The impact of prior therapies on outcomes with trifluridine/tipiracil in patients with metastatic gastric/gastroesophageal junction cancer in the phase III TAGS trial

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INTRODUCTION

- Prognosis is poor for patients with metastatic gastric or gastroesophageal junction cancer (mGC/GEJC), and relapse is frequent after first- and second-line systemic therapies[1-3]
- In the phase III TAGS trial, trifluridine/tipiracil (FTD/TPI) demonstrated survival benefit and manageable safety in patients with mGC/GEJC whose disease progressed after ≥2 prior regimens[4]
  - Based on these data, FTD/TPI was approved as a third- or later-line treatment for mGC/GEJC[5]
- Here, we examined whether prior treatment with ramucirumab (RAM), RAM plus paclitaxel (PAC), or irinotecan (IRI), standard second-line treatments for mGC/GEJC, influenced efficacy/safety outcomes in the phase III TAGS trial

METHODS

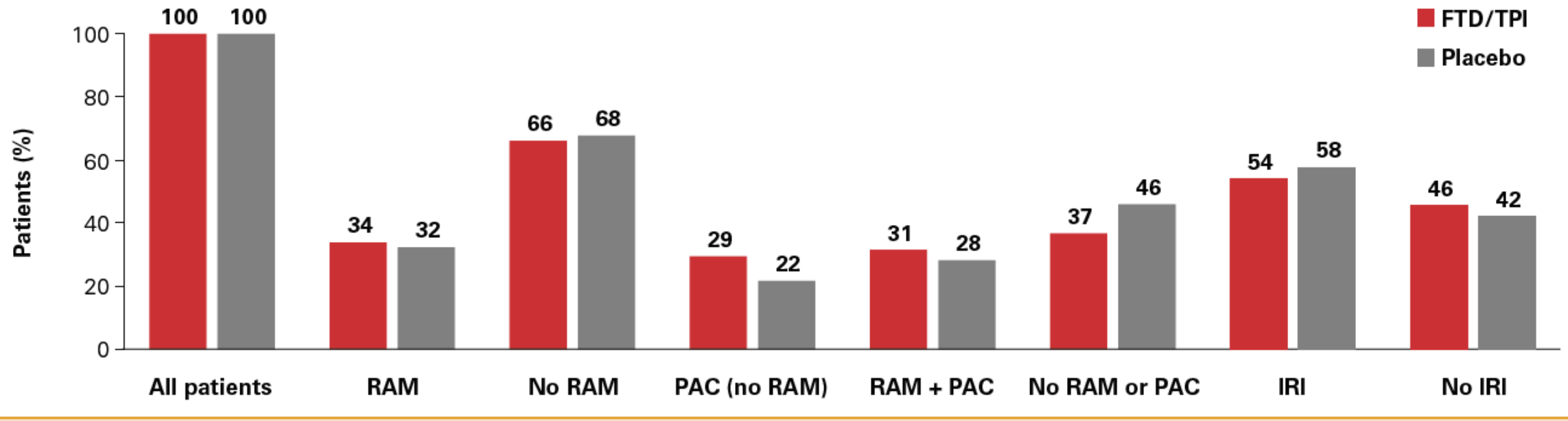
- Patients in the TAGS trial were categorized into 7 subgroups based on prior treatment received:
  - RAM (alone or in combination with other agents)
  - No RAM
  - PAC but no RAM
  - RAM + PAC (sequentially or in combination)
  - Neither PAC nor RAM
  - IRI (alone or in combination with other agents)
  - No IRI
- The first 2 subgroups (prior RAM and no prior RAM) were prespecified, but the others were evaluated post hoc
  - These analyses were not powered for statistical significance

RESULTS

Patient population

- Overall, the patterns of prior therapy received were balanced between the treatment arms (**Figure 1**); additional demographic data are provided in Supplementary Tables S1 and S2
  - Only 3% of all patients received prior RAM without receiving prior PAC

Figure 1. Subgroups by prior therapy[a]



FTD/TPI, trifluridine/tipiracil; IRI, irinotecan; PAC, paclitaxel; RAM, ramucirumab.
[a]Percentages of patients in the FTD/TPI (n=337) and placebo groups (n=170).

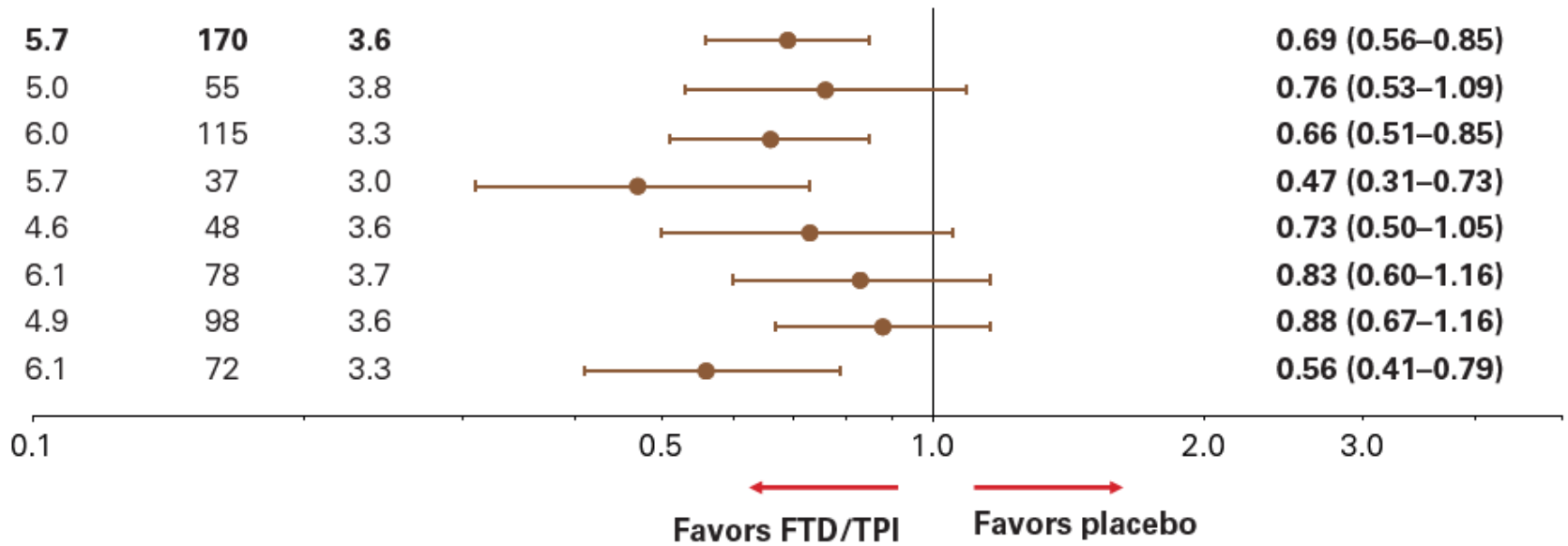
RESULTS

Efficacy

- Regardless of prior therapy received, FTD/TPI treatment was associated with overall survival (OS) and progression-free survival (PFS) benefit compared with placebo (**Figures 2** and **3**; Supplementary Figures S1 and S2)
- In a separate analysis of patients who were randomized to FTD/TPI (Supplementary Figure S3), OS was comparable between patients who received the following:
  - Prior RAM plus PAC and those who received neither PAC nor RAM
    - Hazard ratio (HR), 1.15; 95% CI, 0.84–1.58
  - Prior PAC (but no RAM) and those who received neither PAC nor RAM
    - HR, 0.91; 95% CI, 0.66–1.25
- Similar results were observed with PFS in these subgroups (Supplementary Figure S3)
- Survival outcomes in the IRI and no IRI subgroups were consistent with the overall population; however, OS and PFS in the FTD/TPI arm were somewhat longer in patients who did not receive prior IRI (Supplementary Figure S4)
  - In the IRI vs no IRI subgroups (FTD/TPI arm), the OS HR was 1.47 (95% CI, 1.13–1.92) and the PFS HR was 1.51 (95% CI, 1.19–1.91)

Figure 2. OS by prior therapy

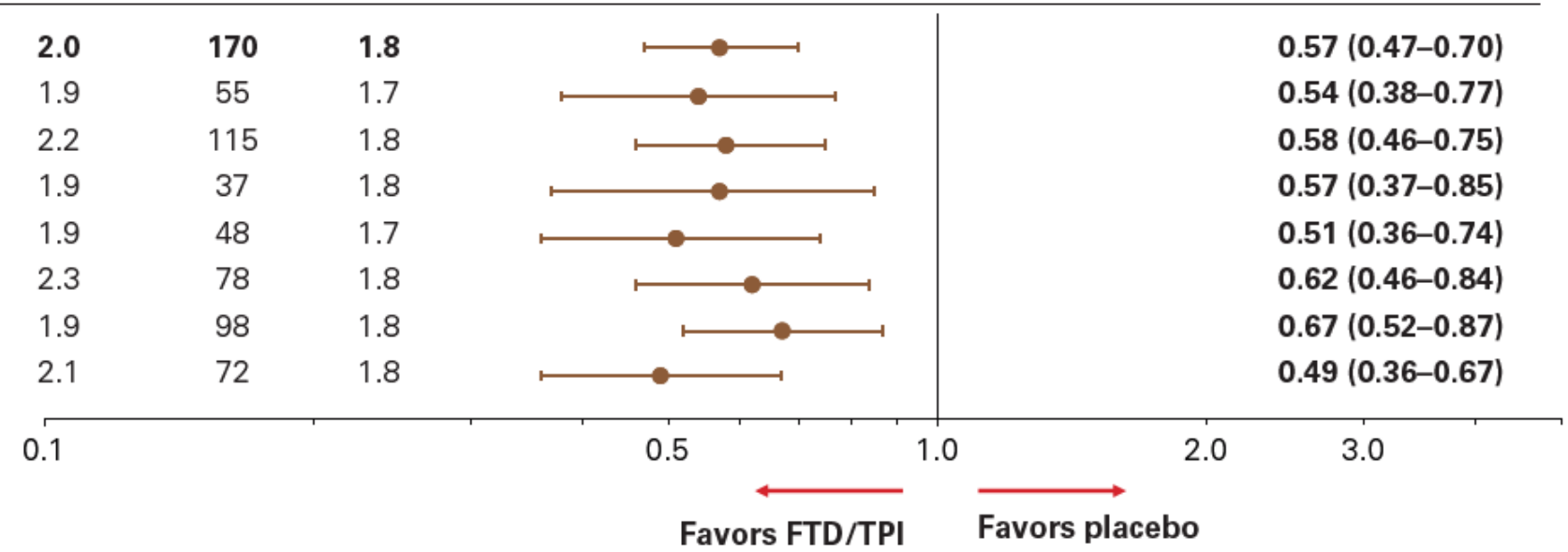
Subgroup	FTD/TPI n	FTD/TPI Median OS, months	Placebo n	Placebo Median OS, months	OS HR (95% CI)
All patients	**337**	**5.7**	**170**	**3.6**	**0.69 (0.56–0.85)**
RAM	114	5.0	55	3.8	**0.76 (0.53–1.09)**
No RAM	223	6.0	115	3.3	**0.66 (0.51–0.85)**
PAC (no RAM)	99	5.7	37	3.0	**0.47 (0.31–0.73)**
PAC + RAM	106	4.6	48	3.6	**0.73 (0.50–1.05)**
No PAC or RAM	124	6.1	78	3.7	**0.83 (0.60–1.16)**
IRI	183	4.9	98	3.6	**0.88 (0.67–1.16)**
No IRI	154	6.1	72	3.3	**0.56 (0.41–0.79)**



CI, confidence interval; FTD/TPI, trifluridine/tipiracil; HR, hazard ratio; IRI, irinotecan; OS, overall survival; PAC, paclitaxel; RAM, ramucirumab.

Figure 3. PFS by prior therapy

Subgroup	FTD/TPI n	FTD/TPI Median PFS, months	Placebo n	Placebo Median PFS, months	PFS HR (95% CI)
All patients	**337**	**2.0**	**170**	**1.8**	**0.57 (0.47–0.70)**
RAM	114	1.9	55	1.7	**0.54 (0.38–0.77)**
No RAM	223	2.2	115	1.8	**0.58 (0.46–0.75)**
PAC (no RAM)	99	1.9	37	1.8	**0.57 (0.37–0.85)**
PAC + RAM	106	1.9	48	1.7	**0.51 (0.36–0.74)**
No PAC or RAM	124	2.3	78	1.8	**0.62 (0.46–0.84)**
IRI	183	1.9	98	1.8	**0.67 (0.52–0.87)**
No IRI	154	2.1	72	1.8	**0.49 (0.36–0.67)**



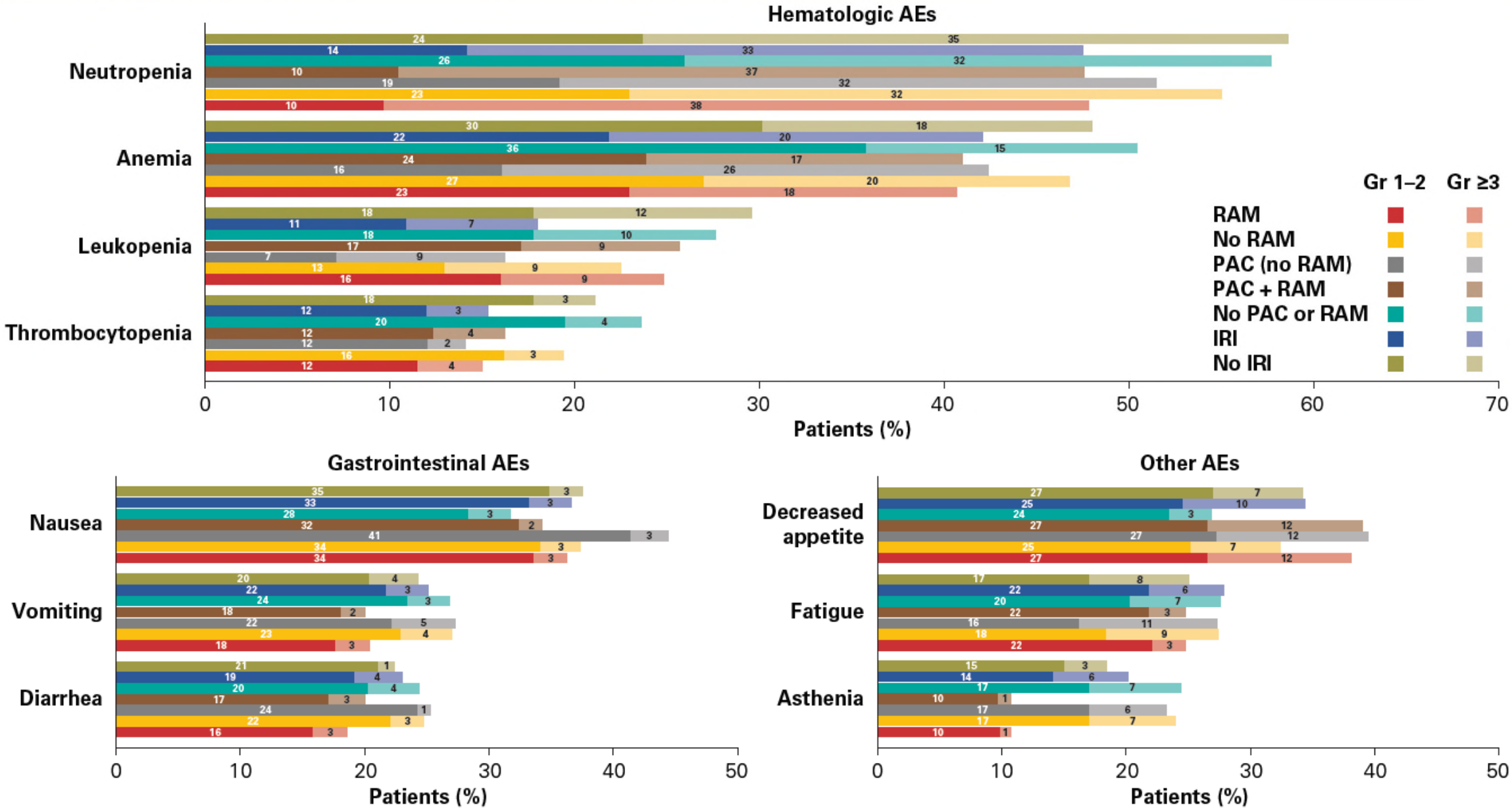
CI, confidence interval; FTD/TPI, trifluridine/tipiracil; HR, hazard ratio; IRI, irinotecan; PAC, paclitaxel; PFS, progression-free survival; RAM, ramucirumab.

RESULTS

Safety

- The FTD/TPI safety profile was consistent across all prior therapy subgroups (**Figure 4**)
  - Similar overall incidences of grade ≥3 AEs (ranging from 76% to 83%) were observed
  - Marginal variations were noted in hematologic AE incidences: rates were slightly higher in patients who had not previously received either PAC, RAM or IRI (**Figure 4**)

Figure 4. AE[a] incidences in FTD/TPI-treated patients by prior therapy



AE, adverse event; FTD/TPI, trifluridine/tipiracil; Gr, grade; IRI, irinotecan; PAC, paclitaxel; RAM, ramucirumab.
[a]AEs of any cause.

CONCLUSIONS

- Trifluridine/tipiracil administered as third- or later-line treatment in patients with mGC/GEJC improved survival outcomes compared with placebo and was tolerable regardless of the type of previous therapy patients had received
  - There was a trend towards longer OS and PFS in patients who had not previously received IRI, RAM, or PAC

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APPENDIX SLIDES

Table S1. Patient baseline characteristics

		RAM		No RAM		PAC (no RAM)		PAC + RAM	
		FTD/TPI (n=114)	Placebo (n=55)	FTD/TPI (n=223)	Placebo (n=115)	FTD/TPI (n=99)	Placebo (n=37)	FTD/TPI (n=106)	Placebo (n=48)
Age, years	Median (range)	65 (37–81)	65 (42–80)	63 (24–89)	61 (32–82)	63 (27–89)	63 (39–79)	65 (37–81)	66 (42–80)
Sex, %	Male	73	75	76	66	81	70	74	77
Geographic region, %	USA, Europe, or Australia	70	58	95	97	91	92	71	58
	Japan	30	42	5	3	9	8	29	42
Primary cancer type, %	Gastric	70	69	71	72	66	65	69	67
	GEJ	30	31	29	26	34	30	31	33
	Both	0	0	0	2	0	5	0	0
ECOG PS at baseline, %	0	37	44	36	38	33	38	35	44
	1	63	56	64	62	67	62	65	56
Previous gastrectomy, %	Yes	50	47	40	42	42	51	50	48
	No	50	53	60	58	58	49	50	52
No. of prior regimens, %	2	25	15	44	49	30	41	25	17
	3	34	35	43	36	48	38	35	31
	≥4	41	51	13	16	21	22	40	52
Baseline renal function, %	Normal (≥90 mL/min)	36	35	42	43	43	51	37	33
	Mild RI (60–89 mL/min)	46	42	39	42	34	27	45	40
	Moderate RI (30–59 mL/min)	16	24	18	13	21	19	16	27
	Severe RI (<30 mL/min)	1	0	<1	1	1	0	1	0
	Missing	1	0	<1	2	0	3	1	0

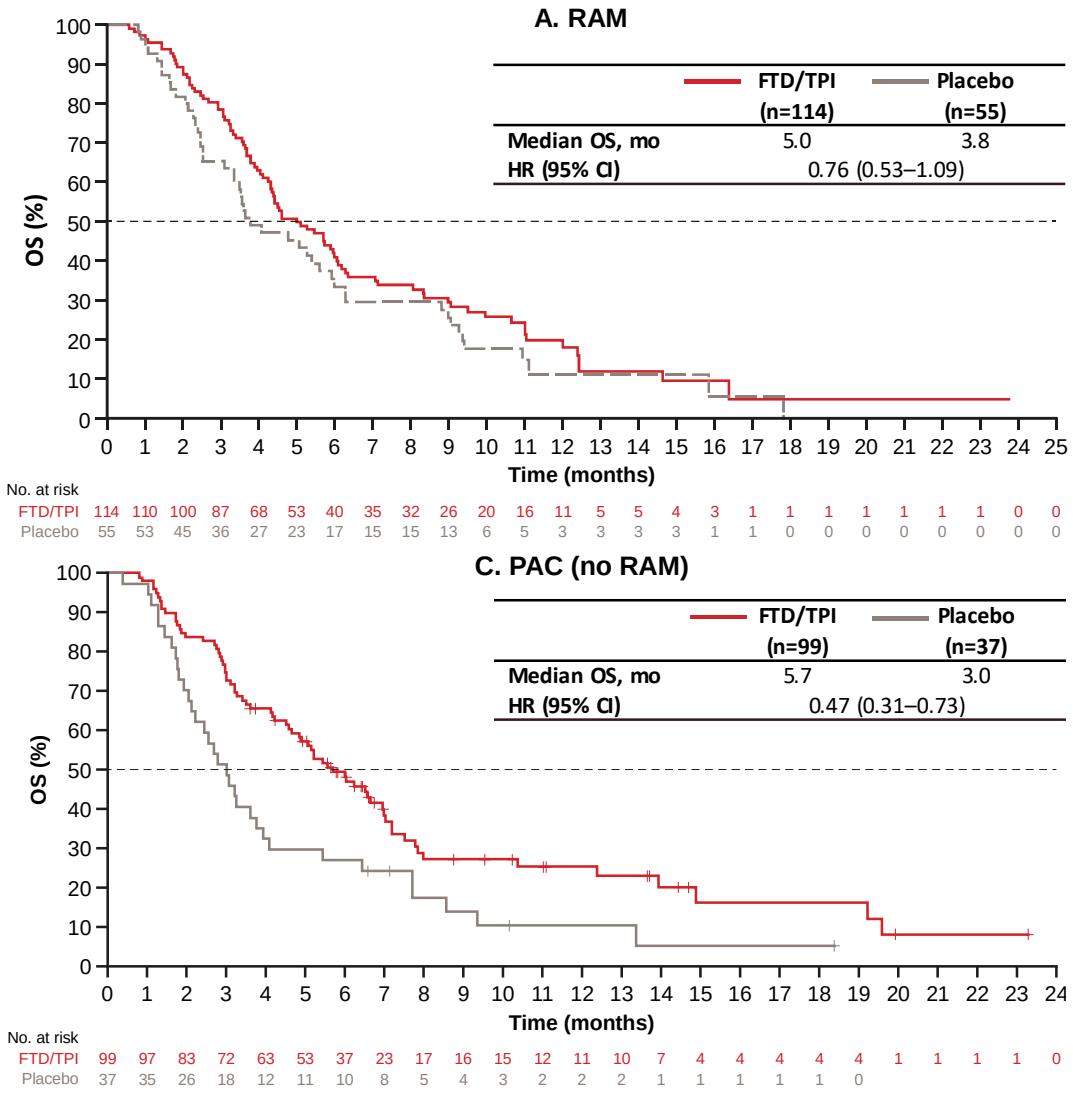
ECOG PS, Eastern Cooperative Oncology Group performance status; FTD/TPI, trifluridine/tipiracil; GEJ, gastroesophageal junction cancer; PAC, paclitaxel; RAM, ramucirumab; RI, renal impairment; USA, United States of America.

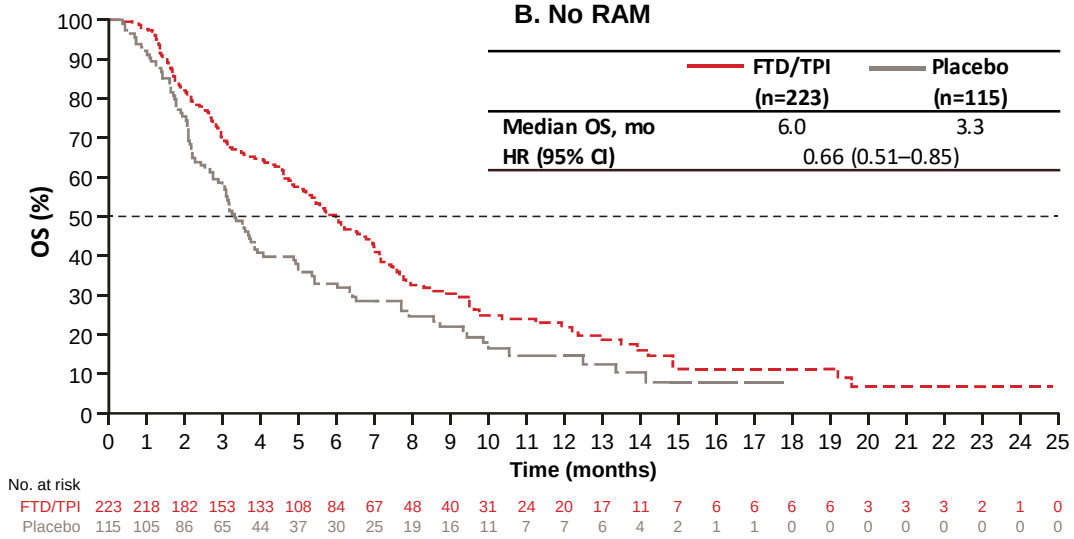
Table S2. Patient baseline characteristics

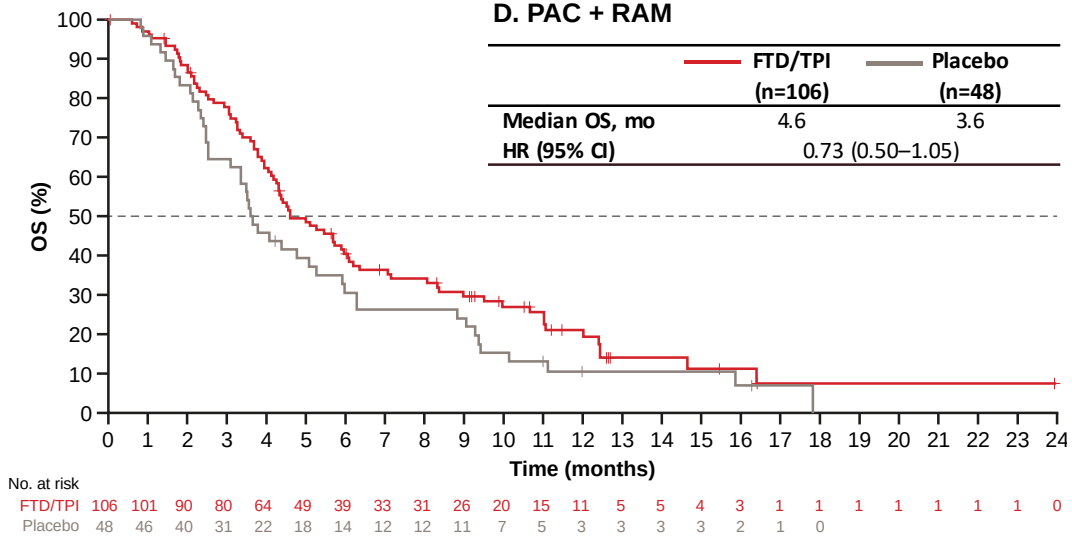
		No PAC or RAM		IRI		No IRI	
		FTD/TPI (n=124)	Placebo (n=78)	FTD/TPI (n=183)	Placebo (n=98)	FTD/TPI (n=154)	Placebo (n=72)
Age, years	Median (range)	64 (24–83)	60 (32–82)	64 (24–83)	64 (39–82)	63 (38–89)	61 (32–79)
Sex, %	Male	72	64	74	74	75	61
Geographic region, %	USA, Europe, or Australia	98	99	81	77	93	94
	Japan	2	1	19	23	7	6
Primary cancer type, %	Gastric	76	76	71	71	71	71
	GEJ	24	24	29	28	29	28
	Both	0	0	0	1	0	1
ECOG PS at baseline, %	0	39	38	34	41	39	39
	1	61	62	66	59	61	61
Previous gastrectomy, %	Yes	39	37	44	44	44	43
	No	61	63	56	56	56	57
No. of prior regimens, %	2	55	53	16	19	63	62
	3	38	35	51	39	26	31
	≥4	7	13	33	42	11	7
Baseline renal function, %	Normal (≥90 mL/min)	40	38	39	39	40	42
	Mild RI (60–89 mL/min)	44	49	43	45	41	38
	Moderate RI (30–59 mL/min)	15	10	17	15	18	18
	Severe RI (<30 mL/min)	0	1	1	0	0	1
	Missing	1	1	0	1	1	1

ECOG PS, Eastern Cooperative Oncology Group performance status; FTD/TPI, trifluridine/tipiracil; GEJ, gastroesophageal junction cancer; IRI, irinotecan; PAC, paclitaxel; RAM, ramucirumab; RI, renal impairment; USA, United States of America.

Figure S1. OS by prior therapy







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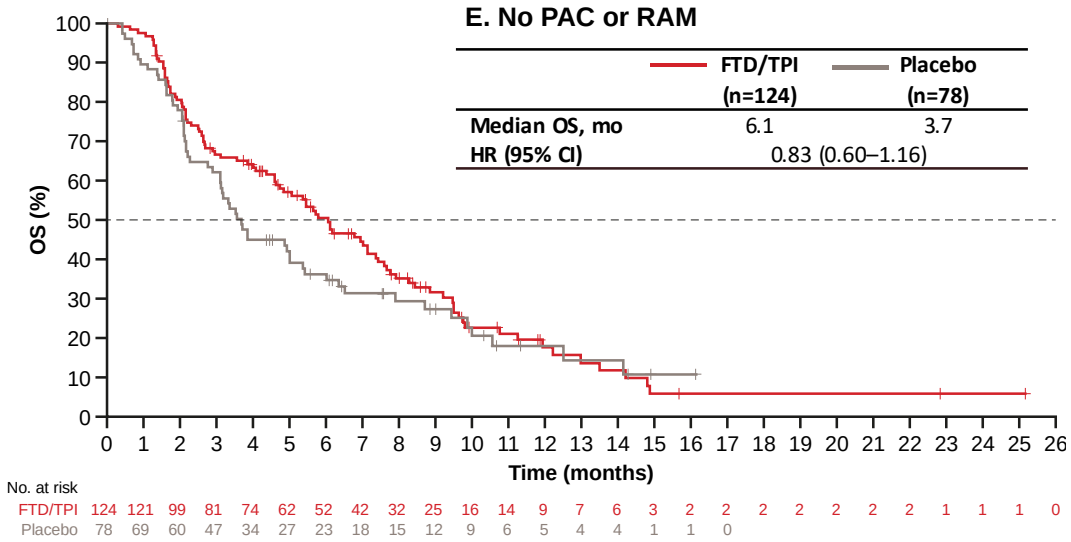
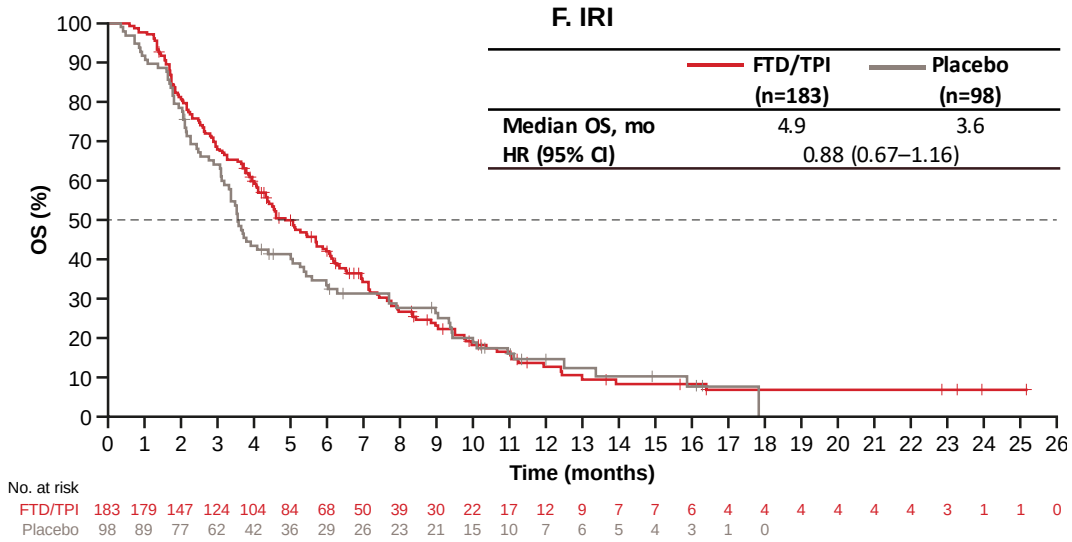
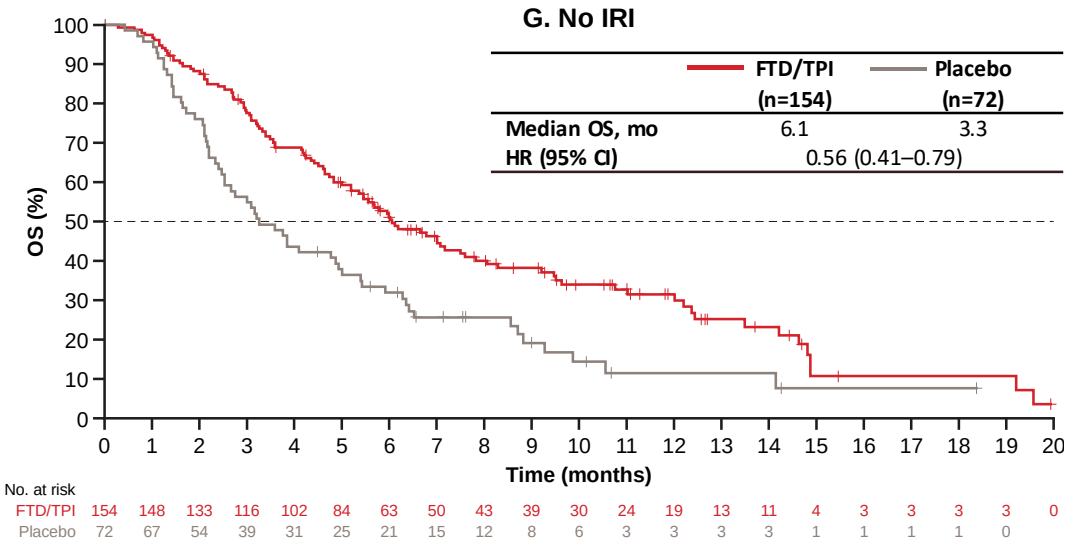
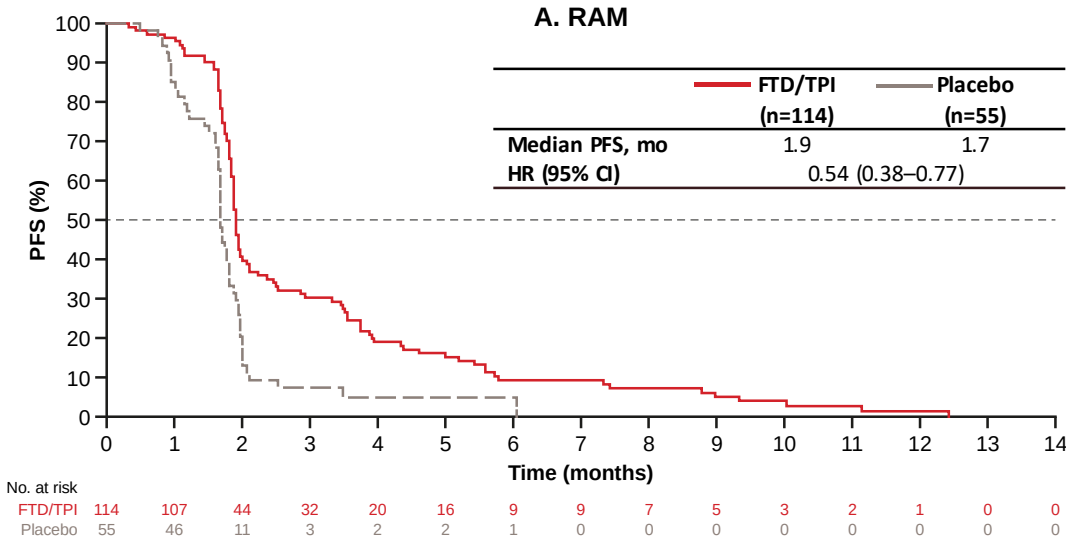


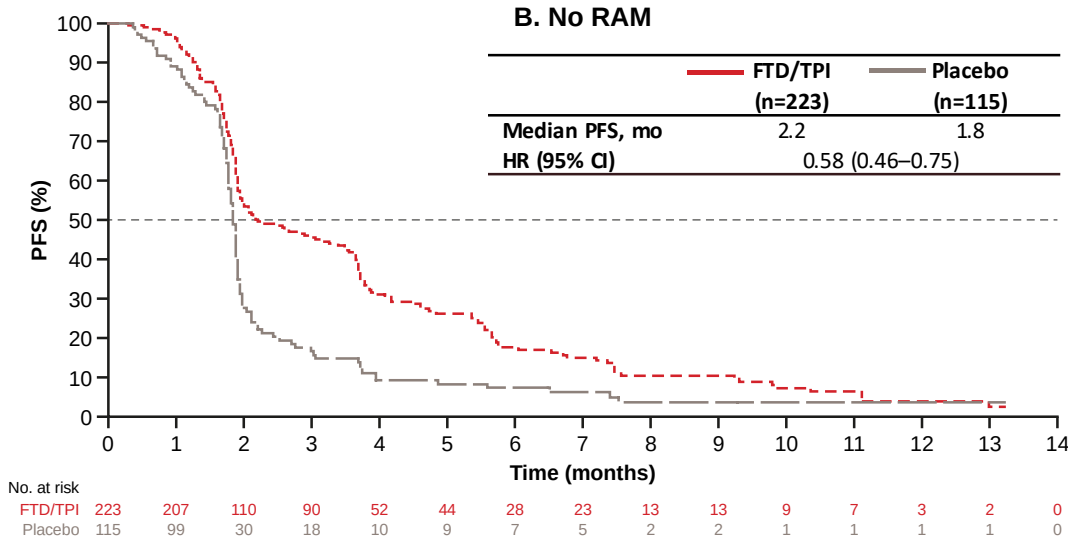


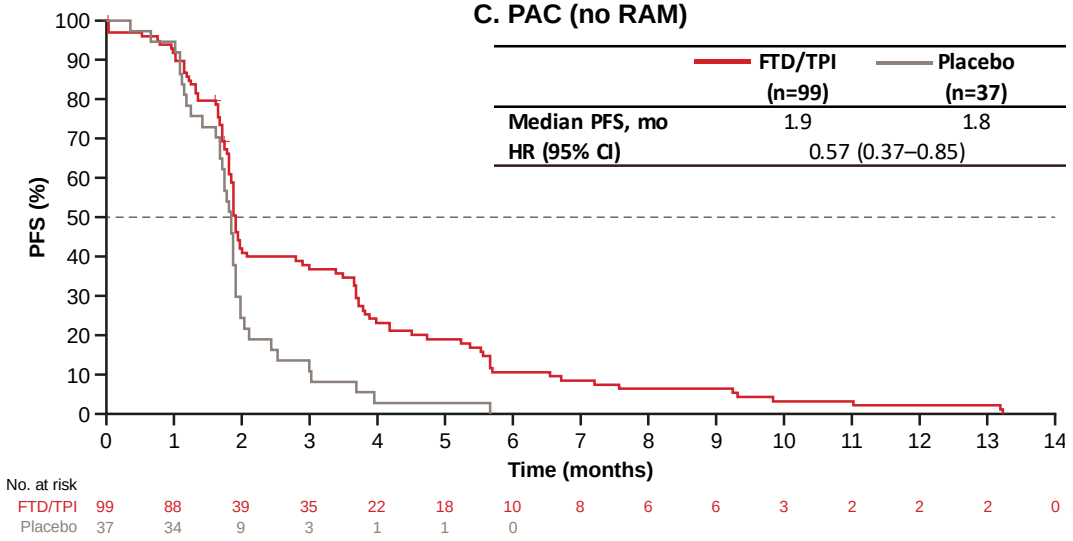


FTD/TPI, trifluridine/tipiracil; IRI, irinotecan; PAC, paclitaxel; RAM, ramucirumab.

Figure S2. PFS by prior therapy







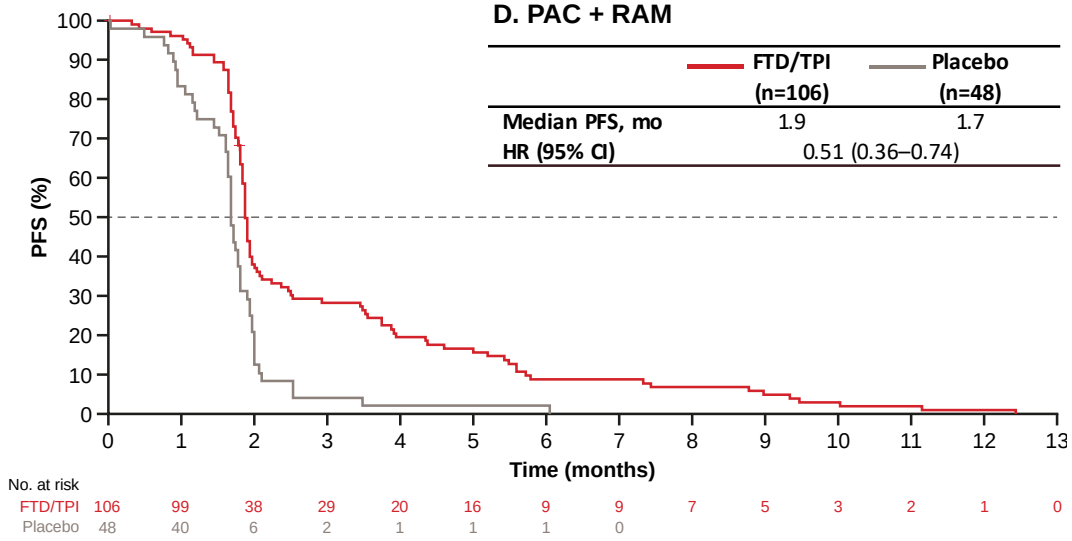
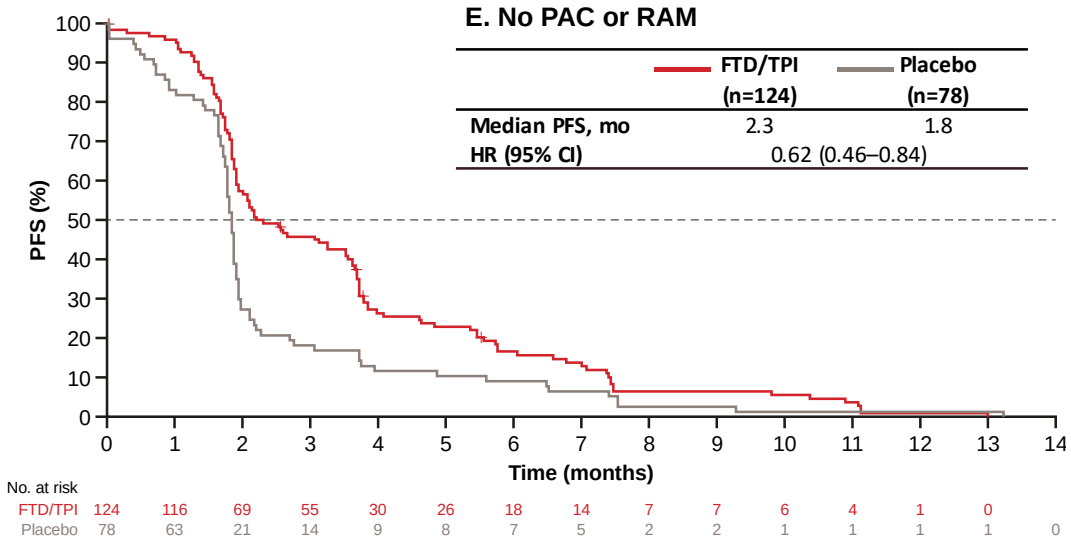
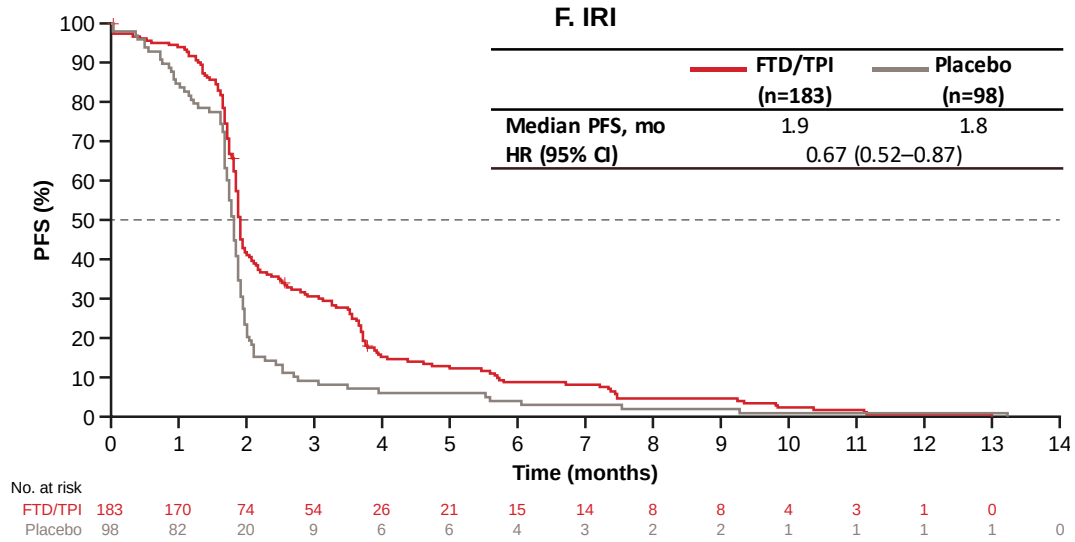
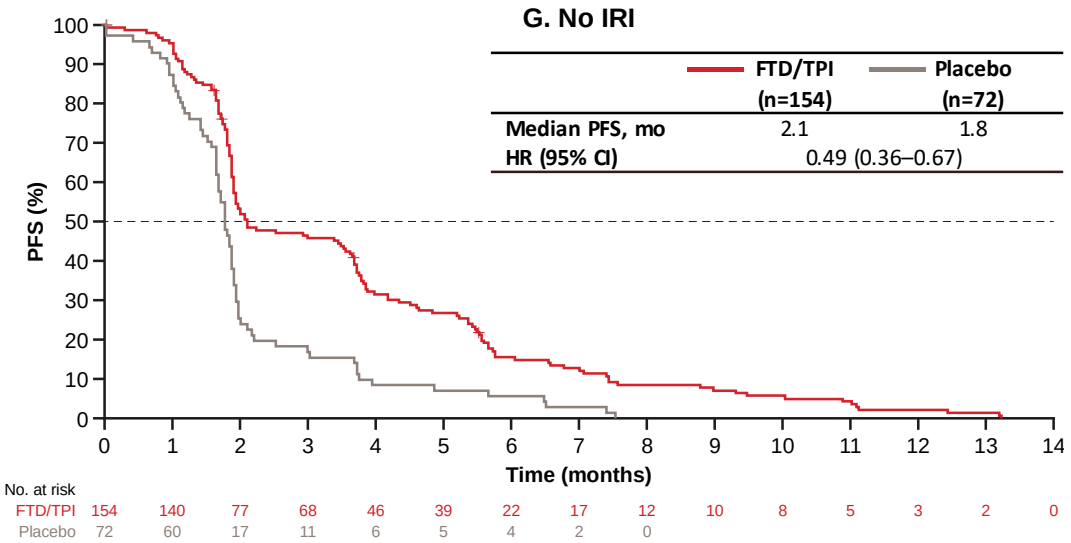


Figure S2. PFS by prior therapy

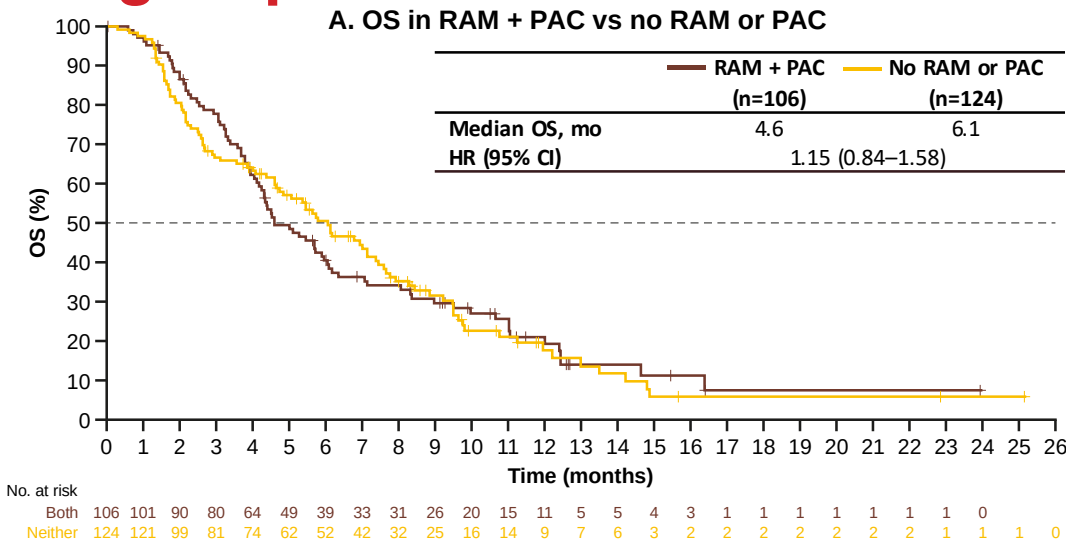


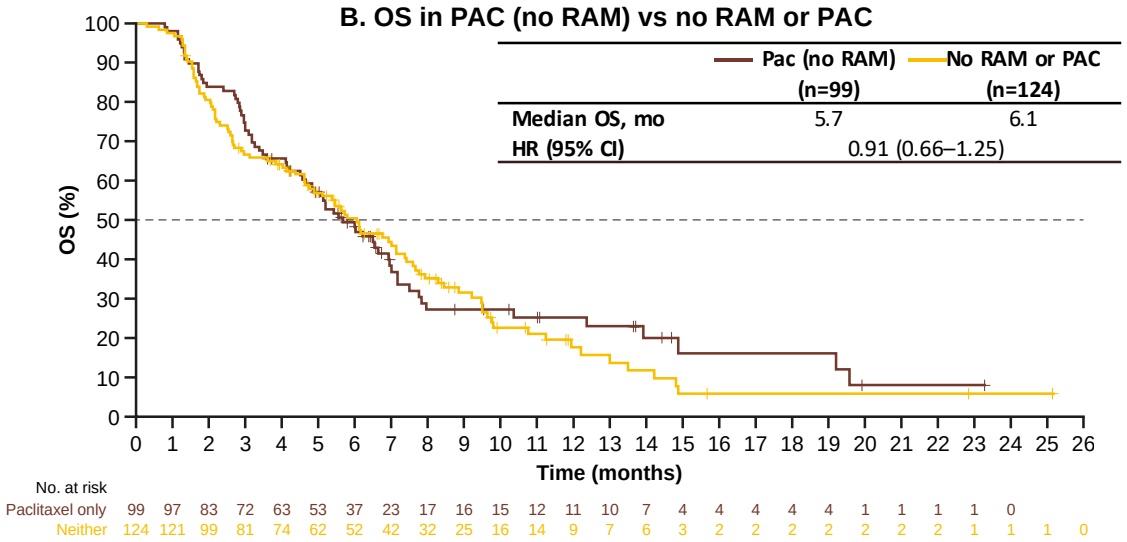


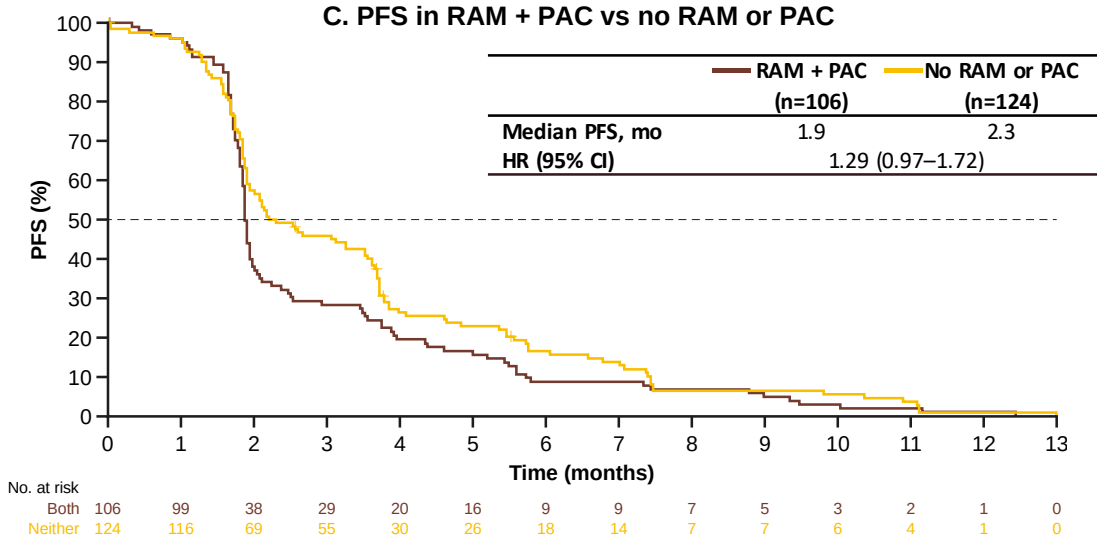


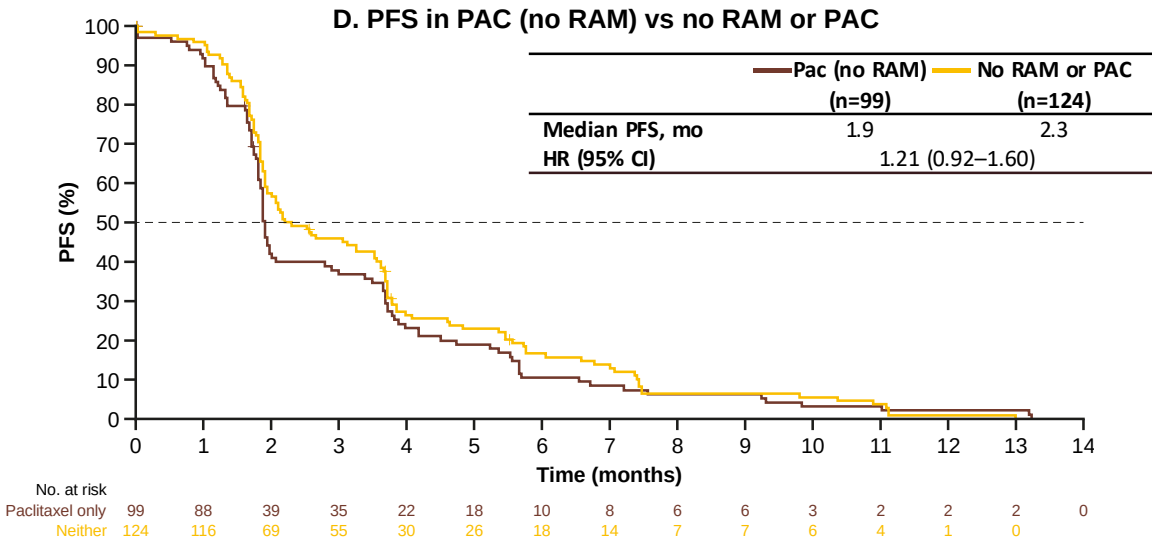
FTD/TPI, trifluridine/tipiracil; IRI, irinotecan; PAC, paclitaxel; RAM, ramucirumab.

Figure S3. OS and PFS with FTD/TPI treatment: comparison between subgroups



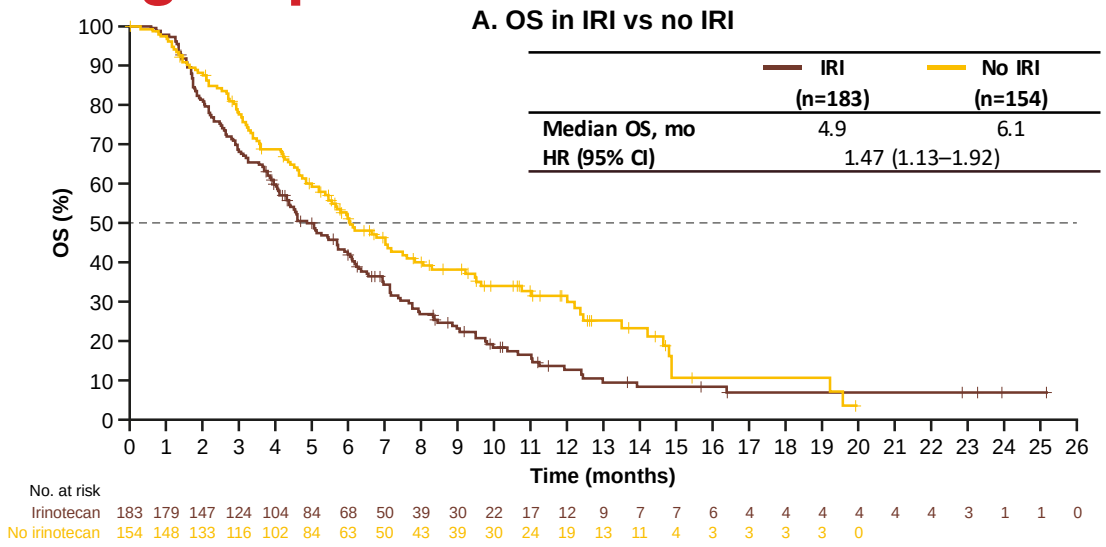


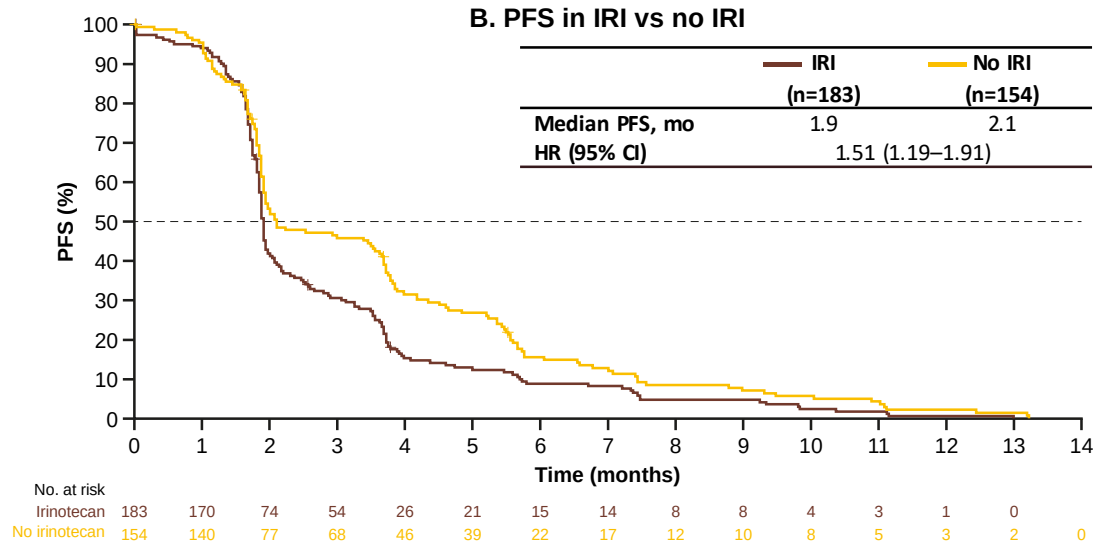




FTD/TPI, trifluridine/tipiracil; PAC, paclitaxel; RAM, ramucirumab.

Figure S4. OS and PFS with FTD/TPI treatment: comparison between subgroups





FTD/TPI, trifluridine/tipiracil; IRI, irinotecan.