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#1402 MO Evaluating Pathological response to guide adjuvant FLOT chemotherapy in gastroesophageal cancer (SPACE-FLOT)

LBA 60 Phase 3 study of SHR-1701 versus placebo in combination with chemo as first-line (1L) therapy for HER2-negative gastric/gastroesophageal junction adenocarcinoma (G/GEJA)

Assoc. Prof. Radka Lordick Obermannová, MD, PhD

Masaryk Memorial Cancer Institute, Brno, Czech Republic

MO Masaryk Memorial Cancer Institute

DECLARATION OF INTERESTS

Dr Radka Lordick Obermannová, PhD

Lectures and consulting: BMS, Merck, MSD, Servier, GSK, Astellas
Research support for the institution: Roche
Employment and membership in societies:
Masaryk Memorial Cancer Institute, Department of Comprehensive Cancer
EORTC (Lead of the Task Force of oesophageal and gastric cancer within the EORTC GI Tract)
CZECRINonco (Chair of Academic Clinical Trials Network)

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Evaluating Pathological response to guide adjuvant FLOT chemotherapy in gastroesophageal cancer (SPACE-FLOT)

An international cohort study of real-world data

Margaret Lee
On behalf of the SPACE-FLOT investigators
Melbourne, Australia

Can pathological response to neoadjuvant FLOT guide adjuvant FLOT therapy based upon survival outcomes stratified by TRG?

SPACE-FLOT is an international cohort study of real-world data

43 Hospitals
12 Countries

Australia
New Zealand
England
Ireland
Sweden
France
Italy
Netherlands
India
Malaysia
Singapore
Canada

Eligible Population
N=1887

- Non metastatic GEJ/gastric adenocarcinoma
- Neoadjuvant FLOT chemotherapy
- Curative resection

Minimal pathological response N=459	Adjuvant FLOT N=272
	No adjuvant N=187
Partial pathological response N=1207	Adjuvant FLOT N=847
	No adjuvant N=360
Complete pathological response N=221	Adjuvant FLOT N=136
	No adjuvant N=85

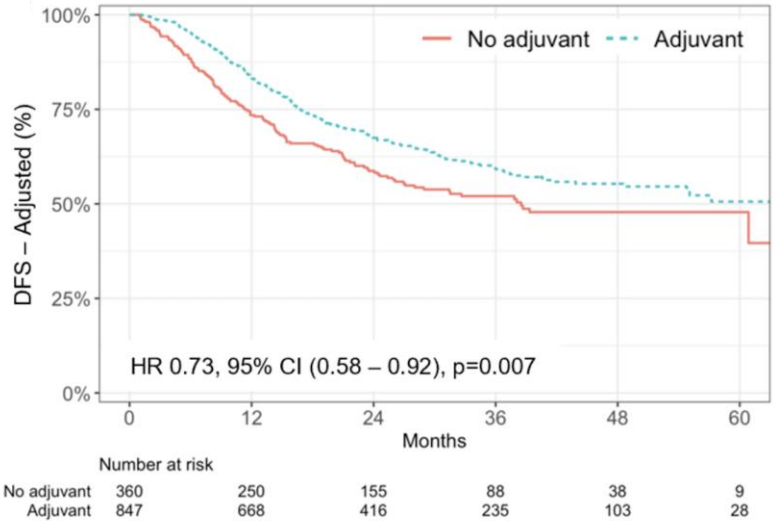
Endpoints and Statistical Considerations

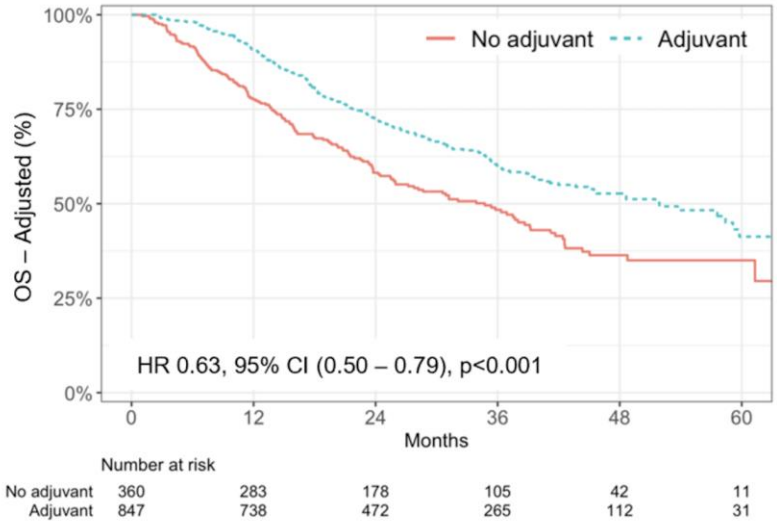
- Primary: DFS
- Powered for 15% difference in 2-year DFS across all three TRG categories
- Secondary: OS
- DFS and OS with log-rank and multivariate Cox-regression analysis
- Propensity score matched analysis

Radka Lordick Obermannová

Results

Partial Pathological Response to Neoadjuvant FLOT

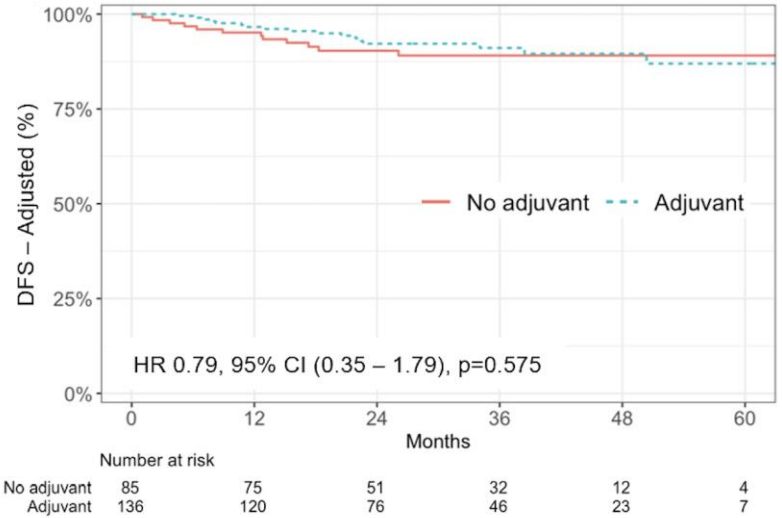


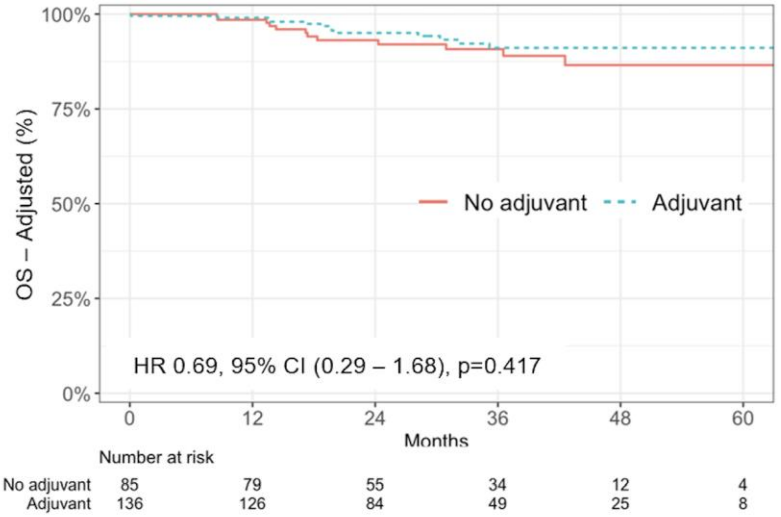


- Adjuvant FLOT provided a **significant improvement in DFS and OS** for partial responders
- Findings validated with propensity score matched analysis

Results

Complete Pathological Response to Neoadjuvant FLOT

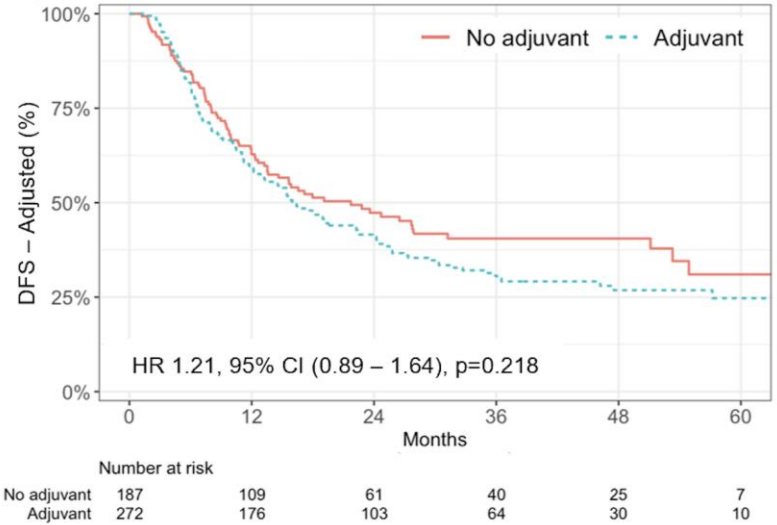


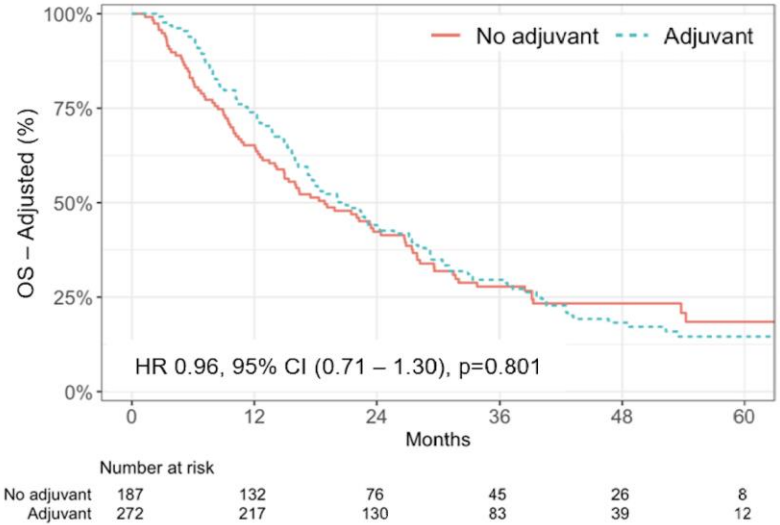


- Adjuvant FLOT **did not improve DFS and OS** for complete responders
- Findings validated with propensity score matched analysis

Results

Minimal Pathological Response to Neoadjuvant FLOT





- Adjuvant FLOT **did not improve DFS or OS** for minimal responders
- Findings validated with propensity score matched analysis

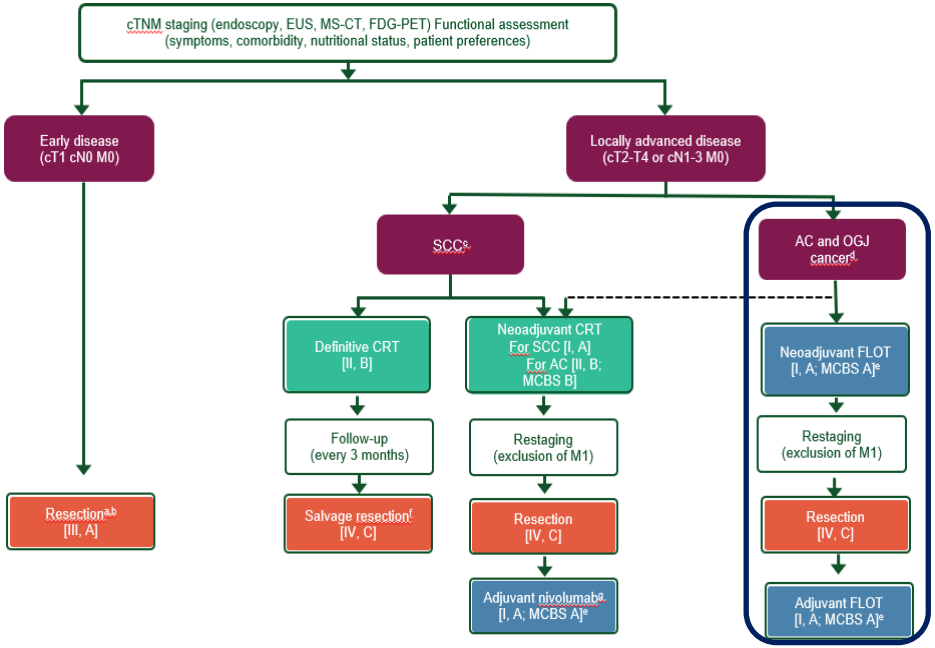
Potential implications for clinical practice

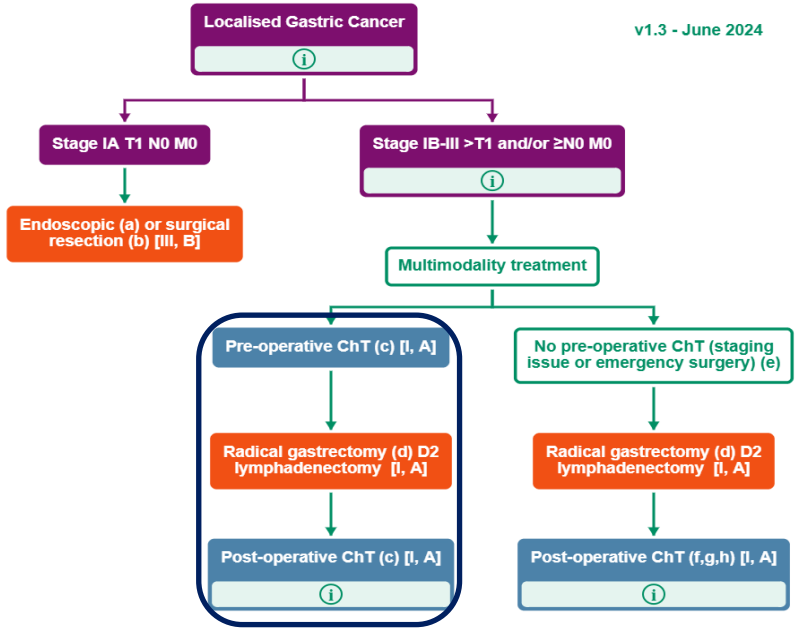
Pathological Response	Adjuvant FLOT Benefit	Recommendations based on SPACE-FLOT
Complete pathological response	No DFS/OS benefit	Consider no adjuvant FLOT
Partial pathological response	DFS/OS benefit	Strongly support adjuvant FLOT
Minimal pathological response	No DFS/OS benefit	Consider no adjuvant FLOT

Can we use this suggestion for our daily practice?

Treatment standard for localized GEJ/G cancer

ESMO GUIDELINES

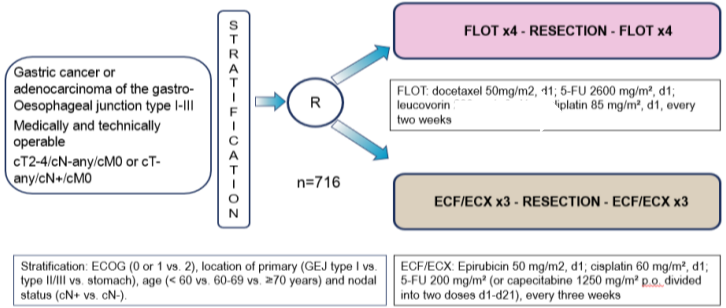


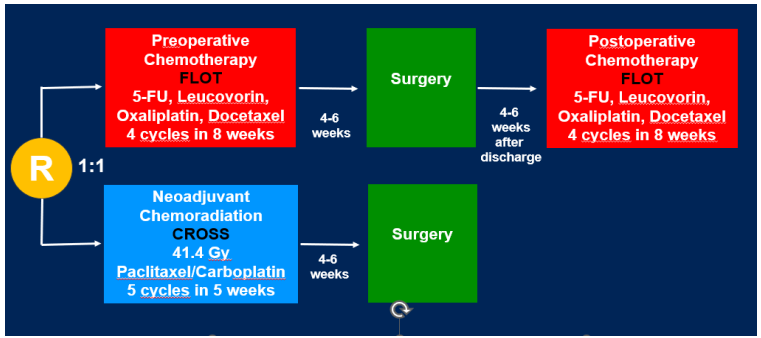


Obermannová R et al eUPdate 2024: In progress
Lordick F et al. https://www.esmo.org/living-guidelines/esmo-gastric-cancer-living-guideline

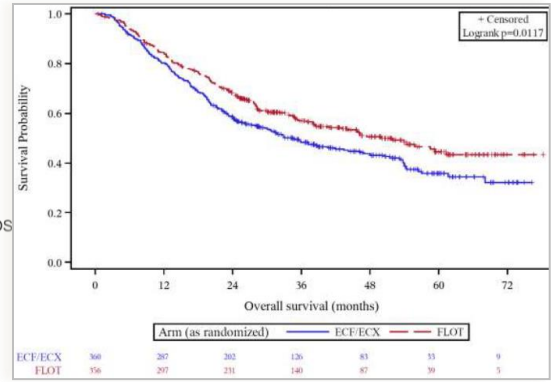
Treatment standard for localized GEJ/G cancer

FLOT-4 and ESOPEC

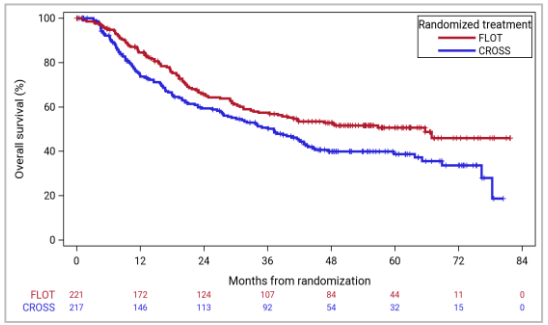




Primary endpoint OS (ITT)



Projected OS rates		
	ECF/X	FLOT
2 year	59%	68%
3 year	48%	57%
5 year	36%	45%



	FLOT	CROSS
Events	97	121
Median OS(mo)	66	37
3-year OS rate	57.4%	50.7%
5-year OS rate	50.6%	38.7%

Al Batran SE et al. The Lancet, 2019; Hoeppner J et al. # LBA 1 ASCO 2024

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Can we use this suggestion for our daily practice?

- Study design
- Baseline characteristics
- Standardisation of treatment evaluation
- TRG evaluation

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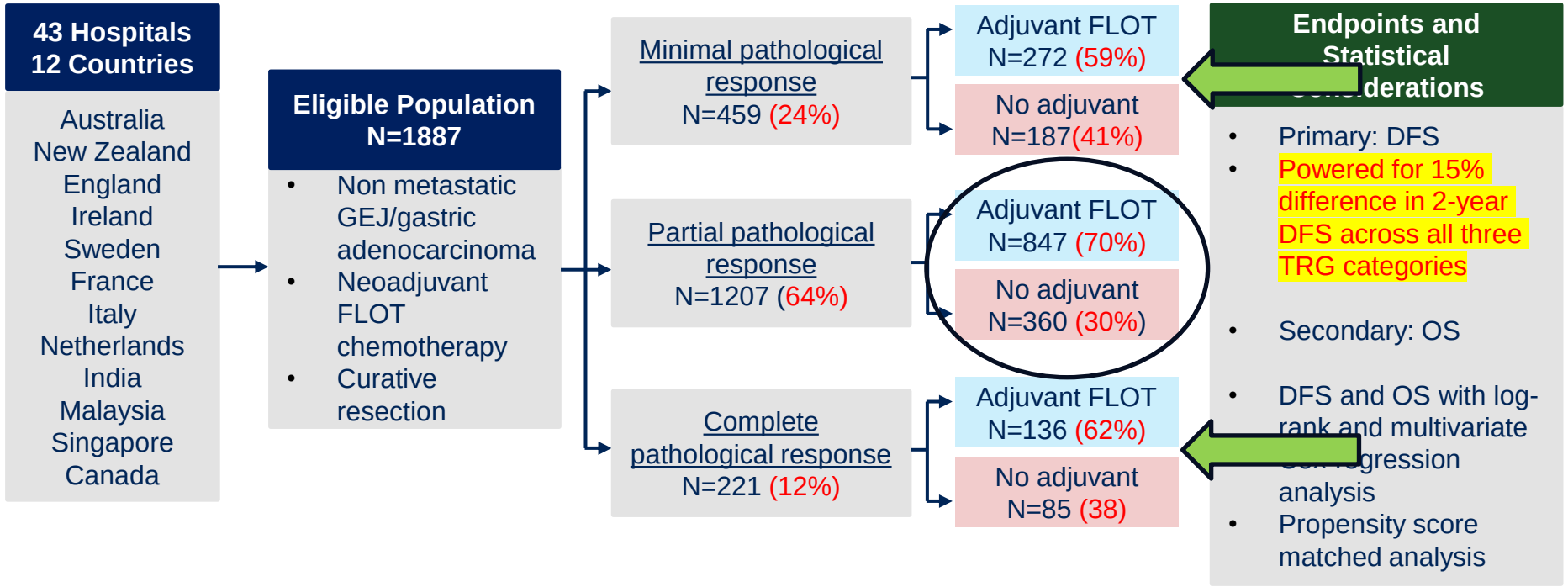
Can we used the real data to take treatment decision after surgery?

STUDY DESIGN



*Gastric only)

Can we use this suggestion for our daily practice?

- Study design
- Baseline characteristics
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- TRG evaluation

Can we used the real data to take treatment decision after surgery?

BASELINE CHARACTERISTICS

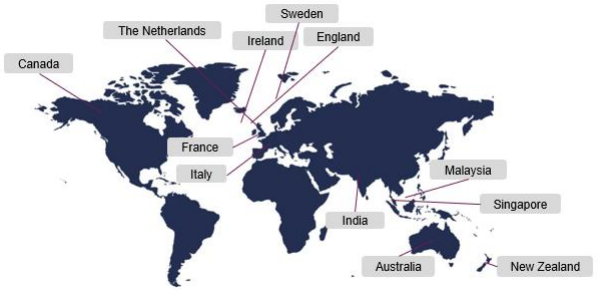
		Adjuvant FLOT N=1255	No adjuvant N=632	p-value
Age, mean (years)		61.6	65.6	<0.001
Male, N (%)		941 (75.0)	475 (75.2)	0.955
Charlson Co-morbidity Index, median (IQR)		2 (1-3)	3 (2-4)	<0.001
ECOG at time of surgery, median (IQR)		0 (0-1)	0 (0-1)	0.003
Completed neoadjuvant FLOTx4, N (%)		1127 (89.8%)	437 (69.1)	<0.001
Primary tumor location, N (%)	GEJ	733 (58.4)	450 (71.2)	<0.001
	Gastric	522 (41.6)	182 (28.8)	
Histology type*, N (%)	Intestinal	343 (27.3)	161 (25.5)	0.349
	Diffuse	251 (20.0)	95 (15.0)	
	Mixed/unspecified	661 (52.7)	376 (59.5)	
cT status, N (%)	cT1	58 (4.6)	21 (3.3)	0.220
	cT2-3	1016 (81.0)	531 (84.0)	
	cT4	181 (14.4)	80 (12.7)	
cN+ status, N (%)		640 (4.6)	333 (3.3)	0.495
ECOG at recurrence, median (IQR)		1 (0-2)	1 (1-2)	<0.001

Can we use this suggestion for our daily practice?

- Study design
- Baseline characteristics
- Standardisation of treatment evaluation
- TRG evaluation

TRG evaluation

- The main issues on the histopathologic evaluation of TRG:
- Intra-and inter-observer variability
- Lack of uniform protocol
- No validated biomarker



Summary of TRG systems

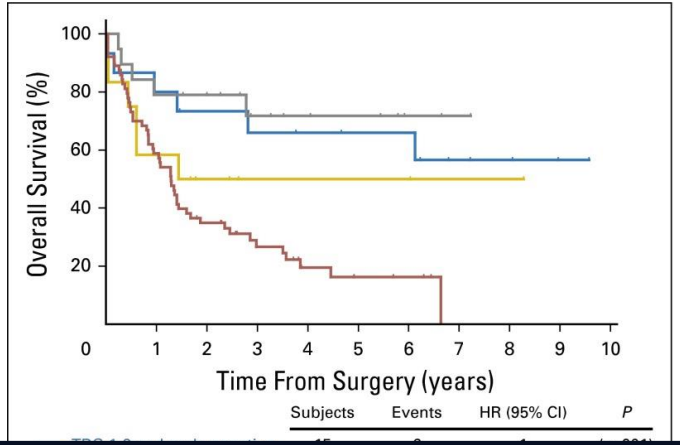
Regression grade	Relation between tumor and fibrosis			Proportion of residual tumor	
	Mandard	Dworak	Ryan	Becker	JGCA
Complete	TRG1; no residual cancer cell, total fibrosis	TRG4; no tumor cells, only fibrotic mass		TRG1a; 0% residual tumor	TRG3; 0% residual tumor
Subtotal	TRG2; rare residual cancer cells, scattered through the fibrosis	TRG3; difficult to find tumor cells microscopically, which scattered in fibrotic tissue	TRG1; no or rare residual cancer cells	TRG1b; <10% residual tumor	TRG2; 1–33% residual tumor
Partial	TRG3; more residual cancer cells, but outgrown by fibrosis	TRG2; easy to find tumor cells microscopically, with dominantly fibrotic changes	TRG2; more residual cancer cells	TRG2; 10–50% Residual tumor	TRG1b; 34–66% residual tumor
No response	TRG4; residual cancer cells outgrowing fibrosis TRG5; absence of regressive changes	TRG1; dominant tumor mass with obvious fibrosis TRG0; no regression	TRG3; residual cancer cells outgrowing fibrosis or no regression	TRG3; >50% residual tumor	TRG1a; >67% residual tumor TRG0; 100% residual tumor

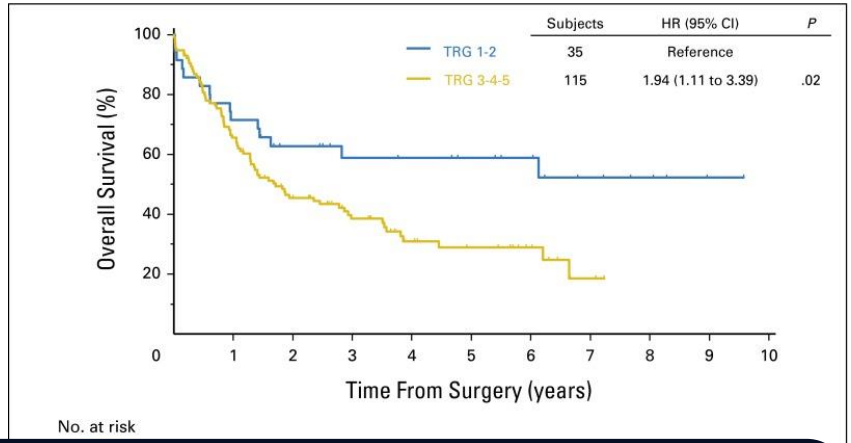
TRG, tumor regression grade; JGCA, Japanese Gastric Cancer Association.

Garbarino GM et al Digestive Medicine Research, 2023;6:2.

Can pathological response to ChT guide adjuvant therapy based on survival outcomes stratified by TRG?

Results from Phase III MAGIC TRIAL





Lymph node metastases and not pathologic response to chemotherapy was the only independent predictor of survival after chemotherapy plus resection in the MAGIC trial.

What did we learn from FLOT-4 and ESOPEC?

Postoperative	FLOT	ESOPEC
Node-positive (N+)	51%	48.7%
R1 resection	16%	5.2%
Pts at high risk of recurrence	67%	53.9%

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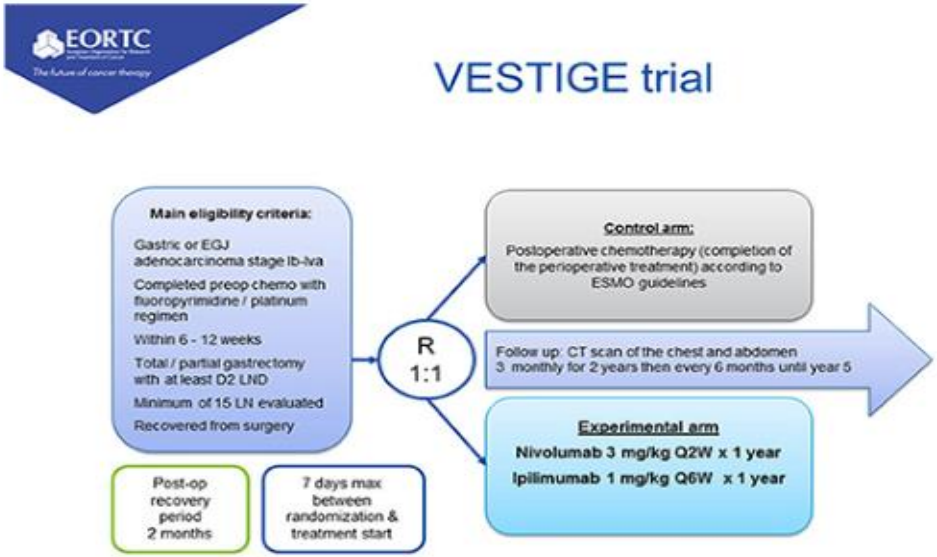
Al Batran SE et al. The Lancet, 2019; Hoeppner J et al. # LBA 1 ASCO 2024

EORTC 1707 VESTIGE study

Adjuvant immunotherapy for high-risk patients (ypTN+ and or R1), phase II study



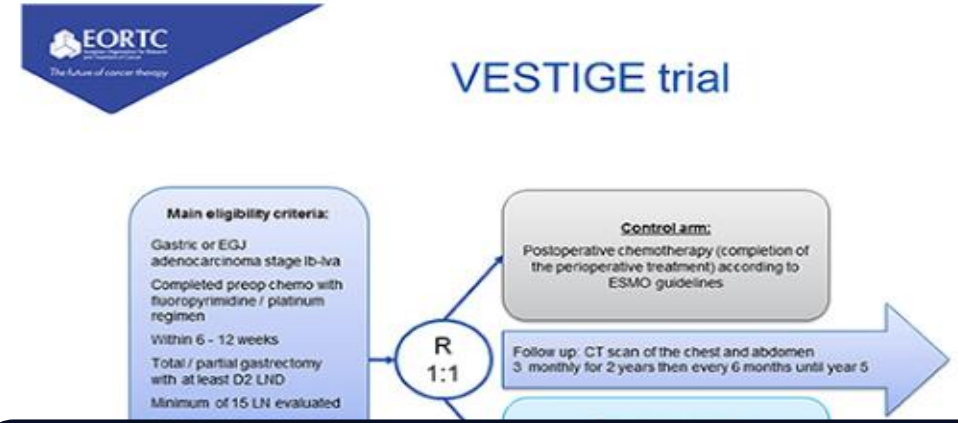
Primary objective: DFS in patients with AJCC 8th edition stage Ib-IVa gastric and esophagogastric (EG) junctional adenocarcinoma

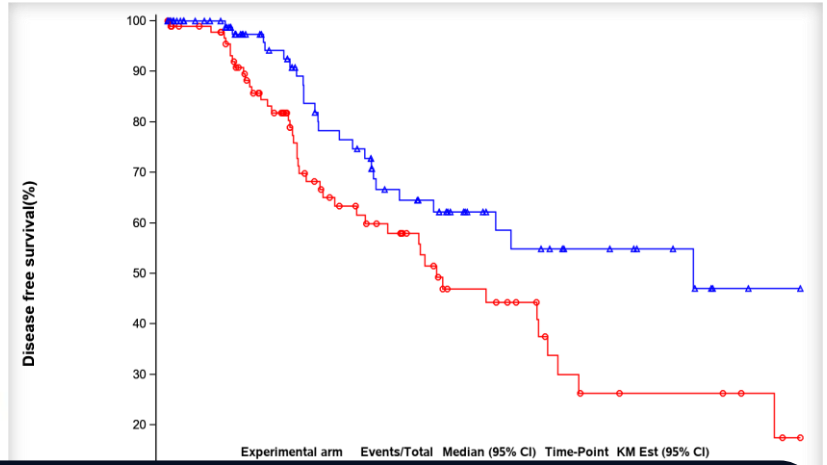
Patient population: high risk of recurrence (defined by ypN1-3 and/or R1 status) following neoadjuvant chemotherapy and resection.

Smyth EC et a. Front. Oncol., Sec. Gastrointestinal Cancers Vol: 9 - 2019

EORTC 1707 VESTIGE study

Adjuvant immunotherapy for high-risk patients (ypTN+ and or R1), phase II study





Data from EORTC 1707 Vestige suggest that patients
with poor prognosis (ypN+or R1) following neoadjuvant FLOT benefit from adjuvant FLOT

Smyth EC et a. Front. Oncol., Sec. Gastrointestinal Cancers Vol: 9 - 2019
Smyth EC et. al. Annals of Oncology, 2023, ISSN: 0923-7534, Vol: 34, S182-S183

Can we use this suggestion for our daily practice?

- Study design

„Retrospective, not based on randomized comparison but on RWE“

- Baseline characteristics

„Imbalances in important prognostic factors"

- Standardisation of treatment evaluation

„No standardized response evaluation,TRG is not a validated biomarker“

- Diagnostic and surgical approach

„Differences between center standards and expertise“

- Powered for a 15% difference in 2-year DFS across all three TRG categories

„In terms of statistics, they may have missed smaller but clinically meaningful differences“

Conclusion

Pathological Response	Adjuvant FLOT Benefit	Recommendations based on SPACE-FLOT
Complete pathological response	No DFS/OS benefit	Consider no adjuvant FLOT „Questionnable“
Partial pathological response	DFS/OS benefit	Strongly support adjuvant FLOT
Minimal pathological response	No DFS/OS benefit	Consider no adjuvant FLOT Adjuvant FLOT based on EORTC VESTIGE still seems to be the best option

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Phase 3 study of SHR-1701 versus placebo in combination with chemo as first-line (1L) therapy for HER2-negative gastric/gastroesophageal junction adenocarcinoma (G/GEJA)

Zhi Peng[1], Jufeng Wang[2], Yanqiao Zhang[3], Hongli Li[4], Qun Zhao[5], Xiaodong Zhu[6], Shaozhong Wei[7], Ying Cheng[8], Wenhui Yang[9], Jun Yao[10], Mingjun Zhang[11], Lin Xie[12], Xizhi Zhang[13], Ping Zhao[14], Changlu Hu[15], Jingdong Zhang[16], Zhigao Wang[17], Wenliang Wang[17], Hongxia Han[17], Lin Shen[1]*

*Leading Principal Investigator

[1]Department of Gastrointestinal Oncology, Key laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital & Institute, Beijing, China; [2]Department of Digestive Diseases 2, Henan Cancer Hospital, Zhengzhou, China; [3]Gastroenterology Department, Harbin Medical University Cancer Hospital, Harbin, China; [4]Gastrointestinal Medical Oncology, Tianjin Medical University Cancer Institution & Hospital, Tianjin, China; [5]Third Department of Surgery, The Fourth Hospital of Hebei Medical University, Shijiazhuang, China; [6]Medical oncology, Fudan University Shanghai Cancer Center, Shanghai, China; [7]Gastrointestinal Surgery, Hubei Cancer Hospital, Wuhan, China; [8]Department of Medical Oncology, Jilin Cancer Hospital, Changchun, China; [9]Gastroenterology Department, Shanxi Cancer Hospital, Taiyuan, China; [10]Oncology Department, The First Affiliated Hospital of Henan University of Science and Technology, Luoyang, China; [11]Oncology Department, The Second Hospital of Anhui medical university, Hefei, China; [12]Gastrooncology Department, Yunnan Cancer Hospital & Third Affiliated Hospital of Kunming Medical University, Kunming, China; [13]Oncology Department, North Jiangsu People's Hospital, Yangzhou, China; [14]Gastrointestinal Surgery, Sichuan Cancer Hospital, Chengdu, China; [15]Department of Chemotherapy Oncology, Anhui Provincial Hospital, Hefei, China; [16]Department of Digestive Diseases 2, Liaoning Cancer Hospital and Institute, Shenyang, China; [17]Clinical Research & Development, Jiangsu Hengrui Pharmaceuticals Co., Ltd., Shanghai, China

Dual inhibition of TGF-β and PD-L1: a novel approach to cancer treatment

Rationale for dual target: bispecific antibody

- Only 20% of tumours respond to anti-PD-L1 treatment in the long term
- TGF-β signaling in the TME is associated with resistance to anti-PD-L1 therapies

- In a preclinical studies, blockade of TGF-β signaling:
  - reduced the number of immunosuppressive regulatory T cells,
  - increased the number of effector T cells, and restored sensitivity to anti–PD-L1 therapy

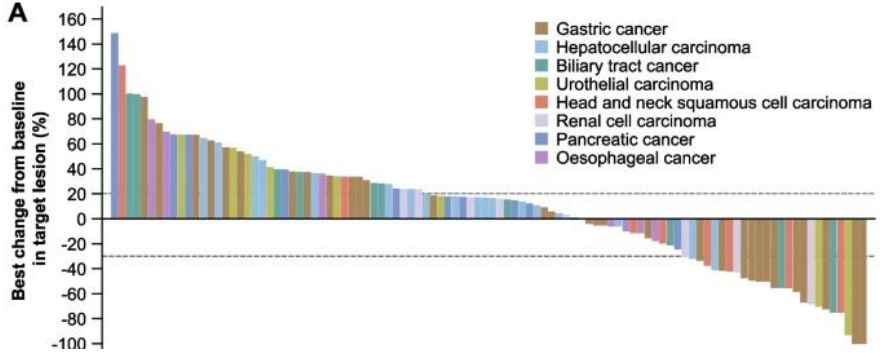
SHR-1701 is a bifunctional fusion protein composed of an IgG4 monoclonal antibody targeting PD-L1 fused with the extracellular domain of the TGF-β receptor II.

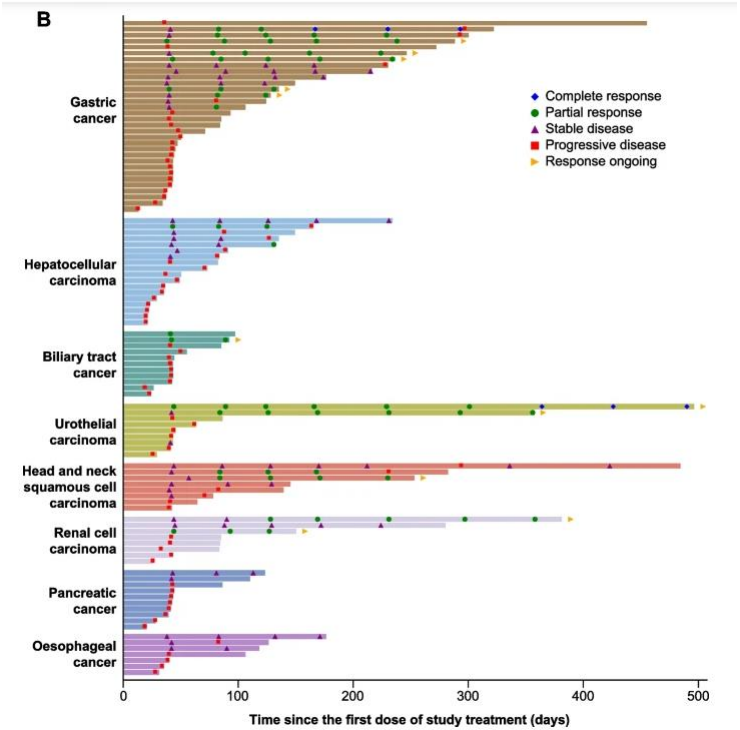
Gulley JL, et al. Mol Oncol. 2022; 16: 2117–2134
Pan W, et al. Int J Oral Sci. 2019 Nov 5;11(3):30

SHR- 1701 in phase I gastric cancer cohort

No DLT in MTD assessment

Fig. 2





The most favorable efficacy was shown in the GC cohort, with an ORR of 20.0% (95% CI, 8.4–36.9) per RECIST v1.1 and 25.7% (95% CI, 12.5–43.3) per iRECIST.

Liu, D., Zhou, J., Wang, Y. et al. BMC Med 20, 408 (2022)

SHR- 1701 treatment related adverse events

Phase I Study

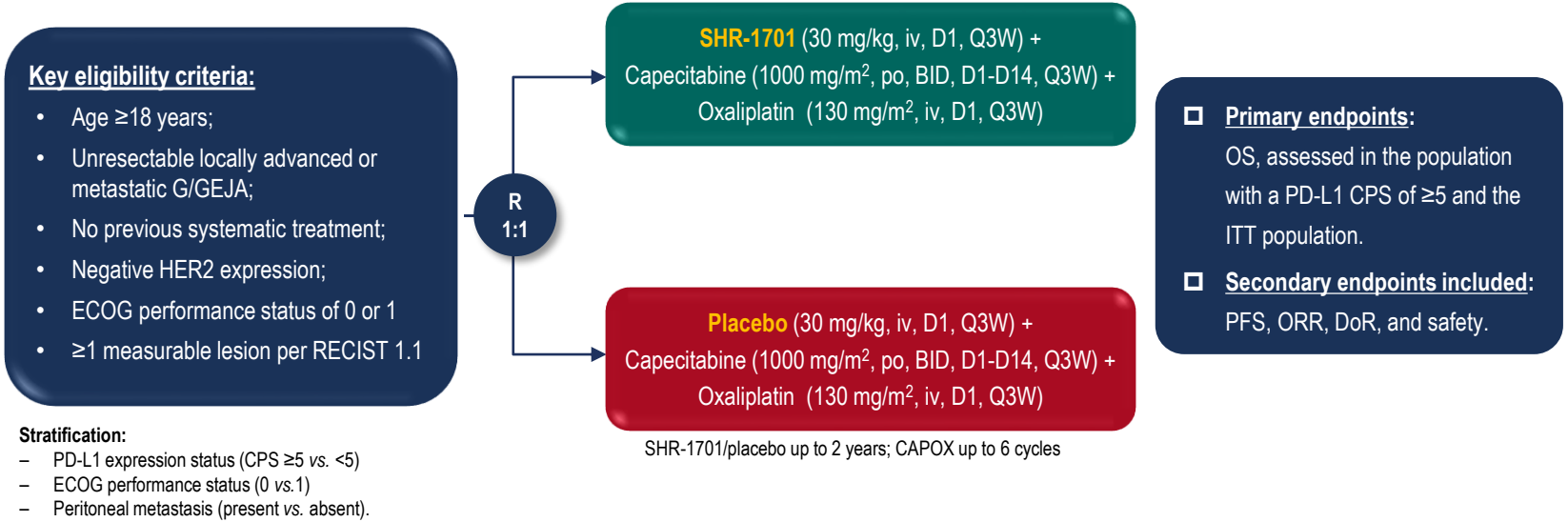
	All patients (*N*=171)				
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Any	120 (70%)	34 (20%)	49 (29%)	27 (16%)	7 (4%)
Aspartate aminotransferase increased	40 (23%)	30 (18%)	5 (3%)	4 (2%)	1 (<1%)
Alanine aminotransferase increased	29 (17%)	22 (13%)	5 (3%)	1 (<1%)	1 (<1%)
Anemia	26 (15%)	9 (5%)	12 (7%)	5 (3%)	0
Hypothyroidism	19 (11%)	9 (5%)	10 (6%)	0	0
Rash	18 (11%)	10 (6%)	4 (2%)	4 (2%)	0
Blood bilirubin increased	18 (11%)	13 (8%)	4 (2%)	1 (<1%)	0
Protein urine present	15 (9%)	6 (4%)	9 (5%)	0	0
Bilirubin conjugated increased	14 (8%)	9 (5%)	3 (2%)	2 (1%)	0
Asthenia	13 (8%)	8 (5%)	4 (2%)	1 (<1%)	0
Gamma-glutamyltransferase increased	12 (7%)	3 (2%)	3 (2%)	5 (3%)	1 (<1%)
Decreased appetite	12 (7%)	9 (5%)	3 (2%)	0	0
Pyrexia	11 (6%)	7 (4%)	4 (2%)	0	0
Pruritus	10 (6%)	7 (4%)	2 (1%)	1 (<1%)	0
Hyponatremia	9 (5%)	4 (2%)	0	4 (2%)	1 (<1%)
Blood alkaline phosphatase increased	9 (5%)	5 (3%)	3 (2%)	1 (<1%)	0
Platelet count decreased	9 (5%)	5 (3%)	4 (2%)	0	0
Gingival bleeding	9 (5%)	5 (3%)	4 (2%)	0	0
Proteinuria	9 (5%)	7 (4%)	2 (1%)	0	0

Data are present as *n* (%). Treatment-related adverse events that occurred in at least 5% of all treated patients are listed. Three (2%) grade 5 events were considered to be treatment related by the investigators, including one (<1%) caused by pneumonia and two (1%) unknown deaths

Liu, D., Zhou, J., Wang, Y. et al. BMC Med 20, 408 (2022).

Study design

- **A multicenter, 2-part, phase 3 study (ClinicalTrials.gov, NCT04950322).**
  - Safety and tolerability exploration part 1: recommended dose of SHR-1701 was 30 mg/kg Q3W, when combined with CAPOX.
  - Multicenter, randomized, double-blind, part 2 aimed to assess the addition of SHR-1701 to CAPOX.



SHR-1701/placebo up to 2 years; CAPOX up to 6 cycles

Stratification:
- PD-L1 expression status (CPS ≥5 *vs.* <5)
- ECOG performance status (0 *vs.*1)
- Peritoneal metastasis (present *vs.* absent).

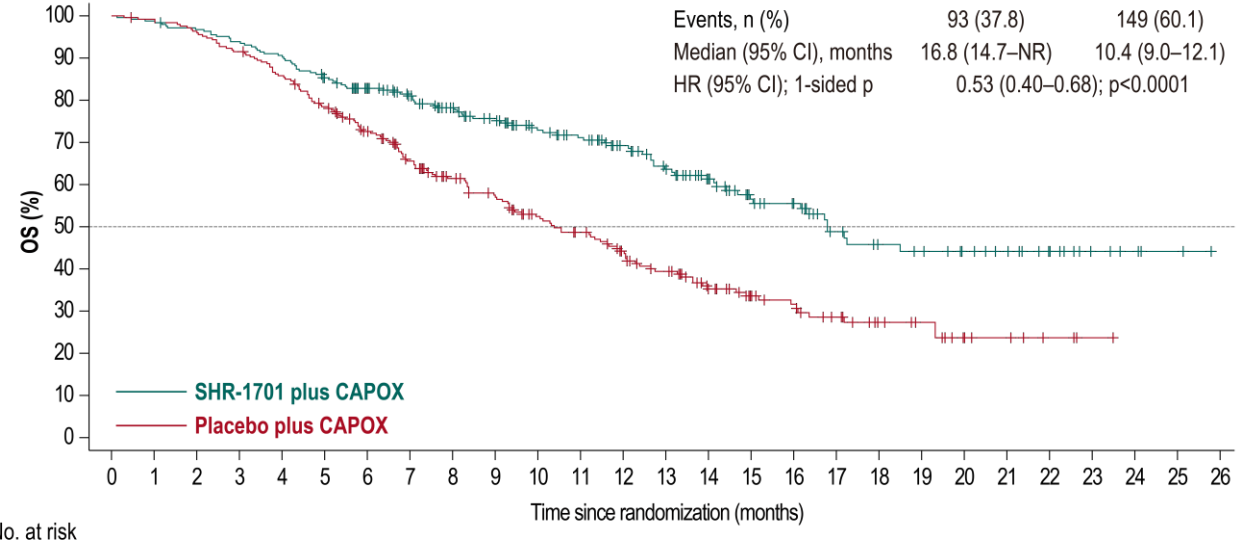
The E1L3N PD-L1 IHC assay was used as the companion diagnostic test for PD-L1 expression.
CAPOX, capecitabine and oxaliplatin; ECOG, Eastern Cooperative Oncology Group; RECIST, Response Evaluation Criteria in Solid Tumors; CPS, combined positive score; ITT, intention-to-treat population; OS, overall survival; PFS, progression-free survival; ORR, objective response rate; DoR, duration of response.

Baseline characteristics

	PD-L1 CPS ≥5		ITT	
	SHR-1701 plus CAPOX (N=246)	Placebo plus CAPOX (N=248)	SHR-1701 plus CAPOX (N=365)	Placebo plus CAPOX (N=366)
Age, median (range), years	62 (24–80)	64 (26–78)	63 (24–80)	62 (26–78)
Male, n (%)	193 (78.5)	183 (73.8)	285 (78.1)	274 (74.9)
ECOG performance status, n (%)				
0	59 (24.0)	60 (24.2)	89 (24.4)	91 (24.9)
1	187 (76.0)	188 (75.8)	276 (75.6)	275 (75.1)
Primary tumour location, n (%)				
Gastric	192 (78.0)	200 (80.6)	288 (78.9)	286 (78.1)
Gastroesophageal junction	54 (22.0)	48 (19.4)	77 (21.1)	80 (21.9)
Peritoneal metastasis, n (%)	84 (34.1)	83 (33.5)	124 (34.0)	123 (33.6)
Disease status, n (%)				
Metastatic	241 (98.0)	238 (96.0)	355 (97.3)	353 (96.4)
Locally advanced	4 (1.6)	10 (4.0)	9 (2.5)	13 (3.6)
Locally recurrent	1 (0.4)	0	1 (0.3)	0
Histological subtype (Lauren classification), n (%)				
Diffuse	25 (10.2)	25 (10.1)	41 (11.2)	39 (10.7)
Intestinal	165 (67.1)	155 (62.5)	249 (68.2)	230 (62.8)
Mix	50 (20.3)	63 (25.4)	66 (18.1)	86 (23.5)
Unknown	6 (2.4)	5 (2.0)	9 (2.5)	11 (3.0)
Microsatellite instability status, n (%)				
High	4 (1.6)	4 (1.6)	6 (1.6)	4 (1.1)
Low or microsatellite stable	156 (63.4)	167 (67.3)	226 (61.9)	226 (61.7)
Unknown	86 (35.0)	77 (31.0)	133 (36.4)	136 (37.2)

OS in the PD-L1 CPS ≥5 population

– Median follow-up: 13.6 months*

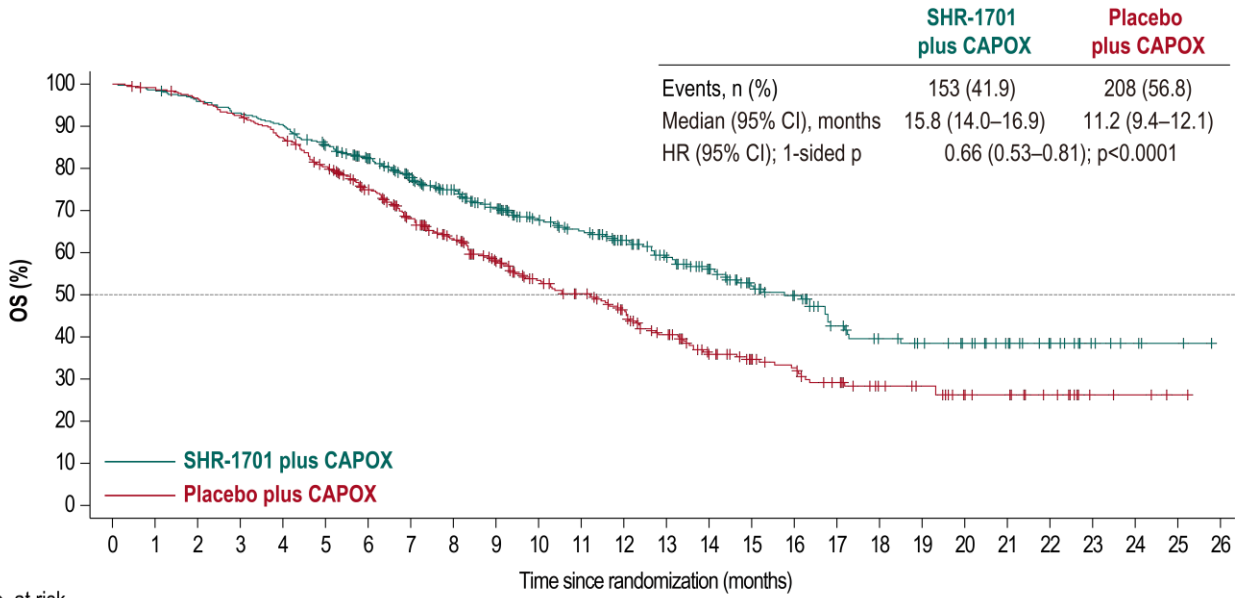


No. at risk

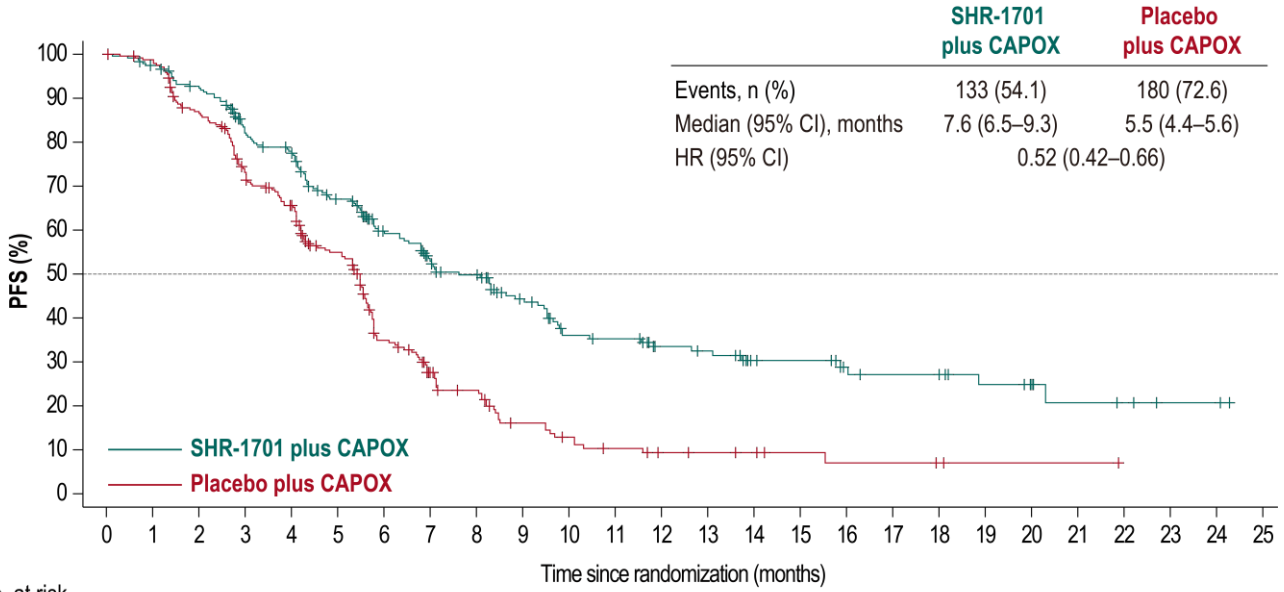
SHR-1701 plus CAPOX	246	243	237	230	222	206	190	176	156	144	126	118	102	88	70	54	48	34	28	26	21	18	12	6	4	2	0
Placebo plus CAPOX	248	245	238	226	211	191	170	146	127	115	98	89	75	63	47	37	32	25	18	15	8	6	3	1	0		

NR, not reached.

OS in the ITT population



PFS per BICR in the PD-L1 CPS ≥5 population

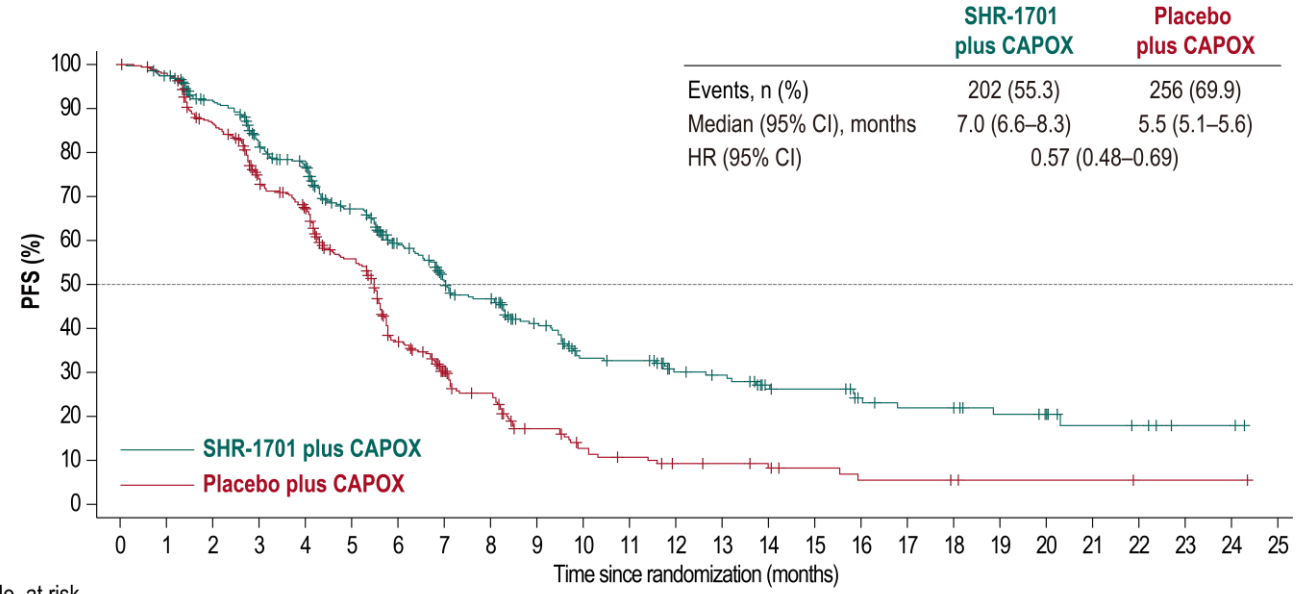


No. at risk

SHR-1701 plus CAPOX	246	228	214	179	168	137	107	86	78	61	46	43	33	31	23	22	17	15	15	11	8	5	4	2	2	0
Placebo plus CAPOX	248	237	203	167	146	112	65	43	33	20	15	11	8	7	6	4	3	3	2	1	1	1	0			

BICR, blinded independent central review.

PFS per BICR in the ITT population



No. at risk

SHR-1701 plus CAPOX	365	340	308	261	240	196	154	119	107	81	60	57	43	40	30	28	22	19	19	14	11	7	6	2	2	0
Placebo plus CAPOX	366	345	296	243	215	163	99	66	49	28	19	15	11	10	8	6	4	4	3	2	2	2	1	1	1	0

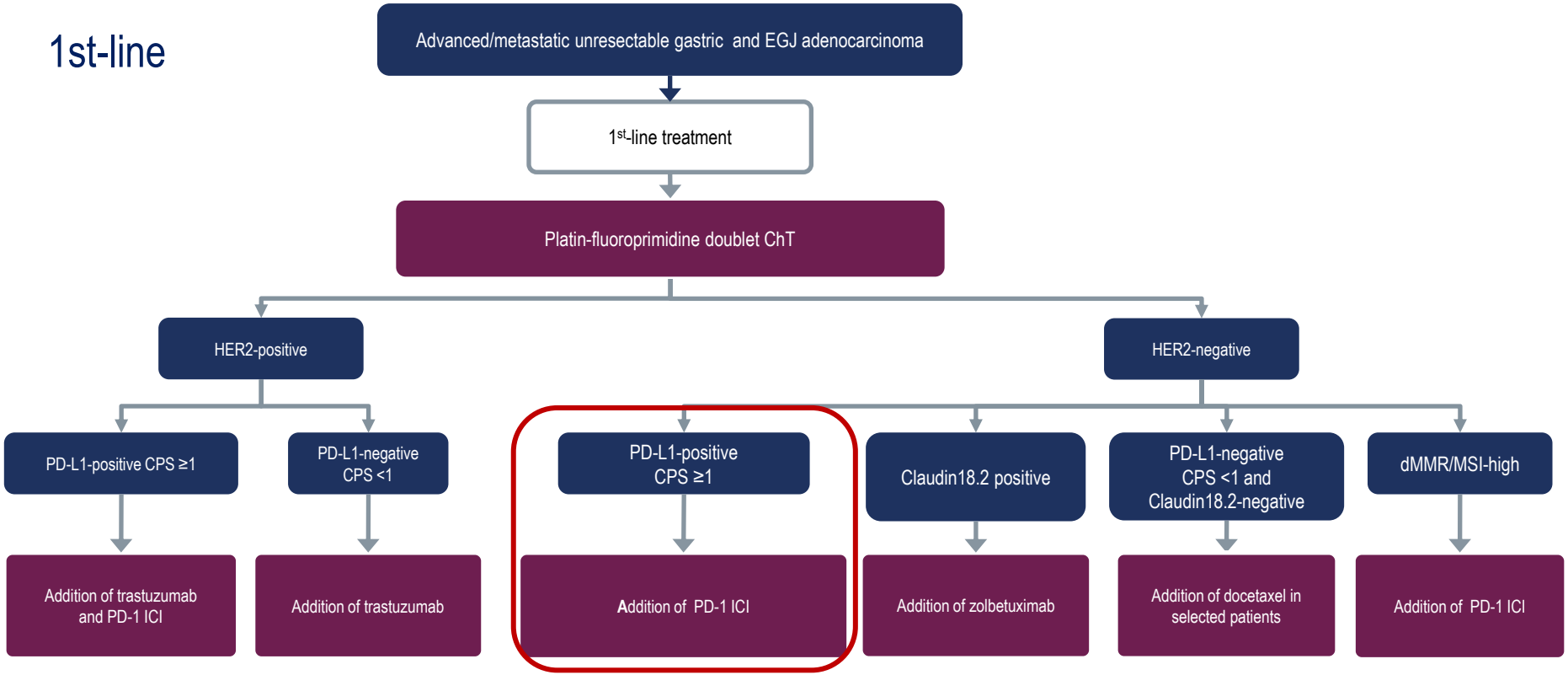
Safety summary

	SHR-1701 plus CAPOX (N=364)	Placebo plus CAPOX (N=366)
TRAEs of any grade	356 (97.8)	360 (98.4)
TRAEs of grade ≥3	228 (62.6)	216 (59.0)
Serious TRAEs	127 (34.9)	88 (24.0)
TRAEs leading to discontinuation of any study medication	38 (10.4)	11 (3.0)
SHR-1701/placebo discontinuation	30 (8.2)	7 (1.9)
CAPOX discontinuation	16 (4.4)	6 (1.6)
TRAEs leading to death	7 (1.9)	4 (1.1)

Data are n (%).

TRAE, treatment-related adverse events.

ESMO GUIDELINES: Standard treatment of metastatic GEJ/G cancer:



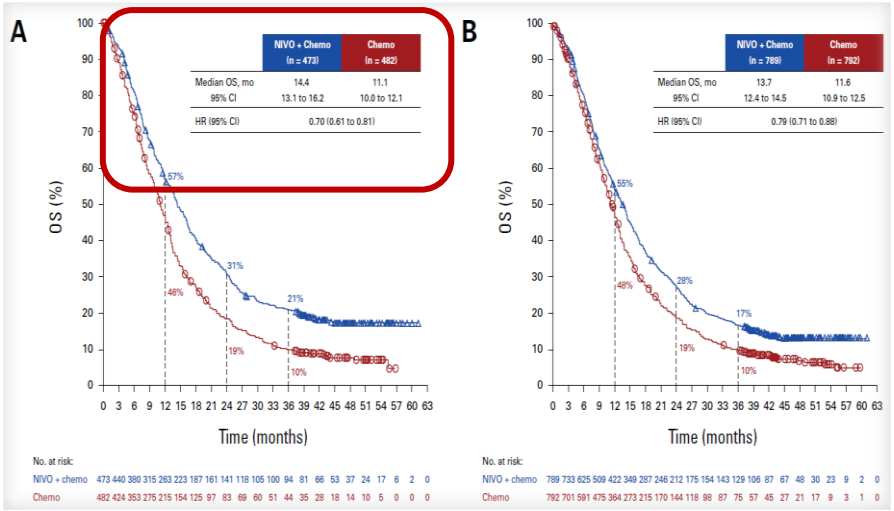
Radka Lordick Obermannová

Lordick F. et al. https://www.esmo.org/living-guidelines/esmo-gastric-cancer-living-guideline

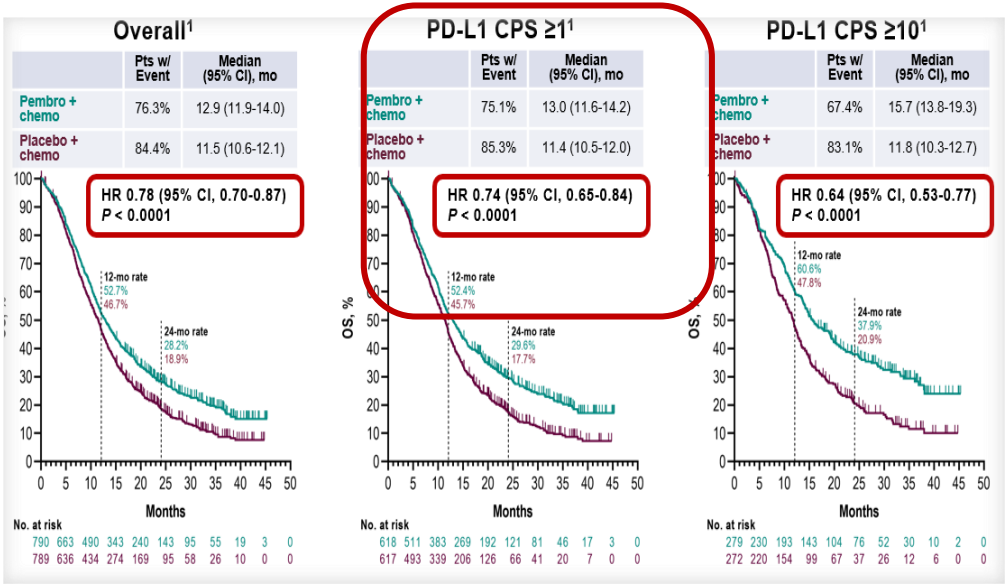
Standard 1st line in HER2 negative GEJ/G cancer

CHECKMATE-649 – OS

PD-L1 ≥ 5 **ALL**



KEYNOTE-859 – OS



Janjigian Y et al. J Clin Oncol. 2024
Rha SY et al. Lancet Oncol. 2023 Nov;24(11):1181-1195

Immunotherapy: 1st line in HER2 negative GEJ/G cancer

Efficacy according to PD-L status

Phase III (HR)	ChM-649 Global antiPD-1 nivolumab	KEYNOTE-859 Global antiPD-1 pembrolizumab	ORIENT-16 Chinese antiPD-1 sintilimab	Rationale 305 Global antiPD-1 tislelizumab	SHR 1701 Chinese antiPD-1 and anti TGF RII
All HR mOS(mo)	0.78 13.7 vs 11.6	0.78 12.9 vs 11.5	0.77 15.2 vs 12.3	0.80 17.2 vs 12.6	0.66 15.8 vs 11.2
CPS < 1	0.95 13.1 vs 12.5	0.92	0.84	NR	NR
CPS ≥ 1	0.75 13.8 vs 11.3	0.74 13.0 vs 11.4	0.73	NR	NR
CPS ≥ 5	0.69 14.4 vs 11.1	NR	0.66 18.4 vs 12.9	0.73 17.8 vs 13.2	0.53 16.8 vs 10.4
CPS ≥ 10	0.66 15.0 vs 10.9	0.64 15.7 vs 11.8	0.56	NR	NR

Janjigian Y et al. J Clin Oncol. 2024, Rha SY et al. Lancet Oncol. 2023 Nov;24(11):11811195, Xu J.et al. JAMA. 2023 Dec 5;330(21):2064-2074, Qiu MZ et al BMJ 2024; 385

Conclusions

Phase 3 study of SHR-1701 versus placebo in combination with chemo as first-line (1L) therapy for HER2-negative gastric/gastroesophageal

- Encouraging data

However:

- No appropriate control arm
- Is toxicity an issue?
- CPS≤5 and MSI population outcomes were not reported
- Effects on a global population unknown
- Short median follow-up of 13.6 months

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Thank you for your kind attention.

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obermannova@mou.cz

Masaryk Memorial Cancer Institute