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5-fluorouracil and oxaliplatin +/- docetaxel in the 1st line treatment of HER2 negative locally advanced unresectable or metastatic gastric or gastro-esophageal junction adenocarcinoma: the phase III GASTFOX study (FFCD-PRODIGE 51)

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FFCD

PRODIGE
PARTENARIAT DE RECHERCHE EN ONCOLOGIE DIGESTIVE

DECLARATION OF INTERESTS

Aziz ZAANAN

Consulting or Advisory Role: Bristol Myers Squibb, MSD, Pierre Fabre, Havas Life, Alira Health, Zymeworks, Astra Zeneca, Daiichi Sankyo, Amgen, Astellas, Lilly, Merck, Roche, Sanofi, Servier, Bayer, BeiGene

Travel, Accommodations, Expenses: Bristol Myers Squibb, MSD, Servier, Pierre Fabre

Research Funding: Amgen, Roche

Background

First-line chemotherapy for unresectable locally advanced or metastatic gastric (G)/ gastroesophageal junction (GEJ) adenocarcinoma

- The preferred first-line (L1) chemotherapy regimen is the combination of a fluoropyrimidine (fluorouracil, capecitabine) and a platinum salt (cisplatin or oxaliplatin), such as FOLFOX regimen[1]

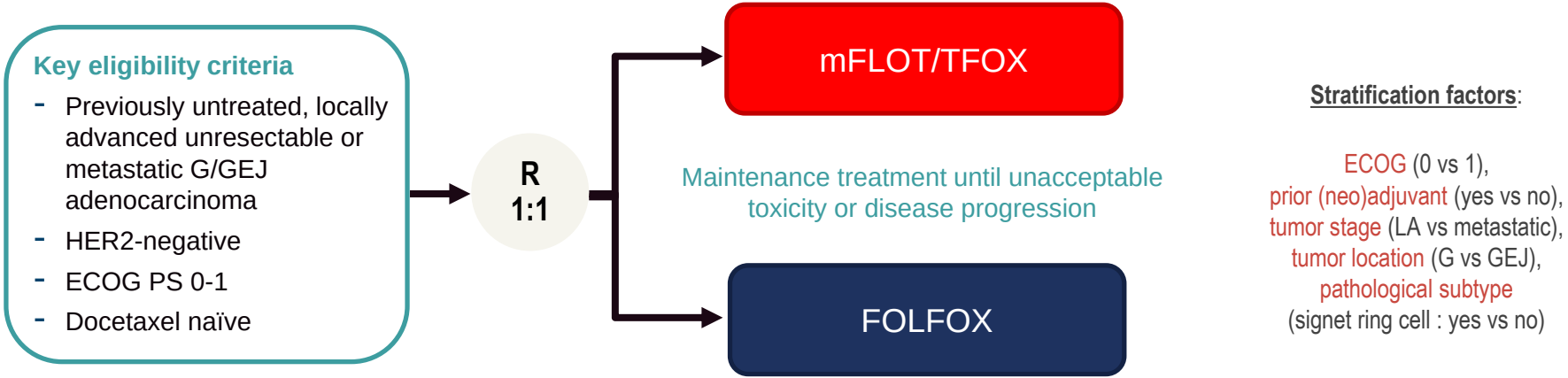
- The triplet FLOT chemotherapy, which is the standard of care for resectable disease[2], has shown promising results in phase II studies[3]

- GASTFOX study assessed the efficacy and safety of a modified FLOT regimen (=TFOX) as L1 in unresectable locally advanced or metastatic G/GEJ adenocarcinoma

(1) Lordick F, et al. Ann Oncol 2022;33:1005-1020. (2) Al-Batran SE, Lancet 2019;393:1948-1957.
(3) Al-Batran SE, et al. Ann Oncol. 2008;19:1882-7.

Study Design

Randomized, multicenter, academic, phase III trial



Stratification factors:

ECOG (0 vs 1),
prior (neo)adjuvant (yes vs no),
tumor stage (LA vs metastatic),
tumor location (G vs GEJ),
pathological subtype
(signet ring cell : yes vs no)

Recruitment period : between December 2016 and December 2022 (96 French cancer centers)

Data cutoff date for PFS and OS analysis : June 2023

Median follow up : 42.8 months

Tumor response assessment by investigator per RECIST v1.1. **LA**, locally advanced; **G**, gastric; **GEJ**, gastroesophageal junction
mFLOT/TFOX: docetaxel 50 mg/m^2, oxaliplatin 85 mg/m^2, folinic acid 400 mg/m^2, 5FU continuous at 2.400 mg/ m^2 46h (**q2w)**
FOLFOX: oxaliplatin 85 mg/m^2, folinic acid 400 mg/m^2, 5FU bolus 400 mg/m^2 followed by 5FU continuous at 2.400 mg/ m^2 46h (**q2w)**

mFLOT/TFOX regimen

Q2W	FOLFOX	mFLOT/TFOX [1]	FLOT [2-3]
Docetaxel	-	50 mg/m^2	50 mg/m^2
Oxaliplatin	85 mg/m^2	85 mg/m^2	85 mg/m^2
5FU bolus	400 mg/m^2	-	-
5FU continuous	2400 mg/m^2 /46h	2400 mg/m^2 /46h	2600 mg/m^2 /24h

(1) Van Cutsem E, ..., Rougier P. Ann Oncol 2015;26: 149-156.
(2) Al-Batran SE, et al. Ann Oncol 2008;19:1882-7. (3) Al-Batran SE, Lancet 2019;393:1948-1957

Statistical Considerations

Primary endpoint :

- progression-free survival (ITT)

Based on a two-sided alpha risk of 5%, a power of 90%, and an expected HR=0.733 in favor to mFLOT/TFOX, 454 events were required

Secondary endpoint :

- PFS on per-protocol (PP) population
- overall survival (ITT and PP)
- objective response rate
- safety & quality of life

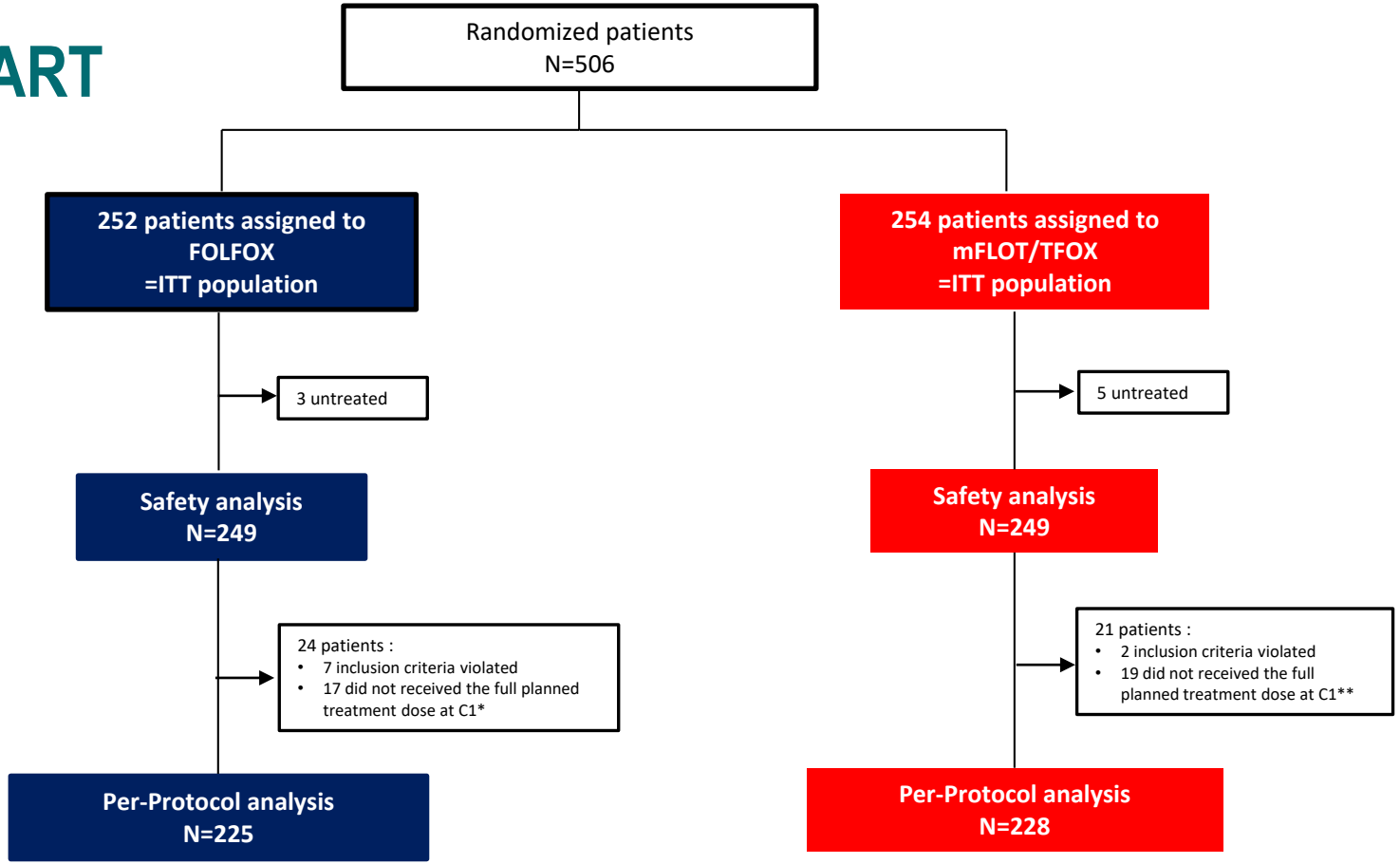
For survival outcomes, HR and 95% CI were estimated by a Cox proportional hazard model.

The Hazard Ratio is appropriate when the HR is constant over the entire study period, and if not, it may be misleading to use the HR model [1-2]

In that case, the restricted mean survival time (RMST), which is the mean survival time up to a specific time point, is more reliable to quantify the survival difference between arms [3-4]

(1) Liang F, Ann Oncol 29:1320–1324, 2018. (2) Pak K et al, JAMA Oncol. 2017;3(12):1692-1696.
(3) Andre T, N Engl J Med 2020; 383:2207-2218. (4) Conroy T, ASCO 2023 prodige 23_LBA3504

FLOW CHART



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* FOLFOX arm: 17 did not received the full planned treatment dose at C1: 0% of the dose on at least one chemotherapy drugs for 3 pts; between 0% and 50% for 4 pts; between 50% and 90% for 10 pts; ** mFLOT/TFOX arm: 19 did not received the full planned treatment dose at C1: 0% of the dose on at least one chemotherapy drugs for 4 pts; between 0% and 50% for 1 pts; between 50% and 90% for 14 pts

BASELINE CHARACTERISTICS

		mFLOT/TFOX N=254	FOLFOX N=252
Age, years (range)	Median	64.55 (31.7-86.7)	63.91 (25.6-84.7)
Sex, n (%)	Male	205 (80.7)	193 (76.6)
ECOG PS, n (%)	0 1	107 (42.1) 147 (57.9)	108 (42.9) 144 (57.1)
Primary tumor location, n (%)	Stomach GEJ	111 (43.7) 143 (56.3)	108 (42.9) 144 (57.1)
Disease stage, n (%)	Metastatic Locally advanced Unknown	245 (96.5) 9 (3.5) 0 (0)	242 (96.0) 8 (3.2) 2 (0.8)
Histological subtype (SRCC), n (%)	Yes No	89 (35.0) 165 (65.0)	88 (34.9) 164 (65.1)
Organs with metastases, n (%)	0-1 ≥2	126 (49.6) 128 (50.4)	133 (52.8) 119 (47.2)
Prior adjuvant/neoadjuvant trt, % (n)		11 (4.3)	20 (7.9)

ECOG PS Eastern Cooperative Oncology Group performance status; **GEJ** gastroesophageal junction; **SRCC** signet ring cell carcinoma

Tumor response analysis

	mFLOT/TFOX N=254	FOLFOX N=252
Evaluable patients[a], n (%)	237 (93.3%)	235 (93.2%)
ORR[b], % (95% CI)	**66.2** (59.8-72.4)	**57.5** (50.9-63.9)
	P=0.04	
Best overall response, n (%)		
CR	16 (6.7%)	19 (8.1%)
PR	141 (59.5%)	116 (49.4%)
SD	62 (26.2%)	60 (25.5%)
PD	18 (7.6%)	40 (17.0%)
Disease control rate, % (95% CI)	**92.4** (88.3-95.4)	**83.0** (77.7-87.6)
	P=0.02	

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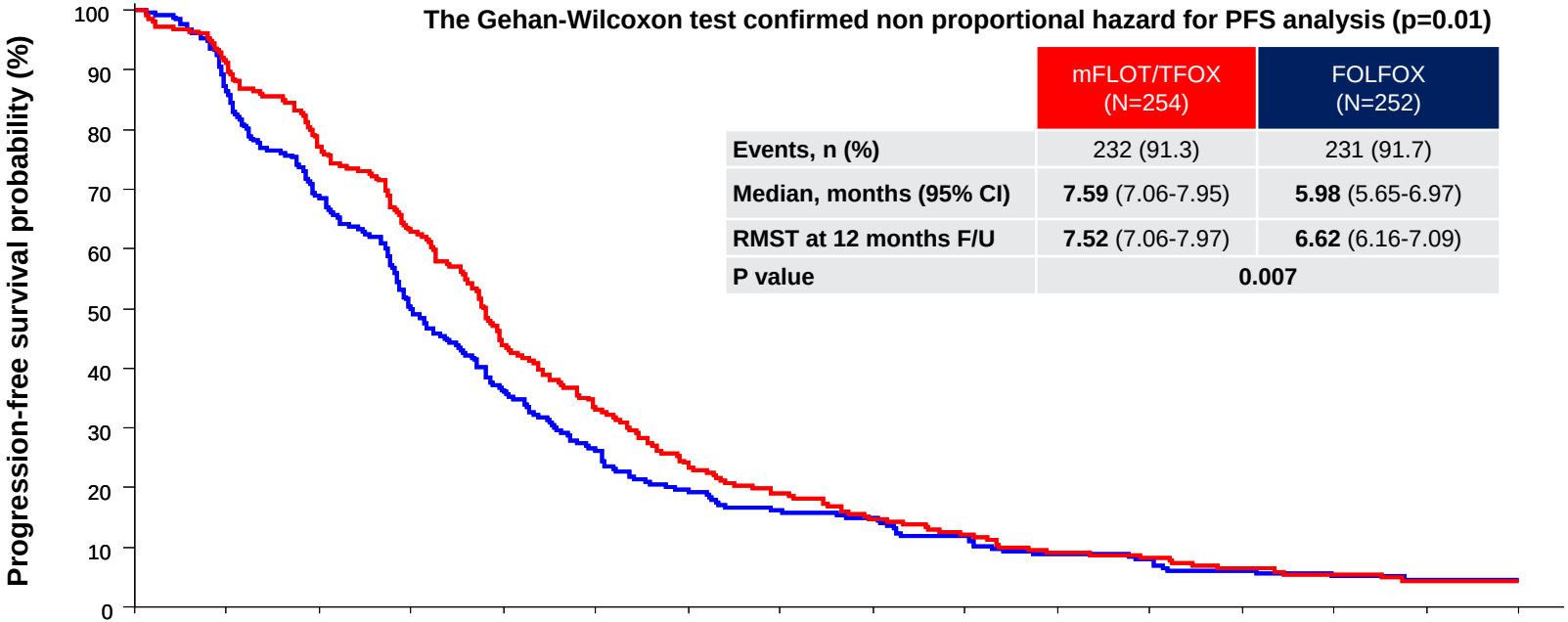
[a]Patients with measurable disease according RECIST criteria version 1.1; Non evaluable patients included those who had postbaseline tumor assessment but without measurable disease, or patients who had no postbaseline tumor assessments due to death, withdrawal of consent, lost to follow up, or any other reasons. [b]ORR is defined as the percentage of patients with CR/PR. P value was evaluated by Chi-Square.
ORR, Objective response rate; **CR** complete response; **PD** progressive disease; **PR** partial response; **SD** stable disease.

Progression-free survival

Intention-to-treat (ITT)

The Gehan-Wilcoxon test confirmed non proportional hazard for PFS analysis (p=0.01)

	mFLOT/TFOX (N=254)	FOLFOX (N=252)
Events, n (%)	232 (91.3)	231 (91.7)
Median, months (95% CI)	**7.59** (7.06-7.95)	**5.98** (5.65-6.97)
RMST at 12 months F/U	**7.52** (7.06-7.97)	**6.62** (6.16-7.09)
P value	**0.007**	



N at risk

FOLFOX	252	217	173	123	87	61	45	37	34	27	20	18	12	10	8	8
mFLOT/TFOX	254	228	191	153	106	78	56	45	34	28	21	18	13	11	9	8

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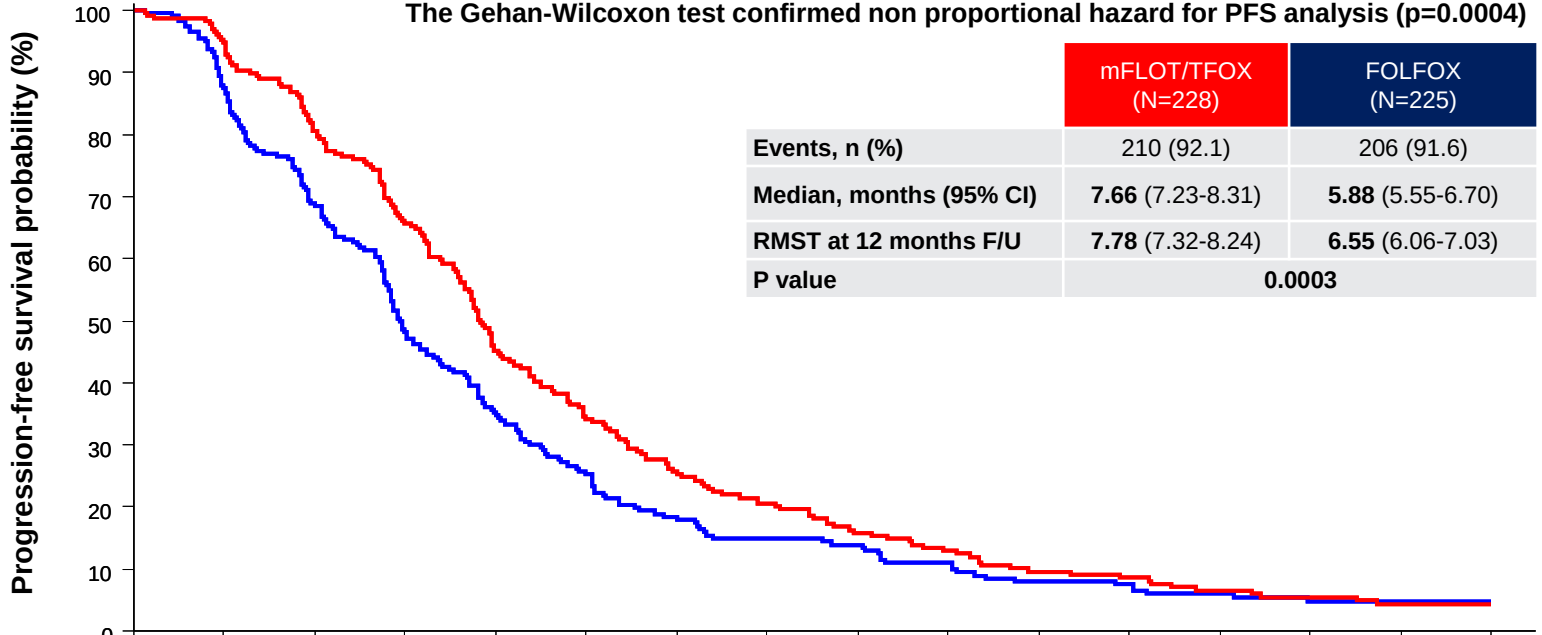
RMST, Restricted mean survival time (mean survival time up to a specific endpoint).
The 12 months time point was chosen to reflect the patients'median PFS follow-up (F/U)

Progression-free survival

Per-protocol (PP)

The Gehan-Wilcoxon test confirmed non proportional hazard for PFS analysis (p=0.0004)

	mFLOT/TFOX (N=228)	FOLFOX (N=225)
Events, n (%)	210 (92.1)	206 (91.6)
Median, months (95% CI)	**7.66** (7.23-8.31)	**5.88** (5.55-6.70)
RMST at 12 months F/U	**7.78** (7.32-8.24)	**6.55** (6.06-7.03)
P value	**0.0003**	



N at risk

FOLFOX	225	197	155	106	75	52	37	30	28	22	16	15	10	8	7	7
mFLOT/TFOX	228	215	181	145	99	73	55	44	33	27	20	17	12	10	8	8

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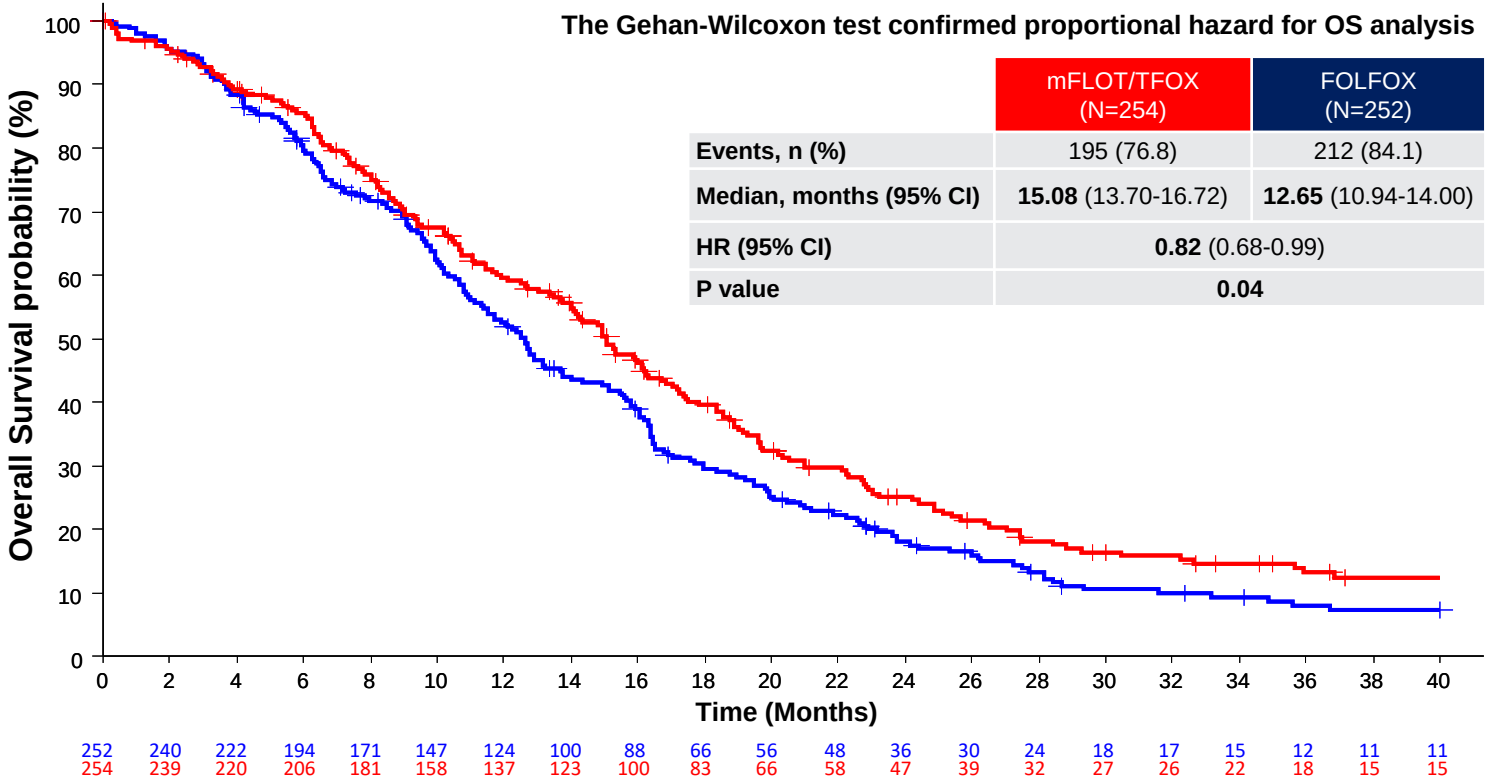
RMST, Restricted mean survival time (mean survival time up to a specific endpoint).
The 12 months time point was chosen to reflect the patients'median PFS follow-up (F/U)

Overall survival

Intention-to-treat (ITT)



The Gehan-Wilcoxon test confirmed proportional hazard for OS analysis

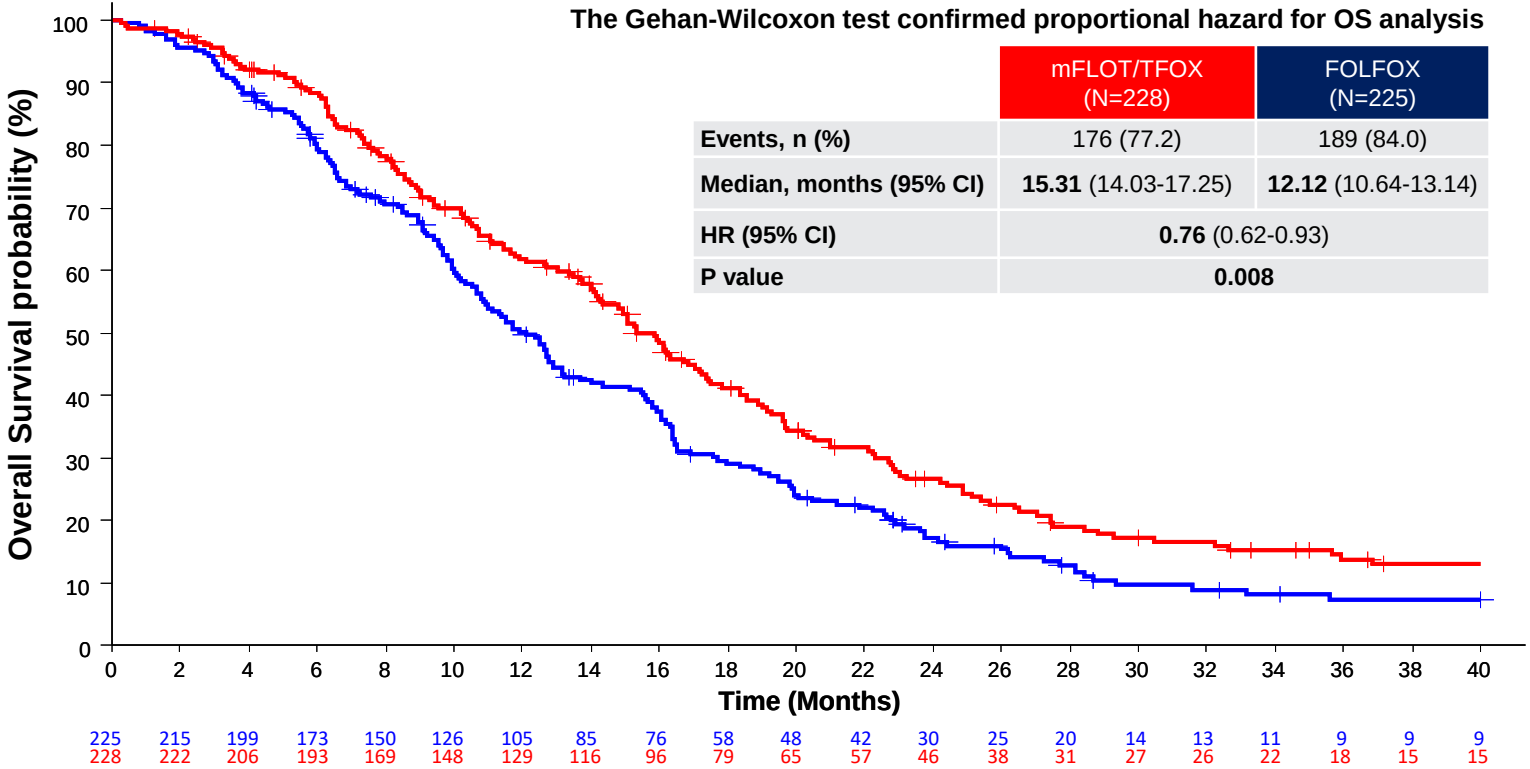
	mFLOT/TFOX (N=254)	FOLFOX (N=252)
Events, n (%)	195 (76.8)	212 (84.1)
Median, months (95% CI)	**15.08** (13.70-16.72)	**12.65** (10.94-14.00)
HR (95% CI)	**0.82** (0.68-0.99)	
P value	**0.04**	

N at Risk

FOLFOX	252	240	222	194	171	147	124	100	88	66	56	48	36	30	24	18	17	15	12	11	11
mFLOT/TFOX	254	239	220	206	181	158	137	123	100	83	66	58	47	39	32	27	26	22	18	15	15

Overall survival

Per-protocol (PP)



The Gehan-Wilcoxon test confirmed proportional hazard for OS analysis

	mFLOT/TFOX (N=228)	FOLFOX (N=225)
Events, n (%)	176 (77.2)	189 (84.0)
Median, months (95% CI)	**15.31** (14.03-17.25)	**12.12** (10.64-13.14)
HR (95% CI)	**0.76** (0.62-0.93)	
P value	**0.008**	

N at Risk

FOLFOX	225	215	199	173	150	126	105	85	76	58	48	42	30	25	20	14	13	11	9	9	9
mFLOT/TFOX	228	222	206	193	169	148	129	116	96	79	65	57	46	38	31	27	26	22	18	15	15

Most common Treatment-Emergent Adverse Events (TEAEs) Reported in ≥20% of patients

	mFLOT/TFOX (N=249)			FOLFOX (N=249)			P value* (difference grade 3-4)
	Grade 1-2 N (%)	Grade 3 N (%)	Grade 4 N (%)	Grade 1-2 N (%)	Grade 3 N (%)	Grade 4 N (%)	
Hematologic							
Anemia	168 (67.5)	15 (6.0)	3 (1.2)	154 (61.8)	7 (2.8)	3 (1.2)	NS
Thrombocytopenia	115 (46.2)	6 (2.4)		134 (53.8)	7 (2.8)		NS
Neutropenia	44 (17.7)	45 (18.1)	20 (8.0)	68 (27.3)	33 (13.3)	11 (4.4)	0.02
Febrile neutropenia	-	7 (2.8)		-	4 (1.6)		NS
Non Hematologic							
Peripheral neuropathy	127 (51.0)	79 (31.7)		161 (64.7)	47 (18.9)	2 (0.8)	0.02
Diarrhoea	146 (58.6)	32 (12.9)	4 (1.6)	83 (33.3)	16 (6.4)		0.03
Nausea	153 (61.4)	10 (4.0)		143 (57.4)	11 (4.4)		NS
Vomiting	99 (39.8)	12 (4.8)		70 (28.1)	8 (3.2)		NS
Stomatitis	79 (31.7)	3 (1.2)	1 (0.4)	53 (21.3)	1 (0.4)		NS
Fatigue	174 (69.9)	38 (15.3)		164 (65.9)	18 (7.2)		0.005
Toxic death †	-	2 (<1)		-	1 (<1)		NS

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Toxicity was evaluated on the safety set population.
† Toxic death was defined as a chemotherapy-related toxicity resulting in death.
***** P value : difference in grade 3-4 toxicities between mFLOT/TFOX and FOLFOX was evaluated by Chi-Square

Conclusions

- mFLOT/TFOX demonstrated statistically significant and clinically meaningful improvement in PFS, OS, and ORR versus FOLFOX in patients with advanced HER2 negative G/GEJ adenocarcinomas

- Safety profile of mFLOT/TFOX was manageable and consistent with prior studies

mFLOT/TFOX can be considered as a new 1L treatment option for patients eligible for a triplet regimen

- At least for patients with PD-L1 and CLDN18.2 negative tumors
- Next step : mFLOT/TFOX + immunotherapy or zolbetuximab (GASTFOX-2 trial)

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  - Statistical analysis : K. Le Malicot

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