THE EFFECT OF TRIFLURIDINE/TIPIRACIL IN PATIENTS TREATED IN RECOURSE BY PROGNOSTIC FACTORS AT BASELINE: AN EXPLORATORY ANALYSIS

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Supplementary material

Table S1 Treatment duration and dose delays/reductions

	GPC subgroup		PPC subgroup	
	FTD/TPI (n=261)	**Placebo (n=125)**	**FTD/TPI (n=272)**	**Placebo (n=140)**
No. of cycles				
Mean (SD)	4.1 (2.9)	2.5 (1.8)	2.8 (2.0)	2.1 (1.1)
Median (range)	3 (1–18)	2 (1–16)	2 (1–11)	2 (1–8)
Treatment duration, weeks				
Mean (SD)	18.3 (13.9)	10.2 (7.5)	12.2 (8.7)	8.5 (4.3)
Median (range)	13 (4–80)	8.1 (4–66)	8.4 (4–49)	8.1 (4–32)
Delays or dose reductions, n (%)				
Delay in ≥1 cycle[a]	140 (53.6)	7 (5.6)	105 (38.6)	7 (5.0)
≥1 dose reduction	47 (18.0)	0	26 (9.6)	3 (2.1)

FTD/TPI, trifluridine/tipiracil; GPC, good prognostic characteristics; PPC, poor prognostic characteristics; SD, standard deviation.
GPC was defined as <3 metastatic sites and ≥18 months since first metastasis.

[a]A delay of ≥4 days in initiation of ≥1 cycle.

Table S2 The effect of various prognostic factors on OS at 6 and 12 months

	6 month OS FTD/TPI /Placebo	**12 month OS** FTD/TPI /Placebo	**6 month OS** FTD/TPI /Placebo	**12 month OS** FTD/TPI /Placebo
	ITT RECOURSE			
Overall	57.8% / 43.5%	26.6% / 17.6%		
GPC subgroup	71.7% / 53.9%	37.5% / 25.2%		
PPC subgroup	44.4% / 34.1%	15.3% / 10.7%		
	No liver metastases		Liver metastases	
GPC subgroup	83.4% / 71.0%	65.1% / 34.8%	64.8% / 40.1%	22.1% / 17.3%
PPC subgroup	62.7% / 52.4%	36.1% / 22.2%	41.7% / 31.0%	12.4% / 8.7%
	No lung metastases		Lung metastases	
GPC subgroup	73.8% / 60.0%	30.8% / 19.5%	70.6% / 52.3%	41.2% / 27.0%
PPC subgroup	38.5% / 37.5%	11.9% / 16.7%	46.0% / 33.5%	16.2% / 9.8%
	No lymph metastases		Lymph metastases	
GPC subgroup	71.3% / 53.3%	36.4% / 27.8%	73.6% / 55.8%	41.5% / 19.1%
PPC subgroup	40.8% / 32.0%	16.8% / 7.7%	47.2% / 35.3%	14.7% / 12.3%
	No peritoneal metastases		Peritoneal metastases	
GPC subgroup	70.3% / 54.1%	35.6% / 26.1%	89.5% / 50.0%	59.8% / 0.0%
PPC subgroup	44.1% / 35.0%	16.0% / 10.5%	45.4% / 31.7%	13.6% / 11.3%
	ECOG PS = 0		ECOG PS = 1	
GPC subgroup	76.4% / 59.4%	41.3% / 30.4%	64.7% / 45.0%	31.5% / 16.2%
PPC subgroup	56.1% / 40.2%	20.1% / 17.0%	31.7% / 28.2%	10.1% / 5.5%
	Age <65 years		Age ≥65 years	
GPC subgroup	72.6% / 54.8%	38.8% / 26.8%	70.7% / 52.6%	36.2% / 23.2%
PPC subgroup	44.3% / 36.7%	14.0% / 9.8%	44.9% / 31.1%	16.6% / 11.5%
	KRAS wild type		*KRAS* mutant	
GPC subgroup	71.7% / 53.5%	33.0% / 19.5%	71.9% / 54.4%	43.1% / 29.7%
PPC subgroup	51.9% / 37.6%	18.5% / 10.7%	38.6% / 30.8%	12.9% / 11.8%

ECOG PS, Eastern Cooperative Oncology Group performance status; FTD/TPI, trifluridine/tipiracil; GPC, good prognostic characteristics; ITT, intent to treat; OS, overall survival; PPC, poor prognostic characteristics.
GPC was defined as <3 metastatic sites and ≥18 months since first metastasis.

Table S3 The effect of various prognostic factors on PFS at 3, 6 and 9 months

	3 month PFS FTD/TPI /Placebo	**6 month PFS** FTD/TPI /Placebo	**9 month PFS** FTD/TPI /Placebo	**3 month PFS** FTD/TPI /Placebo	**6 month PFS** FTD/TPI /Placebo	**9 month PFS** FTD-TPI /Placebo
	ITT RECOURSE					
Overall	40.9%/ 13.0%	15.1% / 1.4%	7.7% / 1.4%			
GPC subgroup	51.1% / 14.5%	22.4% / 1.9%	12.1% / 1.9%			
PPC subgroup	31.0% / 11.6%	7.9% / 0.9%	3.3% / NE			
	No liver metastases			Liver metastases		
GPC subgroup	66.9% / 26.2%	35.9% / 4.3%	20.7% / 4.3%	41.9% / 4.7%	14.5% / 0.0%	7.1% / 0.0%
PPC subgroup	37.6% / 30.6%	17.6% / 0.0%	6.6% / 0.0%	30.1% / 8.2%	6.6% / 1.1%	2.8% / NE
	No lung metastases			Lung metastases		
GPC subgroup	47.5% / 20.0%	18.4% / 4.0%	11.9% / 4.0%	53.0% / 13.1%	24.5% / 1.3%	12.3% / 1.3%
PPC subgroup	20.4% / 13.0%	4.7% / 0.0%	2.3% / 0.0%	33.6% / 11.3%	8.8% / 0.9%	3.5% / NE
	No lymph metastases			Lymph metastases		
GPC subgroup	49.9% / 13.6%	21.3% / 1.4%	12.8% / 1.4%	55.9% / 17.4%	26.6% / 3.5%	9.2% / 3.5%
PPC subgroup	34.9% / 7.7%	9.0% / 0.0%	2.3% / 0.0%	28.0% / 14.2%	7.3% / 1.3%	4.4% / NE
	No peritoneal metastases			Peritoneal metastases		
GPC subgroup	49.5% / 15.3%	21.7% / 2.0%	11.7% / 2.0%	73.0% / 0.0%	32.7% / 0.0%	17.5% / 0.0%
PPC subgroup	32.6% / 12.2%	8.8% / 0.0%	3.4% / 0.0%	26.5% / 10.3%	5.9% / 2.6%	2.9% / NE
	ECOG PS = 0			ECOG PS = 1		
GPC subgroup	53.7% /13.7%	22.2% / 2.7%	12.2% / 2.7%	47.2% / 15.7%	22.7% / 0.0%	11.9%/0.0%
PPC subgroup	35.8% / 16.4%	9.6% / 0.0%	4.7% / 0.0%	25.8% / 7.2%	6.2% / 1.4%	1.7% / NE
	Age <65 years			Age ≥65 years		
GPC subgroup	50.1% / 16.3%	18.6% / 1.8%	7.0% / 1.8%	52.2% / 12.1%	26.9% / 2.0%	18.3% / 2.0%
PPC subgroup	26.1% / 13.6%	7.1% / 2.0%	2.1% / NE	38.1% / 9.6%	9.1% / 0.0%	4.6% / 0.0%
	KRAS wild type			*KRAS* mutant		
GPC subgroup	51.1% / 16.8%	20.3% / 1.9%	13.4% / 1.9%	51.2% / 12.5%	25.1% / 2.1%	10.5% / 2.1%
PPC subgroup	33.3% / 16.5%	8.8% / 2.5%	2.9% / NE	29.2% /7.3%	7.2% / 0.0%	3.9% / 0.0%

ECOG PS, Eastern Cooperative Oncology Group performance status; FTD/TPI, trifluridine/tipiracil; GPC, good prognostic characteristics; ITT, intent to treat; NE, not evaluable; PFS, progression-free survival.
GPC was defined as <3 metastatic sites and ≥18 months since first metastasis.

Table S4 Baseline patient demographics and clinical characteristics in RECOURSE patients in the GPC subgroup (number of metastatic sites <3 and time since 1st metastasis ≥18 months) with no liver metastasis at randomisation (n=153).

	Trifluridine/tipiracil		Placebo	
	GPC subgroup (n=261)	**GPC no liver met subgroup (n=97)**	**GPC subgroup (n=125)**	**GPC no liver met subgroup (n=56)**
Median age, years	64.0	64.0	63.0	61.0
Patient age, n (%)				
<65 years	137 (52.5)	52(53.6)	72 (57.6)	36(64.3)
65 to <75 years	105 (40.2)	37(38.1)	43 (34.4)	16(28.6)
≥75 years	19 (7.3)	8(8.2)	10 (8.0)	4(7.1)
Gender, n (%)				
Females	97 (37.2)	38(39.2)	47 (37.6)	22(39.3)
Male	164 (62.8)	59(60.8)	78 (62.4)	34(60.7)
Race, n (%)				
Asian	91 (34.9)	35(36.1)	43 (34.4)	26(46.4)
Other	170 (65.1)	62 (63.9)	82 (65.6)	30 (53.6)
ECOG PS, n (%)				
0	158 (60.5)	59(60.8)	77 (61.6)	32(57.1)
1	103 (39.5)	38(39.2)	48 (38.4)	24(42.9)
KRAS status, n (%)				
Mutant	119 (45.6)	49(50.5)	64 (51.2)	26(46.4)
Wild type	142 (54.4)	48(49.5)	61 (48.8)	30(53.6)
Time since diagnosis of metastasis, n (%)				
<18 months	0	0	0	0
≥18 months	261 (100.0)	97(100.0)	125 (100.0)	56(100.0)
Number of prior regimens, n (%)				
2	26 (10.0)	7(7.2)	15 (12.0)	6(10.7)
3	50 (19.2)	11(11.3)	18 (14.4)	6(10.7)
≥4	185 (70.9)	79(81.4)	92 (73.6)	44(78.6)
Number of metastatic sites, n (%)				
1–2	261 (100.0)	97(100.0)	125 (100.0)	56(100.0)
≥3	0	0	0	0
Site of Lesion				
Liver	164(62.8)	0	69(55.2)	0
Lung	172(65.9)	74(76.3)	100(80.0)	47(83.9)
Lymph	53(20.3)	37(38.1)	32(25.6)	24(42.9)

Peritoneum	19(7.3)	14(14.4)	6(4.8)	6(10.7)
Primary site of disease, n (%)				
Colon	171 (65.5)	57(58.8)	63 (50.4)	25(44.6)
Rectum	90 (34.5)	40(41.2)	62 (49.6)	31(55.4)

ECOG PS, Eastern Cooperative Oncology Group performance status; GPC, good prognostic characteristics

Table S5 Adverse events occurring in ≥10% of patients in any group

AEs, n (%)	FTD/TPI				Placebo			
	GPC subgroup (n=261)		PPC subgroup (n=272)		GPC subgroup (n=125)		PPC subgroup (n=140)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Any AE	257 (98.5)	171 (65.5)	267 (98.2)	199 (73.2)	115 (92.0)	57 (45.6)	132 (94.3)	80 (57.1)
Blood disorders or laboratory investigations								
Anaemia	109 (41.8)	46 (17.6)	105 (38.6)	40 (14.7)	9 (7.2)	2 (1.6)	13 (9.3)	5 (3.6)
Neutrophil count decrease	87 (33.3)	56 (21.5)	61 (22.4)	29 (10.7)	1 (0.8)	0	0	0
Neutropenia	85 (32.6)	62 (23.8)	71 (26.1)	45 (16.5)	0	0	0	0
WBC decrease	82 (31.4)	32 (12.3)	64 (23.5)	23 (8.5)	1 (0.8)	0	0	0
Platelet count decrease	47 (18.0)	7 (2.7)	34 (12.5)	6 (2.2)	2 (1.6)	0	4 (2.9)	0
Blood ALP increase	22 (8.4)	4 (1.5)	25 (9.2)	14 (15.1)	9 (7.2)	5 (4.0)	17 (12.1)	8 (5.7)
Weight loss	20 (7.7)	0	21 (7.7)	1 (0.4)	9 (7.2)	0	18 (12.9)	0
Gastrointestinal disorders								
Nausea	130 (49.8)	4 (1.5)	128 (47.1)	6 (2.2)	29 (23.2)	1 (0.8)	34 (24.3)	2 (1.4)
Diarrhoea	86 (33.0)	7 (2.7)	84 (30.9)	9 (3.3)	13 (10.4)	0	20 (14.3)	1 (0.7)
Vomiting	73 (28.0)	6 (2.3)	75 (27.6)	5 (1.8)	14 (11.2)	1 (0.8)	24 (17.1)	0
Constipation	39 (14.9)	1 (0.4)	42 (15.4)	0	18 (4.4)	1 (0.8)	22 (15.7)	2 (1.4)
Abdominal pain	36 (13.8)	1 (0.4)	43 (15.8)	10 (3.7)	10 (8.0)	3 (2.4)	26 (18.6)	7 (5.0)

AEs, n (%)	FTD/TPI				Placebo			
	GPC subgroup (n=261)		PPC subgroup (n=272)		GPC subgroup (n=125)		PPC subgroup (n=140)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Metabolism and nutrition disorders								
Decreased appetite	91 (34.9)	9 (3.4)	117 (43.0)	10 (3.7)	28 (22.4)	6 (4.8)	50 (35.7)	7 (5.0)
General disorders								
Fatigue	90 (34.5)	9 (3.4)	98 (36.0)	12 (4.4)	22 (17.6)	3 (2.4)	40 (28.6)	12 (8.6)
Asthenia	50 (19.2)	9 (3.4)	47 (17.3)	9 (3.3)	17 (13.6)	4 (3.2)	13 (9.3)	4 (2.9)
Pyrexia	42 (16.1)	1 (0.4)	56 (20.6)	5 (1.8)	11 (8.8)	0	26 (18.6)	1 (0.7)
Peripheral oedema	26 (10.0)	0	27 (9.9)	1 (0.4)	8 (6.4)	0	19 (13.6)	2 (1.4)
Respiratory or thoracic disorders								
Cough	32 (12.3)	2 (0.8)	25 (9.2)	0	18 (14.4)	0	12 (8.6)	2 (1.4)
Dyspnoea	25 (9.6)	5 (1.9)	31 (11.4)	9 (3.3)	17 (13.6)	4 (3.2)	17 (12.1)	6 (4.3)
Skin and subcutaneous tissue disorders								
Alopecia	27 (10.3)	0	9 (3.3)	0	0	0	3 (2.1)	0

AE, adverse event; ALP, alkaline phosphatase; FTD/TPI, trifluridine/tipiracil; GPC, good prognostic characteristics; PPC, poor prognostic characteristics; WBC, white blood cell.

GPC was defined as <3 metastatic sites and ≥18 months since first metastasis.

Figure S1 Overall survival in RECOURSE patients in the GPC subgroup (number of metastatic sites <3 and time since first metastasis ≥18 months) with no liver metastasis at randomisation (n=153) receiving trifluridine/tipiracil (blue) or placebo (red).

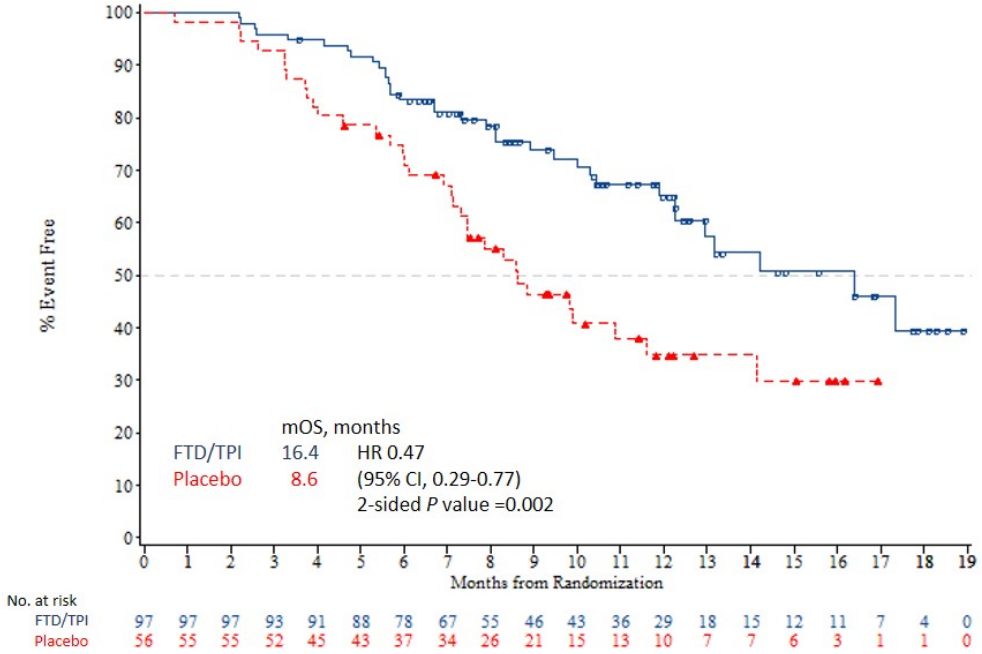

Figure S2 Progression-free survival in RECOURSE patients in the GPC subgroup (number of metastatic sites <3 and time since first metastasis ≥18 months) with no liver metastasis at randomisation (n=153) receiving trifluridine/tipiracil (blue) or placebo (red).

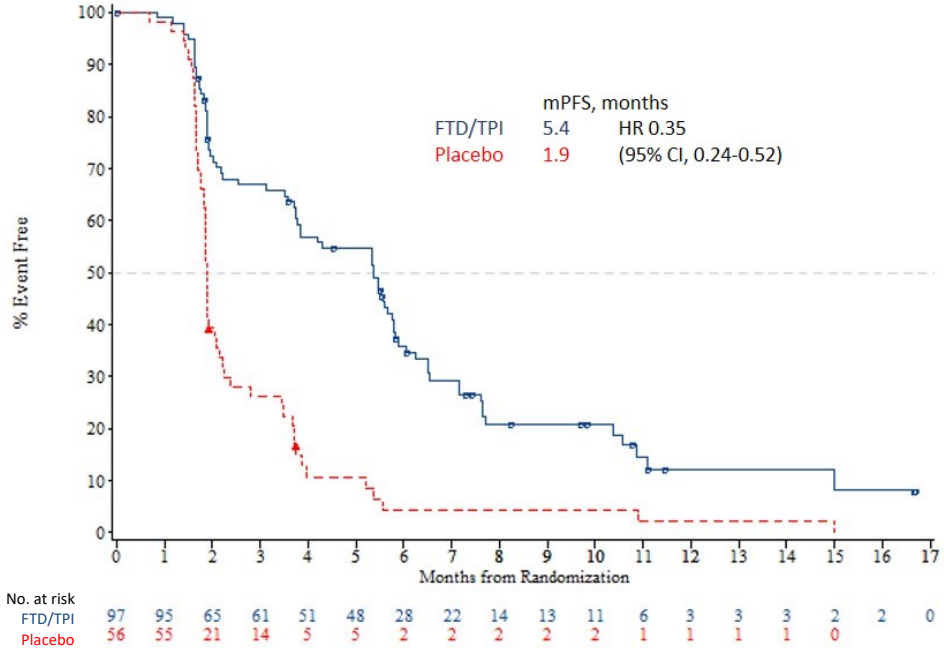

Figure S3 Time to Eastern Cooperative Oncology Group Performance Status ≥2 in RECOURSE patients in the GPC subgroup (number of metastatic sites <3 and time since first metastasis ≥18 months) with no liver metastasis at randomisation (n=153) receiving trifluridine/tipiracil (blue) or placebo (red).