



A phase I, open-label study evaluating the safety and pharmacokinetics of trifluridine/tipiracil in patients with advanced solid tumors and varying degrees of renal impairment

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Abstract

Purpose Trifluridine/tipiracil (FTD/TPI) is approved for advanced colorectal and gastric/gastroesophageal cancer; however, data in patients with renal impairment (RI) are limited. This phase I study evaluated FTD/TPI in patients with advanced solid tumors and varying degrees of RI to develop dosing guidance.

Methods Patients were enrolled into normal renal function ($\text{CrCl} \geq 90$ mL/min), mild RI (CrCl 60–89 mL/min), or moderate RI (CrCl 30–59 mL/min) cohorts and administered the recommended FTD/TPI dose (35 mg/m² twice daily, days 1–5 and 8–12; 28-day cycle). Based on interim pharmacokinetics/safety data, patients with severe RI (CrCl 15–29 mL/min) were enrolled and received FTD/TPI 20 mg/m² twice daily.

Results Forty-three patients (normal renal function [$n = 12$]; mild RI [$n = 12$]; moderate RI [$n = 11$]; severe RI [$n = 8$]) were enrolled and treated. At steady state, compared to values in patients with normal renal function, FTD area under the curve (AUC) was not significantly different in patients with RI, but TPI AUC was significantly higher and increased with RI severity. FTD/TPI safety profile was consistent with prior experience, but grade ≥ 3 adverse events (AEs) were more frequent in the RI cohorts (83.3% [mild], 90.9% [moderate], 75.0% [severe], and normal [50.0%]). Hematologic AEs (anemia and neutropenia) were more frequent with RI. Overall, seven patients discontinued because of unrelated, nonhematologic AEs.

Conclusion FTD/TPI is safe and tolerable at the recommended 35 mg/m² dose in patients with mild/moderate RI and at the reduced 20 mg/m² dose in patients with severe RI.

Trial registration NCT02301117, registration date: November 21, 2014.

Keywords Trifluridine/tipiracil · TAS-102 · Renal impairment · Safety · Pharmacokinetics

Introduction

Trifluridine and tipiracil (FTD/TPI) is an oral cytotoxic chemotherapy comprising trifluridine (FTD), a thymidine-based antineoplastic nucleoside analog, and tipiracil (TPI), a thymidine phosphorylase inhibitor, formulated at a molar ratio of 1.0:0.5 [1]. TPI significantly improves the oral bioavailability of FTD by inhibiting its degradation by thymidine

phosphorylase, thereby increasing its systemic exposure [1, 2].

FTD/TPI demonstrated antitumor activity and tolerability in phase I–II clinical trials across a range of tumor types [3–7]. Pharmacokinetic analyses of FTD/TPI, including a mass balance study in patients with solid tumors, showed that following oral administration, both FTD and TPI are rapidly absorbed, with median times to maximum observed plasma concentration (T_{max}) values ranging from 1 to 2 h, and are eliminated with a half-life of 1.5–4.0 h [4, 5, 8]. FTD is mainly eliminated via metabolism by thymidine phosphorylase to the inactive metabolite trifluoromethyluracil (FTY); < 3% of FTD was found unchanged in the urine/feces [8, 9]. This suggested that the main pathway of elimination

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of FTD is nonrenal. However, TPI is mostly eliminated via renal excretion; 27% of TPI was found unchanged in the urine [4, 5, 8, 9].

In the phase III RECURSE and TAGS trials [10, 11], FTD/TPI demonstrated significantly improved survival versus placebo, and a tolerable safety profile in patients with treatment-refractory, metastatic colorectal, gastric, or gastroesophageal cancer. The most frequent adverse events (AEs) associated with FTD/TPI use were hematologic, including neutropenia and anemia. In both trials, FTD/TPI was dosed at 35 mg/m² twice daily (BID) on days 1–5 and 8–12 of a 28-day cycle (administered orally within 1 h after a meal), with days 13–28 constituting the recovery period. Based on these results [10, 11], FTD/TPI was approved for both indications.

A significant proportion of patients with advanced solid tumors have renal impairment (RI) as defined by a creatinine clearance (CrCl) value < 90 mL/min [12–14]. RI alters drug pharmacokinetics not only by impairing urinary clearance but also by affecting drug absorption, metabolism, and distribution. Studies in cancer patients with RI have shown that the pharmacokinetics of many anticancer drugs are significantly altered by RI, and some patients experienced higher incidences of AEs associated with overexposure [12, 13]. These studies demonstrate the need for dosing adjustments of anticancer therapy in patients with RI. As TPI is primarily eliminated by urinary excretion, RI is expected to impact TPI excretion and increase its exposure, and consequently, increase FTD exposure. Patients with RI may require FTD/TPI dosing adjustments. However, data on FTD/TPI use in patients with RI are limited; the phase III clinical trials were not designed to assess the use of FTD/TPI in patients with RI, and patients with moderate to severe RI were underrepresented in these trials [10, 11]. Therefore, further research was needed to develop dosing recommendations for FTD/TPI in patients with RI.

This phase I study was conducted to evaluate the pharmacokinetics and safety of FTD/TPI in patients with advanced solid tumors and normal renal function or varying degrees of RI, and thereby develop guidance for making dosing adjustments in patients with RI.

Methods

Study design, treatment, and endpoints

This was a phase I open-label study (Clinicaltrials.gov registration: NCT02301117) in patients with advanced solid tumors and varying degrees of RI or normal renal function. This study consisted of 2 parts: a pharmacokinetic part (cycle 1) and an extension part (cycle 2 onwards; Supplementary Fig. S1). The estimated CrCl by the Cockcroft–Gault

equation was used to categorize patients into cohorts based on their degree of RI [15]. CrCl was tested within 7 days prior to starting the study medication, and patients on dialysis were excluded. This was not designed as a dose-finding study, and patients were enrolled based on baseline renal function. Patients were initially enrolled into one of three cohorts (cohorts 1–3) according to their baseline renal function at study entry: normal renal function (CrCl ≥ 90 mL/min), mild RI (CrCl 60–89 mL/min), or moderate RI (CrCl 30–59 mL/min). In the pharmacokinetic part, patients in cohorts 1–3 received the same FTD/TPI dose as patients in the phase III TAGS and RECURSE trials (35 mg/m² BID on days 1–5 and 8–12 of a 28-day cycle). Subgroup data from an earlier phase II study [16; data on file] and from the phase III RECURSE trial [17] indicated tolerability of the 35 mg/m² BID dose in patients with mild or moderate RI. Therefore, these patients received the recommended FTD/TPI dose. Study medication was administered orally, within 1 h after a meal.

Dose selection and enrollment in the severe RI cohort

An interim safety and pharmacokinetic assessment was conducted (cutoff date: December 21, 2015) after patients in cohorts 1–3 had completed cycle 1 (the pharmacokinetic part). Safety results obtained were consistent with previous observations [10, 11, 16–18; data on file]. Although treatment-related grade ≥ 3 AEs occurred more frequently in the moderate RI cohort (46%) than in the mild RI or the normal renal function cohort (17% each), the discontinuation rate after cycle 1 was ≈ 20% in each cohort and was not biased by RI. Pharmacokinetic data suggested an increase in FTD area under the curve from 0 to 12 h (AUC_{0–12}) of approximately 15% and 50% in patients with mild and moderate impairment, respectively, compared with that in patients with normal renal function, indicating a correlation between FTD oral clearance (CL/F) and renal function. Regression analysis with the formula $FTD\ CL/F = 0.3432 \times CrCl^{0.4870}$ extrapolated the CL/F in patients with severe RI (CrCl 15–29 mL/min) to be approximately half that in patients with normal renal function. Based on pharmacokinetic analysis in cohorts 1–3, 20 mg/m² BID was designated to have comparable exposure in patients with severe RI as the recommended 35 mg/m² BID dose in patients with normal renal function and was considered to have an adequate safety margin. Therefore, the dose level for the fourth, severe RI cohort was chosen as 20 mg/m² BID, on the same dosing schedule as the other cohorts. Initially, patients in the severe RI cohort were enrolled one at a time to ensure safety and tolerability. After the third patient had completed cycle 1, the remaining patients were enrolled in parallel. Patients in all cohorts who

had completed cycle 1 (in the pharmacokinetic part of the study) were eligible to enter the extension part.

In the extension part, patients continued to receive FTD/TPI at the same dose and schedule as cycle 1 until disease progression, unacceptable toxicity (described later), or the patient's request or physician's decision to withdraw. The primary objectives of the study were: (1) to assess the safety and tolerability of FTD/TPI in patients with advanced solid tumors and varying degrees of RI and (2) to compare the plasma pharmacokinetic profile of FTD and TPI in patients with normal renal function to those with varying degrees of RI, to evaluate the impact of RI on the pharmacokinetic profile of FTD and TPI.

Patients

Adult patients with advanced solid tumors (except breast cancer), normal renal function or varying degrees of RI (as described above), and not on dialysis were eligible for enrollment. Other inclusion criteria included an Eastern Cooperative Oncology Group performance status (ECOG PS) of 2 or lower, ability to take oral medications, and adequate organ function (including a hemoglobin of ≥ 9.0 g/dL and absolute neutrophil count of $\geq 1.5 \times 10^9/L$). Key exclusion criteria were prior FTD/TPI treatment, serious illness (including brain metastases, active infection, and uncontrolled diabetes), major surgery, extended field radiation, or therapy with an investigational agent ≤ 4 weeks of the treatment start date.

This study was conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines, and approval was obtained from each institution's review board or ethics committee. All patients provided written informed consent prior to participation in the trial.

Safety assessments and criteria for dosing modifications or treatment discontinuation

AEs were recorded from the time of enrollment into the study until 30 days after the last study drug dose and were graded according to National Cancer Institute Common Terminology Criteria version 4.03.

In case of toxicity, a maximum of 3 dose reductions (by 5 mg/m^2 per dose) were permitted to a minimum of 20 mg/m^2 BID for patients in the normal renal function and mild and moderate RI cohorts and a maximum of 1 dose reduction (by 5 mg/m^2 per dose) down to 15 mg/m^2 was permitted for patients in the severe RI cohort.

Patients with uncomplicated grade ≤ 3 hematologic toxicities (neutropenia or thrombocytopenia) did not require dose reductions. The FTD/TPI dose was held if neutrophil count was $< 500/\text{mm}^3$ or platelet count was $< 50,000/\text{mm}^3$. For all patients with decreases in neutrophil and/or platelet counts, the next cycle of study treatment was not started until the

resumption criteria (a neutrophil count of $\geq 1500/\text{mm}^3$ or a platelet count of $\geq 75,000/\text{mm}^3$) were met. Those patients with complicated grade ≥ 3 neutropenia or thrombocytopenia were administered supportive medications (hematopoietic growth factors) or were considered for a dose reduction in the next cycle, or both, depending on the severity of the event. Patients who experienced grade 4 neutropenia or thrombocytopenia that resulted in a > 1 -week delay of the start of the next cycle were started at a reduced dose in the next cycle.

In case of nonhematologic toxicities, dosing was interrupted for the first three occurrences of grade ≥ 3 AEs and was resumed (once the AE resolved to baseline grade) at the next reduced dose level in the next dosing cycle. At the fourth occurrence of the grade ≥ 3 event, treatment was discontinued.

FTD/TPI treatment was permanently discontinued for one or more of the following reasons: an irreversible, treatment-related, grade 4 clinically relevant event; the fourth occurrence of a treatment-related, grade 3, nonhematologic AE; or an AE that required more than 3 dose reductions of FTD/TPI, a dose reduction below 15 mg/m^2 BID for patients with severe RI, or a maximum dose delay of > 28 days from the scheduled start date of the next cycle.

Pharmacokinetic assessments

Blood samples were collected on days 1 and 12 of cycle 1 for measurement of plasma concentrations of FTD/TPI within 30 min prior to the dose (0 h), and 0.5, 1, 2, 4, 6, 8, 10, and 12 h after dose. Urine samples were collected prior to administration of the morning dose, and from 0 through 12 h after dose. The concentrations of FTD, FTY, and TPI in plasma and urine were measured using validated liquid chromatography-tandem mass spectrometry methods, as previously described [19]. The range of quantification for FTD was 5.00–5000 ng/mL, and twofold and fivefold dilutions were accurately quantitated. The range of quantification for TPI was 0.200–200 ng/mL. The accuracy values (relative error) for within-day and between-day reproducibility were -4.0% to 3.0% and -4.0% to 2.4% , respectively, for FTD, and -3.0% to 3.8% and 1.0 to 4.0% , respectively, for TPI.

Pharmacokinetic endpoints and analyses

All pharmacokinetic data were analyzed using the Phoenix WinNonlin (Version 7; Certara LP, Princeton, NJ, USA) software. Noncompartmental methods using actual sampling times were applied for calculating the following plasma pharmacokinetic parameters for FTD and TPI: maximum observed plasma concentration (C_{max}); area under the plasma concentration–time curve from time 0 to the last measurable plasma concentration estimated by

the linear trapezoidal rule (AUC_{0-last}), to infinity calculated for day 1 (AUC_{0-inf}), and to end of dosing interval for day 12 only (AUC_{tau}); apparent terminal phase elimination half-life ($t_{1/2}$); terminal elimination oral clearance for day 1 (CL/F); steady-state oral clearance for day 12 (CL_{ss}/F); and apparent volume of distribution (V_d/F). The accumulation ratio of C_{max} ($R_{C_{max}}$) was calculated as the ratio of C_{max} (day 12)/ C_{max} (day 1) and the accumulation ratio of AUC_{0-last} ($R_{AUC_{0-last}}$) was calculated as the ratio of AUC_{0-last} (day 12)/ AUC_{0-last} (day 1).

To determine an appropriate dose for patients with severe RI, a regression analysis between actual CrCl and CL/F values on Day 12 collected from patients with normal renal function, and mild and moderate RI was performed using the power model. According to the following power formula, CL/F at each RI level was calculated, and then the dose for patients with severe RI to provide the similar AUC with that for patients with normal renal function was estimated. The regression analysis was performed by the Taiho pharmacokinetic team.

$$FTD\ CL/F\ (L/h) = 0.3432 \times CrCl^{0.4870}$$

Urine pharmacokinetic endpoints and parameters are described in Supplementary Methods.

Statistical analysis

Sample size considerations were based on the typical sample size (6–8 patients per cohort) recommended for RI studies [20]. Accounting for the individual variability in pharmacokinetic parameters (with a maximum covariance of 50%) and assuming a 25% dropout rate, it was estimated that for each cohort, 12 patients would need to be enrolled to obtain 9 evaluable patients. In the severe RI cohort, data from six evaluable patients were considered adequate for pharmacokinetic analysis.

The safety population comprised all patients who received at least 1 dose of FTD/TPI, and the pharmacokinetic analysis population comprised patients in the safety population with at least one concentration measurement on day 1, day 12, or both.

Plasma concentrations of FTD or TPI below the lower limit of quantification (LLOQ) in the predose samples or in early time points were set at 0. The collection time of the predose sample was set to 0, and actual postdose sampling times were expressed relative to the time of dosing. Plasma concentrations below the LLOQ in terminal samples or in the middle of the curve flanked by measurable concentrations were treated as missing values.

Effect of RI on FTD/TPI pharmacokinetics

Plasma pharmacokinetic parameters (C_{max} , AUC_{0-inf} , AUC_{0-last} , and AUC_{tau}) were analyzed by one-way analysis of variance (one-way ANOVA) using the categorical RI groups as class variables after the parameters were log-transformed, and comparisons were made between the normal renal function group and each of the RI groups. Point estimates of geometric mean ratios (GMRs) with their corresponding 90% confidence intervals (CIs) were constructed and back-transformed from the log-scale to express the estimates as ratios (each RI group to the control group). All analyses were carried out with Phoenix WinNonlin[®] software (Version 7.0, Certara LP; Princeton, New Jersey, USA) or SAS[®] statistical software, version 9.3 or a later version.

Results

Patient population

A total of 43 patients (12 patients with normal renal function, and 12, 11, and 8 patients with mild, moderate, and severe RI, respectively) were enrolled across 15 sites in the United States, Serbia, and the Czech Republic from March 2015 to November 2018. All patients received at least 1 dose of study drug. At data cutoff (January 31, 2019), 42 patients (98%) had discontinued (1 during the pharmacokinetic part, 7 prior to entering the extension part, and 34 during the extension part). Most discontinuations were due to disease progression (31 patients; 72%) or withdrawal of consent (6 patients; 14%).

Most patients were white (33/43; 76.7%); the median age was 64.0 years, and most patients (38/43; 88.4%) had gastrointestinal cancers (colorectal [$n=22$], liver [$n=6$], pancreas [$n=5$], gastric [$n=3$], and appendix [$n=2$]). Median CrCl was 105.7 mL/min in the normal renal function cohort, and 70.1, 43.1, and 24.4 mL/min in the mild, moderate, and severe RI cohorts, respectively (Table 1). Mean baseline albumin was comparable across cohorts, ranging from 35.4 to 38.3 g/L. Nearly all patients (41/43; 95.3%) had received prior anticancer therapy, with 58.1% having received ≥ 3 prior regimens.

Pharmacokinetics

Among 41 patients who were included in the pharmacokinetic analysis, pharmacokinetic concentration data were available for 40 patients on day 1 of cycle 1, 38 patients on day 12 of cycle 1, and 37 patients at both time points. The reasons for the exclusion of patients from the

Table 1 Patient baseline characteristics

	Normal RF (<i>n</i> = 12)	Mild RI (<i>n</i> = 12)	Moderate RI (<i>n</i> = 11)	Severe RI (<i>n</i> = 8)	Overall (<i>N</i> = 43)
Age, years					
Median (range)	54.5 (29–67)	68.0 (53–78)	72.0 (45–86)	69.0 (55–83)	64.0 (29–86)
Sex, <i>n</i> (%)					
Male	5 (41.7)	8 (66.7)	5 (45.5)	4 (50.0)	22 (51.2)
Female	7 (58.3)	4 (33.3)	6 (54.5)	4 (50.0)	21 (48.8)
Race, <i>n</i> (%)					
White	9 (75.0)	9 (75.0)	8 (72.7)	7 (87.5)	33 (76.7)
Black	2 (16.7)	0	1 (9.1)	1 (12.5)	4 (9.3)
Asian	1 (8.3)	3 (25.0)	1 (9.1)	0	5 (11.6)
Other	0	0	1 (9.1)	0	1 (2.3)
Mean body surface area (SD), m ²	1.81 (0.30)	1.81 (0.21)	1.83 (0.26)	1.89 (0.11)	1.83 (0.23)
Creatinine clearance, mL/min					
Mean (SD)	122.9 (43.5)	71.3 (7.9)	46.0 (8.4)	23.9 (4.5)	70.4 (43.5)
Median (range)	105.7 (90.7–236.6)	70.1 (61.6–81.6)	43.1 (32.5–58.8)	24.4 (16.0–29.7)	63.8 (16.0–236.6)
Mean baseline albumin (SD), g/L	38.2 (4.2)	38.3 (5.2)	35.4 (5.9)	37.0 (7.7)	37.3 (5.6)
Prior anticancer therapy, <i>n</i> (%)					
Adjuvant	12 (100)	12 (100)	10 (90.9)	7 (87.5)	41 (95.3)
For metastatic disease	6 (50.0)	2 (16.7)	4 (36.4)	1 (12.5)	13 (30.2)
Neoadjuvant	10 (83.3)	12 (100)	8 (72.7)	7 (87.5)	37 (86.0)
Neoadjuvant	1 (8.3)	2 (16.7)	3 (27.3)	0	6 (14.0)
No. of prior regimens, <i>n</i> (%)					
1	0	3 (25.0)	1 (9.1)	4 (50.0)	8 (18.6)
2	2 (16.7)	1 (8.3)	4 (36.4)	0	7 (16.3)
≥ 3	10 (83.3)	8 (66.7)	5 (45.5)	2 (25.0)	25 (58.1)

All patients in the normal RF, mild RI, and moderate RI cohorts received FTD/TPI 35 mg/m² BID, whereas patients in the severe RI cohort received FTD/TPI 20 mg/m² BID

RF renal function, RI renal impairment, SD standard deviation

pharmacokinetic analysis are listed in Supplementary Table S1.

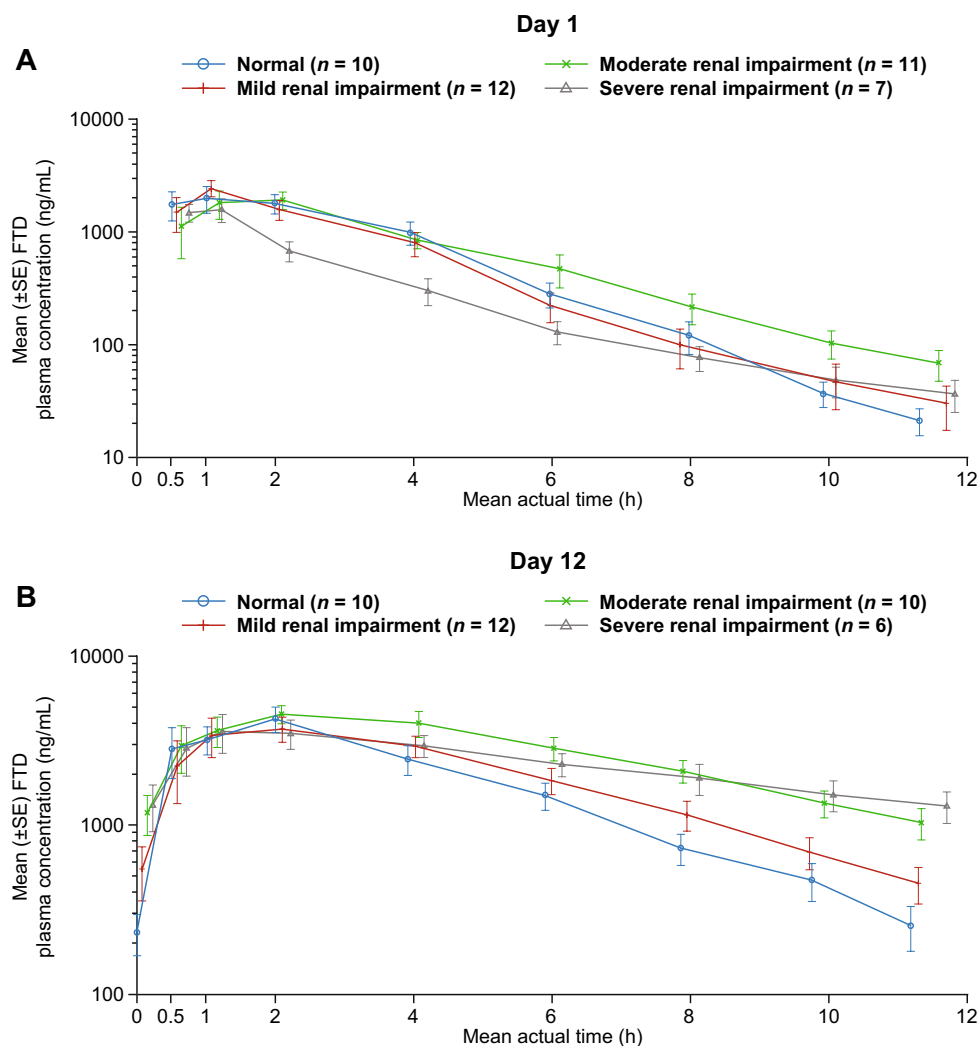
Mean plasma concentration–time profiles of FTD and TPI are shown in Figs. 1, 2, respectively, after the administration of the first dose (day 1, cycle 1) or multiple doses (day 12, cycle 1). On day 1, cycle 1, the mean plasma concentrations of FTD were comparable in the normal renal function, mild RI, and moderate RI cohorts, but were lower in the severe RI cohort. On day 12, cycle 1, the mean FTD concentration was lower in the normal renal function cohort than in the RI cohorts. The mean TPI plasma concentration was lowest in the normal renal function cohort and increased with the severity of RI on both days 1 and 12 of cycle 1.

Following the first dose of FTD/TPI (day 1, cycle 1), mean AUC values of FTD were similar between the normal renal function and the mild/moderate RI cohorts but was significantly lower in the severe RI cohort than the normal renal function cohort, which was consistent with the lower dose administered (− 51% for mean AUC_{0–last} [GMR, 0.49; 90% CI, 0.33–0.73]; − 50% for mean AUC_{0–inf} [GMR, 0.50; 90% CI, 0.33–0.76]; all *P* values < 0.05; Tables 2, 3). After

multiple doses of FTD/TPI (day 12, cycle 1), compared with the normal renal function cohort, FTD AUC values were nearly unchanged in the mild cohort (by − 1% for both AUC_{0–last} and AUC_{tau}), and somewhat increased in the moderate and severe RI cohorts (by + 56% for AUC_{0–last} and AUC_{tau} for the moderate RI cohort; + 37% [AUC_{0–last}] and + 45% [AUC_{tau}] for the severe RI cohort), but these differences were not statistically significant (all *P* values > 0.05; Table 3). Mean accumulation ratios of AUC_{0–last} increased with increasing RI (ranging from 2.80 to 6.09) on day 12 (Table 2).

FTD C_{max} values followed a similar trend. After the first dose, mean FTD C_{max} values were similar in the normal renal function, mild RI, and moderate RI cohorts but were somewhat decreased in the severe RI cohort (− 38%; GMR, 0.62), consistent with the lower dosing in this cohort. Following multiple doses, the differences in C_{max} values between the normal renal function and RI cohorts were not significant; GMRs ranged from 0.84 to 1.19 (all *P* values > 0.05) on day 12 (Table 3).

Fig. 1 Mean plasma concentration–time profile of FTD (pharmacokinetic population) on **A** day 1 and **B** day 12 of cycle 1. FTD trifluridine, SE standard error. Note: the lower limit for concentration in the log-linear scale is 0.01 ng/mL. Standard error bar values lower than 0.01 ng/mL are shown at 0.01 ng/mL



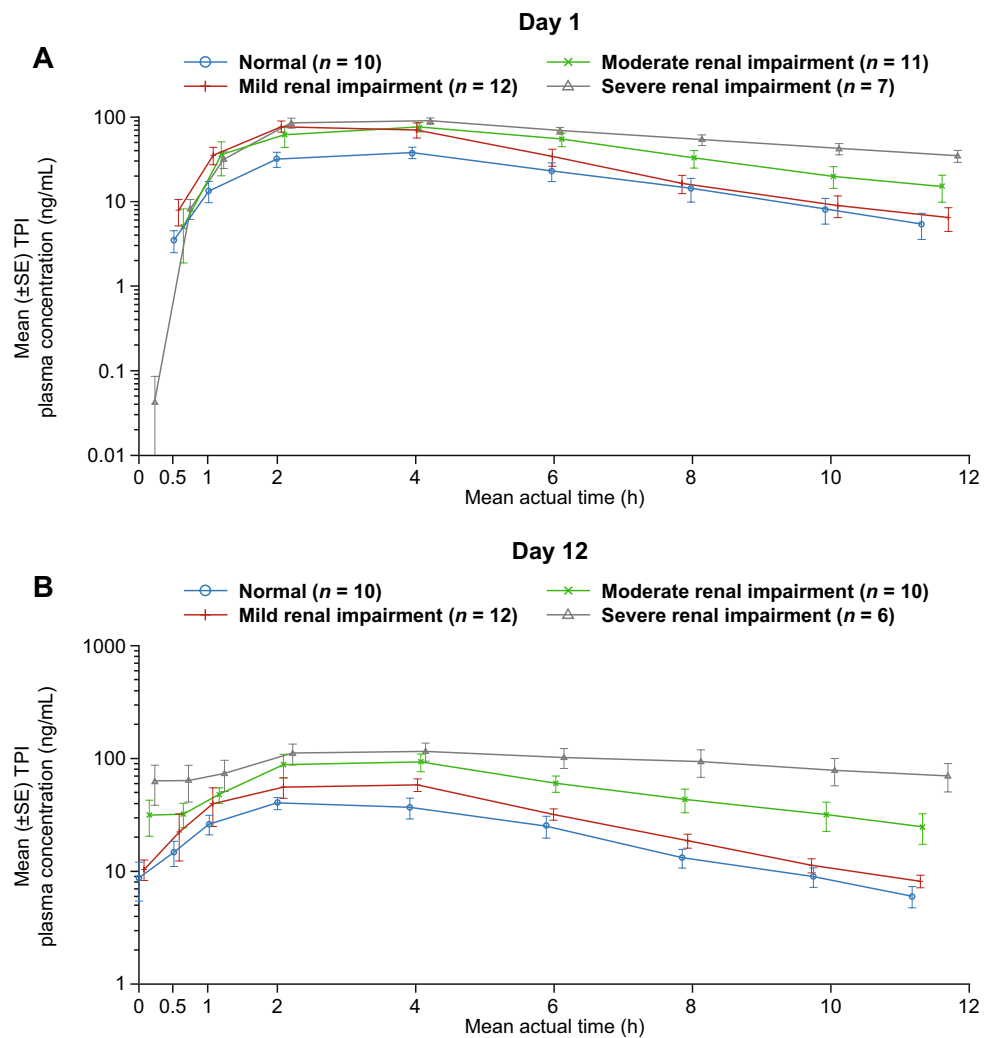
Mean CL/F and CL_{ss}/F values for FTD showed the opposite trend to AUC values. Whereas mean CL/F values were similar across cohorts on day 1, a decreasing trend in mean CL_{ss}/F was noted with increasing RI on day 12 (Table 2). On both days, mean clearance values were not significantly different between the normal renal function and RI cohorts (Table 3).

On the other hand, TPI plasma exposures significantly increased with the severity of RI on both days 1 and 12 of cycle 1 and were lowest in the normal renal function cohort. On day 1, mean AUC_{0–last} values were increased by +65% (GMR, 1.65; 90% CI, 1.16–2.36; $P < 0.05$), +121% (GMR, 2.21; 90% CI, 1.54–3.18; $P < 0.05$), and +224% (GMR, 3.24; 90% CI, 2.15–4.89; $P < 0.05$) in the mild RI, moderate RI, and severe RI cohorts, respectively, compared with the normal renal function cohort. After multiple doses on day 12, mean AUC_{0–last} values were increased by +42% (GMR, 1.42; 90% CI, 1.00–2.03), +139% (GMR, 2.39; 90% CI, 1.65–3.47; $P < 0.05$), and +308% (GMR, 4.08; 90%

CI, 2.66–6.26) in the mild RI, moderate RI, and severe RI cohorts, respectively, compared with the normal renal function cohort (Table 3). Trends in AUC_{inf} and AUC_{tau} were consistent with AUC_{0–last}, although these values were not calculable in almost all patients in the severe RI cohort (Tables 2, 3). No marked accumulation in AUC_{0–last} was observed in TPI on day 12 (Table 2). Similar to AUC values, mean C_{max} values for TPI were significantly higher in the RI cohorts than in the normal renal function cohort on both day 1 (ranging from +91% to +113%) and day 12 (ranging from +51% to +158%), and these values increased with the severity of RI (Tables 2, 3).

Mean CL/F (day 1, cycle 1) and CL_{ss}/F values (day 12, cycle 1) for TPI were significantly lower in the mild and moderate RI cohorts than in the normal renal function cohort; GMRs were 0.66 ($P = 0.0748$) and 0.48 for CL/F and 0.65 and 0.48 for CL_{ss}/F (all the other P values < 0.05 ; Table 3). Mean clearance was not calculable for most patients in the severe RI cohort (Table 2).

Fig. 2 Mean plasma concentration–time profile of TPI (pharmacokinetic population) on **A** day 1 and **B** day 12 of cycle 1. *SE* standard error, *TPI* tipiracil. Note: the lower limit for concentration in the log-linear scale is 0.01 ng/mL. Standard error bar values lower than 0.01 ng/mL are shown at 0.01 ng/mL



Urine pharmacokinetic findings for FTD and TPI are shown in Supplementary Table S2 and are described in the Supplement.

Safety

All enrolled patients received at least one dose of FTD/TPI and were evaluable for safety ($N=43$). The median treatment duration was 60 days (range, 1–306) for the overall population (42.0, 78.0, 71.0, and 52.5 days for the normal renal function and mild, moderate, and severe RI cohorts, respectively). Median relative dose intensity (ratio of delivered to planned) was 86.0% for the overall population (89.8%, 85.2%, 83.2%, and 91.0% for the various cohorts), and the median number of cycles completed were similar (2.0; range, 2.0–3.0) across cohorts (Supplementary Table S3).

Overall, 37 patients (86.0%) experienced a treatment-related AE, and 32 patients (74.4%) had a grade ≥ 3 AE of any causality. The overall incidence of any-cause grade ≥ 3 AEs was higher in the RI cohorts (83.3%, 90.9%, and 75.0%

in the mild, moderate, and severe RI cohorts, respectively) than in the normal renal function cohort (50.0%); incidences of most grade ≥ 3 AEs were comparable in the severe and mild RI cohorts (Table 4 and Supplementary Table S4). The incidence of serious AEs was higher in the mild (58.3%) and moderate RI cohorts (45.5%) than in the normal renal function cohort (33.3%). Overall, the most common serious AEs were sepsis ($n=4$), acute renal failure ($n=3$), and small-intestinal obstruction and pneumonia ($n=2$, each).

Overall, 5 patients (1 with mild RI, 2 with moderate RI, and 2 with severe RI) had one dose reduction each. In 4 patients, the dose reductions were reported during cycle 2, and one patient in the severe RI cohort had a dose reduction during cycle 9. Seven patients (16.3%) discontinued because of AEs, none of which were related to treatment. These discontinuations included 1 patient in the normal renal function cohort (due to decreased appetite), 3 patients in the mild RI cohort (due to abdominal pain, insomnia, and acute renal failure; $n=1$ each), 2 patients in the moderate RI cohort (both due to small-intestinal obstruction), and 1 patient in

Table 2 Plasma pharmacokinetic parameters for FTD/TPI on days 1 and 12 of cycle 1: descriptive statistics

	FTD															
	Normal RF						TPI									
	Mild RI		Moderate RI		Severe RI		Normal RF		Mild RI		Moderate RI		Severe RI			
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD		
Day 1																
C_{max} , ng/mL	10	2514 (66.6)	12	2896 (46.8)	11	2494 (49.4)	7	1557 (63.4)	10	43.67 (37.9)	12	83.56 (60.5)	11	93.14 (42.7)	7	91.16 (30.6)
AUC_{0-inf} , h*ng/mL	10	7311 (45.3)	12	6772 (47.5)	11	7464 (46.8)	7	3674 (76.8)	9	210.11 (51.5)	11	327.82 (70.6)	10	465.46 (39.5)	1	819.59 (NA)
AUC_{0-last} , h*ng/mL	10	7253 (46.2)	12	6671 (46.5)	11	7296 (46.1)	7	3528 (74.1)	10	204.91 (46.4)	12	338.97 (76.2)	11	453.45 (41.6)	7	664.85 (25.3)
CL/F, L/h	10	8.72 ± 4.19	12	10.05 ± 5.96	11	9.17 ± 4.86	7	12.69 ± 12.41	9	147.90 ± 80.75	11	104.95 ± 86.18	10	64.62 ± 18.57	1	20.11 ± NA
$T_{1/2}$, h	10	1.21 ± 0.38	12	2.22 ± 1.15	11	1.92 ± 0.43	7	2.78 ± 1.43	9	2.20 ± 0.50	11	2.44 ± 0.76	10	2.59 ± 0.42	1	4.00 ± NA
Vd/F, L	10	13.18 (55.9)	12	26.38 (53.6)	11	22.39 (49.8)	7	33.58 (27.0)	9	403.56 (70.4)	11	290.84 (89.6)	10	228.86 (33.5)	1	(NA)
Day 12																
C_{max} , ng/mL	10	4684 (52.4)	12	4041 (73.3)	10	5563 (46.4)	6	3930 (36.2)	10	44.84 (45.5)	12	67.92 (58.8)	10	101.67 (47.1)	6	115.49 (52.1)
AUC_{tau} , h*ng/mL	10	19,004 (37.2)	12	18,740 (77.2)	8	29,581 (25.1)	3	27,495 (59.3)	9	230.74 (41.1)	10	388.17 (27.8)	8	519.10 (67.0)	2	1655.74 (40.8)
AUC_{0-last} , h*ng/mL	10	18,715 (35.9)	12	18,505 (76.5)	10	29,270 (40.3)	6	25,619 (40.4)	10	232.84 (39.1)	12	331.28 (47.7)	10	557.39 (61.9)	6	950.59 (63.2)
CLSS/F, L/h	10	3.29 ± 1.12	12	4.07 ± 3.54	8	2.10 ± 0.41	1	1.90 ± NA	9	128.32 ± 58.13	10	78.88 ± 21.15	8	61.97 ± 32.74	0	–
$T_{1/2}$, h	10	2.23 ± 0.98	12	2.25 ± 0.76	8	2.98 ± 0.91	1	3.30 ± NA	9	2.77 ± 0.88	10	2.49 ± 0.74	8	2.95 ± 0.50	0	–
R_{Cmax}	9	1.89 (65.8)	12	1.40 (66.6)	10	2.17 (51.8)	6	2.29 (35.5)	9	1.10 (43.9)	12	0.81 (53.2)	10	1.13 (41.1)	6	1.28 (46.4)
$R_{AUC0-last}$	9	2.60 (43.9)	12	2.77 (44.6)	10	4.04 (41.2)	6	5.74 (39.5)	9	1.20 (46.1)	12	0.98 (44.7)	10	1.26 (46.0)	6	1.46 (43.0)

All data shown are geometric mean (CV %), with the exception of CL/F, CLSS/F, and $T_{1/2}$, which are arithmetic mean ± SD

AUC_{0-last} area under the plasma concentration–time curve from time 0 to last measurable plasma concentration estimated by the linear trapezoidal rule, AUC_{0-inf} area under the plasma concentration–time curve from time 0 to infinity, AUC_{tau} area under the plasma concentration–time curve from time 0 to the end of dosing interval, CL/F oral clearance, CLSS/F steady-state oral clearance, C_{max} maximum observed plasma concentration, FTD trifluridine, NA not applicable, R_{Cmax} accumulation ratio calculated as ratio of C_{max} (day 12)/ C_{max} (day 1), RF renal function, RI renal impairment, $T_{1/2}$ apparent terminal phase elimination half-life, TPI tipiracil, Vd/F apparent volume of distribution

Table 3 Plasma pharmacokinetic parameters: effect of renal impairment

Parameter	Cohort	FTD			TPI		
		<i>n</i>	Geometric mean	Ratio vs normal cohort (90% CI) ^a	<i>n</i>	Geometric mean	Ratio vs normal cohort (90% CI) ^a
C_{max} , ng/mL Day 1	Normal RF	10	2514		10	43.67	
	Mild RI	12	2896	1.15 (0.79–1.68)	12	83.56	1.91 (1.40–2.62)
	Moderate RI	11	2494	0.99 (0.68–1.45)	11	93.14	2.13 (1.55–2.94)
	Severe RI	7	1557	0.62 (0.40–0.95)	7	91.16	2.09 (1.45–3.00)
C_{max} , ng/mL Day 12	Normal RF	10	4684		10	44.84	
	Mild RI	12	4041	0.86 (0.59–1.26)	12	67.92	1.51 (1.07–2.15)
	Moderate RI	10	5563	1.19 (0.80–1.76)	10	101.67	2.27 (1.57–3.27)
	Severe RI	6	3930	0.84 (0.53–1.32)	6	115.49	2.58 (1.69–3.93)
AUC_{0-last} , h*ng/mL Day 1	Normal RF	10	7253		10	204.91	
	Mild RI	12	6671	0.92 (0.65–1.31)	12	338.97	1.65 (1.16–2.36)
	Moderate RI	11	7296	1.01 (0.70–1.44)	11	453.45	2.21 (1.54–3.18)
	Severe RI	7	3528	0.49 (0.33–0.73)	7	664.85	3.24 (2.15–4.89)
AUC_{0-last} , h*ng/mL Day 12	Normal RF	10	18,715		10	232.84	
	Mild RI	12	18,505	0.99 (0.69–1.41)	12	331.28	1.42 (1.00–2.03)
	Moderate RI	10	29,270	1.56 (1.08–2.27)	10	557.39	2.39 (1.65–3.47)
	Severe RI	6	25,619	1.37 (0.89–2.11)	6	950.59	4.08 (2.66–6.26)
AUC_{0-inf} , h*ng/mL Day 1	Normal RF	10	7311		9	210.11	
	Mild RI	12	6772	0.93 (0.65–1.32)	11	327.82	1.56 (1.05–2.32)
	Moderate RI	11	7464	1.02 (0.71–1.47)	10	465.46	2.22 (1.48–3.32)
	Severe RI	7	3674	0.50 (0.33–0.76)	1	819.59	3.90 (1.54–9.88)
AUC_{tau} , h*ng/mL Day 12	Normal RF	10	19,004		9	230.74	
	Mild RI	12	18,740	0.99 (0.68–1.42)	10	388.17	1.68 (1.20–2.36)
	Moderate RI	8	29,581	1.56 (1.04–2.33)	8	519.10	2.25 (1.57–3.22)
	Severe RI	3	27,495	1.45 (0.82–2.54)	2	1655.74	7.18 (4.03–12.78)
CL/F , L/h Day 1	Normal RF	10	7.99		9	130.51	
	Mild RI	12	9.05	1.13 (0.80–1.61)	11	86.40	0.66 (0.45–0.97)
	Moderate RI	11	8.26	1.03 (0.72–1.48)	10	62.09	0.48 (0.32–0.70)
	Severe RI	7	9.90	1.24 (0.83–1.86)	1	20.11	0.15 (0.06–0.37)
CL_{ss}/F , L/h Day 12	Normal RF	10	3.09		9	116.82	
	Mild RI	12	3.27	1.06 (0.75–1.49)	10	75.94	0.65 (0.47–0.91)
	Moderate RI	8	2.07	0.67 (0.46–0.98)	8	55.52	0.48 (0.33–0.69)
	Severe RI	1	1.90	0.61 (0.26–1.43)	0	–	–

All patients in the normal RF, mild RI, and moderate RI cohorts received FTD/TPI 35 mg/m² BID, whereas patients in the severe RI cohort received FTD/TPI 20 mg/m² BID

AUC_{0-last} area under the plasma concentration–time curve from time 0 to last measurable plasma concentration estimated by the linear trapezoidal rule, AUC_{0-inf} area under the plasma concentration–time curve from time 0 to infinity, AUC_{tau} area under the plasma concentration–time curve from time 0 to the end of dosing interval, *BID* twice daily, CL/F oral clearance, CL_{ss}/F steady-state oral clearance, C_{max} maximum observed plasma concentration, *FTD* trifluridine, *RF* renal function, *RI* renal impairment, *TPI* tipiracil

^aBack-transformed from the log-scale to express the estimates as ratios

^bBased on ANOVA model comparing each renal impairment cohort with the normal renal function cohort

the severe RI cohort (dehydration, fatigue, muscular weakness, and dyspnea). There were no deaths during the study.

In all patients, the most common AEs of any cause and grade were fatigue (55.8%), decreased appetite (48.8%), nausea (48.8%), anemia (39.5%), vomiting (34.9%), dehydration (27.9%), and diarrhea and dyspnea (25.6% each). Grade ≥ 3 AEs occurring in $\geq 10\%$ of all patients were anemia and

decreased neutrophil count (16.3% each) and neutropenia (11.6%). The only notable difference in AE incidences between the RI cohorts and the normal cohort pertained to anemia and neutropenia, which trended higher in the mild RI (any-grade anemia, 25.0%; any-grade neutropenia, 16.7%), moderate RI (72.7% and 27.3%, respectively), and severe RI cohorts (50.0% and 25.0%, respectively) than in

Table 4 Safety summary

	Normal RF (<i>n</i> = 12)	Mild RI (<i>n</i> = 12)	Moderate RI (<i>n</i> = 11)	Severe RI (<i>n</i> = 8)
Any-cause AEs	12 (100)	12 (100)	11 (100)	8 (100)
Any-cause serious AEs	4 (33.3)	7 (58.3)	5 (45.5)	3 (37.5)
Any-cause grade ≥ 3 AEs	6 (50.0)	10 (83.3)	10 (90.9)	6 (75.0)
Treatment-related AEs	10 (83.3)	10 (83.3)	11 (100)	6 (75.0)
Any-cause AEs leading to discontinuation	1 (8.3)	3 (25.0)	2 (18.2)	1 (12.5)
Any-cause AEs with outcome of death	0	0	0	0
Most common AEs of any grade in $\geq 25\%$ of patients in any cohort				
Nausea	9 (75.0)	6 (50.0)	4 (36.4)	2 (25.0)
Decreased appetite	6 (50.0)	6 (50.0)	5 (45.5)	4 (50.0)
Vomiting	5 (41.7)	5 (41.7)	4 (36.4)	1 (12.5)
Fatigue	4 (33.3)	10 (83.3)	7 (63.6)	3 (37.5)
Abdominal pain	3 (25.0)	4 (33.3)	1 (9.1)	2 (25.0)
Constipation	3 (25.0)	3 (25.0)	1 (9.1)	3 (37.5)
Abdominal distension	2 (16.7)	1 (8.3)	2 (18.2)	0
Anemia	2 (16.7)	3 (25.0)	8 (72.7)	4 (50.0)
Cough	2 (16.7)	3 (25.0)	3 (27.3)	0
Decreased neutrophil count	2 (16.7)	5 (41.7)	2 (18.2)	0
Diarrhea	2 (16.7)	4 (33.3)	2 (18.2)	3 (37.5)
Dyspnea	2 (16.7)	4 (33.3)	3 (27.3)	2 (25.0)
Pruritus	2 (16.7)	3 (25.0)	2 (18.2)	0
Decreased white blood cell count	1 (8.3)	1 (8.3)	3 (27.3)	1 (12.5)
Dehydration	1 (8.3)	6 (50.0)	2 (18.2)	3 (37.5)
Dizziness	1 (8.3)	0	3 (27.3)	1 (12.5)
Muscular weakness	1 (8.3)	2 (16.7)	1 (9.1)	2 (25.0)
Neutropenia	1 (8.3)	2 (16.7)	3 (27.3)	2 (25.0)
Pyrexia	1 (8.3)	3 (25.0)	1 (9.1)	2 (25.0)
Urinary tract infection	1 (8.3)	0	3 (27.3)	1 (12.5)
Peripheral edema	0	2 (16.7)	1 (9.1)	2 (25.0)
Increased blood creatinine	0	0	3 (27.3)	0

All data are shown as numbers (%) unless otherwise noted. All patients in the normal RF, mild RI, and moderate RI cohorts received FTD/TPI 35 mg/m² BID, whereas patients in the severe RI cohort received FTD/TPI 20 mg/m² BID

AE adverse event, BID twice daily, RF renal function, RI renal impairment

the normal renal function cohort (16.7% and 8.3%, respectively). Grade ≥ 3 hematologic AEs led to dose interruptions in 1, 5, and 2 patients in the normal renal function, mild RI, and moderate RI cohorts, respectively; no dose interruptions due to hematologic toxicities were reported in the severe RI cohort. No patients had dose reductions due to grade ≥ 3 hematologic toxicities. Overall, no treatment discontinuations due to hematologic toxicities were reported.

Discussion

In view of the limited data available for FTD/TPI activity/safety in patients with RI, this phase I study was designed to provide guidance for FTD/TPI dosing in patients with advanced tumors and varying degrees of RI. In this study,

patients with mild and moderate RI received 35 mg/m² BID (on days 1–5 and 8–12 of a 28-day cycle), the recommended dose for patients with normal renal function, based on safety data in earlier phase II and III trials showing tolerability in patients with mild/moderate RI [16–18; data on file]. Based on the interim pharmacokinetic and safety data obtained from cohorts 1–3 in cycle 1, the dose for the severe RI cohort was designated as 20 mg/m² BID (on days 1–5 and 8–12 of a 28-day cycle).

Given that absorbed TPI is mainly eliminated by urinary excretion [4, 5, 8], RI was expected to increase TPI exposure and thereby, enhance FTD exposure. In this study, the evaluation of FTD's and TPI's pharmacokinetic parameters in patients with RI or normal renal function indicated a significant effect of RI on TPI exposures. However, the effect of mild or moderate RI on FTD exposures was relatively

marginal. Following administration of the first dose, FTD plasma concentrations and exposures were lower in the severe RI cohort than in the normal cohort, which reflected the lower dose that was administered. At steady state, no significant differences were observed in FTD plasma exposures between patients with RI and those in the normal cohort, although FTD plasma exposures showed a trend of increase with increased RI (mean accumulation ratio of AUC_{0-last} in the severe RI cohort was nearly twofold that in the normal renal function cohort). It is to be noted that the steady-state plasma exposures of FTD in patients in the severe RI cohort who received FTD/TPI at a lower starting dose (20 mg/m² BID) were similar to those observed in patients in the mild and moderate RI cohorts who received FTD/TPI at 35 mg/m² BID. In contrast to FTD, significant increases in TPI plasma exposures were observed in all RI cohorts compared with the normal renal function cohort, both after administration of the first dose and at steady state. Plasma exposures of TPI (C_{max} and AUCs) increased with the severity of RI, and the mean clearance decreased with severity. However, TPI accumulation ratios ($R_{AUC0-last}$ and R_{Cmax}) did not increase appreciably with RI.

RI may also affect the pharmacokinetics of chemotherapeutic agents through other indirect effects on nonrenal clearance, including absorption or hepatic metabolism [12, 13]. However, an earlier study evaluating FTD/TPI in patients with varying degrees of hepatic impairment showed that FTD and TPI exposures were not increased by hepatic impairment [18], which suggested that changes in nonrenal clearance may have a limited impact on exposure of FTD or TPI when administered together as FTD/TPI.

Study treatment exposure (median number of initiated/completed cycles; relative dose intensity) was comparable across cohorts, indicating that renal function did not have an impact on treatment compliance. The overall safety profile of FTD/TPI observed in this study was consistent with previous observations, and no new safety concerns were observed, which suggested that the increased TPI exposures did not impact the safety profile of FTD/TPI. Study discontinuation was overwhelmingly related to disease progression, not toxicity, and no AE-related deaths occurred. In patients with mild or moderate RI, FTD/TPI at 35 mg/m² BID resulted in a higher frequency of grade ≥ 3 toxicities and serious AEs than in those with normal renal function, although incidences of any-grade treatment-related AEs were not increased in these cohorts. There were no clinically meaningful differences in the FTD/TPI safety profile between patients with severe RI who received an adjusted 20 mg/m² BID dose and those with mild or moderate RI who received the regular dose, indicating that this reduced dose was tolerable in patients with severe RI. The frequency of grade ≥ 3 hematologic AEs, including anemia and neutropenia, trended higher in patients with RI than in those with normal renal function, although

the small numbers of patients precluded any real comparison of AE rates between the cohorts. The increased incidence of grade ≥ 3 anemia in patients with severe RI could be partly explained by the decreased erythropoietin production and impaired iron absorption in these patients [21], which predispose them to anemia. Heme-related AEs were managed with dose interruptions (which were more frequent in the mild RI cohort), and no permanent discontinuations of treatment due to heme-related AEs were reported across cohorts.

These observations are consistent with results from post hoc subgroup analyses of FTD/TPI safety in patients with mild or moderate RI in the phase III RECURSE and TAGS trials [17, 18]. In both trials, the rates of hematologic toxicities (in particular, neutropenia and anemia) were higher in patients with mild or moderate RI. However, these AEs were managed with dosing modifications and supportive medications. Nearly all cases of grade ≥ 3 neutropenia resolved; median times to resolution were similar in patients with normal renal function and in those with RI [18]. Overall, these data indicate that heme-related AEs can be monitored and managed in patients with RI without the need for treatment discontinuation.

One important limitation in this study was the small sample sizes of the cohorts. Although this sample size was sufficient to study the effects of RI on FTD/TPI pharmacokinetics, robust comparisons of safety could not be performed. In addition, plasma protein unbound fractions of FTD and TPI were not quantitated. Given that FTD mainly binds to albumin [9] and albumin is a significant covariate of FTD clearance [22], the effect of hypoalbuminemia, including that of ongoing renal dysfunction on the evaluation of FTD pharmacokinetics, could not be ruled out. However, in this study, baseline albumin levels were comparable between the normal renal function and the RI cohorts. In addition, there were no clinically meaningful changes in albumin or other lab parameters from baseline to the last study visit in any cohort, and there were no renal function-dependent changes in these parameters, which indicated the absence of significant worsening of renal function during the study. Therefore, it is unlikely that the evaluation of FTD/TPI pharmacokinetics was affected by changes in albumin levels or worsening of renal function.

In conclusion, the results of this study indicate that FTD/TPI at the recommended dose of 35 mg/m² BID was tolerable in patients with advanced solid tumors and mild or moderate RI, with no unexpected safety concerns noted. Even with increased TPI exposures, FTD steady-state plasma exposures in patients with RI were comparable to those in patients with normal renal function. Although these patients may receive the recommended dose without the need for dosing adjustments, they should be closely monitored for toxicity, particularly hematologic toxicity. The reduced FTD/TPI starting dose of 20 mg/m² BID was

found to be tolerable and appropriate for patients with advanced solid tumors and severe RI, and no meaningful changes in safety were noted between the severe RI cohort at the adjusted dose and the mild or moderate RI cohorts at the recommended dose. On the basis of these results, the FTD/TPI dosage for patients with severe RI has been recommended as 20 mg/m² BID on days 1–5 and days 8–12 of each 28-day cycle, allowing for a dose reduction to 15 mg/m² in case of intolerability [9].

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Code availability Phoenix WinNonlin[®] software (Version 7.0, Certara LP; Princeton, New Jersey, USA) or SAS[®] statistical software, version 9.3 or a later version.

Declarations

Conflict of interest M.W.S. reports research funding from Incyte, Lexicon, NGM Bio, Nourscom, Tesaro, and Yivia. C.R.B. is part of the speaker bureau for Taiho Oncology Inc. M.G.F. received research grant funding (to institution) from Amgen, AstraZeneca, and Novartis; has served on the advisory board of Amgen, Array Biopharma, Bayer, and Pfizer; is part of the speakers bureau for Amgen and Guardant360, and reports honoraria from Amgen. M.A.R. received research funding from Taiho Oncology, Inc, during the conduct of the study and from Celgene Corporation and the National Cancer Institute, outside the submitted work. K.H., I.Y., K.A.B., and Y.H. are employees of Taiho Oncology, Inc. K.A.B. is a former employee and a stockholder of Eli Lilly. L.R. received research funding from Taiho Oncology, Inc. W.S., L.P., S.K., T.J.G., D.R.S., J.S., V.S., and B.Z. have no financial disclosures to report.

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Consent to participate Informed consent was obtained from all individual participants included in the study.


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