Proxies of quality of life in metastatic colorectal cancer: analyses in the RECOURSE trial

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ABSTRACT

Background In the pivotal phase III, randomised, double-blind, placebo-controlled RECOURSE study, treatment with trifluridine/tipiracil was well tolerated and associated with prolonged progression-free and overall survival in patients with metastatic colorectal cancer (mCRC). There was no formal analysis of quality of life (QoL) in RECOURSE. The aim of the present analysis was to assess proxies of QoL during the RECOURSE treatment period, in terms of adverse events (AEs) likely to affect QoL and Eastern Cooperative Oncology Group performance status (ECOG PS).

Patients and methods Enrolled patients had documented, previously treated (≥2 prior chemotherapy lines) mCRC and an ECOG PS of 0 or 1. Patients received best supportive care plus trifluridine/tipiracil 35 mg/m² twice daily (n=534) or placebo (n=266) in a 28-day cycle. AEs analysed included nausea, vomiting, diarrhoea, dysgeusia and fatigue/asthenia. ECOG PS was determined at baseline, on day 1 of each treatment cycle, at treatment end and 30 days post-treatment discontinuation.

Results AEs that affect QoL were more frequent in patients treated with trifluridine/tipiracil than placebo. Median treatment duration for patients experiencing at least one of these AEs was longer than that observed for the overall RECOURSE population (trifluridine/tipiracil: 12 vs 7 weeks; placebo: 10 vs 6 weeks). Versus placebo, the duration of most AEs was longer in trifluridine/tipiracil recipients; however, all AEs except nausea and vomiting occupied a lower proportion of the total treatment period. Of the patients who had their PS recorded at discontinuation, PS was maintained in 67% and 63% of cases.

Conclusions Analysis of ECOG PS and AEs thought to affect QoL in the RECOURSE patient population suggests that trifluridine/tipiracil treatment does not result in a deterioration of patient QoL versus placebo.

INTRODUCTION

Globally, colorectal cancer (CRC) is the third most commonly diagnosed cancer (~10% of new cases) and is responsible for 8% of cancer-related deaths.1 It is now well known that quality of life (QoL) is an important issue for individuals with cancer, with QoL affected by both the disease and therapies used to...
treat the disease. In advanced CRC, the main aims of treatment are to prolong overall survival (OS) and maintain QoL.

Analysis of QoL assessment in trials of advanced CRC has shown that formal assessment of QoL occurred in only 27% of phase III trials conducted between 2007 and 2014. Despite this lack of formal analysis, investigation of patient symptoms and treatment-related side effects remains important in the study of cancer treatments and as part of high-quality, patient-centred care. Primarily, physician-rated, functional performance status (PS) and patient-reported adverse events (AEs) are used to assess these treatment effects. Data suggest a significant correlation between PS and patient-reported AEs, both in cancer in general and in advanced CRC specifically, including both measures deteriorating concurrently in patients with advanced CRC.

Trifluridine/tipiracil is a combination of the thymidine-based nucleoside analogue trifluridine and the thymidine phosphorylase inhibitor tipiracil. Trifluridine/tipiracil inhibits thymidylate synthase, disrupting DNA synthesis, but its predominant antitumour activity results from the incorporation of trifluridine into DNA, while tipiracil improves trifluridine bioavailability. Trifluridine/tipiracil is approved in the USA and Europe for the treatment of patients with metastatic CRC (mCRC) who have been previously treated with currently available therapies. In Japan, it is indicated for the treatment of unresectable advanced or recurrent CRC.

The efficacy and safety of trifluridine/tipiracil in patients with refractory mCRC have been investigated in the large, international RECOURSE (Randomized, Double-Blind, Phase 3 Study of TAS-102 plus Best Supportive Care (BSC) versus Placebo plus BSC in Patients with Metastatic Colorectal Cancer Refractory to Standard Chemotherapies) study. Median OS in RECOURSE was significantly longer in patients treated with trifluridine/tipiracil plus BSC versus placebo plus BSC (7.1 vs 5.3 months; HR: 0.68; 95% CI 0.58 to 0.81; p<0.001). Median progression-free survival (PFS) was 2.0 vs 1.7 months (HR: 0.48; 95% CI 0.41 to 0.57; p<0.001). Common AEs in the RECOURSE population included dysgeusia, gastrointestinal AEs (nausea and vomiting, diarrhoea) and fatigue/asthenia. These AEs are considered likely to affect QoL.

| Adverse event     | Trifluridine/tipiracil (n=533) | Placebo (n=265) |
|-------------------|--------------------------------|-----------------|
|                   | Overall incidence, % | Highest grade | Incidence at highest grade, n (%) | Overall incidence, % | Highest grade | Incidence at highest grade, n (%) |
| Nausea            | 48.4 | 3 | 10 (1.9) | 23.8 | 3 | 3 (1.1) |
| Vomiting          | 27.8 | 3 | 11 (2.1) | 14.3 | 3 | 1 (0.4) |
| Diarrhoea         | 31.9 | 4 | 16 (3.0)* | 12.5 | 3 | 1 (0.4) |
| Dysgeusia         | 6.8  | 2 | 3 (0.6)  | 2.3  | 2 | 1 (0.4) |
| Fatigue           | 35.3 | 3 | 21 (3.9) | 23.4 | 3 | 15 (5.7) |
| Asthenia          | 18.2 | 3 | 18 (3.4) | 11.3 | 3 | 8 (3.0) |

*One incidence of grade 4 diarrhoea was observed in trifluridine/tipiracil patients. This number indicates the total number of grade 3 and 4 diarrhoea events.

![Figure 1](image_url)
No formal assessment of QoL was undertaken in the RECOURSE study. Therefore, the aim of the present analysis was to assess AEs likely to affect QoL during the course of the trial and Eastern Cooperative Oncology Group (ECOG) PS.

**METHODS**

**RECOURSE study design, patient population and treatment regimen**

Detailed methods of the RECOURSE study have been previously published. Briefly, RECOURSE was a phase III, randomised, double-blind, placebo-controlled trial conducted in Japan, Europe, the USA and Australia. Patients enrolled were those with documented mCRC treated with ≥2 prior lines of standard chemotherapy (including anti-epidermal growth factor receptor antibody if KRAS wild-type) and an ECOG PS of 0 or 1. All patients received BSC and either trifluridine/tipiracil or placebo on days 1–5 and 8–12 of each 28-day cycle. Trifluridine/tipiracil was administered at a dose of 35 mg/m² twice daily, and three dose reductions (in 5 mg/m² steps) were allowed.

Patients continued study treatment until disease progression, death, unacceptable toxicity or patient refusal of treatment. Patients were evaluated every 2 weeks during the treatment period and every 8 weeks from treatment cessation until the trial data collection cut-off date or death.

**Collection of AE and PS data**

AEs were classified and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, V.4.03. PS was evaluated using the ECOG score at baseline, on day 1 of each treatment cycle, at the end of treatment and 30 days after treatment discontinuation. Patients who died (PS=5) before treatment discontinuation were not included in the analysis of PS at discontinuation.

**Statistical analysis**

AEs for all patients who received at least one dose of study drug were summarised using descriptive statistics. The AEs included in this analysis were those of high prevalence and which were likely to affect QoL: nausea and vomiting, diarrhoea, dysgeusia and fatigue/asthenia. ECOG PS at treatment discontinuation (ECOG scores of 0–4) was compared with PS at baseline in the trifluridine/tipiracil and placebo groups using descriptive statistics. Time to worsening of ECOG PS was analysed in the intent-to-treat population using a two-sided, stratified log-rank test, and basing the HR and two-sided 95% CIs on a stratified Cox model and associated Kaplan-Meier survival estimates. SAS V.9.1 was used for statistical analyses.

**RESULTS**

**Patient population**

RECOURSE enrolled 800 patients, with 534 and 266 randomised to trifluridine/tipiracil and placebo, respectively. The characteristics of the population have been previously described; the main characteristics were as follows: median age 63 years, ~61% male and predominantly white (~57%) or Asian (~34%). ECOG PS was 0 or 1 in ~55% and ~45% of patients, respectively. The colon was the primary site of disease in the majority (~62% of
each group), and most patients (79%) were 18 months or more from a diagnosis of first metastases. The mean (±SD) duration patients received the study drug was 12.7±12.0 weeks in the trifluridine/tipiracil group and 6.8±6.1 weeks in the placebo group.

**AEs affecting QoL**
Trifluridine/tipiracil patients were more likely to experience AEs that affect QoL than placebo patients (table 1). The overall incidence in the RECURSSE population as well as incidence at the highest grade are given for each AE likely to affect QoL.

The frequency of AEs was higher during cycle 1 than in subsequent cycles for patients treated with trifluridine/tipiracil (figure 1).

The median treatment duration for all patients in the RECURSSE study was 6.7 weeks for the trifluridine/tipiracil patients and 5.7 weeks for the placebo patients (figure 2). Notably, the median treatment duration for patients experiencing at least one AE likely to affect QoL

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**Figure 3** Median duration of adverse events experienced in the RECURSSE trial presented in (A) days and (B) proportion of the treatment period.
was longer than that for the whole RECOURSE population regardless of treatment allocation (figure 2). Patients in the trifluridine/tipiracil group had longer median treatment durations than patients in the placebo group.

While most of the AEs experienced by trifluridine/tipiracil recipients were of longer duration than those experienced by placebo recipients (figure 3A), the AEs occupied a lower proportion of the total treatment period (with the exception of nausea/vomiting) (figure 3B).

**PS at discontinuation**

A total of 759 patients had their PS recorded at discontinuation (table 2). Two hundred and seventy-eight and 146 patients receiving trifluridine/tipiracil and placebo, respectively, had a PS of 0 at baseline; 180 (65%) and 86 (60%) of these patients maintained a PS of 0 at discontinuation. Of the patients receiving trifluridine/tipiracil or placebo with a PS of 1 at baseline (n=218 and n=117), 152 (70%) and 80 (68%) had a PS of 1 at discontinuation; overall, 67% and 63% of trifluridine/tipiracil and placebo recipients maintained their PS throughout the study. The percentage of patients with a PS of 1 at baseline who improved to PS 0 at discontinuation was 4% in the trifluridine/tipiracil group and 3% in the placebo group. Overall, the percentage of patients who were at PS 0 or 1 at treatment discontinuation was 84% and 81% in the trifluridine/tipiracil and placebo groups, respectively. In addition, trifluridine/tipiracil significantly delayed the median time to an ECOG PS of ≥2 versus placebo (5.7 vs 4.0 months; HR: 0.66; 95% CI 0.56 to 0.78; p<0.001).14

**DISCUSSION**

No formal assessment of QoL was performed during the RECOURSE study. The present analysis aimed to assess the type, timing and duration of AEs known to affect QoL and changes in physician-rated functional PS, and use these endpoints as surrogates for QoL in the RECOURSE population. Evidence suggests that chemotherapy-induced nausea and vomiting, diarrhoea, dysgeusia and fatigue/asthenia can have a significant negative impact on patients’ QoL.15–18 These AEs were reported more frequently in the trifluridine/tipiracil group than in the placebo group in RECOURSE. The majority of these AEs were mild to moderate in severity, and did not affect treatment continuity in a substantial way, being managed by dose reductions and/or treatment delays rather than hospitalisation.14 21 These AEs are expected in patients treated with a thymidine nucleotide analogue,21 are predictable and reversible, and were managed appropriately during RECOURSE.

Patients experiencing AEs that affect their QoL might be expected to discontinue therapy at a higher rate than those who were not; however, patients in RECOURSE who experienced these AEs had a longer treatment duration than the overall population, and the duration of these AEs was generally a lower proportion of the total treatment duration in patients receiving trifluridine/tipiracil than in those receiving placebo. These data indicate that patients treated with trifluridine/tipiracil remained in the study longer than those treated with placebo despite a higher likelihood of experiencing more frequent AEs of a longer duration that may have affected their QoL.

The original RECOURSE analysis showed that worsening of baseline PS from 0 to 1 to ≥2 was delayed in patients receiving trifluridine/tipiracil versus placebo.14 PS was unchanged in 67% of patients treated with trifluridine/tipiracil, which was a similar proportion to that seen in the placebo group (63%), suggesting that PS was maintained in patients treated with trifluridine/tipiracil despite a higher level of AEs versus placebo.

Assessment of QoL in clinical trials of cancer drugs is difficult, being hampered by patient and physician subjectivity, complexity and patient adherence.22 Over the past 20 years, formal assessment of QoL in advanced CRC has decreased such that during 1998–2006, 46% of trials formally assessed QoL, while during 2007–2014 this decreased to 27% of studies (p=0.04).2 Use of surrogate endpoints to assess efficacy in cancer studies can be a risk, with evidence suggesting that approvals based on endpoints such as tumour shrinkage or PFS can result in agents used for treatment that have no benefits on either OS and/or QoL.23 In contrast, several studies indicate that PS is related to QoL. In a study of patients with pancreatic cancer, those with a worse PS self-reported a worse QoL,24 while another analysis of patients with metastatic non-small cell lung cancer found that higher QoL was significantly associated with good PS, and patients who demonstrated a decline in QoL also had a decline in PS (p=0.0001 for both).25 A systematic review found good correlation between PS and patient-reported AEs (including QoL), and suggested that assessment of PS and patient-reported AEs may lead to more effective patient care.6 Deteriorating PS has been associated with a worsening of QoL-related symptoms such as fatigue, nausea and diarrhoea.7

The limitations of the current analysis include the subjective nature of QoL analysis, and the fact that using PS at discontinuation as a surrogate for QoL has not been validated and is not formally recognised. The strength of the analysis is its consistency. The lack of PS deterioration at discontinuation, plus the longer treatment duration in patients experiencing AEs thought to

### Table 2 Changes in Eastern Cooperative Oncology Group performance status from baseline to treatment discontinuation in the RECOURSE trial

| Baseline performance status | Trifluridine/tipiracil | Placebo |
|-----------------------------|------------------------|---------|
| 0 (n=278)                   | 180 (65)               | 86 (60) |
| 1 (n=218)                   | 78 (28)                | 43 (30) |
| 2                           | 13 (5)                 | 13 (9)  |
| 3                           | 6 (2)                  | 4 (3)   |
| 4                           | 1 (0.4)                | 1 (0.5) |

**Performance status at discontinuation, n (%)**

| Baseline performance status | Trifluridine/tipiracil | Placebo |
|-----------------------------|------------------------|---------|
| 0 (n=146)                   | 8 (4)                  | 4 (3)   |
| 1 (n=117)                   | 152 (70)               | 80 (68) |
| 2                           | 40 (18)                | 22 (19) |
| 3                           | 17 (8)                 | 8 (7)   |
| 4                           | 1 (0.5)                | 0       |

**Group performance status from baseline to treatment discontinuation**

| Group performance status | Baseline | Discontinuation |
|--------------------------|----------|-----------------|
| Placebo                  | 13 (5)   | 4 (3)           |
| Trifluridine/tipiracil   | 180 (65) | 4 (3)           |
affect QoL, suggests that, in the RECORESE patients, treatment with trifluridine/tipiracil did not affect their QoL to the extent where they wished to leave the study. In addition, a separate analysis using the Quality-adjusted Time Without Symptoms of Disease or Toxicity (QTWIST) method\textsuperscript{26} has shown an improvement in quality-adjusted survival in patients treated with trifluridine/tipiracil versus placebo.\textsuperscript{27}

In conclusion, analysis of PS and AEs thought to affect QoL in the RECORESE patient population suggests that trifluridine/tipiracil treatment does not result in a deterioration of patient QoL versus placebo while prolonging OS. Formal assessment of QoL for trifluridine/tipiracil is currently underway in an observational, early-access programme.\textsuperscript{26}

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