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Chemotherapy for Advanced Gastric Cancer

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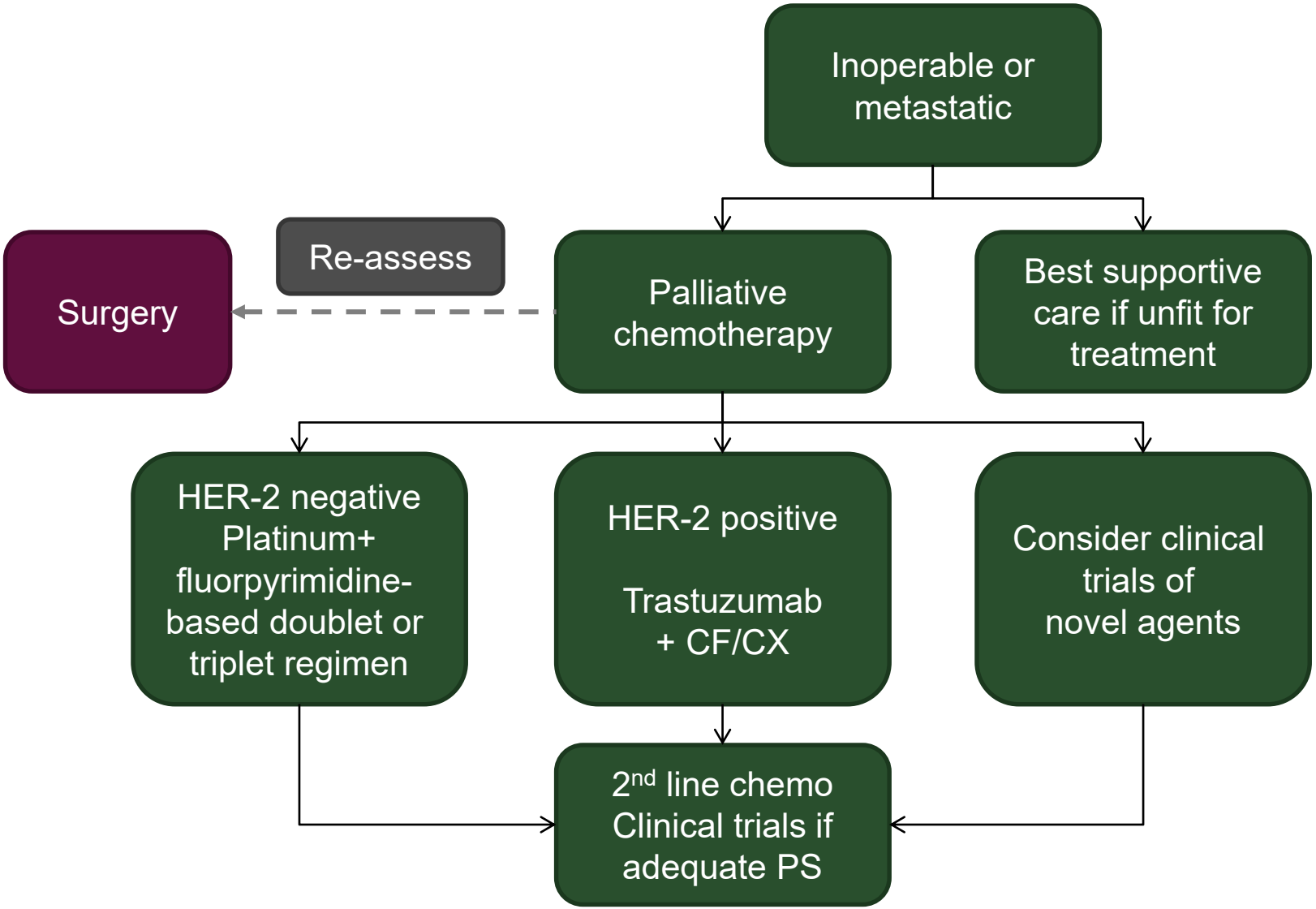
Treatment for advanced gastric cancer: What is standard of care? ESMO guidelines



Smyth EC, et al. Ann Oncol 2016;27(Suppl 5):38–49. By permission of the European Society of Medical Oncology

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Treatment for metastatic/unresectable gastric cancer: Active agents in first line

- Based upon superiority trials:
  - 5-FU
  - Cisplatin
  - Docetaxel
  - Trastuzumab
- Based upon non-inferiority trials
  - Oxaliplatin
  - Capecitabine
  - S1
  - Irinotecan

Cervantes A, et al. Cancer Treat Rev 2012; 39:60-67

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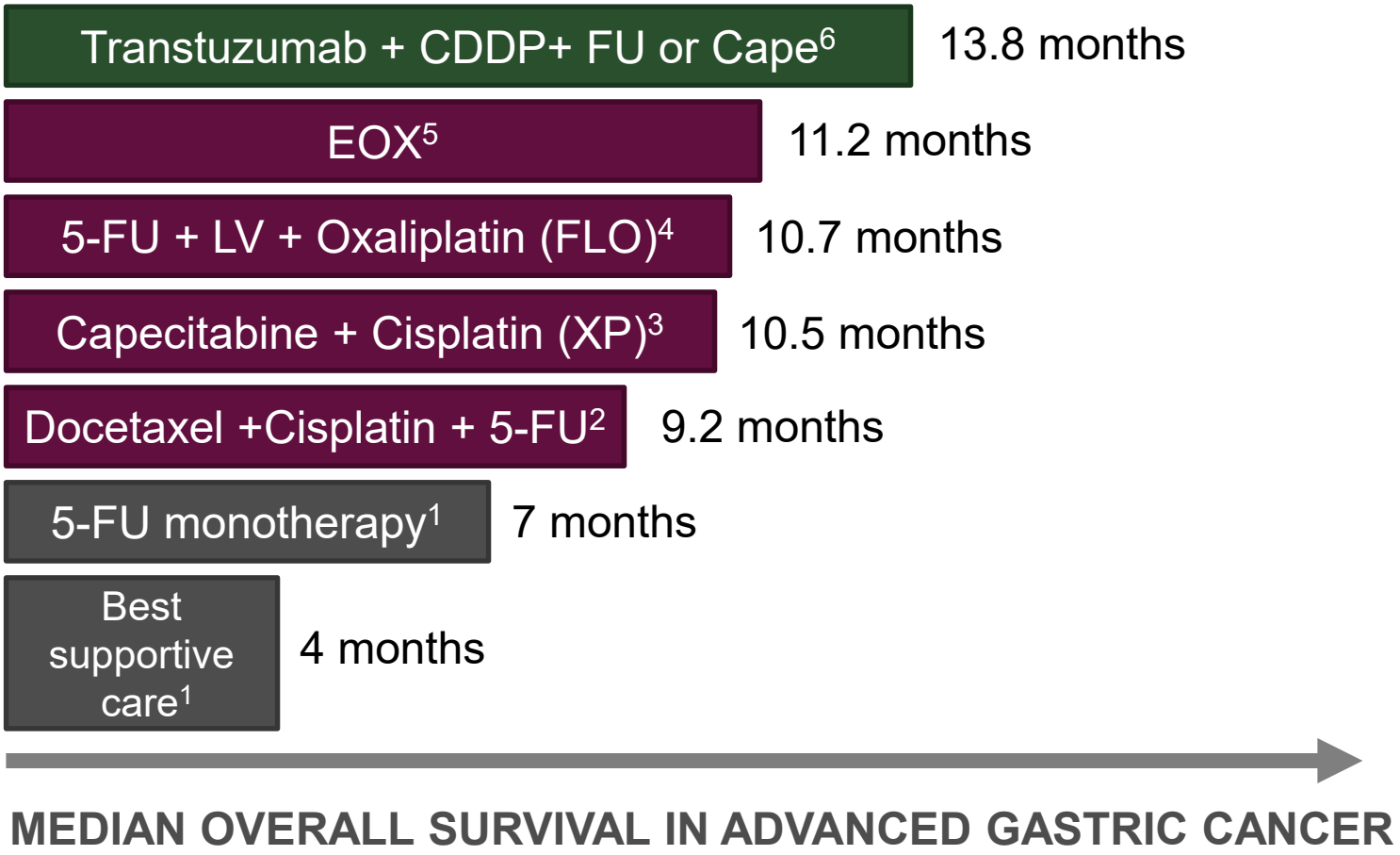
Have we made any progress in the treatment of advanced gastric cancer?



1. Wagner A, et al. JCO 2006. 2. van Cutsem E, et al. J Clin Oncol 2006;24:4991–4997. 3.Kang YK et al, Ann Oncol 2009; 20:666–73. 4. Al Batran SE, et al. J Clin Oncol 2008;26:1435–1442. 5. Cunningham D, et al. N Engl J Med 2008;358:36-46. 6. Bang YJ, et al. Lancet 2010;376:687–697
EOX: Epirubicin/Oxaliplatin/Capecitabine.

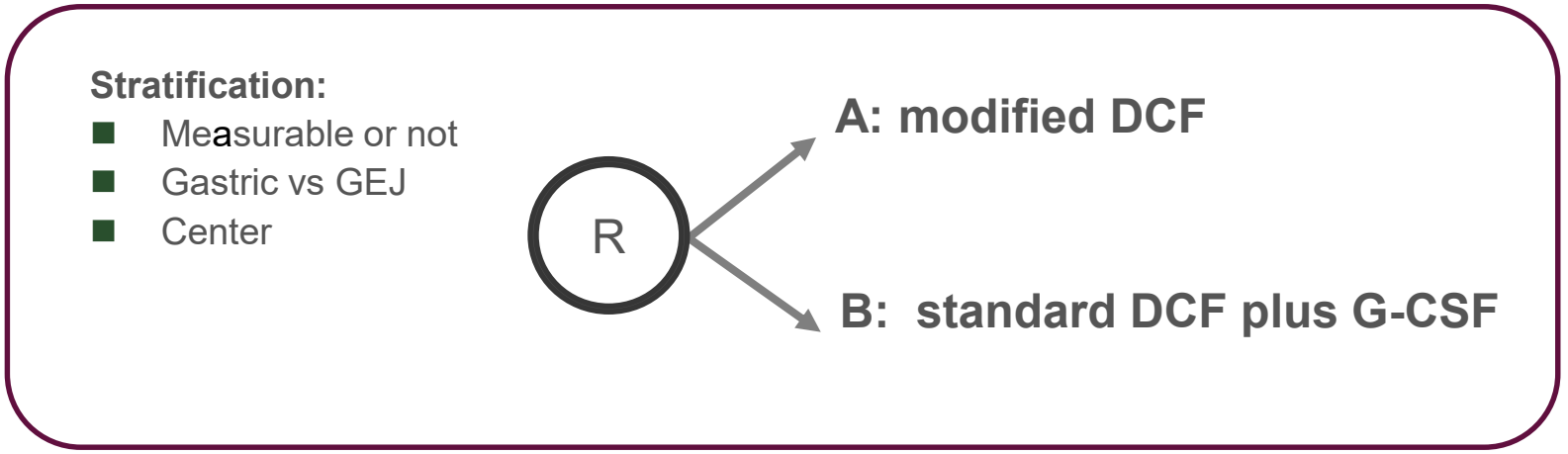
FFCD-GERCOR-FNCLCC 03-07 Phase III Study. FOLFIRI vs ECF in advanced gastric cancer

- **Objective II:** Response Rate (RR), PFS and OS

	ECF N=209	FOLFIRI n=207	p value
TTF (months)	4.2	5,1	0.008
RR 1st RR 2nd	39.2% 10.1%	37.8% 13.7%	n.s.
PFS (months) Median range	5.29 4.53-6.31	5.75 5.19-6.74	0.96
OS (months) Median range	9.49 8.77-11.14	9.72 8.54-11.27	0.95

Guimbaud R, et al. J Clin Oncol 2014;32:3520–3526

Phase II Study of modified DCF vs DCF plus G-CSF in advanced gastric cancer



- **Objective :** 6 months-PFS
- **Objectives II:**
  - RR, OS, Toxicity

Shah MA, et al. J Clin Oncol 2015;33:3874–3879

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Phase II Study of modified DCF vs DCF plus G-CSF in advanced gastric cancer

Table 1. Randomly Assigned Treatment

Drug	Dose (mg/m^2)	Schedule
Arm A (mDCF)		
Docetaxel	40	Day 1 IVPB (60 minutes)
Leucovorin	400	Day 1 IVPB (30 minutes)
Fluorouracil	400	Day 1 IVP
Fluorouracil	1,000 (per day)	IVCI daily × 2 days
Cisplatin	40	Day 2 or 3 IVPB (30 minutes)
Arm B (parent DCF plus G-CSF)		
Docetaxel	75	Day 1 IVPB (60 minutes)
Cisplatin	75	Day 1 IVPB (60 minutes)
Fluorouracil	750 (per day)	IVCI daily × 5 days
Neulasta*	6 mg	Subcutaneous on day 8, 9, or 10
Neupogen*	300 or 480 μg†	Subcutaneous × 7 days (days 10 to 17)

Shah MA, et al. J Clin Oncol 2015;33:3874–3879

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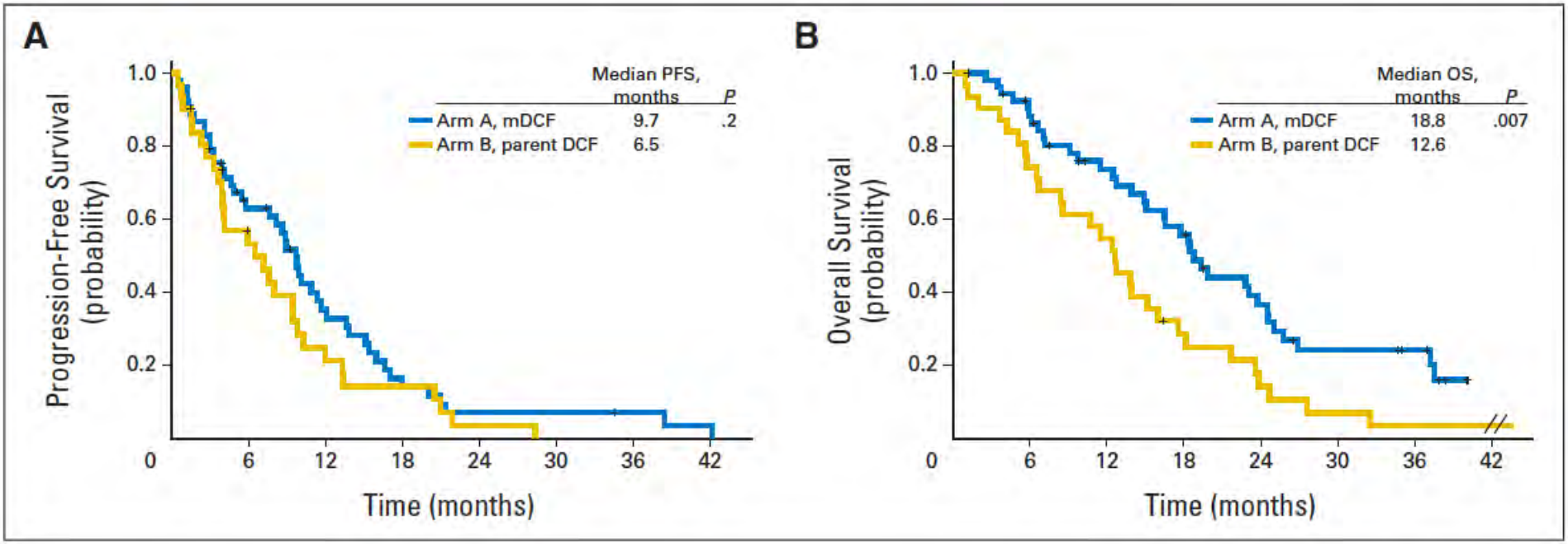
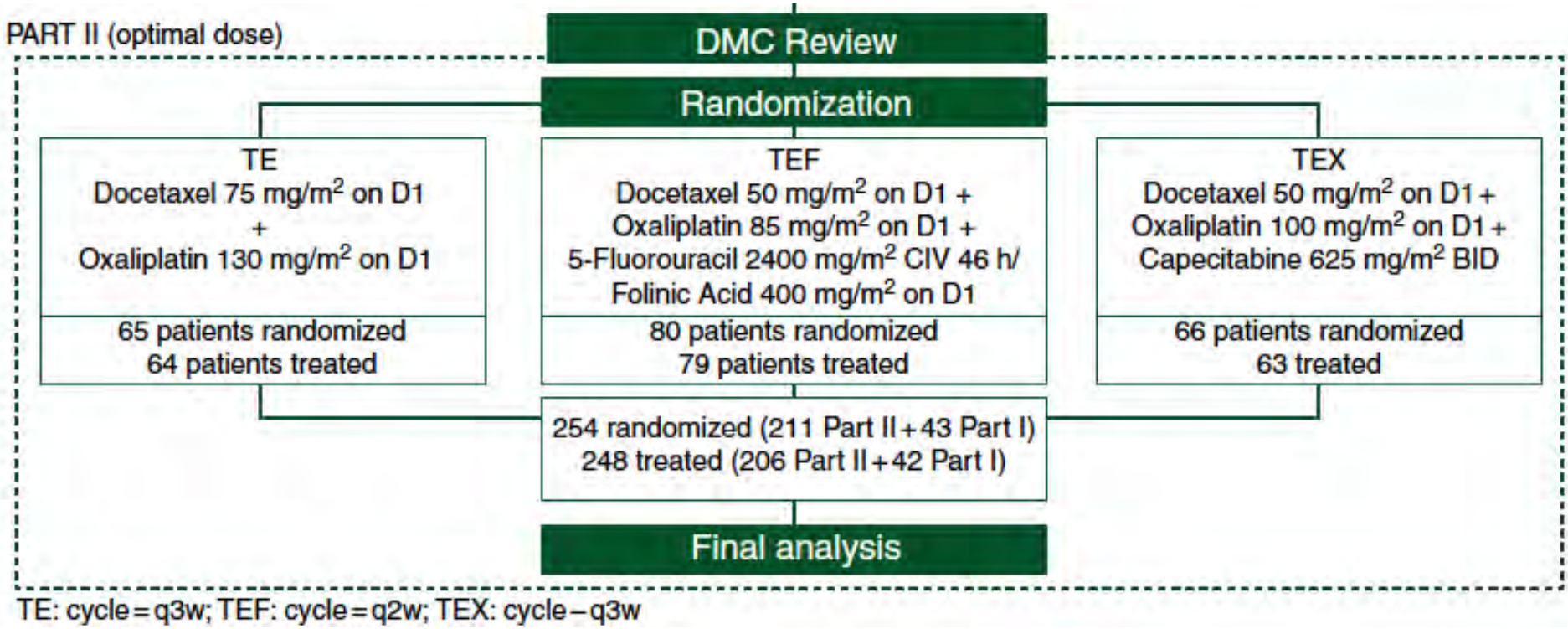
Phase II Study of modified DCF vs DCF plus G-CSF in advanced gastric cancer



Shah MA, et al. J Clin Oncol 2015;33:3874–3879

Docetaxel + Oxaliplatin + 5FU-LV/Capecitabine
TE vs TEF vs TEX



Van Cutsem E, et al. Ann Oncol 2015;26:149–156.

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Docetaxel + Oxaliplatin + 5FU-LV/Capecitabine TE vs TEF vs TEX

Treatment	Patients nr	RR %	95% CI	PFS months	95% CI	OS months	95% CI
TE	79	23,1	14,3-34,0	4,50	3,68-5,32	8,97	7,79-10,9
TEX	86	25,6	16,6-36,6	5,55	4,30-6,37	11,30	8,08-14,0
TEF	89	**46.6**	35,9-57,5	**7,66**	6,97-9,40	**14,59**	11,7-21,8

Van Cutsem E, et al. Ann Oncol 2015;26:149–156.

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Gastric cancer: Second line chemotherapy. Trials comparing BSC versus active treatment

Trial author	Year	Patients random (n)	Treatment	Response rate (%)	HR OS	P value	Gain in median survival
Thuss-Patience, et al.[1]	2011	40 1:1	Irinotecan	NR SD 58%	0.48	0.0023	2.4 months
Kang, et al.[2]	2012	193 2:1	Irinotecan Docetaxel	NR	0.65	0.004	1.3 months
Ford, et al.[3]	2014	168 1:1	Docetaxel	NR	0.67	0.01	1.6 months

1. Thuss-Patience PC, et al. Eur J Cancer 2011;47:2306–2314.
2. Kang JH, et al. J Clin Oncol 2012;30:1513–1518.
3. Ford HE, et al. Lancet Oncol 2014;15:78–86.

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Gastric cancer second line chemotherapy: Docetaxel vs BSC (COUGAR-02 Trial) is improving survival

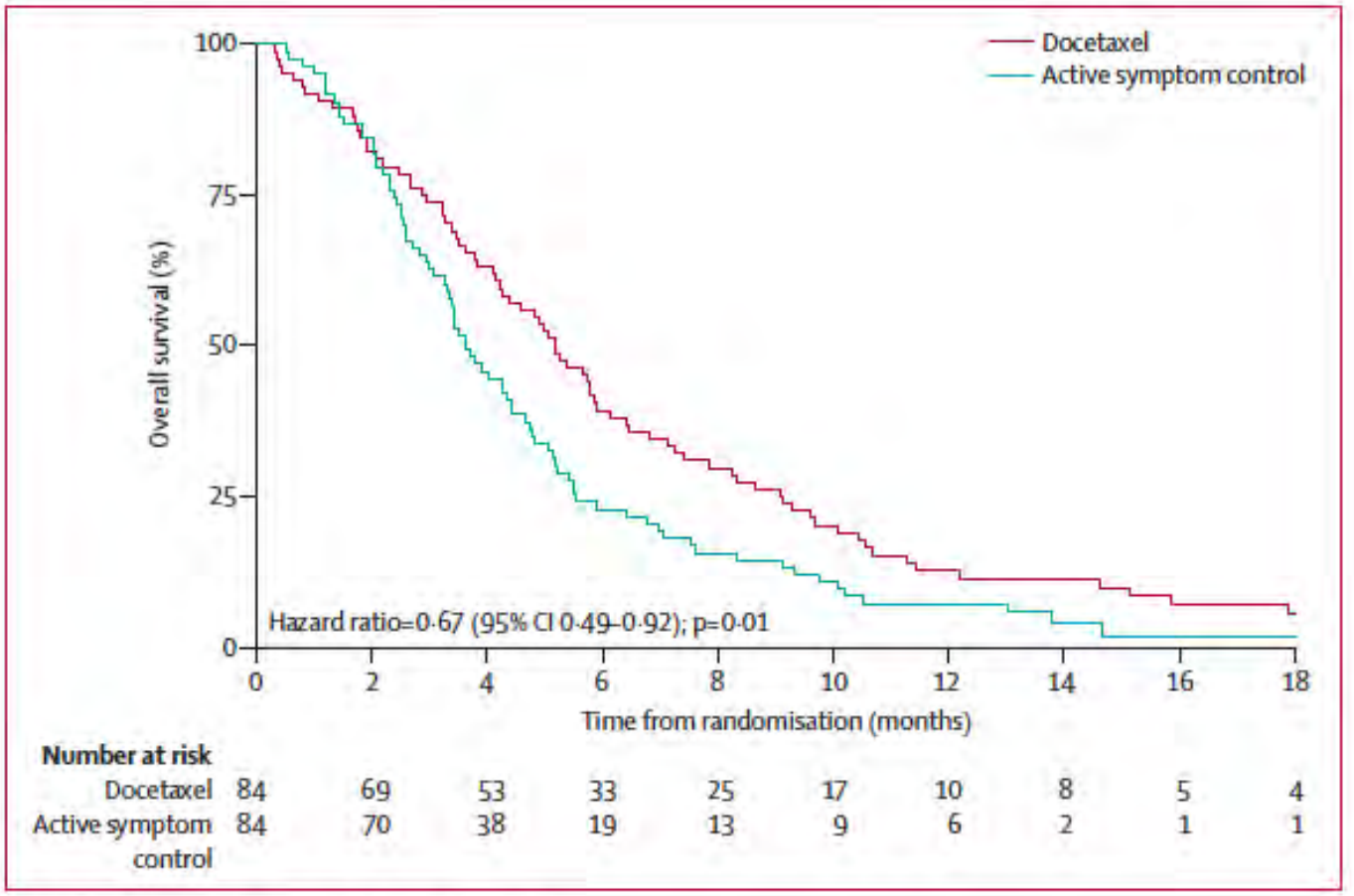

Figure 2: **Kaplan-Meier plot of overall survival**

Ford HE, et al. Lancet Oncol 2014;15:78-86.

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Gastric cancer: Second line chemotherapy trials comparing BSC versus active treatment

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Otshu, et al[4]	2013	656 2:1	Everolimus	0.90	0.124	0.9 months
Fuchs, et al[5]	2014	355 2:1	Ramucirumab	0.77	0.047	1.4 months

1. Thuss-Patience PC, et al. Eur J Cancer 2011;47:2306–2314. 2. Kang JH, et al. J Clin Oncol 2012;30:1513–1518.
3. Ford HE, et al. Lancet Oncol 2014;15:78–86. 4. Otshu A. et al. J Clin Oncol 2013;31:3935–3943. 5. Fuchs CS, et al. Lancet 2014;383:31–39.

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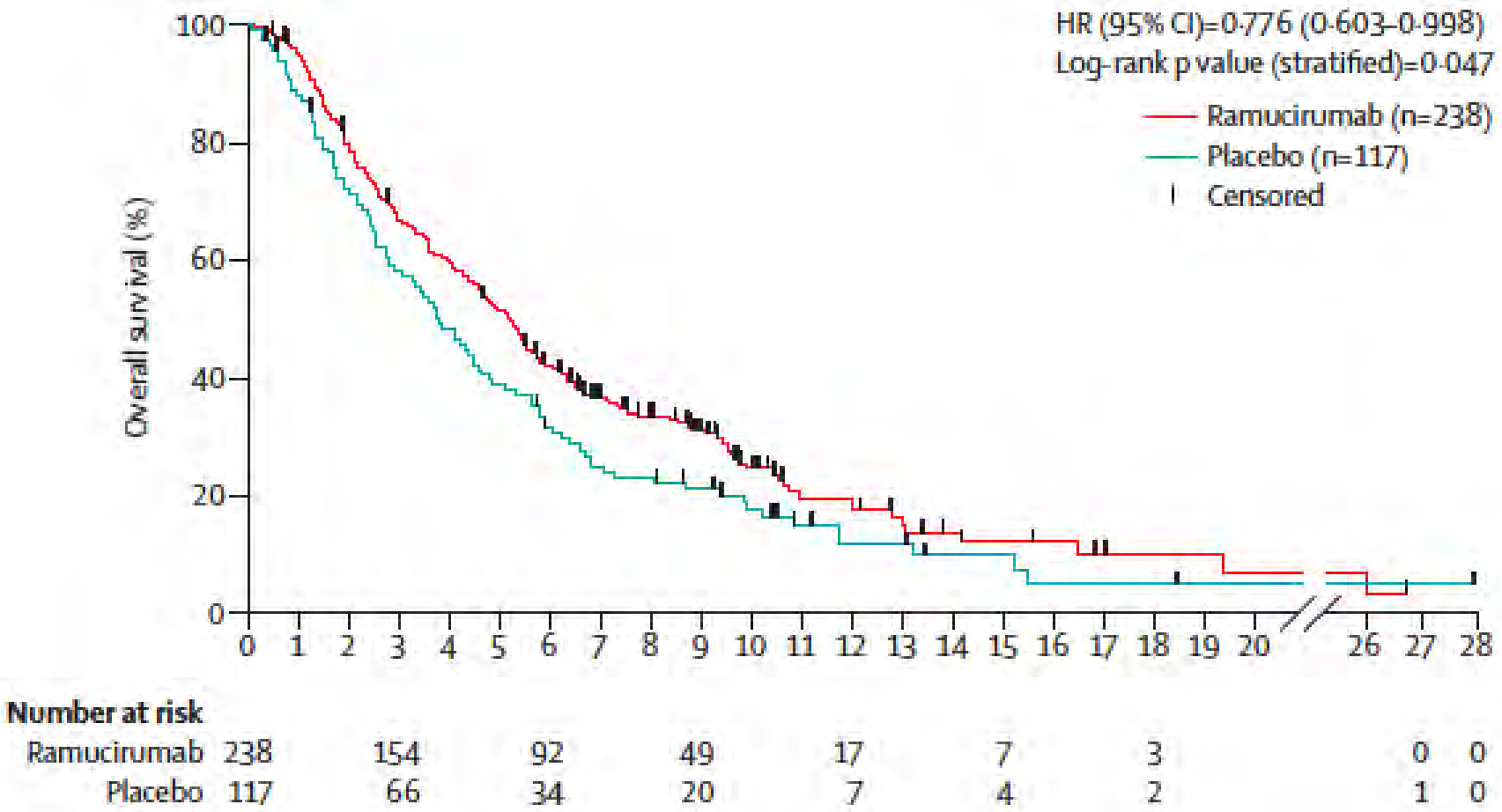
Gastric cancer second line treatment: Ramucirumab vs BSC (REGARD Trial) is improving survival



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Gastric cancer: Second line chemotherapy trials comparing two active treatments

Trial author	Year	Patients (n)	Treatment	HR OS	P value	Gain in median survival
Hironaka, et al.[1]	2013	223	Irinotecan vs paclitaxel	1.13	0.38	0.9 months for irinotecam
Wilke et al.[2]	2014	665	Paclitaxel+/- ramucirumab	0.80	0.017	2.2 months

1. Hironaka S, et al. J Clin Oncol 2013;31:4438–4444.
2. Wilke H, et al. Lancet Oncol 2014;15:1224–1235.

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Gastric cancer: Third or further line therapy randomized trials comparing with BSC or active treatment

Trial author	Year	Patients random (n)	Treatment	HR OS	P value	mOS and Gain in median survival
Tabernero, et al.[1] **KEYNOTE-061 Third line**	2018	507 2:1	**Trifluridine/Tipiracil** vs BSC	0.69	0.0003	5.7 vs 3.6 2.1 months
Bang, et al.[2] **JAVELIN 300 Third or further lines**	2018	371 1:1	**Avelumab** vs Investigator choice of Chemotherapy	1.10	ns	4.6 vs 5.0 -0.4 months
Kang, et al[3] **ATTRACTION-2 Third or further lines**	2017	493 2:1	**Nivolumab** vs BSC	0.63	0.0001	5.26 vs 4.14 1.12 months

1. Tabernero, J. et al. Ann Oncol 2018; 29(suppl_5) LBA nr.2 . 2. Bang YJ, et al. Ann Oncol 2018; doi: 10.1093/annonc/myd264
3. Kang JK, et al. Lancet 2017;390:2461-2471.

TAGS: TAS-102 Gastric Study[a]

Patients with mGC
(including GEJ cancer)
- ≥2 prior regimens:
  - Fluoropyrimidine
  - Platinum
  - Taxane and/or irinotecan
  - HER2 inhibitor, if available, for HER2+ disease
  - Refractory to/intolerant of last prior therapy
- ECOG PS of 0 or 1
- Age ≥18 y (≥20 y in Japan)

Target sample size: 500

R
2:1

FTD/TPI (TAS-102) + BSC
(n=337)
35 mg/m^2 BID orally on days 1–5 and 8–12 of each 28-day cycle

Placebo + BSC
(n=170)
BID orally on days 1–5 and 8–12 of each 28-day cycle

End points
- Primary:
  - OS
- Key secondary:
  - PFS, safety
- Other secondary:
  - ORR
  - DCR
  - QOL
  - Time to ECOG PS ≥2

- 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

Patient Disposition

	FTD/TPI	Placebo
ITT population, n (%)	337 (100)	170 (100)
Randomized, not treated, n	2	2
All treated patients, n (%)	335 (100)	168 (99)
Ongoing at data cutoff	19 (6)	3 (2)
Discontinued study treatment	316 (94)	165 (98)
Disease progression	255 (76)	147 (87)
AE	35 (10)	11 (7)
Withdrew consent, physician's decision, or protocol violation	26 (8)	7 (4)

AE, adverse event; ITT, intent-to-treat

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
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

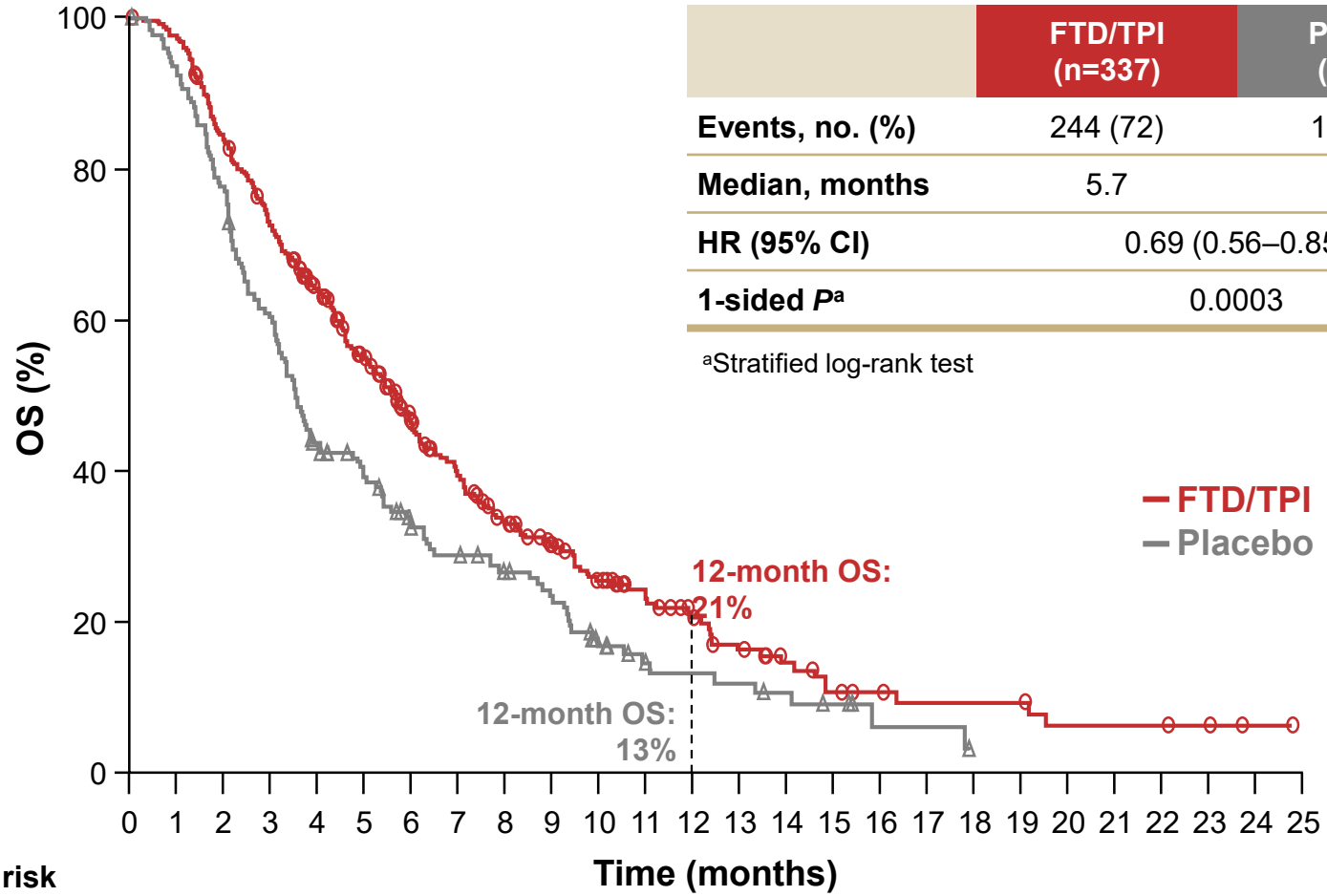
Baseline Disease Characteristics and Post-Study Therapy

		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

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

[a]1 patient did not receive a fluoropyrimidine; [b]All patients received irinotecan or taxane or both

Primary Endpoint – OS

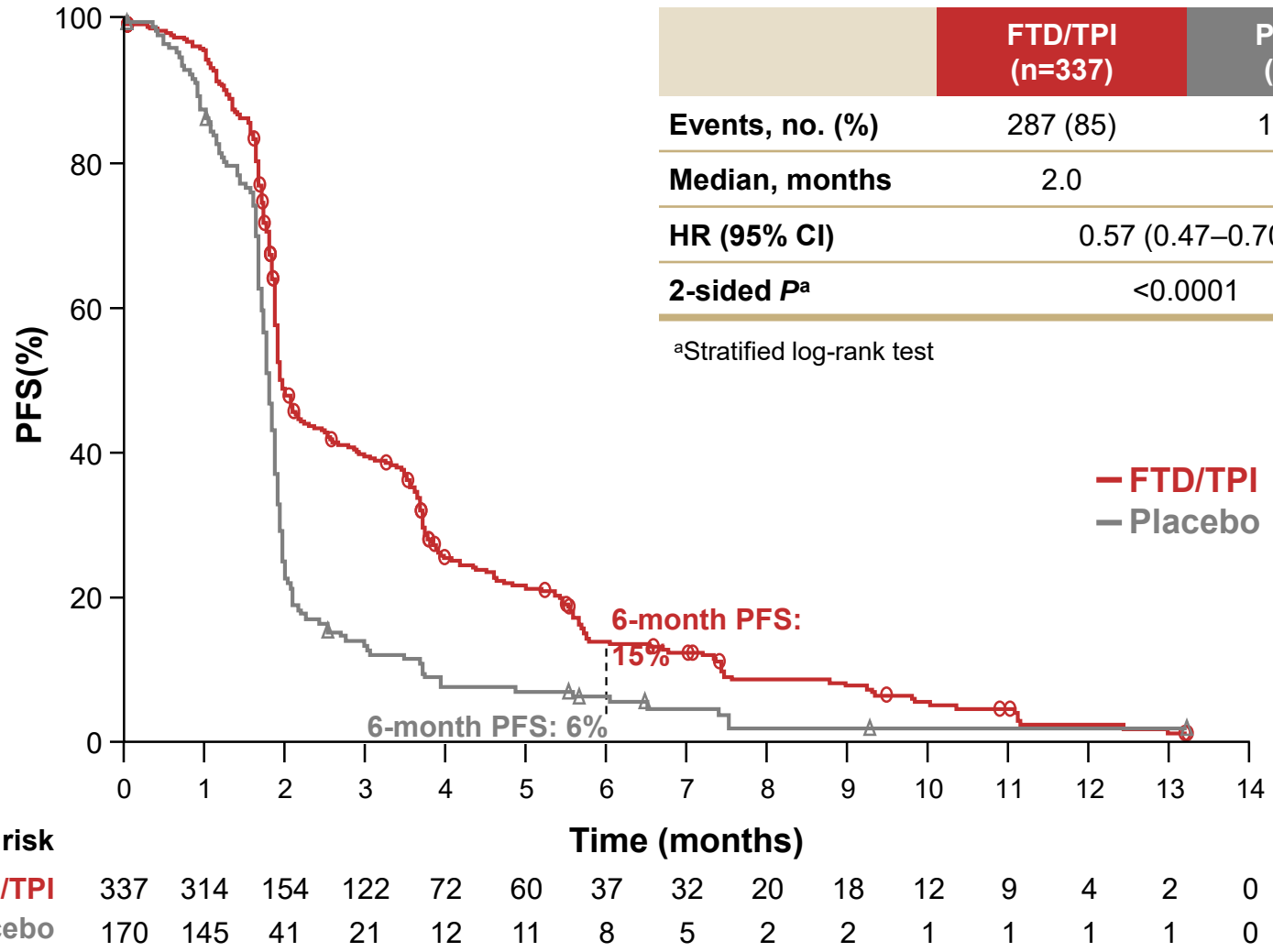


	FTD/TPI (n=337)	Placebo (n=170)
Events, no. (%)	244 (72)	140 (82)
Median, months	5.7	3.6
HR (95% CI)	0.69 (0.56–0.85)	
1-sided *P*[a]	0.0003	

[a]Stratified log-rank test

ITT population

Secondary Endpoint – PFS



	FTD/TPI (n=337)	Placebo (n=170)
Events, no. (%)	287 (85)	156 (92)
Median, months	2.0	1.8
HR (95% CI)	0.57 (0.47–0.70)	
2-sided *P*[a]	<0.0001	

[a]Stratified log-rank test

ITT population

Non-Hematologic AEs in >10% of Patients

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

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	Any grade %	Grade ≥3 %	Any grade %	Grade ≥3 %
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Constipation	13	1	15	2
Dyspnea	7	2	10	4
General physical deterioration	7	7	10	9

All treated patients

Hematologic Laboratory Abnormalities

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

[a]Treated patients with ≥1 post-baseline measurement

[b]Per 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

Conclusions for Flupiridine/Tipiracil

- 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 unilateral)
  - 2.1-month improvement in median OS (5.7 vs 3.6 months)
- FTD/TPI showed a predictable and manageable safety profile, consistent with that seen previously in patients with mCRC
  - No new safety signals were observed in patients with mGC
- FTD/TPI represents an effective treatment option with a manageable safety profile for patients with heavily pretreated mGC

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Advanced Gastric cancer: Conclusions

- Platinum-based chemotherapy as first option, with FOLFIRI as an alternative
- Triplets with Docetaxel in fit patients with excellent PS
- Alternative ways of delivering triplets available
- Second line chemotherapy also prolongs survival in good PS patients (Docetaxel, Irinotecan, Paclitaxel)
- Trifluridine/Tipiracil improves survival in third line
- These statements could also be valid for junctional and lower third esophageal adenocarcinoma