

ORIGINAL ARTICLE

Neutropenia and survival outcomes in metastatic colorectal cancer patients treated with trifluridine/tipiracil in the RECURSE and J003 trials

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Background: The phase II J003 ($N = 169$) and phase III RECURSE ($N = 800$) trials demonstrated a significant improvement in survival with trifluridine (FTD)/tipiracil (TPI) versus placebo in patients with refractory metastatic colorectal cancer. This *post hoc* analysis investigated pharmacokinetic data of FTD/TPI exposure and pharmacodynamic markers, such as chemotherapy-induced neutropenia (CIN) and clinical outcomes.

Patients and methods: A total of 210 patients from RECURSE were enrolled in this substudy. A limited sampling approach was used, with three pharmacokinetic samples drawn on day 12 of cycle 1. Patients were categorized as being above or below the median area under the plasma concentration–time curve (AUC) for FTD and TPI. We conducted a *post hoc* analysis using the entire RECURSE population to determine the correlations between CIN and clinical outcome. We then carried out a similar analysis on the J003 trial to validate the results.

Results: In the RECURSE subset, patients in the high FTD AUC group had a significantly increased CIN risk. Analyses of the entire population demonstrated that FTD/TPI-treated patients with CIN of any grade in cycles 1 and 2 had significantly longer median overall survival (OS) and progression-free survival (PFS) than patients who did not develop CIN and patients in the placebo group. Patients who required an FTD/TPI treatment delay had increased OS and PFS versus those in the placebo group and those who did not develop CIN. Similar results were obtained in the J003 cohort.

Conclusions: In RECURSE, patients with higher FTD drug exposure had an increased CIN risk. FTD/TPI-treated patients who developed CIN had improved OS and PFS versus those in the placebo group and those who did not develop CIN.

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Similar findings were reported in the J003 cohort, thus validating the RECURSE results. The occurrence of CIN may be a useful predictor of treatment outcomes for FTD/TPI-treated patients.

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Key words: chemotherapy-induced neutropenia, FTD/TPI, J003, metastatic colorectal cancer, RECURSE

INTRODUCTION

Trifluridine (FTD)/tipiracil (TPI) is a novel oral therapy comprising an antineoplastic thymidine-based nucleoside analog, FTD, and a thymidine phosphorylase inhibitor, TPI. TPI improves the bioavailability of FTD by inhibiting its catabolism by thymidine phosphorylase, resulting in a 37-fold increase in FTD area under the curve (AUC).^{1,2}

Two trials, J003 (JapicCTI-090880) and RECURSE (NCT01607957), demonstrated that FTD/TPI improved survival in refractory metastatic colorectal cancer (mCRC). The J003 trial, a phase II, randomized, placebo-controlled study in 169 refractory mCRC patients from Japan, demonstrated a 3.4-month overall survival (OS) benefit (9.0 versus 6.6 months) for FTD/TPI-treated patients compared with those receiving placebo.³ Similarly, the phase III, placebo-controlled RECURSE trial of 800 patients with refractory mCRC demonstrated a significant improvement in median OS [7.1 versus 5.3 months; hazard ratio (HR), 0.68; $P < 0.001$] and progression-free survival (PFS) (2.0 versus 1.7 months; HR, 0.48; $P < 0.001$).⁴ The most frequently reported adverse event was chemotherapy-induced neutropenia (CIN), with 67% of patients experiencing at least grade 1 CIN.⁴ Interestingly, a number of groups have recently reported that the onset of CIN is an indication of better treatment outcomes in mCRC patients treated with FTD/TPI,^{5–7} with the development of higher-grade CIN (grade ≥ 3) at any time of FTD/TPI treatment being associated with longer PFS and OS.⁸

To investigate the relationship between FTD/TPI exposure, efficacy, and safety, we carried out a pharmacokinetic (PK) and pharmacodynamic (PD) substudy of the RECURSE trial. We then conducted a *post hoc* analysis using data from the entire RECURSE trial to further characterize the relationship between CIN and the clinical efficacy of FTD/TPI. Following this, we carried out a similar analysis on the J003 trial to validate these results.

METHODS

Study designs

The study designs and FTD/TPI dosing in RECURSE and J003 were similar and have been described previously.^{3,4} Patients received placebo or FTD/TPI 35 mg/m² orally twice daily on days 1–5 and 8–12 of every 28-day cycle.

Assessments

CIN grades were classified according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.⁹ For patients who enrolled in the optional RECURSE PK/PD substudy, blood samples were collected at

steady state on day 12 of cycle 1 at 1, 3, and 6 hours after the morning dose of FTD/TPI. Daily AUC values were estimated using a non-linear mixed-effect modeling program (NONMEM[®] version 7.2.0; ICON plc, Dublin, Ireland) for both FTD and TPI. All data summaries and listings were produced using SAS version 9.1.3 (SAS Institute Inc., Cary, NC). Patients were divided into high versus low AUC groups for both components based on the median daily AUC values of FTD and TPI.

Statistical analysis

Analyses of OS and PFS according to PK parameters and onset of CIN were carried out using a non-stratified Cox regression to estimate HRs. Survival distribution was estimated using the Kaplan–Meier method.

RESULTS

RECURSE patient characteristics

Overall PK/PD population. Of the 800 patients enrolled in RECURSE, 210 participated in this substudy (FTD/TPI $n = 138$; placebo $n = 72$). Patient demographics and baseline characteristics were mostly comparable (supplementary Table S1, available at *Annals of Oncology* online) and generally representative of the overall study.

AUC subgroups. The median (range) FTD AUC was 43.51 (15.2–84.6) $\mu\text{g}\cdot\text{h}/\text{ml}$ and the median (range) TPI AUC was 0.65 (0.2–2.9) $\mu\text{g}\cdot\text{h}/\text{ml}$. The mean age (standard deviation) in the high FTD AUC group was 62.1 (± 10.8) versus 60.6 (± 9.9) years in the low FTD AUC group (supplementary Table S1, available at *Annals of Oncology* online). Approximately twice as many patients in the high FTD and TPI AUC groups had mild (creatinine clearance 60–89 ml/min) and moderate (creatinine clearance 30–59 ml/min) renal impairment at baseline (high FTD: 39.1% mild, 17.4% moderate; high TPI: 37.7% mild, 18.8% moderate) versus the low FTD and TPI AUC groups (low FTD: 15.9% mild, 5.8% moderate; low TPI: 17.4% mild, 4.3% moderate). These differences were statistically significant ($P < 0.0001$), and this association is currently being investigated in an ongoing phase I study (NCT02301117).

FTD/TPI efficacy in the PK/PD population

OS and PFS. In the RECURSE PK/PD subset, patients treated with FTD/TPI also had improved median OS and PFS compared with patients treated with placebo [HR, 0.58; 95% confidence interval (CI), 0.42–0.80 and HR, 0.34; 95% CI, 0.24–0.49, respectively] (Table 1; supplementary Table S2, available at *Annals of Oncology* online).

Median OS tended to be longer in the high versus low FTD AUC groups [9.2 versus 7.2 months, respectively (HR, 0.72;

	FTD			TPI			Overall PK/PD population	
	High FTD AUC (n = 69)	Low FTD AUC (n = 69)	Placebo (n = 72)	High TPI AUC (n = 69)	Low TPI AUC (n = 69)	Placebo (n = 72)	FTD/TPI (n = 138)	Placebo (n = 72)
Median OS, months (95% CI)	9.2 (7.6–10.7)	7.2 (5.0–9.7)	5.6 (4.0–7.3)	7.8 (6.1–10.7)	9.2 (7.2–10.2)	5.6 (4.0–7.3)	8.9 (7.2–9.9)	5.6 (4.0–7.3)
Median PFS, months (95% CI)	3.7 (2.1–3.9)	2.0 (1.9–3.9)	1.8 (1.6–1.8)	2.0 (1.9–3.7)	3.7 (2.1–4.3)	1.8 (1.6–1.8)	3.3 (1.9–3.8)	1.8 (1.6–1.8)
Median time to ECOG PS ≥2, months (95% CI)	7.8 (6.7–9.9)	5.6 (4.4–9.5)		6.3 (5.0–8.8)	7.8 (6.1–9.6)			

AUC, area under the curve; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; FTD, trifluridine; OS, overall survival; PD, pharmacodynamic; PFS, progression-free survival; PK, pharmacokinetic; TPI, tipiracil.

95% CI, 0.46–1.11], but did not reach statistical significance (Figure 1A; Table 1; supplementary Table S2, available at *Annals of Oncology* online). There was no significant difference in median PFS in the high versus low FTD AUC groups (HR, 0.82; 95% CI, 0.57–1.18) (Figure 1C; Table 1; supplementary Table S2, available at *Annals of Oncology* online).

Other efficacy measures. The high FTD AUC group demonstrated a significantly longer time to progression to Eastern Cooperative Oncology Group performance status (ECOG PS) ≥2 than the low AUC group (HR, 0.64; 95% CI, 0.44–0.93) (supplementary Table S2, available at *Annals of Oncology* online). There was a statistically significant trend ($P < 0.05$) towards longer duration of treatment with FTD/TPI in the high versus low FTD AUC groups, with a median total duration of 13.9 versus 6.1 weeks, respectively.

FTD/TPI safety in the AUC subgroups. As expected, the safety profile for FTD/TPI-treated patients within the PK/PD population was similar to that for the overall RECURSE population (supplementary Table S3, available at *Annals of Oncology* online).

There was a greater risk of any-grade and grade ≥3 CIN in the high versus low FTD AUC groups (supplementary Table S3, available at *Annals of Oncology* online). Patients with higher FTD AUC were also more likely to experience grade ≥1 CIN in cycles 1 and 2 (supplementary Tables S4 and S5, available at *Annals of Oncology* online). Any-grade adverse events of interest according to maximum CIN grade in cycles 1 and 2 are listed in supplementary Table S6, available at *Annals of Oncology* online. In the PK/PD cohort, FTD AUC and maximum plasma concentration tended to be numerically higher among those who developed any-grade

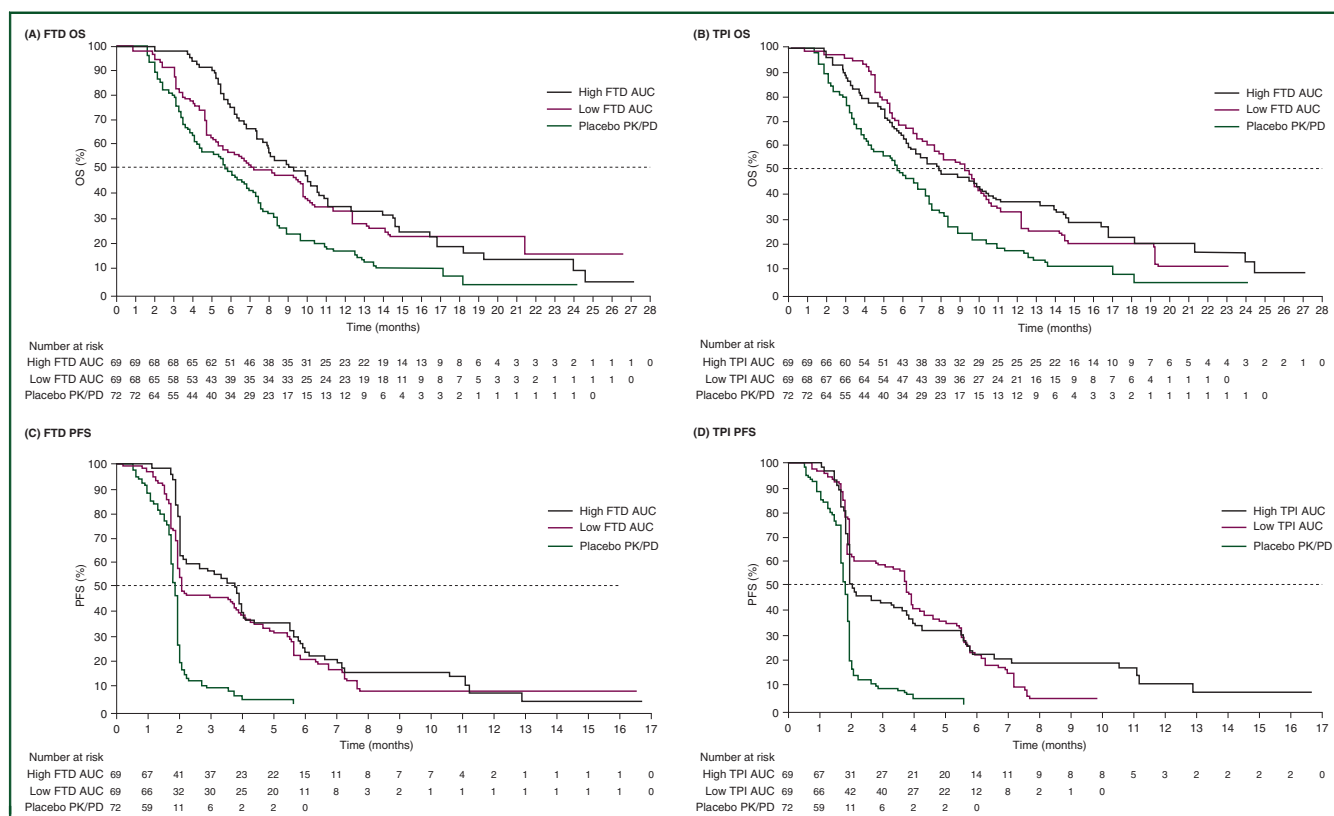


Figure 1. RECURSE: Kaplan–Meier estimates of overall survival (OS) and progression-free survival (PFS) in the pharmacokinetic/pharmacodynamic (PK/PD) population according to high and low area under the curve (AUC) of trifluridine (FTD) (OS: A; PFS: C) or tipiracil (TPI) (OS: B; PFS: D) or placebo treatment.

Treatment end points ^a	CIN grade				Comparison	Univariate comparison, HR (95% CI)*		
	No CIN (n = 205)	Grade ≥1 (n = 329)	Grade 1–2 (n = 168)	Grade ≥3 (n = 161)		Grade ≥1	Grade 1–2	Grade ≥3
Median OS, months	4.4	9.3	9.1	9.8	Versus placebo	0.51 (0.43–0.61)	0.57 (0.46–0.70)	0.48 (0.39–0.60)
					Versus no CIN	0.40 (0.33–0.48)	0.45 (0.36–0.57)	0.38 (0.30–0.48)
Median PFS, months	1.8	3.5	2.1	3.7	Versus placebo	0.36 (0.30–0.43)	0.43 (0.34–0.53)	0.32 (0.25–0.40)
					Versus no CIN	0.50 (0.41–0.61)	0.58 (0.46–0.73)	0.45 (0.35–0.57)
Median time to ECOG PS ≥2, months	3.3	7.4	7.5	7.2	Versus placebo	0.47 (0.39–0.57)	0.47 (0.37–0.59)	0.47 (0.37–0.61)
					Versus no CIN	0.39 (0.31–0.48)	0.40 (0.31–0.52)	0.39 (0.30–0.51)

CI, confidence interval; CIN, chemotherapy-induced neutropenia; ECOG PS, Eastern Cooperative Oncology Group performance status; FTD, trifluridine; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TPI, tipiracil.

^a Kaplan–Meier estimates.

* All comparisons are significant ($P < 0.0001$). Stratified log-rank test (stratification factors: KRAS status, time since diagnosis of first metastasis, region).

CIN versus those who did not (supplementary Table S7, available at *Annals of Oncology* online), but was not statistically significant.

Analysis of CIN and dose delays in RECURSE

Neutropenia. In the entire RECURSE study population, of the patients treated with FTD/TPI, 353 (66%) experienced any-grade CIN and 175 (33%) did not experience CIN (supplementary Table S8, available at *Annals of Oncology* online). The first onset of CIN was generally observed during the first two cycles of study drug treatment (supplementary Table S8, available at *Annals of Oncology* online). Median OS, PFS, and time to ECOG PS ≥2 of FTD/TPI-treated patients with CIN of any grade in cycles 1 and 2 ($n = 329$) were significantly longer than of those without CIN ($n = 205$) [OS: 9.3 versus 4.4 months (HR, 0.40; $P < 0.0001$); PFS: 3.5 versus 1.8 months (HR, 0.50; $P < 0.0001$); time to ECOG PS ≥2: 7.4 versus 3.3 months (HR, 0.39; $P < 0.0001$)] (Table 2). This was particularly true for those with grade ≥3 CIN [OS: 9.8 versus 4.4 months (HR, 0.38; $P < 0.0001$); PFS: 3.7 versus 1.8 months (HR, 0.45; $P < 0.0001$); time to ECOG PS ≥2: 7.2 versus 3.3 months (HR, 0.39; $P < 0.0001$)] (Table 2). A multivariate analysis carried out was also consistent with these results (supplementary Table S9, available at *Annals of Oncology* online). Those treated with FTD/TPI who experienced first

CIN of any grade in cycle ≥2 also had statistically significantly improved median OS versus placebo (9.1 versus 6.3 months; $P < 0.05$), PFS versus placebo (3.5 versus 1.8 months; $P < 0.05$), and time to ECOG PS ≥2 versus placebo (8.1 versus 5.5 months; $P < 0.05$) (supplementary Table S10, available at *Annals of Oncology* online). Patients who developed grade ≥3 CIN during cycle 1 had a nearly twofold increase in median OS compared with patients receiving placebo (10.1 versus 5.3 months; $P < 0.05$) (supplementary Table S11, available at *Annals of Oncology* online).

Onset of grade ≥3 CIN, regardless of timing, indicated significant improvements in OS versus patients receiving placebo and those who did not develop CIN (Figure 2; supplementary Figures S1, S2, S3, and S4; supplementary Table S11, available at *Annals of Oncology* online).

Treatment delays. Patients who required an FTD/TPI treatment delay had a statistically significant increase in OS and PFS compared with those receiving placebo and those who did not have an FTD/TPI treatment delay (both comparisons $P < 0.05$).

Compared with FTD/TPI-treated patients with no treatment delay, the OS HR was 0.18 for a delay of ≥8 days and 0.31 for a delay of 4–7 days ($P < 0.05$) (Table 3). These findings suggest an association between longer dose delays due to CIN and longer improved outcomes.

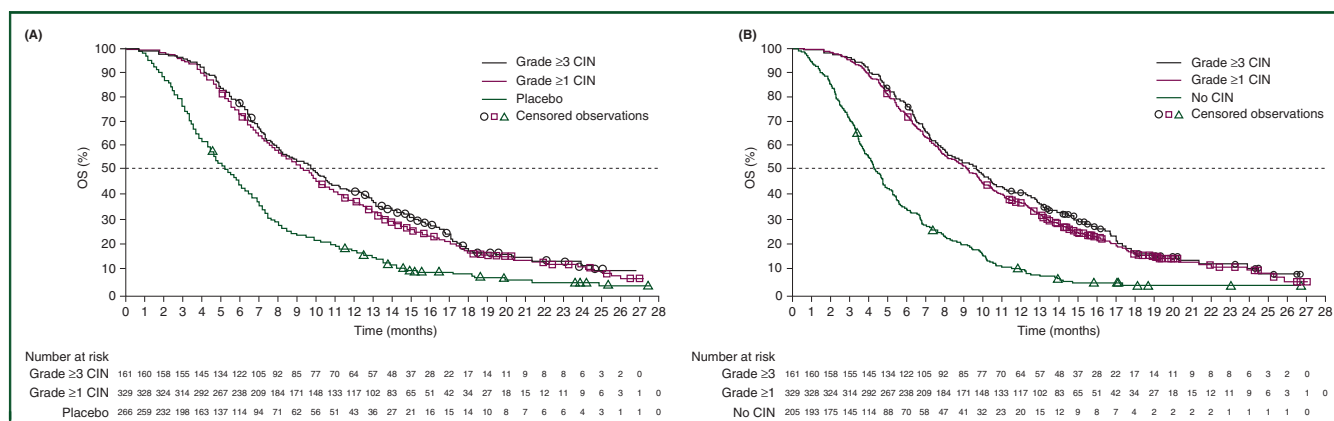


Figure 2. RECURSE: Kaplan–Meier estimates of overall survival (OS) in cycles 1 and 2 according to chemotherapy-induced neutropenia (CIN) grade versus placebo (A) and no CIN (B).

Table 3. Survival and incidence of any-grade CIN in FTD/TPI-treated patients who experienced treatment delays in RECURSE^a

	n (%) ^b	Median OS, months	OS HR versus placebo (95% CI)	OS HR versus no delay (95% CI)	Median PFS, months	PFS HR versus placebo (95% CI)	PFS HR versus no delay (95% CI)	Patients with CIN, n (%) ^c	CIN RR ^d (95% CI)
≥8 days (n = 533)	108 (20.3)	14.4	0.31 (0.23–0.40)*	0.18 (0.13–0.25)*	5.8	0.16 (0.12–0.22)*	0.16 (0.12–0.22)*	96 (88.9)	1.88 (1.64–2.16)*
≥4 and <8 days (n = 533)	137 (25.7)	9.7	0.51 (0.41–0.64)*	0.31 (0.23–0.40)*	3.7	0.33 (0.26–0.41)*	0.33 (0.26–0.42)*	121 (88.3)	1.87 (1.63–2.14)*
None (n = 533)	288 (54.0)	4.9	1.21 (1.01–1.44)**	—	1.8	0.94 (0.78–1.12)	—	136 (47.2)	—
Placebo (n = 265) ^e	265 (100)	5.3	—	—	1.7	—	—	2 (0.8)	—

CI, confidence interval; CIN, chemotherapy-induced neutropenia; FTD, trifluridine; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RR, relative risk; TPI, tipiracil.
^a Across all cycles, 289 patients (54.2%) in the FTD/TPI group had adverse events that resulted in interruptions in dosing, dose delays, and/or dose reductions compared with 36 patients (13.6%) in the placebo group.
^b Percentage of as-treated population in the specific treatment group.
^c Treatment delays may or may not be related to a specific neutropenic event.
^d Relative risk versus no delay.
^e Includes 14 placebo patients (5.3%) who experienced some cycle delay of ≥4 days.
* Indicates significant ($P < 0.05$) improvement in survival for the extent of the dose delay group versus the placebo group.
** Indicates significant ($P < 0.05$) improvement in survival for the placebo group versus the extent of the dose delay group.

Validation of correlation between CIN and survival in J003

For the final survival and CIN analysis of J003, 112 patients were included.³ The median follow-up was 57.5 months, with 167 OS events (98.8% of the total) compared with 123 in the primary analysis.³ Median OS remained unchanged from the primary analysis (FTD/TPI: 9.0 months; placebo: 6.6 months) (supplementary Figure S5, available at *Annals of Oncology* online).

Similar to RECURSE, the first onset of CIN in J003 was generally observed during the first two treatment cycles (supplementary Table S8, available at *Annals of Oncology* online). FTD/TPI-treated patients with CIN of any grade in cycles 1 and 2 had significantly longer OS, PFS, and time to ECOG PS ≥2 than those receiving placebo and those who did not develop CIN (Figure 3; supplementary Table S12; supplementary Figure S6, available at *Annals of Oncology* online). This was particularly true for those with grade ≥3 CIN.

DISCUSSION

In RECURSE, patients who were treated with FTD/TPI and demonstrated higher FTD exposure, as determined by AUC, showed an increased risk of CIN. CIN appears to be primarily a surrogate of effective dosing, but is also associated with improved outcomes over those with lower FTD exposure. Although improvement in OS fell short of statistical significance in the high versus low FTD AUC groups, the time to ECOG PS ≥2 was significantly longer. Taken together, this suggests that relatively high FTD levels in plasma may be associated with better clinical outcomes.

Analysis of RECURSE PK/PD suggests a dose–response relationship between FTD exposure and CIN, in agreement with dose-escalation studies finding that a higher rate of CIN at higher doses of FTD/TPI leads to greater efficacy of the drug.^{10,11} Notably, no such dose–response correlations were observed between FTD exposure and other frequently reported adverse events associated with FTD/TPI, including thrombocytopenia, anemia, and diarrhea. The same association is not thought to be found with TPI alone. TPI is a PK modulator which inhibits thymidine phosphorylase to enhance the systemic exposure to FTD by preventing both gastrointestinal and hepatic metabolism of FTD. The total dose of orally administered TPI will contribute to the inhibition of gastrointestinal metabolism of FTD, whereas only the absorbed fraction of TPI can inhibit hepatic metabolism. This has led to the observation that higher exposure to TPI was not associated with longer OS due to the poor absorption of TPI into the systemic circulation.

The onset of any-grade CIN during cycles 1 and 2 represented an independent predictive marker of significantly longer OS, PFS, and time to ECOG PS ≥2. Grade ≥3 CIN was most strongly correlated with the observed improvement in treatment outcomes for all end points regardless of timing of onset. Longer treatment delays were associated with longer OS and PFS compared with patients receiving placebo and those who did not experience treatment delays, which could suggest that dose density is less important than dose exposure itself.

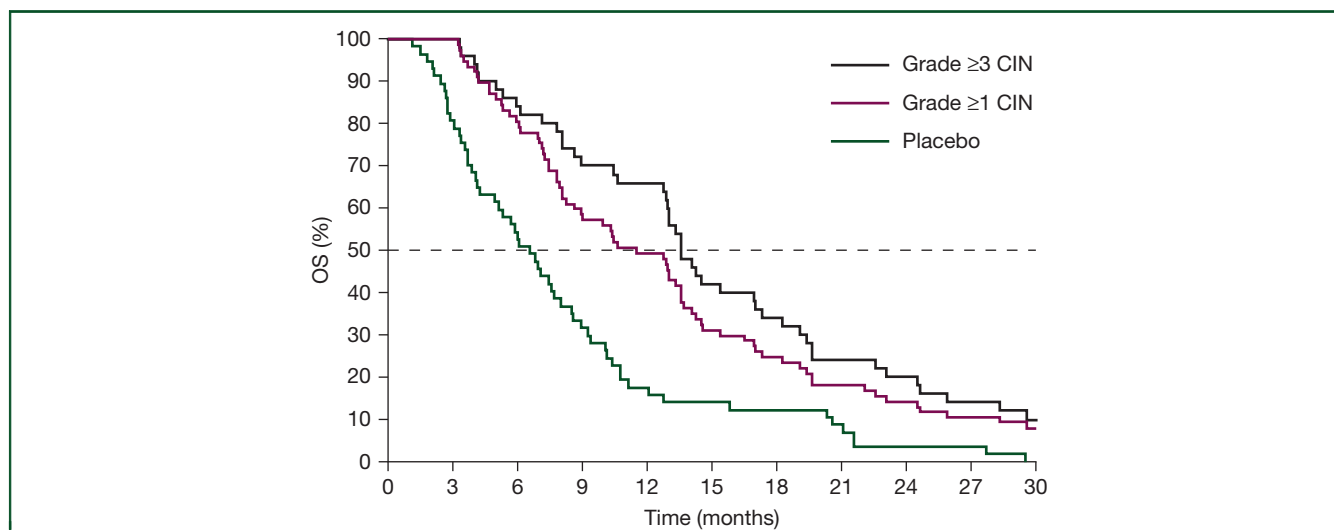


Figure 3. J003: Kaplan–Meier estimates of overall survival (OS) in cycles 1 and 2 according to chemotherapy-induced neutropenia (CIN) grade.

Further, the *post hoc* analysis of J003 demonstrated that CIN was associated with better OS, PFS, and time to ECOG PS worsening in FTD/TPI-treated patients compared with those receiving placebo and those who did not develop CIN. Thus, these analyses of J003 validated the results from RECOURSE, indicating that CIN during the early stages of treatment may act as a surrogate marker for FTD/TPI efficacy in patients with mCRC.

Although severe decreases in neutrophil count pose a risk to patients, CIN can be managed and the rate of febrile neutropenia in RECOURSE was relatively low (4%).⁴ The observations in this trial suggest that the possibility of maintaining higher doses of FTD/TPI could be beneficial to patients. While the RECOURSE and J003 trials were not designed to evaluate this question, it is reasonable that clinicians try to avoid unnecessary FTD/TPI dose reductions. Instead of dose reduction, potential strategies that can maintain the dosages of FTD/TPI include treatment delays (without impact on survival, as demonstrated by our data) and, if CIN does not improve, the appropriate use of granulocyte colony-stimulating factor in a reactive manner.

While this paper supports previous findings of a similar nature,^{5,12,13} the PK/PD analysis and comparison with placebo are new data. Overall, the PK/PD analysis was limited by the small number of patients in the AUC subgroups; sample sizes may have been too small to detect meaningful differences and may well contribute to a false negative due to inadequate power. Additionally, these are not cause-and-effect analyses and are subject to all potential biases of retrospective patient selection not based on baseline characteristics and not consistent with the randomization algorithm. This is a hypothesis-generating study and future analysis should be carried out to expand on these findings.

Conclusions

This PK/PD analysis of RECOURSE suggests that mCRC patients who experience proper dosing of FTD/TPI and therefore achieve higher plasma levels of FTD may experience

improved efficacy outcomes. FTD/TPI-treated patients who developed CIN have a survival advantage over patients receiving placebo and those who did not develop CIN during RECOURSE and J003. CIN, irrespective of the timing of onset, is associated with higher FTD AUC and appears to correlate with improved outcomes when compared with lower FTD AUC, with the most pronounced effect seen in those with grade ≥ 3 CIN. The presence or absence of CIN may be a surrogate marker of the clinical response to FTD/TPI.

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DISCLOSURE

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