 Global Health Status score. Data are mean±SD. Patient numbers refer to patients with evaluable questionnaires/total number of patients still on treatment. EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life questionnaire.

common in both studies, nausea, vomiting and diarrhoea were observed less frequently in PRECONNECT than in the in RECOURSE treatment arm (nausea 30% vs 48%; vomiting 18% vs 28%; and diarrhoea 25% vs 32%).[6] In the current study, there was a slight (<5%) increase in drug-related events in patients aged over 70 years, compared with those aged ≤70 years.

PRECONNECT also confirms the efficacy of trifluridine/tipiracil, with a median PFS of 2.8 months showing consistency with randomised clinical trials.[6 15 16] Unlike the randomised clinical trials, in PRECONNECT, PFS was measured according to local standards for radiological or clinical tumour assessments. However, our post hoc analysis indicated that the median time to first tumour evaluation was 2.1 months in the overall population and in most subgroups of patients except those with ECOG PS 0 (median time to first evaluation was 2.4 months) or ECOG PS 1 (median 1.9 months); this may have led to an overestimation of median PFS. However, patients withdrawn for commercial availability of trifluridine/tipiracil (n=82, 10.3%) were censored for PFS at the time of the last evaluable tumour assessment (at withdrawal at the latest), while remaining on treatment, which may have resulted in an underestimation of PFS.

In PRECONNECT, median PFS was longer in patients who had previously received ≤2 lines of treatment (compared with >2 lines) and in those who had an ECOG PS of 0 (compared with PS of 1) at baseline. It is possible that a longer time interval between tumour evaluations in the ECOG PS subgroups (median 10.4 weeks for ECOG PS 0 vs 8.3 weeks for ECOG PS 1) may have contributed to the difference in PFS in these groups, but not in the subgroups based on number of prior treatment lines, which had a comparable time to first tumour evaluation (median 9.3 weeks in those with ≤2 prior lines of therapy vs 9.0 weeks in those with >2). *RAS* status, primary tumour site and age did not appear to impact PFS, and these subgroups had comparable median intervals to first tumour evaluation. Similarly, no country effect on efficacy or safety was observed in the current study (data not shown). These data support the use of trifluridine/tipiracil as early third-line therapy in patients with refractory mCRC, before any rechallenge with previously used first-line and second-line chemotherapeutic agents, for which the level of evidence is quite low.[2]

Both trifluridine/tipiracil and regorafenib are recommended for third-line treatment of patients with mCRC who have progressed through other available chemotherapies.[2] Although optimal treatment sequencing between the two drugs has not yet been established, a real-world study showed that trifluridine/tipiracil was associated with significantly higher medication adherence and a longer time to discontinuation compared with regorafenib.[18] In a systematic review and meta-analysis that used data from RECOURSE for trifluridine/tipiracil and CONCUR (Asian patients) and CORRECT for regorafenib, trifluridine/tipiracil and regorafenib had similar efficacy; however, regorafenib was associated with significantly more toxicity than trifluridine/tipiracil.[19] Furthermore, trifluridine/tipiracil was dominant over regorafenib in all sensitivity analysis scenarios in a National Institute for Health and Care Excellence validated cost-effectiveness model, which used data from RECOURSE, the similarly designed phase II Japanese trial for trifluridine/tipiracil

and the phase III CORRECT trial for regorafenib.[20] Trifluridine/tipiracil was also shown to be more cost-effective than regorafenib in another study that used data from CORRECT and RECOURSE.[21] However, thus far, only retrospective comparisons of trifluridine/tipiracil and regorafenib in patients with refractory mCRC have been made. Without a direct comparison in a randomised trial, it is difficult to make any firm conclusions regarding the relative efficacy and safety of the two agents.

Treatment goals in this patient population may differ from those of patients receiving earlier lines of therapy[22]; generally, response rates will be lower and maintaining QoL is a well-recognised goal in patients receiving third-line treatment.[22 23] PRECONNECT was the first trial to directly measure QoL with trifluridine/tipiracil in this patient population, and the collected QoL data confirm other analyses that suggested (via proxy measurement) maintenance of QoL during treatment with trifluridine/tipiracil. In RECOURSE, the median time to the deterioration of ECOG PS to ≥2 (a possible proxy measurement of QoL) was significantly longer with trifluridine/tipiracil than placebo (5.7 vs 4.0 months, p<0.001)[6]; the respective time in PRECONNECT was 8.9 months. At the end of treatment in PRECONNECT, 79.8% of patients had maintained an ECOG PS of 0 or 1, allowing new subsequent treatment options. There were no clinically meaningful changes in the mean EORTC QLQ-C30 GHS score at any time point over seven cycles of trifluridine/tipiracil treatment. and the score either improved or did not deteriorate from baseline to end of treatment in 55.9% of patients. Toxicity of late-line cancer therapy can often lead to a decrease in patient QoL, so it is reassuring to have agents available that can control the disease without QoL deterioration. Although the patient population was different, it is interesting to note that QoL was also maintained with trifluridine/tipiracil in patients with heavily pretreated metastatic gastric cancer in TAGS, with no clinically significant deterioration in the mean EORTC QLQ-C30 GHS score.[24]

PRECONNECT is not without limitations; these include the lack of a comparator arm; this is because PRECONNECT was designed to reflect routine clinical practice. In this trial, PFS was assessed by investigators only, according to local standards. Furthermore, although the EORTC QLQ-C30 GHS questionnaire completion rate was high, it was not 100%. There is a possibility that the sickest patients were the ones who did not complete the questionnaire, in which case our assessment of QoL may have been overly optimistic. Finally, PRECONNECT was not designed to collect follow-up data, and therefore, OS was not assessed.

In PRECONNECT, a phase IIIb trial in 793 patients with pretreated mCRC, the safety and efficacy of trifluridine/tipiracil was consistent with that observed in the phase RECOURSE III trial. Additionally, patients' QoL was maintained during treatment with trifluridine/tipiracil, with no clinically meaningful deterioration in QoL observed.

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