



GASTRO
JournalClub

L'importanza della ricerca in Oncologia

10-11 OTTOBRE 2019 - ROMA

VOI Donna Camilla Savelli Hotel - Via Garibaldi, 27

Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial

Lancet Oncol 2018

Published Online

October 21, 2018

[http://dx.doi.org/10.1016/S1470-2045\(18\)30739-3](http://dx.doi.org/10.1016/S1470-2045(18)30739-3)

Kohei Shitara, Toshihiko Doi, Mikhail Dvorkin, Wasat Mansoor, Hendrik-Tobias Arkenau, Aliaksandr Prokharau, Maria Alsina, Michele Ghidini, Catia Faustino, Vera Gorbunova, Edvard Zhavrid, Kazuhiro Nishikawa, Ayumu Hosokawa, Şuayib Yalçın, Kazumasa Fujitani, Giordano D Beretta, Eric Van Cutsem, Robert E Winkler, Lukas Makris, David H Ilson, Josep Tabernero



Dr. Michele Ghidini
U.O. Oncologia Medica

Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico - Milano

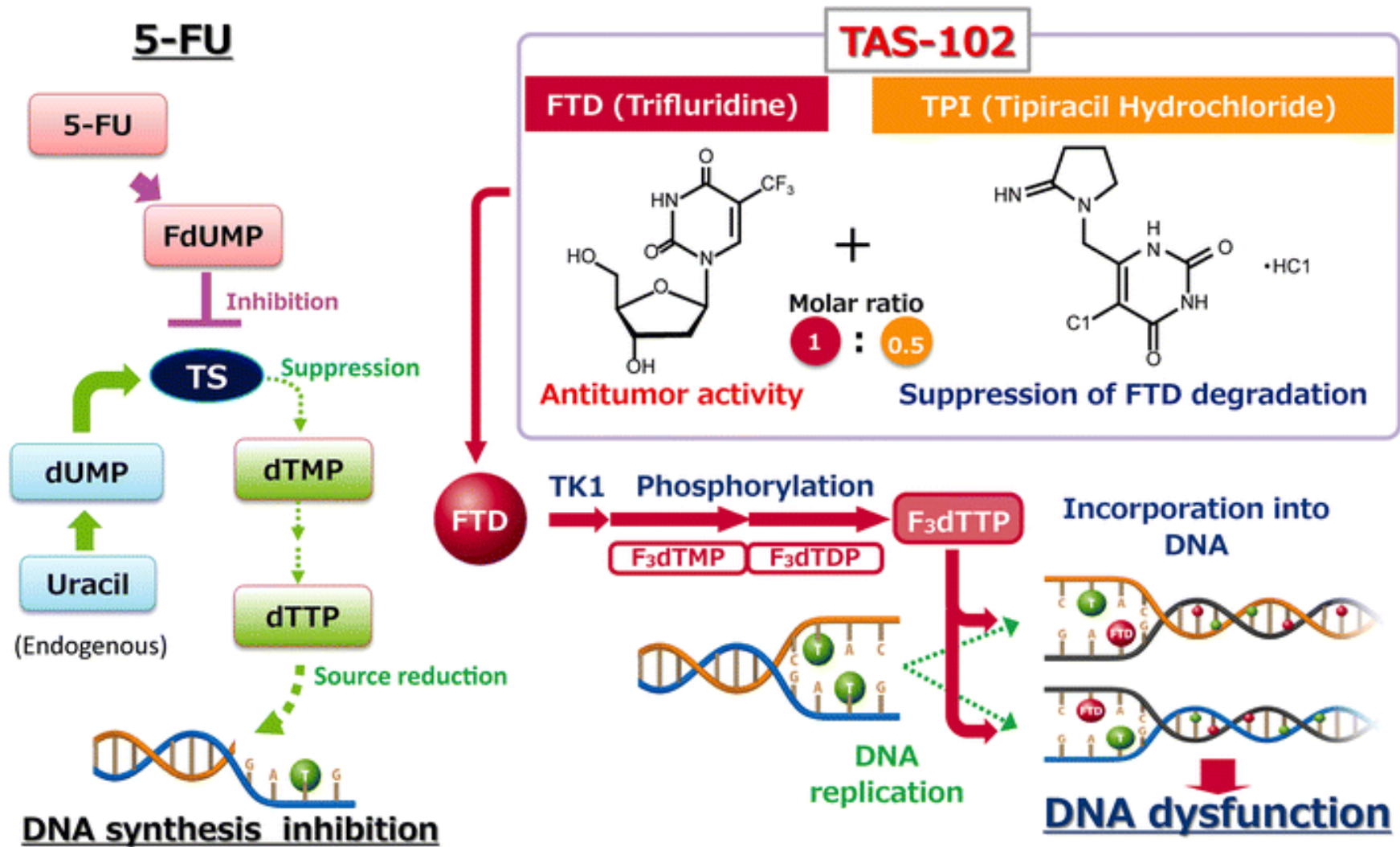


Fondazione IRCCS Ca' Granda
Ospedale Maggiore Policlinico



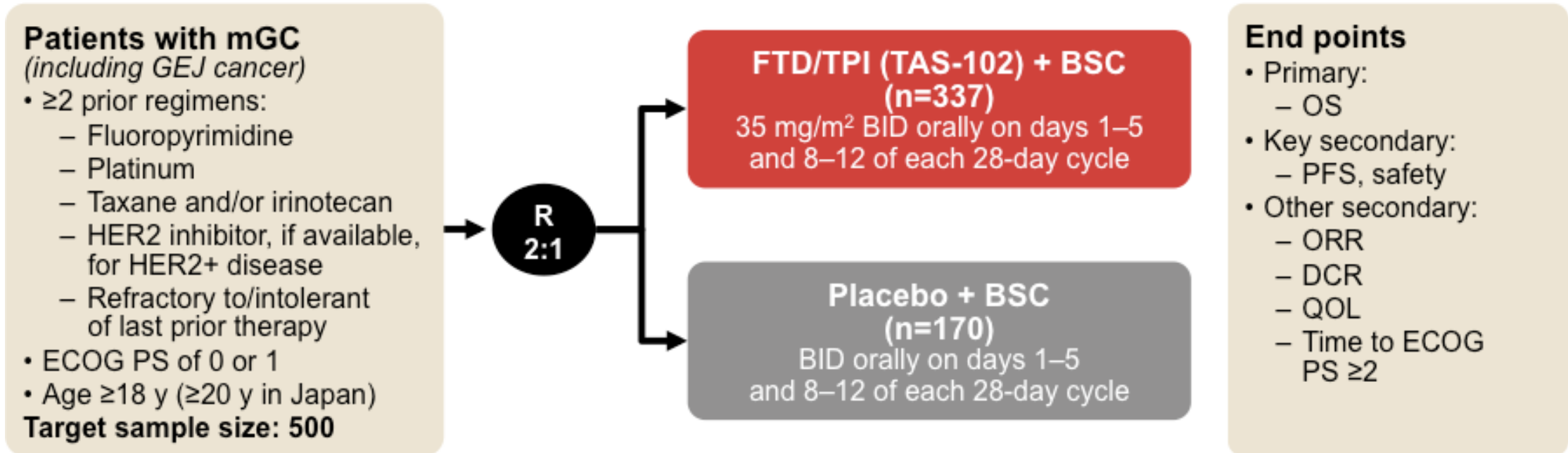

GASTRO
JournalClub

5-FU vs FTD/TPI



Longo-Munoz F et al. Clin Transl Oncol 2017

TAGS: TAS-102 Gastric Study



- Treatment until progression, intolerable toxicity, or patient withdrawal
- Multicenter, randomized, double-blind, placebo-controlled, phase III study
 - Stratification: ECOG PS (0 vs 1), region (Japan vs ROW), prior ramucirumab (yes vs no)
 - Sites: 18 countries, 110 sites; enrollment: February 2016 – January 2018
 - Data cutoff date: March 31, 2018
 - Target 384 events allowed detection of HR for death of 0.70 with 90% power at 1-sided type 1 error of 0.025

BID, twice daily; BSC, best supportive care; GEJ, gastroesophageal junction; QOL, quality of life; ROW, rest of world

Tabernero J, ESMO GI 2018 Barcelona

Baseline demographic and disease characteristics

		FTD/TPI (n=337)	Placebo (n=170)
Age, years; median (range)		64.0 (24–89)	62.5 (32–82)
Gender, %	Male	75	69
	Female	25	31
Geographic region, %	Japan	14	16
	ROW	86	84
ECOG PS, %	0	36	40
	1	64	60
Primary site, %	Gastric	71	71
	GEJ	29	28
	Both	0	1
Prior gastrectomy, %	Yes	44	44
Number of prior regimens, %	2	37	38
	3	40	35
	≥4	23	27

ITT population

Tabernero J, ESMO GI 2018 Barcelona

Baseline disease characteristics, prior and post-study therapies

		FTD/TPI (n=337)	Placebo (n=170)
Number of metastatic sites, %	1-2	46	42
	≥3	54	58
HER2 status, %	Positive	20	16
	Negative	61	62
	Not assessed	18	22
Prior systemic cancer therapeutic agents, %	Fluoropyrimidine	>99 ^a	100
	Platinum	100	100
	Irinotecan ^b	54	58
	Taxane ^b	92	87
	Ramucirumab	34	32
Anti-HER2 therapy	18	14	
Immunotherapy (anti-PD-1/PD-L1)	7	4	
Post-study systemic anticancer therapy, %		25	26

HER-2 status UNK in 100 patients

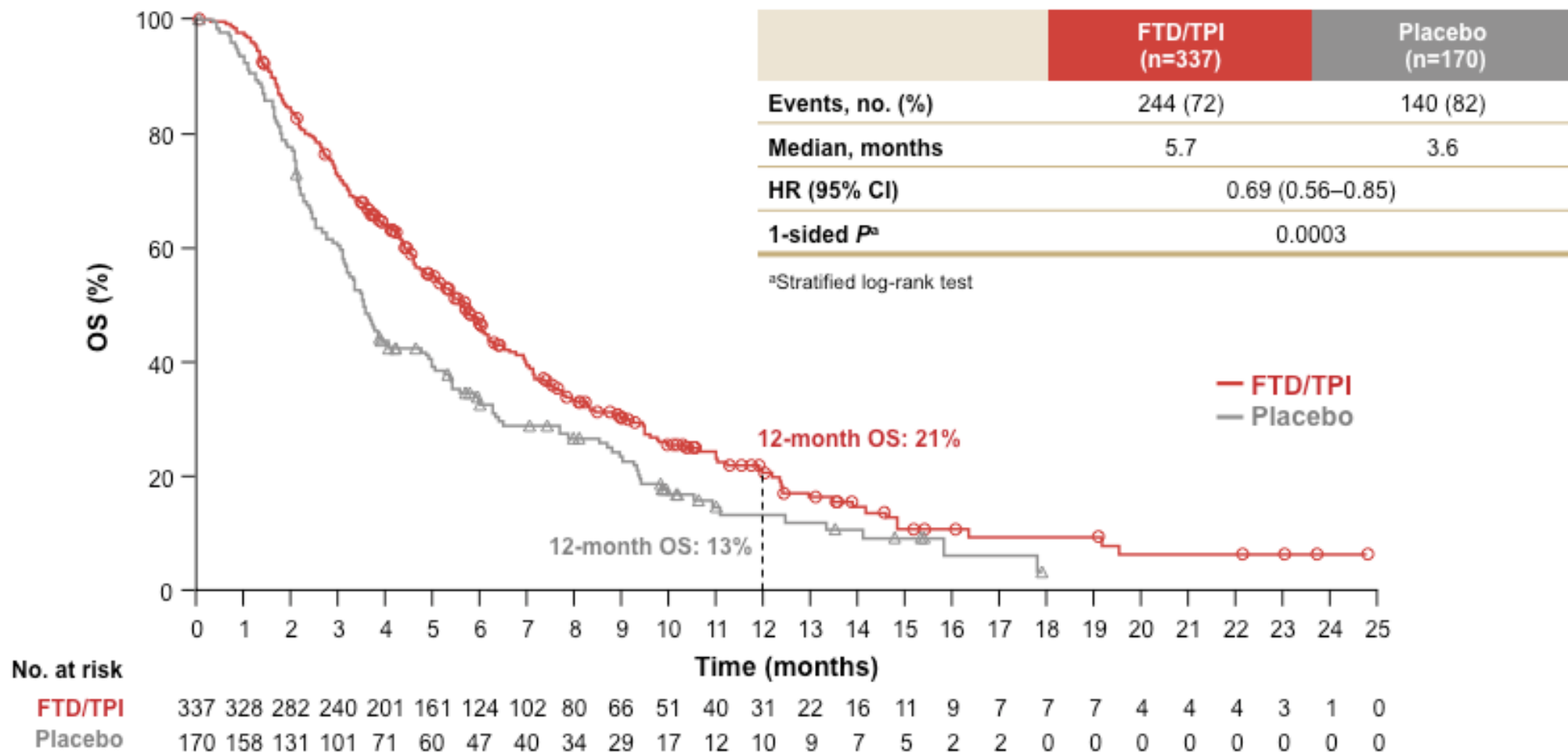
ITT population; PD-1, programmed death-1; PD-L1, programmed death-ligand 1

^a1 patient did not receive a fluoropyrimidine; ^bAll patients received irinotecan or taxane or both

Tabernero J, ESMO GI 2018 Barcelona

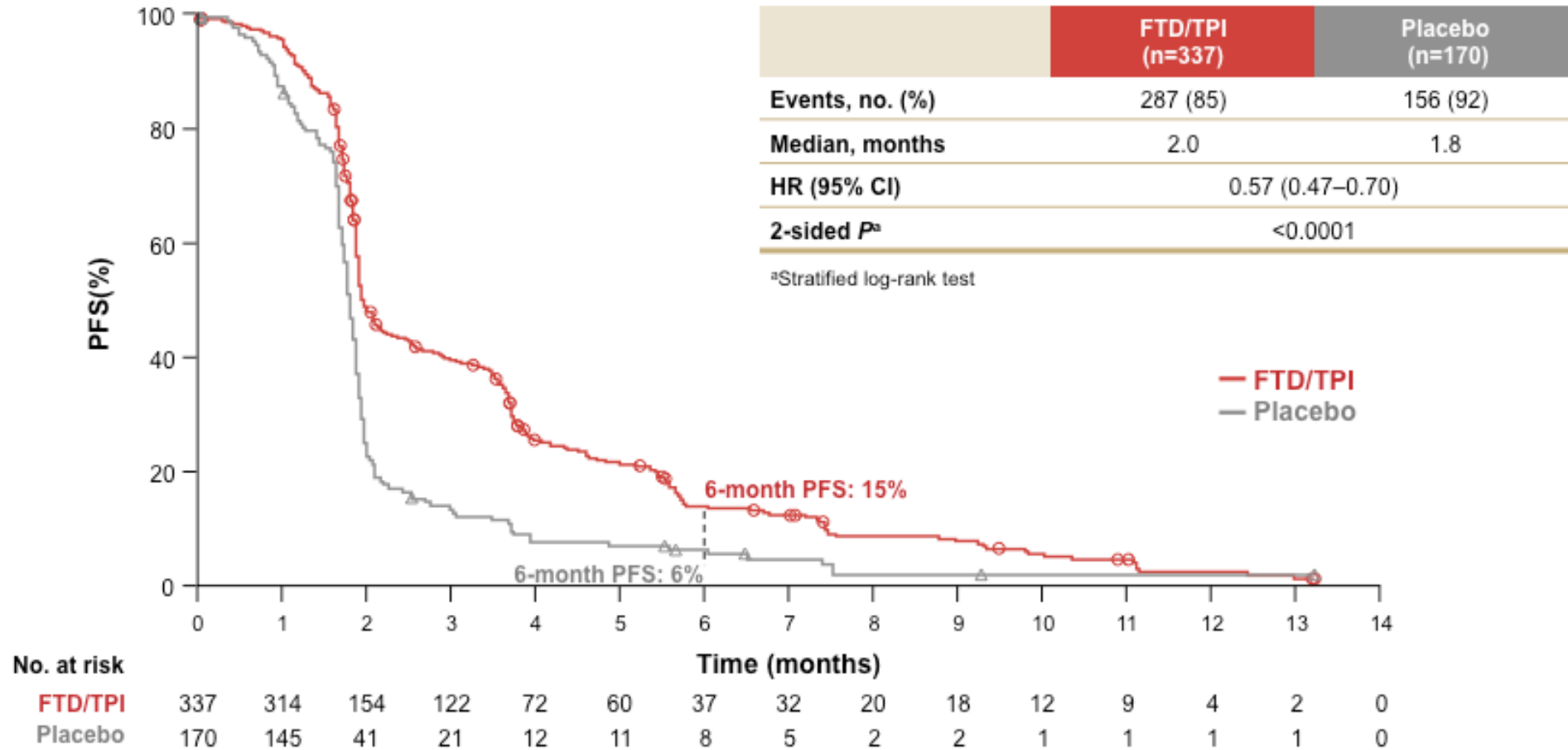


Primary endpoint: OS



Tabernero J, ESMO GI 2018 Barcelona

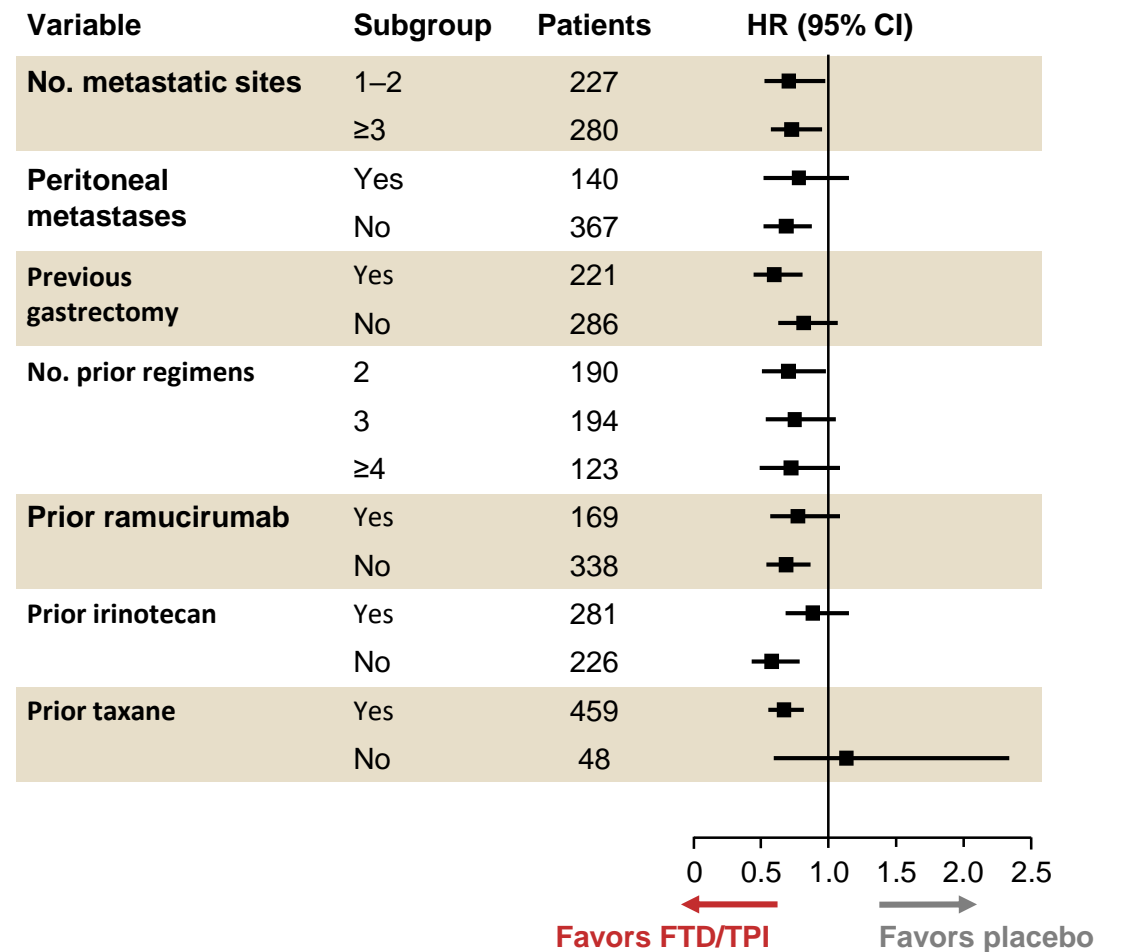
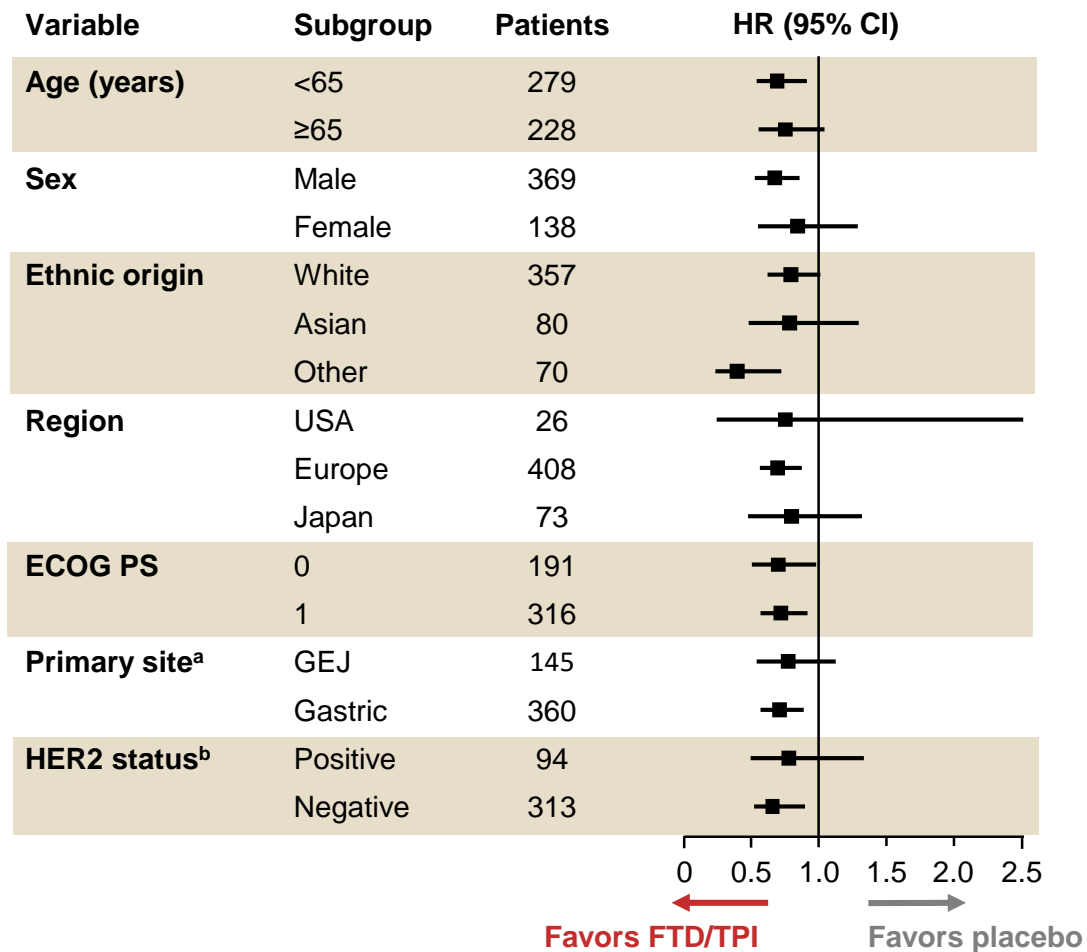
Secondary endpoint: PFS



ITT population

Tabernero J, ESMO GI 2018 Barcelona

OS subgroups analysis



Ilson DH, ASCO GI 2019 S. Francisco

Safety overview

	FTD/TPI (n=335) %	Placebo (n=168) %
Any AE (any cause)	97	93
Grade \geq 3 AE (any cause)	80	58
AE (any cause) leading to discontinuation	13	17
Treatment-related AE	81	57
Treatment-related death	0.3	0.6

All treated patients

Tabernero J, ESMO GI 2018 Barcelona

Non-hematologic AEs

AE	FTD/TPI (n=335)		Placebo (n=168)	
	Any grade %	Grade ≥3 %	Any grade %	Grade ≥3 %
Nausea	37	3	32	3
Decreased appetite	34	9	31	7
Fatigue	27	7	21	6
Vomiting	25	4	20	2
Diarrhea	23	3	14	2
Asthenia	19	5	24	7
Abdominal pain	16	4	18	9
Constipation	13	1	15	2
Dyspnea	7	2	10	4
General physical deterioration	7	7	10	9

All treated patients

Tabernero J, ESMO GI 2018 Barcelona

Hematologic AEs

Laboratory abnormality	FTD/TPI (n=328 ^a)			Placebo (n=162 ^a)		
	Grade 3 %	Grade 4 %	Grade 3/4 %	Grade 3 %	Grade 4 %	Grade 3/4 %
Neutropenia	27	11	38	0	0	0
Leukopenia	19	2	21	0	0	0
Lymphocytopenia	17	2	19	8	0	8
Anemia	19	0 ^b	19	7	0 ^b	7
Thrombocytopenia	4	2	6	0	0	0

^aTreated patients with ≥ 1 post-baseline measurement

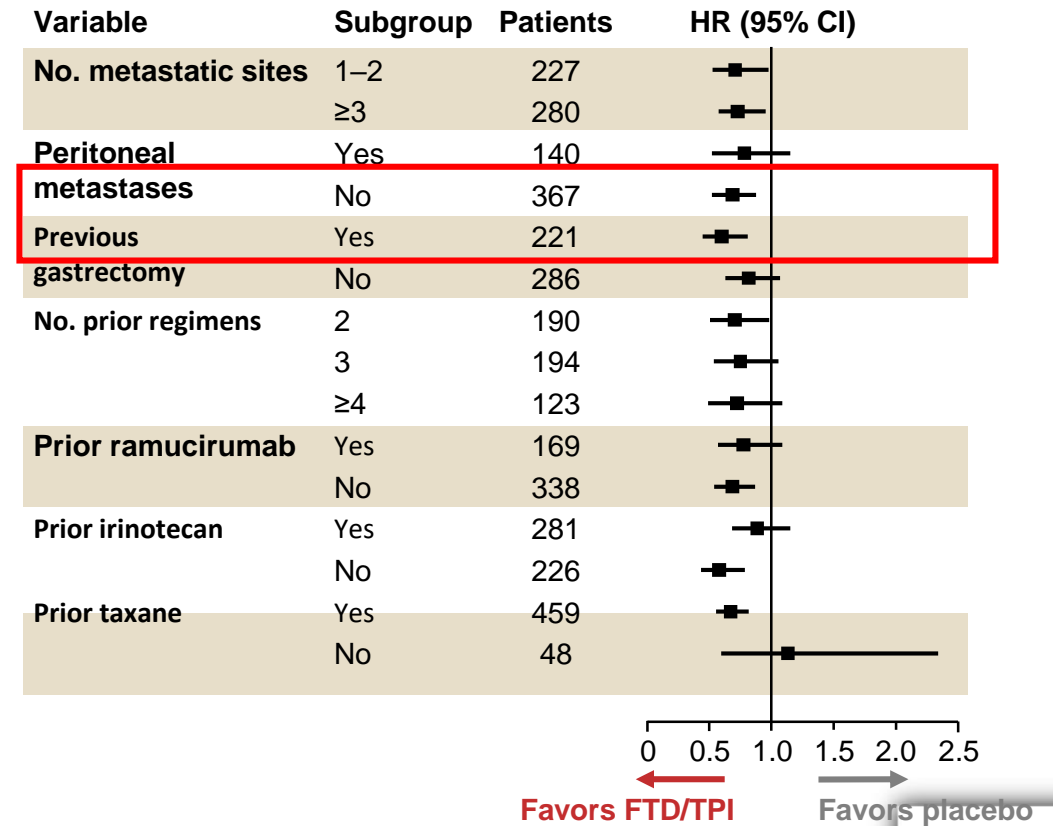
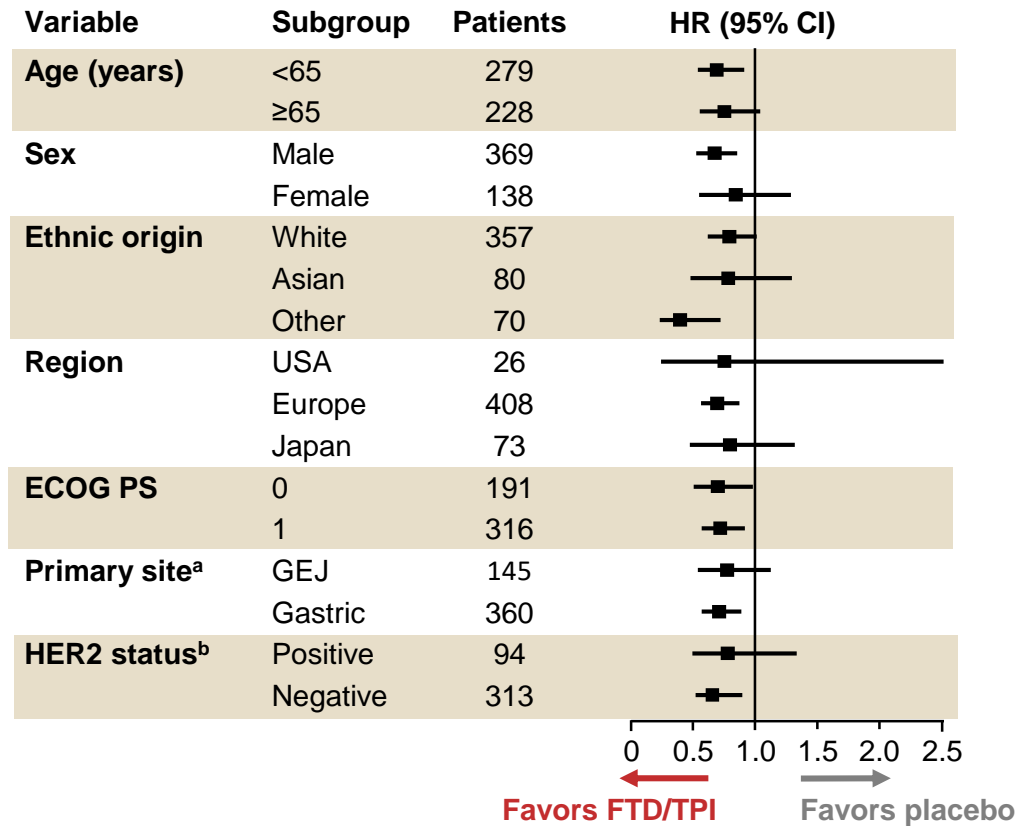
^bPer Common Terminology Criteria for Adverse Events, the highest grade of anemia as a laboratory abnormality is grade 3

- Grade ≥ 3 febrile neutropenia was reported in 6 patients (2%) treated with FTD/TPI

Tabernero J, ESMO GI 2018 Barcelona

Efficacy and safety of trifluridine/tipiracil in patients with metastatic gastric cancer with gastrectomy: Results from a phase 3 study (TAGS)

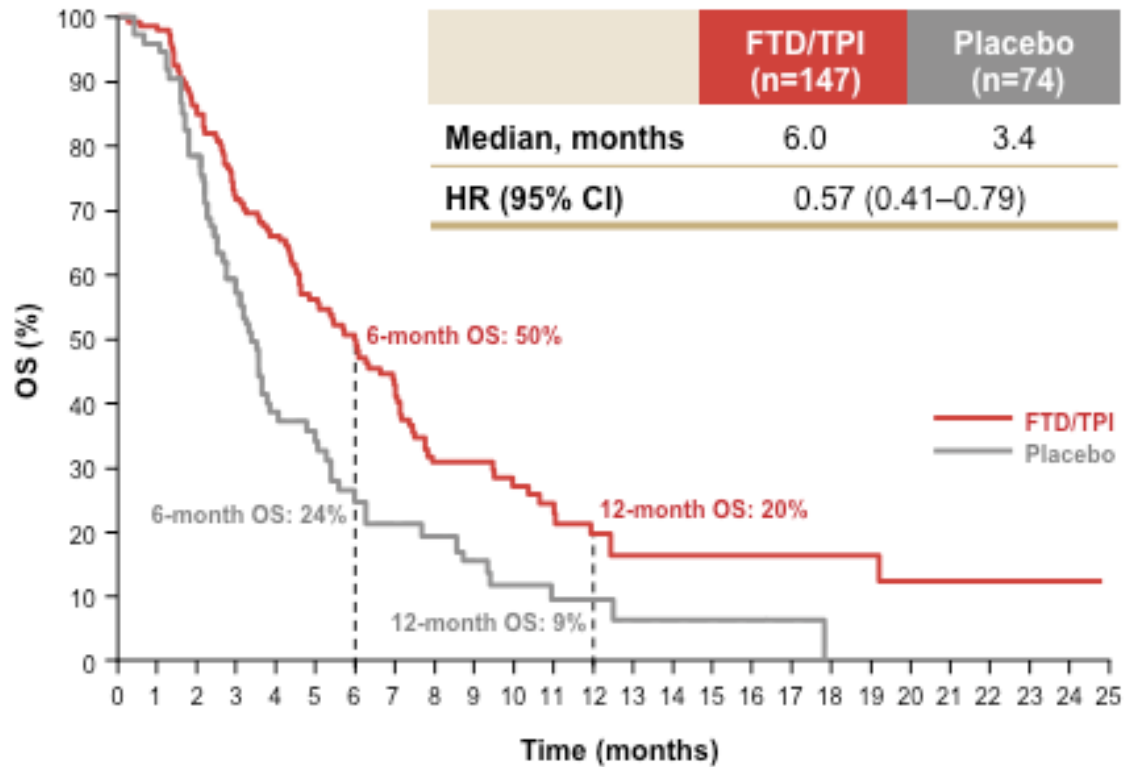
OS subgroups analysis



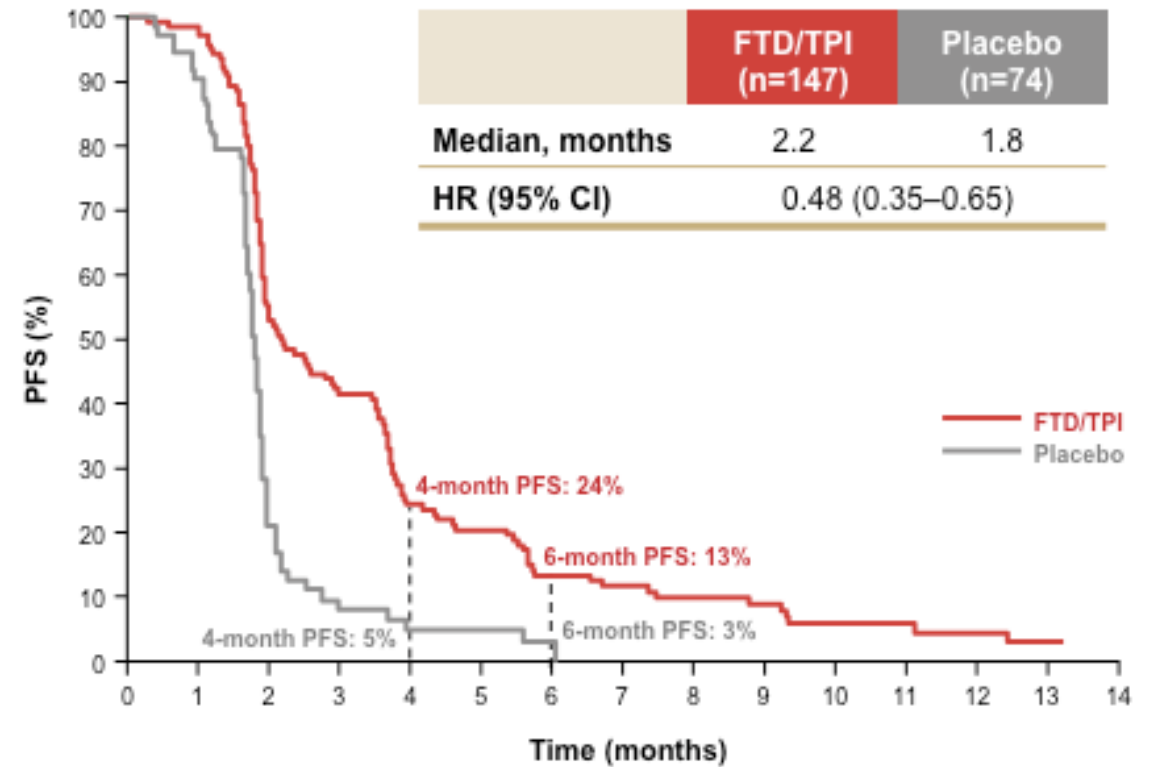
Ilson DH, ASCO GI 2019 S. Francisco

OS and PFS in patients with gastrectomy

OS



PFS



FTD/TPI	147	144	125	103	90	70	59	48	32	27	22	16	12	9	8	7	6	5	5	5	3	3	3	3	1	0
Placebo	74	71	58	42	27	22	14	12	10	8	6	4	3	2	2	2	1	1	0	0	0	0	0	0	0	0

FTD/TPI	147	139	75	54	31	26	17	14	10	9	5	4	3	2	0
Placebo	74	67	15	5	3	3	1	0	0	0	0	0	0	0	0

Ilson DH, ASCO GI 2019 S. Francisco

Treatment exposure in patients with gastrectomy

	Gastrectomy ^a		Overall population ^{a,1}	
	FTD/TPI (n=145)	Placebo (n=73)	FTD/TPI (n=335)	Placebo (n=168)
Mean (SD) dose intensity, mg/m ² /week	145 (28)	159 (23)	148 (27)	155 (28)
Mean (SD) relative dose intensity	0.83 (0.16)	0.91 (0.13)	0.85 (0.15)	0.89 (0.16)
Median (range) cycles initiated per patient	2 (1–14)	2 (1–6)	2 (1–14)	2 (1–16)
Mean (SD) treatment duration, week	12.7 (11.8)	5.8 (4.4)	12.1 (11.5)	7.1 (7.8)

Ilson DH, ASCO GI 2019 S. Francisco


Most common AEs in patients with gastrectomy

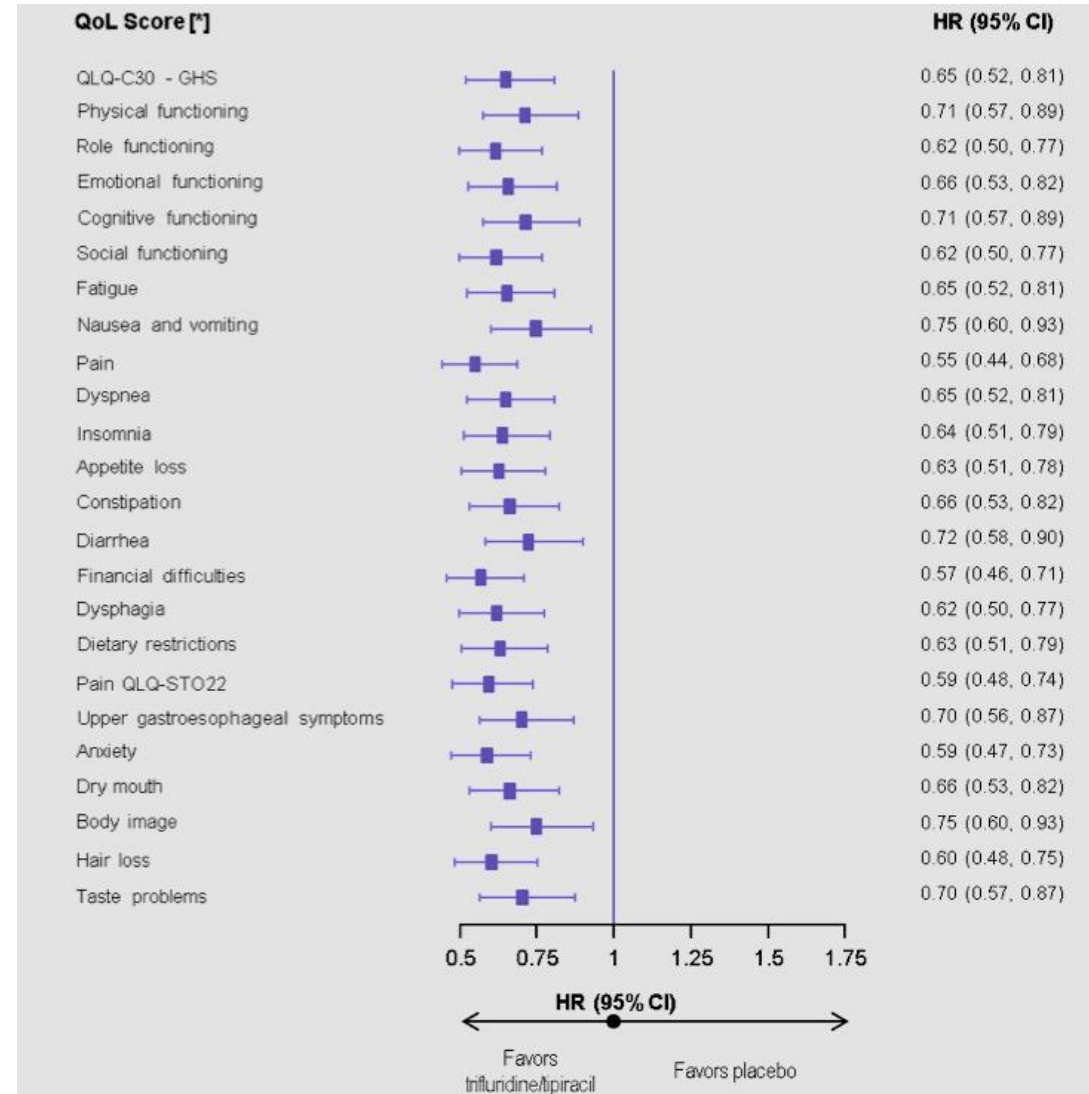
AE	Gastrectomy ^b				Overall population ^{b,1}			
	FTD/TPI (n=145)		Placebo (n=73)		FTD/TPI (n=335)		Placebo (n=168)	
	Any grade %	Grade ≥3 %	Any grade %	Grade ≥3 %	Any grade %	Grade ≥3 %	Any grade %	Grade ≥3 %
Hematologic AEs								
Neutropenia and/or decreased neutrophil count	60	44	1	0	53	34	4	0
Anemia and/or decreased hemoglobin level	53	21	11	4	45	19	19	8
Leukopenia and/or decreased white blood cell count	28	14	1	0	23	9	2	0
Thrombocytopenia and/or decreased platelet count	21	5	1	0	18	3	5	0
Gastrointestinal AEs								
Nausea	39	3	36	4	37	3	32	3
Diarrhea	30	1	16	3	23	3	14	2
Vomiting	25	3	16	1	25	4	20	2
Abdominal pain	18	3	22	10	16	4	18	9
Constipation	12	1	16	3	13	1	15	2
Other AEs								
Decreased appetite	35	8	32	7	34	9	31	7
Fatigue	25	2	22	5	27	7	21	6
Asthenia	21	2	26	7	19	5	24	7
Back pain	10	1	6	1	7	1	7	2

Ilson DH, ASCO GI 2019 S. Francisco

Analysis of symptoms and Health-related QoL scales

Time to deterioration in EORTC QoL scores by ≥ 10 points
(events: death and disease progression)

- ✓ 496 patients with available data
- ✓ Analysis at 6 cycles for FTD/TPI and 3 cycles for placebo
- ✓ No significant deterioration in QLQ-C30 GHS score, EORTC QLQ-C30 functional scale scores and symptoms scores with FTD/TPI
- ✓ **TREND TOWARDS FTD/TPI REDUCING DETERIORATION OF QoL SCORES** 



Alsina M, ASCO 2019 Chicago, abstract #4043

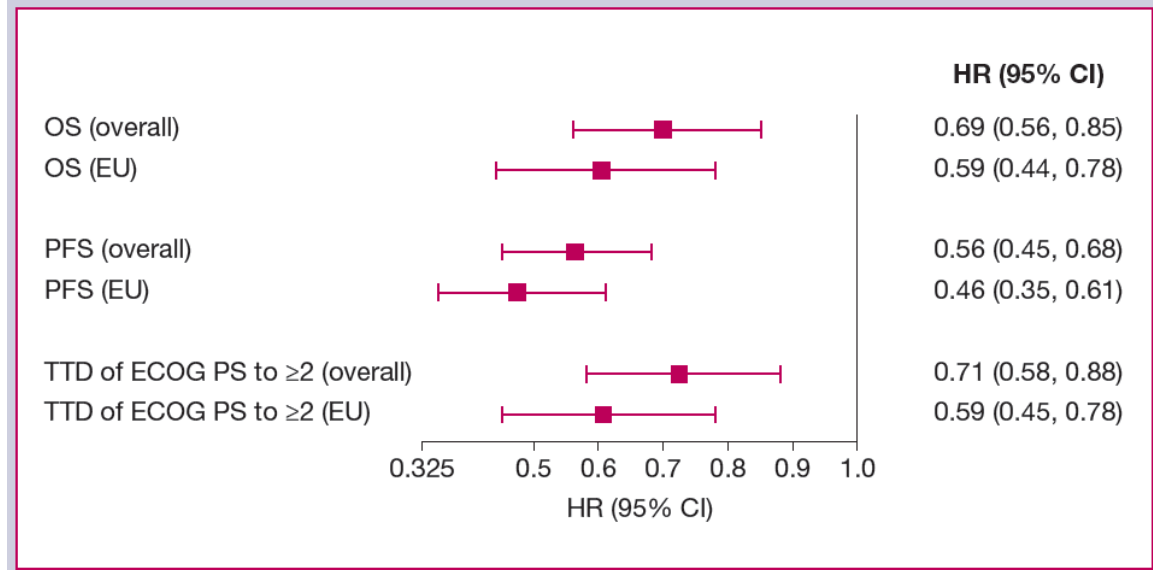
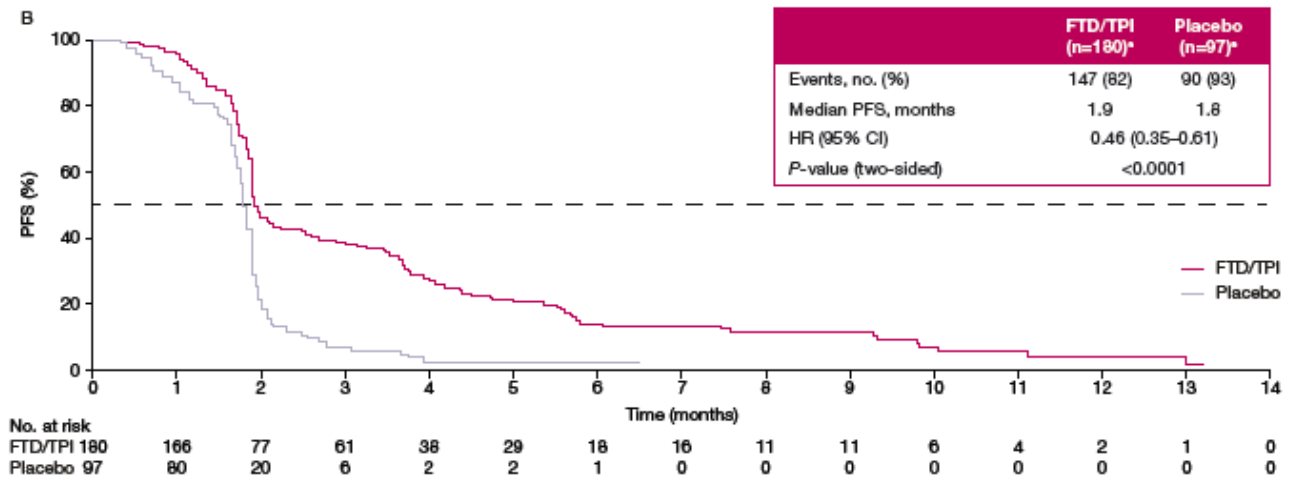
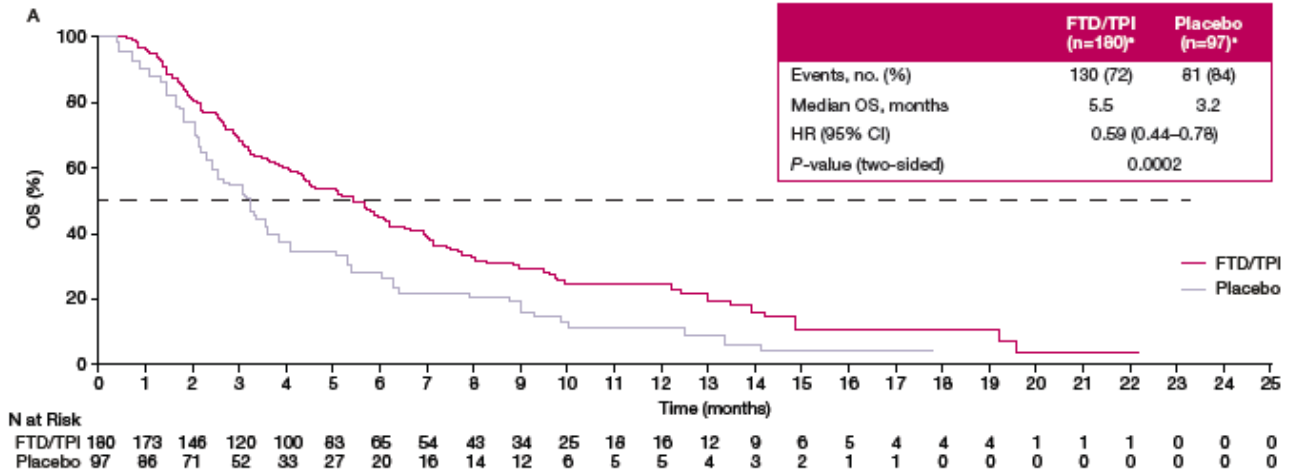
Efficacy and safety in EU patients

	FTD/TPI		Placebo	
	EU subpopulation (N=180)	Overall population (N=337)	EU subpopulation (N=97)	Overall population (N=170)
Age, years; median (range)	64 (38–89)	64 (24–89)	62 (39–82)	62 (32–82)
Male, %	76	75	74	69
ECOG PS, %				
• 0	37	36	42	40
• 1	63	64	58	60
Primary site, %				
• Gastric	64	71	63	71
• GEJ	36	29	35	28
• Both	0	0	2	1
Prior gastrectomy, %	46	44	40	44
Number of prior regimens, %				
• 2	33	37	35	38
• 3	44	40	40	35
• ≥4	23	23	25	27

ECOG PS, European Cooperative Oncology Group performance status; EU, European Union; FTD/TPI, trifluridine/tipiracil; GEJ, gastroesophageal junction.

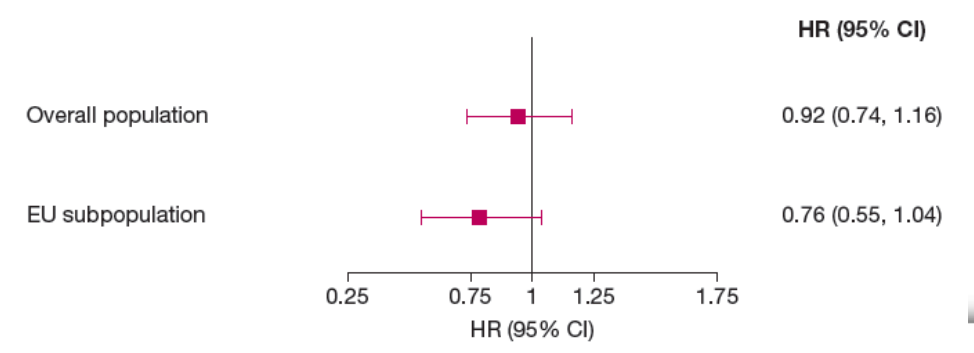
Alsina M, ESMO 2019 Barcelona, abstract #3420

Efficacy and safety in EU patients



CI, confidence interval; ECOG PS, European Cooperative Oncology Group performance status; EU, European Union; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TTD, time to deterioration.

Time to deterioration in EORTC QoL scores by ≥10 points or death



Alsina M, ESMO 2019 Barcelona, abstract #3420

Conclusions

- ✓ FTD/TPI showed a clinically meaningful and statistically significant improvement in OS and PFS compared with placebo in heavily pretreated mGC;
 - 31% reduction in risk of death (HR, 0.69; 95% CI, 0.56–0.85; $P=0.0003$)
 - 2.1-month improvement in median OS (5.7 vs 3.6 months)
- ✓ FTD/TPI prolonged survival versus placebo regardless of gastrectomy;
- ✓ Treatment with FTD/TPI was associated with a positive trend toward a lower risk of QoL deterioration than placebo;
- ✓ FTD/TPI showed a significantly prolonged OS, PFS and time to deterioration in ECOG PS to ≥ 2 also in the EU subpopulation.

October 10, 2019

Efficacy and Safety of Trifluridine/Tipiracil Treatment in Patients With Metastatic Gastric Cancer Who Had Undergone Gastrectomy

Subgroup Analyses of a Randomized Clinical Trial

David H. Ilson, MD, PhD¹; Josep Tabernero, MD, PhD²; Aliaksandr Prokharau, MD³; Hendrik-Tobias Arkenau, MD, PhD⁴; Michele Ghidini, MD, PhD⁵; Kazumasa Fujitani, MD⁶; Eric Van Cutsem, MD, PhD⁷; Peter Thuss-Patience, MD⁸; Giordano D. Beretta, MD⁹; Wasat Mansoor, PhD¹⁰; Edvard Zhavrid, MD¹¹; Maria Alsina, MD²; Ben George, MD¹²; Daniel Catenacci, MD¹³; Sandra McGuigan, MD¹⁴; Lukas Makris, PhD¹⁵; Toshihiko Doi, MD¹⁶; Kohei Shitara, MD¹⁶

[» Author Affiliations](#) | [Article Information](#)

JAMA Oncol. Published online October 10, 2019. doi:10.1001/jamaoncol.2019.3531





michele.ghidini@policlinico.mi.it



GASTRO
JournalClub