The subgroups of the phase III RECOURSE trial of trifluridine/tipiracil (TAS-102) versus placebo with best supportive care in patients with metastatic colorectal cancer

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Abstract

Background: In the phase III RECOURSE trial, trifluridine/tipiracil (TAS-102) extended overall survival (OS) and progression-free survival (PFS) with an acceptable toxicity profile in patients with metastatic colorectal cancer refractory or intolerant to standard therapies. The present analysis investigated the efficacy and safety of trifluridine/tipiracil in RECOURSE subgroups.

Methods: Primary and key secondary end-points were evaluated using a Cox proportional hazards model in prespecified subgroups, including geographical subregion (United States of America [USA], European Union [EU], Japan), age (<65 years, 65 years) and v-Ki-ras2 Kirsten rat sarcoma 2 viral oncogene homologue (*KRAS*) status (wild type, mutant). Safety and tolerability were reported with descriptive statistics.

Results: Eight-hundred patients were enrolled: USA, n = 99; EU, n = 403; Japan, n = 266. Patients aged 65 years and those with mutant *KRAS* tumours comprised 44% and 51% of all patients in the subregions, respectively. Final OS analysis (including 89% of events, compared with 72% in the initial analysis) confirmed the survival benefit associated with trifluridine/tipiracil, with a hazard ratio (HR) of 0.69 (95% confidence interval [CI] 0.59–0.81; P = 0.0001). Median OS in the three regions was 6.5–7.8 months in the trifluridine/tipiracil arm and 4.3–6.7 months in the placebo arm (USA: HR 0.56; 95% CI 0.34–0.94; P = 0.0277; EU: HR 0.62; 95% CI 0.48–0.80; P = 0.0002; Japan: HR 0.75; 95% CI 0.57–1.00; P = 0.0470). Median PFS was 2.0–2.8 months for trifluridine/tipiracil and 1.7–1.8 months for placebo; HRs favoured trifluridine/tipiracil in all regions. Similar clinical benefits of trifluridine/tipiracil were observed in elderly patients and in those with mutant *KRAS* tumours. There were no marked differences among subregions in terms of safety and tolerability.

Conclusions: Trifluridine/tipiracil was effective in all subgroups, regardless of age, geographical origin or *KRAS* status.

This trial is registered with ClinicalTrials.gov: NCT01607957.

Keywords

1. Introduction

Trifluridine/tipiracil (TAS-102, Lonsurf®; Taiho Oncology Inc., Princeton, NJ, USA) is an orally administered chemotherapy consisting of the antineoplastic thymidine-based nucleoside analogue trifluridine, and a thymidine phosphorylase inhibitor, tipiracil, at a molar ratio of 1:0.5 (weight ratio, 1:0.471). The primary cytotoxic mechanism of trifluridine is through incorporation into DNA, leading to DNA dysfunction and damage [1–3]. The

addition of tipiracil improves the bioavailability of trifluridine by inhibiting its catabolism by thymidine phosphorylase [4].

Trifluridine/tipiracil has shown promise in a number of clinical trials, particularly in metastatic colorectal cancer [5–10]. In the phase III RECOURSE trial (NCT01607957), which was conducted in patients with metastatic colorectal cancer refractory to standard therapies, including fluoropyrimidines, irinotecan and oxaliplatin, treatment with trifluridine/tipiracil resulted in a significant improvement in median overall survival (OS) compared with placebo (7.1 versus 5.3 months; hazard ratio [HR] 0.68; P < 0.0001) and in median progression-free survival (PFS) (2.0 versus 1.7 months; HR 0.48; P < 0.0001) [5]. Trifluridine/tipiracil was well tolerated, with few serious adverse events (AEs) reported; neutropenia was the most frequently observed AE. Many patients in this trial [5], as well as all patients in the prior phase II trial [10], were Japanese. Therefore, it is of interest to compare the efficacy and safety of trifluridine/ tipiracil in Western populations with those reported from Japan. The current analyses were performed to further evaluate trifluridine/ tipiracil compared with placebo among different patient groups, including geographical subregions, older patients aged 65 and 70 years, and v-Ki-ras2 Kirsten rat sarcoma 2 viral oncogene homologue (*KRAS*) status.

2. Patients and methods

2.1. Study design

The RECOURSE trial design has been previously described in detail (Supplementary Fig. 1) [5]. Briefly, RECOURSE was a global, phase III, multicentre, randomised, double-blind, placebo-controlled trial comparing trifluridine/tipiracil plus best supportive care on the one hand with placebo plus best supportive care on the other. Patients were stratified according to (1) *KRAS* status (wild type, mutant), (2) time since diagnosis of first metastasis (<18 months, 18 months) and (3) geographical region (Japan and Western [United States of America (USA), European Union (EU) including United Kingdom, and Australia]), and randomly assigned in a 2:1 ratio to receive trifluridine/tipiracil or placebo. Here, we assess results based on geographical subregions (Japan, USA and EU) and outcomes related to age and *KRAS* status. Patients were randomised at 21 different sites in the USA, 20 in Japan and 55 across the EU. Australia was omitted from this analysis because of the small number of enrolled patients (n = 32).

2.2. Patients

Patients with biopsy-proven/documented adenocarcinoma of the colon or rectum who had received two or more regimens of standard chemotherapies for metastatic disease were eligible for randomisation. For more details, please see the supplementary methods.

2.3. End-points

The primary end-point was OS, defined as the time from randomisation to death from any cause. Secondary end-points included PFS (time from randomisation to first radiographical confirmation of disease progression or death from any cause), overall response rate

(proportion of patients with complete or partial response) and safety. Measurements are described in the supplementary methods.

2.4. Statistical analysis

The study protocol included a prespecified analysis of outcomes and safety according to geographical subregion, *KRAS* status and potential prognostic/predictive factors, including age <65 versus 65 years and <70 versus 70 years. OS and PFS were analysed in the intention-to-treat population in each geographical subregion with the use of a two-sided, stratified, logrank test, with the HR and two-sided 95% confidence intervals (CIs) based on a stratified Cox proportional hazards model and the associated Kaplan–Meier survival estimates. Median follow-up time for survival was calculated by means of the reverse Kaplan–Meier method. AEs and laboratory abnormalities were summarised for all patients who received at least one dose of study drug. The number and percentage of patients hospitalised, reason for hospitalisation and total duration of hospitalisation were summarised descriptively by treatment group for each region. *Ad hoc* analyses of outcomes across subregions according to age 65 years, age 70 years and *KRAS* status were also conducted using the same methodology.

The original results of RECOURSE were based on a cut-off date of 24th January 2014 [5]. A further analysis of OS outcomes was performed based on final survival data as of 8th October 2014 and is presented here. Additionally, a multivariate model of potential prognostic factors was developed to create a prognostic index for OS, and included *KRAS* status, time since diagnosis of first metastasis, geographical subregion, v-raf murine sarcoma viral oncogene homologue B1 (*BRAF*) status, age, race, gender, primary tumour site, Eastern Cooperative Oncology Group performance status (ECOG PS), number of prior regimens and number of metastatic sites [11].

3. Results

3.1. Baseline characteristics

Of the 800 patients (excluding the 32 from Australia) enrolled in the RECOURSE trial, 99, 403 and 266 were enrolled in the USA, EU and Japan, respectively. Baseline characteristics for patients randomised within these subregions are shown in Table 1. Elderly patients aged 65 and 70 years represented 44% and 23% of all patients enrolled within the three geographical subregions, respectively; patients with mutant *KRAS* tumours accounted for 51% of patients. There were some differences in the racial profile of patients from these subregions, with US and EU patients being predominantly Caucasian, and Japanese patients being Asian. More than 60% of patients in the EU and Japan were male individuals compared with approximately 50% in the USA. In Japan, the primary tumour site was evenly divided between colon and rectum, while in the EU, and particularly in the USA, the majority of primary tumour sites were in the colon. Japanese patients appeared to have less symptomatic disease, with 71% having an ECOG PS of 0 compared with 41% in the USA and 51% in the EU. In addition, 75.2% of Japanese patients had a normal baseline estimated glomerular filtration rate compared with 48% in the USA and 56% in the EU.

3.2. Efficacy

Median OS in the three geographical subregions ranged from 6.5 months in the USA to 7.8 in Japan in the trifluridine/tipiracil arm and from 4.3 months in the USA to 6.7 in Japan in the placebo arm (Fig. 1A and B). Although the longest median OS was observed in Japan, the improvement was greater in the USA and the EU with HRs of 0.56 (95% CI 0.34–0.94; P = 0.0277) and 0.62 (95% CI 0.48–0.80; P = 0.0002), respectively, compared with 0.75 (95% CI 0.57–1.00; P = 0.047) in Japan. Similar trends were reported for PFS, with HRs favouring trifluridine/tipiracil in all three geographical subregions (Fig. 1C and D).

At the time of the data cut-off for the final survival analysis (8th October 2014), 89% of the 800 patients randomised had died, accounting for 138 additional deaths to the 574 (72%) previously included in the original analysis [6]. Median OS in this updated analysis was 7.2 months for trifluridine/tipiracil versus 5.2 months for placebo, with an HR of 0.69 (95% CI 0.59–0.81; P < 0.0001) (Fig. 2). Although the median OS benefit was slightly longer than in the original analysis (2.0 versus 1.8 months), the outcome pattern remains consistent with the original analysis [5]. The final prognostic risk model identified primary tumour site (colon versus rectum), ECOG PS and number of metastatic sites as prognostic risk factors, in addition to the three stratification factors that were included by default. When patients were divided into quartiles by OS according to these prognostic risk factors, the median OS ranged from 4.6 to 10.5 months in the highest- and lowest-risk quartiles, respectively, in the trifluridine/tipiracil arm, and from 3.5 to 7.1 months, respectively, in the placebo arm (Supplementary Table 1). The HR favoured trifluridine/tipiracil over placebo in all quartiles, ranging from 0.67 in the lowest-risk quartile to 0.56 in the highest-risk quartile. Survival rates 1 year after randomisation in this final analysis were 27.1% (95% CI 23.3–30.9) and 16.6% (95% CI 12.4–21.4) in the trifluridine/tipiracil and placebo arms, respectively.

Table 2 depicts HRs for OS and PFS for patients aged 65 years overall and in the USA, the EU and Japan. Median OS for patients aged 65 years was 7.0 months in the trifluridine/tipiracil arm, significantly longer than the 4.6 months reported in the placebo arm (HR 0.62; 95% CI 0.48–0.80; P = 0.0002). Similar to the population as a whole, the outcome results favoured trifluridine/tipiracil for OS and PFS in each region. Importantly, results for these elderly patients were similar to those for the overall population in each subregion, consistent with the prognostic model that had rejected age as a prognostic factor. Similar results were noted in an analysis of all patients aged 70 years across all three regions; median OS in this age group was 7.0 months in the trifluridine/tipiracil arm compared with 4.7 in the placebo arm (HR 0.65; 95% CI 0.45–0.94; P = 0.0231). HRs for OS and PFS by *KRAS* are shown in Table 3. OS was longer for patients with wild-type *KRAS* than for those with mutant *KRAS* in both the trifluridine/tipiracil and placebo arms overall and among all regions; HRs for OS favoured trifluridine/ tipiracil over placebo regardless of *KRAS* status, although this benefit for patients with mutant *KRAS* did not reach statistical significance (P = 0.0712). PFS was significantly longer for wild-type and mutant *KRAS* (both P < 0.0001) in the population as a whole; HRs again favoured trifluridine/tipiracil but did not reach statistical significance in all subregions.

3.3. Safety and hospitalisation

There were no significant differences among the US, EU and Japanese subgroups and the overall population with respect to the incidence of AEs, grade 3 AEs, serious AEs or hospitalisations (Table 4). Almost all patients experienced an AE, with 98.5%, 96.9% and 99.4% of trifluridine/tipiracil patients and 91.6%, 100% and 92.0% of placebo patients having at least one AE of any grade in EU, US and Japanese subgroups, respectively. The incidence of AEs and haematological laboratory abnormalities of grade 3, which were reported in 5% of patients in any subregion, are shown in Table 4. The most commonly reported AEs were neutropenia in the USA and EU and anaemia in Japan, but there were no consistent differences between Asian and Western populations with respect to grade 3 or 4 clinical AEs or haematological abnormalities.

Table 4 also provides details of hospitalisation for any reason in the RECOURSE trial by subregion. Although there were no important differences in hospitalisation rates in association with trifluridine/tipiracil treatment, there was a slightly higher number of hospitalisations within the placebo cohort in Japan compared with the USA and EU. The hospitalisation rate was higher in the placebo arm than in the trifluridine/tipiracil arm in all regions. Duration of hospital stay was also longer in each region for the placebo arm than for the trifluridine/tipiracil arm. Median length of stay was longer in Japan than in the USA and the EU for both trifluridine/tipiracil and placebo arms. Serious AEs were the most common reason for hospitalisation.

4. Discussion

The efficacy and safety of trifluridine/tipiracil were similar across all three geographical subregions (USA, EU and Japan) and were consistent with the overall RECOURSE population. Improved OS and PFS were observed overall and within each geographical subgroup randomised to trifluridine/tipiracil versus placebo, with an acceptable safety profile. Notably, OS in both the trifluridine/tipiracil and placebo groups in Japan was somewhat longer than that observed in the same treatment groups in the other regions (7.8 versus 6.5–6.8 months for trifluridine/tipiracil; 6.8 versus 4.3–4.9 months for placebo). This result was consistent with what had been observed in an earlier phase II study conducted in a similar Japanese population in which the observed median OS values were 9.0 and 6.6 months in the trifluridine/tipiracil and placebo groups, respectively (HR 0.56; 95% CI 0.39–0.81; P = 0.011) [10].

Differences in baseline characteristics were observed between the Western and Japanese populations in the RECOURSE trial, which may help to explain regional differences in OS. As expected, the Japanese population was entirely Asian, whereas the US and EU populations were predominantly Caucasian. The similarity in efficacy among these regions encourages the generalised applicability of the results. Patients enrolled in Japan were more likely to have an ECOG PS of 0 and have a normal estimated glomerular filtration rate than patients enrolled in the USA or the EU, perhaps suggesting that Japanese patients had less advanced disease at study enrolment than their Western counterparts. This may explain the better prognosis at baseline and longer OS and PFS in both the trifluridine/tipiracil and placebo arms in Japan.

This updated survival analysis is based on reports of clinical events in 89% of randomised patients compared with the initial analysis that was based on reports of clinical events in 72% of such individuals [5]. The reported HR of 0.69 (95% CI 0.59–0.81; P < 0.0001) from this analysis, compared with 0.68 (95% CI 0.58–0.81; P < 0.001) in the original analysis, reveals that the OS benefit with trifluridine/tipiracil was maintained, with median OS increasing from 1.8 to 2.0 months. This survival benefit appears to be present in all patients regardless of their prognostic status at the time of trial entry. The prognostic risk model developed identified primary tumour site, ECOG PS and number of metastatic sites as meaningful prognostic risk factors, in addition to the default stratification factors, which included *KRAS* status, time since diagnosis of first metastasis and geographical subregion. A number of attempts have been made in recent years to develop prognostic risk models for metastatic colorectal cancer [12–15]. Although there are differences in methodology and patient populations among these analyses, ECOG PS, *KRAS* status and number of metastatic sites are factors common to many models. *KRAS* status was included in the model developed here by default as it was a stratification factor; however, our results demonstrated that patients with wild-type *KRAS* generally had a better overall outcome than those with mutant *KRAS* tumours. The importance of *KRAS* as a prognostic factor outside the context of targeted treatment is controversial [12], although some studies have demonstrated poorer outcomes in patients with *KRAS* mutations at codon 12 and in those with metastatic disease [16,17]. The model developed here is somewhat different from other models as it did not include treatment, allowing for the evaluation of trifluridine/tipiracil in different prognostic groups. Results showed all patients benefited equally from trifluridine/ tipiracil, regardless of risk factor (including *KRAS* status), with no effect from the prognostic index. HRs for OS and PFS favoured trifluridine/tipiracil over placebo irrespective of *KRAS* status. However, these differences did not reach statistical significance in every subgroup across geographical regions, indicating that the decision to treat with trifluridine/tipiracil should not be influenced by prognostic factors if patients have a suitable physical condition with adequate organ function consistent with the entry criteria for this study. Results for patients aged 65 and 70 years were similar to those for the general population overall and in each subregion, indicating that trifluridine/tipiracil is a tolerable treatment option in older patients.

Trifluridine/tipiracil was generally well tolerated in the RECOURSE trial, with few differences among subregions. Any differences in the incidence of individual AEs between the Western and Japanese populations may be due to variations in the interpretation of terms used to define certain events, rather than any true differences in tolerability. For instance, the rate of neutropenia in Japan was reported as being substantially lower than elsewhere, although the rates of reduced neutrophil counts and febrile neutropenia were similar. Hospitalisation rates and reasons for hospitalisation were similar across subregions, and were consistently lower for trifluridine/tipiracil than for placebo. However, the median length of stay following hospitalisation for both treatment groups was longer in Japan, perhaps due to the lower cost of hospitalisation in this region.

Although the analysis of efficacy in geographical subregions was preplanned, the comparisons in this study are limited by the low number of patients in some subregions. Notably, the number of patients enrolled in the US subregion (n = 99) was substantially

lower than that in the EU or Japanese subregions (n = 403 and n = 266, respectively). Therefore, despite being stratified by geographical area (Japan versus USA, EU and Australia combined), sample sizes may have been too small to detect differences between trifluridine/tipiracil and placebo in or between subregions. This issue may be compounded when examining *ad hoc* analyses of subpopulations, such as elderly patients, within these subregions.

5. Conclusion

OS and PFS benefits were observed in patients randomised to trifluridine/tipiracil compared with placebo in the USA, the EU and Japan, and were consistent with the results from the overall RECOURSE trial, with an acceptable safety profile. These benefits were observed in all defined prognostic subgroups, including elderly subpopulations. Overall, the results of this analysis provide confidence that trifluridine/tipiracil is safe and effective, regardless of age, *KRAS* status, racial/ethnic differences or other regional differences in geographically disparate patient populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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(A)
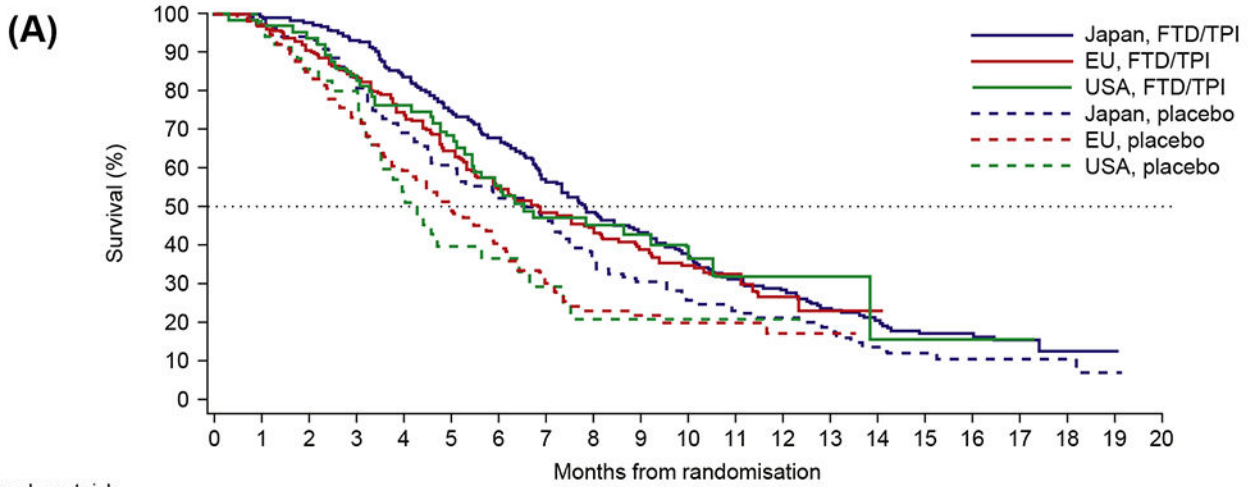
Number at risk:

Japan, FTD/TPI	178	176	174	166	149	133	119	101	85	78	66	56	50	39	31	22	18	12	7	0
EU, FTD/TPI	271	263	246	225	197	166	136	88	59	42	35	26	10	3	0					
USA, FTD/TPI	64	62	60	53	49	43	33	29	24	16	10	5	4	2	1	1	1	1	0	
Japan, placebo	88	87	83	71	61	53	46	41	31	27	23	21	18	14	10	9	5	3	3	0
EU, placebo	132	128	110	94	77	61	45	29	17	16	12	8	5	1	0					
USA, placebo	35	34	30	26	18	14	12	7	5	3	2	2	1	0						

ITT	USA		EU		Japan	
	FTD/TPI (n=64)	Placebo (n=35)	FTD/TPI (n=271)	Placebo (n=132)	FTD/TPI (n=178)	Placebo (n=88)
Median OS, months	6.5	4.3	6.8	4.9	7.8	6.7
OS HR (95% CI)	0.56 (0.34–0.94)		0.62 (0.48–0.80)		0.75 (0.57–1.00)	
P value	0.0277		0.0002		0.047	

(B)

Geographical subregion	Favours FTD/TPI ← → Favours placebo	Patients with events, total patients; hazard ratio (95% CI); median (FTD/TPI, placebo)
Japan		227, 266; 0.75 (0.57–1.00); 7.8, 6.7
EU		255, 403; 0.62 (0.48–0.80); 6.8, 4.9
USA		65, 99; 0.56 (0.34–0.94); 6.5, 4.3

(C)
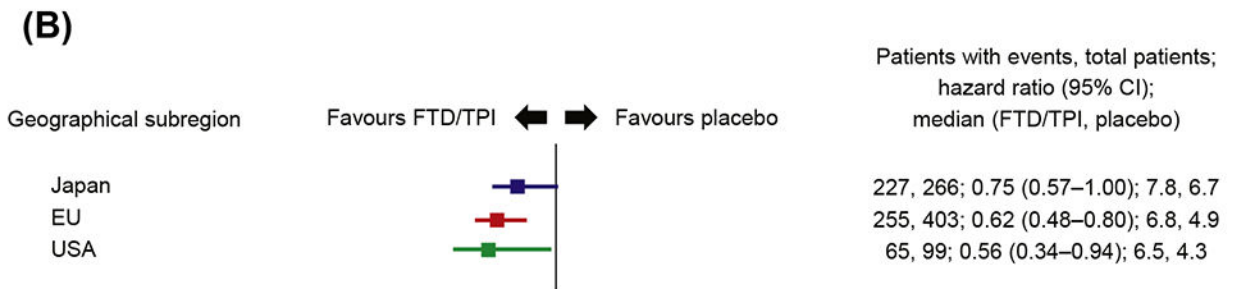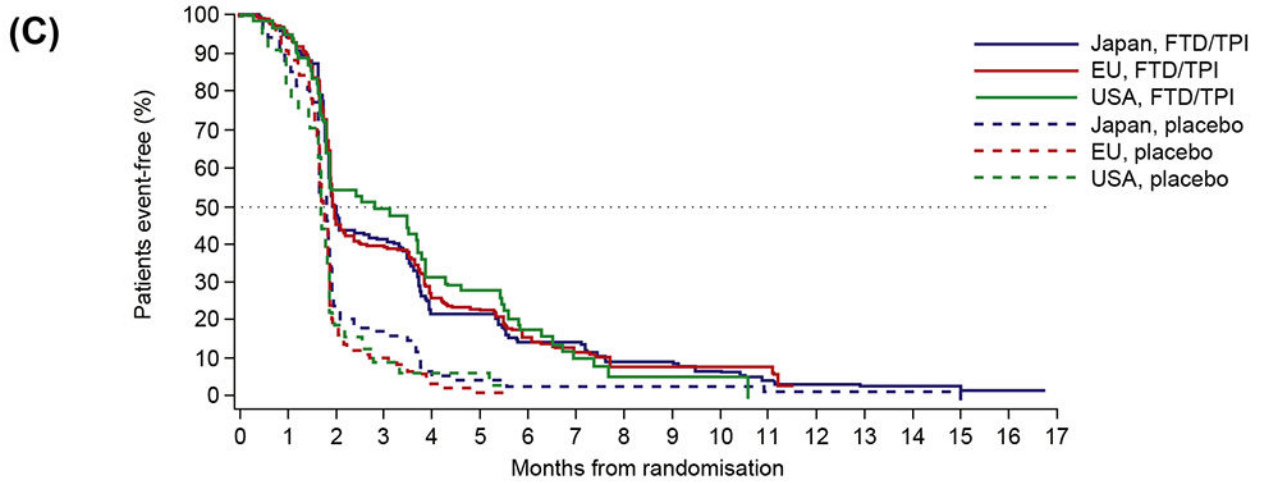
Number at risk:

Japan, FTD/TPI	178	167	83	72	38	38	25	25	16	15	11	7	5	4	4	2	2	0
EU, FTD/TPI	271	246	115	97	63	51	30	21	12	9	6	4	0					
USA, FTD/TPI	64	58	33	30	18	16	10	5	2	2	1	0						
Japan, placebo	88	77	20	15	4	3	2	2	2	2	2	1	1	1	1	0		
EU, placebo	132	115	21	12	3	1	0											
USA, placebo	35	26	6	3	2	2	0											

ITT	USA		EU		Japan	
	FTD/TPI (n=64)	Placebo (n=35)	FTD/TPI (n=271)	Placebo (n=132)	FTD/TPI (n=178)	Placebo (n=88)
Median PFS, months	2.8	1.7	2.0	1.7	2.0	1.8
PFS HR (95% CI)	0.43 (0.26–0.69)		0.41 (0.33–0.52)		0.58 (0.44–0.75)	
P value	0.0004		<0.0001		<0.0001	

(D)

Patients with events, total patients; hazard ratio (95% CI); median (FTD/TPI, placebo)

Geographical subregion — Favours FTD/TPI ← → Favours placebo

Geographical subregion	
Japan	258, 266; 0.58 (0.44–0.75); 2.0, 1.8
EU	349, 403; 0.41 (0.33–0.52); 2.0, 1.7
USA	88, 99; 0.43 (0.26–0.69); 2.8, 1.7
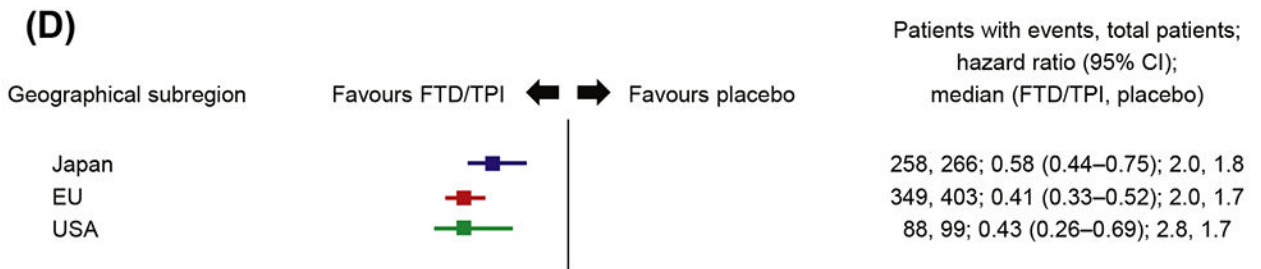
Fig. 1. Kaplan–Meier curves and forest plots for overall survival (OS) and progression-free survival (PFS).

(**A**) Kaplan–Meier curve for OS by geographical subregion; (**B**) forest plot for OS by geographical subregion; (**C**) Kaplan–Meier curve for PFS by geographical subregion; (**D**) forest plot for PFS by geographical subregion. Abbreviations: CI, confidence interval; FTD/TPI, trifluridine/tipiracil; HR, hazard ratio; ITT, intention-to-treat.

Fig. 2. Overall survival as of 8th October 2014 (intention-to-treat population).
Abbreviations: CI, confidence interval; FTD/TPI, trifluridine/tipiracil; HR, hazard ratio; OS, overall survival.

Table 1

Baseline characteristics: geographical subgroups in RECOURSE.

	USA		EU		Japan	
	FTD/TPI (n = 64)	Placebo (n = 35)	FTD/TPI (n = 271)	Placebo (n = 132)	FTD/TPI (n = 178)	Placebo (n = 88)
Male, n (%)	31 (48.4)	18 (51.4)	167 (61.6)	82 (62.1)	113 (63.5)	58 (65.9)
Age, years, mean (SD)	60.2 (11.86)	58.5 (11.02)	61.8 (9.98)	62.1 (10.42)	61.9 (10.09)	62.1 (10.40)
Race, n (%)						
Caucasian	56 (87.5)	27 (77.1)	229 (84.5)	119 (90.2)	0	0
Black/African-American	3 (4.7)	5 (14.3)	1 (0.4)	0	0	0
Asian	5 (7.8)	3 (8.6)	1 (0.4)	1 (0.8)	178 (100)	88 (100)
Primary tumour site, n (%)						
Colon	47 (73.4)	27 (77.1)	176 (64.9)	81 (61.4)	100 (56.2)	45 (51.1)
Rectum	17 (26.6)	8 (22.9)	95 (35.1)	51 (38.6)	78 (43.8)	43 (48.9)
ECOG PS, n (%)						
0	28 (43.8)	13 (37.1)	138 (50.9)	68 (51.5)	128 (71.9)	60 (68.2)
1	36 (56.3)	22 (62.9)	133 (49.1)	64 (48.5)	50 (28.1)	28 (31.8)
KRAS status[a], n (%)						
Wild type	35 (54.7)	17 (48.6)	123 (45.4)	68 (51.5)	94 (52.8)	40 (45.5)
Mutant	29 (45.3)	18 (51.4)	148 (54.6)	64 (48.5)	84 (47.2)	48 (54.5)
Time since diagnosis of first metastasis[a], n (%)						
<18 months	14 (21.9)	11 (31.4)	61 (22.5)	24 (18.2)	33 (18.5)	17 (19.3)
≥18 months	50 (78.1)	24 (68.6)	210 (77.5)	108 (81.8)	145 (81.5)	71 (80.7)
Baseline renal function[b], n (%)						
Normal (CrCL ≥90 ml/min/1.73 m^2)	43 (67.2)	16 (45.7)	164 (60.5)	72 (54.5)	86 (48.3)	46 (52.3)
Mild impairment (CrCL 60–89 ml/min/1.73 m^2)	16 (25.0)	17 (48.6)	86 (31.7)	41 (31.1)	70 (39.3)	33 (37.5)
Moderate impairment (CrCL 30–59 ml/min/1.73 m^2)	5 (7.8)	2 (5.7)	21 (7.7)	16 (12.1)	20 (11.2)	9 (10.2)
Missing	0	0	0	3 (2.3)	2 (1.1)	0
Baseline eGFR[c], n (%)						
Normal (CrCL ≥90 ml/min/1.73 m^2)	34 (53.1)	14 (40.0)	153 (56.5)	72 (54.5)	135 (75.8)	65 (73.9)
Mild impairment (CrCL 60–89 ml/min/1.73 m^2)	24 (37.5)	17 (48.6)	92 (33.9)	42 (31.8)	30 (16.9)	21 (23.9)

	USA		EU		Japan	
	FTD/TPI (n = 64)	**Placebo (n = 35)**	**FTD/TPI (n = 271)**	**Placebo (n = 132)**	**FTD/TPI (n = 178)**	**Placebo (n = 88)**
Moderate impairment (CrCL 30–59 ml/min/1.73 m^2)	5 (7.8)	3 (8.6)	18 (6.6)	12 (9.1)	9 (5.1)	1 (1.1)
Missing	1 (1.6)	1 (2.9)	8 (3.0)	6 (4.5)	4 (2.2)	1 (1.1)

Abbreviations: CrCL, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; eGFR, estimated glomerular filtration rate; FTD/TPI, trifluridine/tipiracil; SD, standard deviation.

[a]As randomised.

[b]CrCL based on Cockcroft-Gault using baseline creatinine.

[c]eGFR (ml/min/1.73 m^2) = 175 × (baseline creatinine)$^{-1.154}$ × (age)$^{-0.203}$ × (0.742 if female) × (1.212 if African-American).

Table 2

OS and PFS in RECOURSE in elderly patients aged ≥65 years overall and by geographical subregion (ITT population).

ITT	USA		EU		Japan		Overall	
	FTD/TPI (n = 27)	Placebo (n = 14)	FTD/TPI (n = 115)	Placebo (n = 61)	FTD/TPI (n = 86)	Placebo (n = 39)	FTD/TPI (n = 234)	Placebo (n = 118)
Median OS, months	7.8	4.0	6.3	4.4	7.8	6.8	7.0	4.6
OS HR (95% CI)	0.31 (0.13–0.79)		0.59 (0.40–0.86)		0.72 (0.47–1.09)		0.62 (0.48–0.80)	
P value	0.0099		0.0054		0.1143		0.0002	
Median PFS, months	3.9	1.6	2.1	1.8	2.0	1.8	2.1	1.8
PFS HR (95% CI)	0.24 (0.10–0.61)		0.37 (0.26–0.53)		0.52 (0.35–0.78)		0.41 (0.32–0.52)	
P value	0.0013		<0.0001		0.0013		<0.0001	

Abbreviations: CI, confidence interval; FTD/TPI, trifluridine/tipiracil; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival.

Table 3

OS and PFS in RECOURSE by *KRAS* status overall and in geographical subregions (ITT population).

ITT	USA		EU		Japan		Overall	
	FTD/TPI	Placebo	FTD/TPI	Placebo	FTD/TPI	Placebo	FTD/TPI	Placebo
Wild-type *KRAS*, n	35	17	123	68	94	40	262	131
Median OS, months	6.7	4.3	8.8	5.5	9.0	6.8	8.0	5.7
OS HR (95% CI)	0.44 (0.22–0.87)		0.56 (0.38–0.81)		0.65 (0.44–0.96)		0.58 (0.45–0.74)	
P value	0.0152		0.0019		0.0309		<0.0001	
Median PFS, months	2.8	1.7	2.0	1.7	2.1	1.8	2.1	1.7
PFS HR (95% CI)	0.51 (0.26–1.02)		0.40 (0.28–0.56)		0.58 (0.39–0.84)		0.48 (0.38–0.60)	
P value	0.0533		<0.0001		0.0041		0.0001	
Mutant *KRAS*, n	29	18	148	64	84	48	272	135
Median OS, months	6.3	4.2	6.0	4.7	7.1	6.2	6.5	4.9
OS HR (95% CI)	0.77 (0.35–1.70)		0.68 (0.48–0.97)		0.87 (0.59–1.28)		0.80 (0.63–1.02)	
P value	0.5209		0.0345		0.4730		0.0712	
Median PFS, months	3.1	1.7	1.9	1.8	1.9	1.8	1.9	1.8
PFS HR (95% CI)	0.35 (0.17–0.70)		0.43 (0.31–0.59)		0.58 (0.40–0.84)		0.49 (0.39–0.61)	
P value	0.0021		<0.0001		0.0037		<0.0001	

Abbreviations: FTD/TPI, trifluridine/tipiracil; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival.

Table 4

Adverse events and haematological laboratory abnormalities of grade ≥3 occurring in >5%, any group (as-treated population).

n (%)	USA		EU		Japan	
	FTD/TPI (n = 64)	Placebo (n = 35)	FTD/TPI (n = 270)	Placebo (n = 131)	FTD/TPI (n = 178)	Placebo (n = 88)
Abdominal pain	3 (4.7)	4 (11.4)	5 (1.9)	4 (3.1)	1 (0.6)	1 (1.1)
Anaemia	9 (14.1)	2 (5.7)	35 (13.0)	2 (1.5)	41 (23.0)	3 (3.4)
Aspartate aminotransferase increased	2 (3.1)	2 (5.7)	3 (1.1)	1 (0.8)	2 (1.1)	4 (4.5)
Asthenia	0	0	18 (6.7)	8 (6.1)	0	0
Blood alkaline phosphatase increased	2 (3.1)	4 (11.4)	9 (3.3)	5 (3.8)	7 (3.9)	4 (4.5)
Blood bilirubin increased	2 (3.1)	0	13 (4.8)	7 (5.3)	6 (3.4)	2 (2.3)
Decreased appetite	0	1 (2.9)	9 (3.3)	5 (3.8)	10 (5.6)	7 (8.0)
Dyspnoea	1 (1.6)	0	13 (4.8)	7 (5.3)	0	3 (3.4)
Fatigue	3 (4.7)	3 (8.6)	12 (4.4)	6 (4.6)	5 (2.8)	6 (6.8)
Febrile neutropenia	4 (6.3)	0	6 (2.2)	0	10 (5.6)	0
Gamma-glutamyltransferase increased	1 (1.6)	0	9 (3.3)	7 (5.3)	7 (3.9)	3 (3.4)
General physical health deterioration	0	0	15 (5.6)	9 (6.9)	3 (1.7)	3 (3.4)
Hepatic failure	1 (1.6)	2 (5.7)	2 (0.7)	2 (1.5)	0	4 (4.5)
Hyperbilirubinaemia	2 (3.1)	2 (5.7)	8 (3.0)	2 (1.5)	1 (0.6)	0
Hypoalbuminaemia	1 (1.6)	2 (5.7)	2 (0.7)	0	1 (0.6)	0
Hypokalaemia	6 (9.4)	0	5 (1.9)	2 (1.5)	1 (0.6)	0
Leukopenia	4 (6.3)	0	9 (3.3)	0	0	0
Neutropenia	20 (31.3)	0	79 (29.3)	0	3 (1.7)	0
Peripheral oedema	0	2 (5.7)	0	0	1 (0.6)	0
Tumour pain	0	0	1 (0.4)	0	2 (1.1)	5 (5.7)
Vomiting	3 (4.7)	0	5 (1.9)	1 (0.8)	3 (1.7)	0
Haematological laboratory abnormalities						
Haemoglobin	15 (23.8)	2 (5.7)	39 (14.6)	3 (2.3)	41 (23.0)	3 (3.4)
Lymphocytes	17 (27.0)	3 (8.6)	41 (15.6)	11 (8.6)	47 (26.4)	11 (12.5)
Neutrophils	28 (44.4)	0	100 (37.3)	0	67 (37.6)	0
Platelets	5 (7.9)	0	11 (4.1)	0	11 (6.2)	1 (1.1)
Leukocytes	18 (28.6)	0	50 (18.7)	0	43 (24.2)	0

n (%)	USA		EU		Japan	
	FTD/TPI (n = 64)	Placebo (n = 35)	FTD/TPI (n = 270)	Placebo (n = 131)	FTD/TPI (n = 178)	Placebo (n = 88)
Hospitalisations						
Total hospitalisations	17 (26.6)	12 (34.3)	84 (31.1)	45 (34.4)	52 (29.2)	36 (40.9)
Median total days hospitalised	7.0	10.5	7.5	9.0	13.0	19.5
Median hospitalisation ratio [a]	0.09	0.19	0.11	0.20	0.19	0.30
Reason for hospitalisation						
Serious adverse event	16 (25.0)	10 (28.6)	79 (29.3)	41 (31.3)	45 (25.3)	34 (38.6)
Febrile neutropenia	4 (6.3)	0	4(1.5)	0	6 (3.4)	0
Elective preplanned surgery alone	0	0	3(1.1)	0	1 (0.6)	0
Hospice/palliative care alone	0	1 (2.9)	1 (0.4)	3 (2.3)	2(1.1)	2 (2.3)
Palliative radiation alone	0	1 (2.9)	0	0	0	0
Other	1 (1.6)	2 (5.7)	8 (3.0)	4 (3.1)	5 (2.8)	2 (2.3)

Abbreviation: FTD/TPI, trifluridine/tipiracil.

[a] Total days hospitalised divided by total days followed.