Carcinoma Gastrico Metastatico
Impatto di ASCO23 sul *continuum* of care

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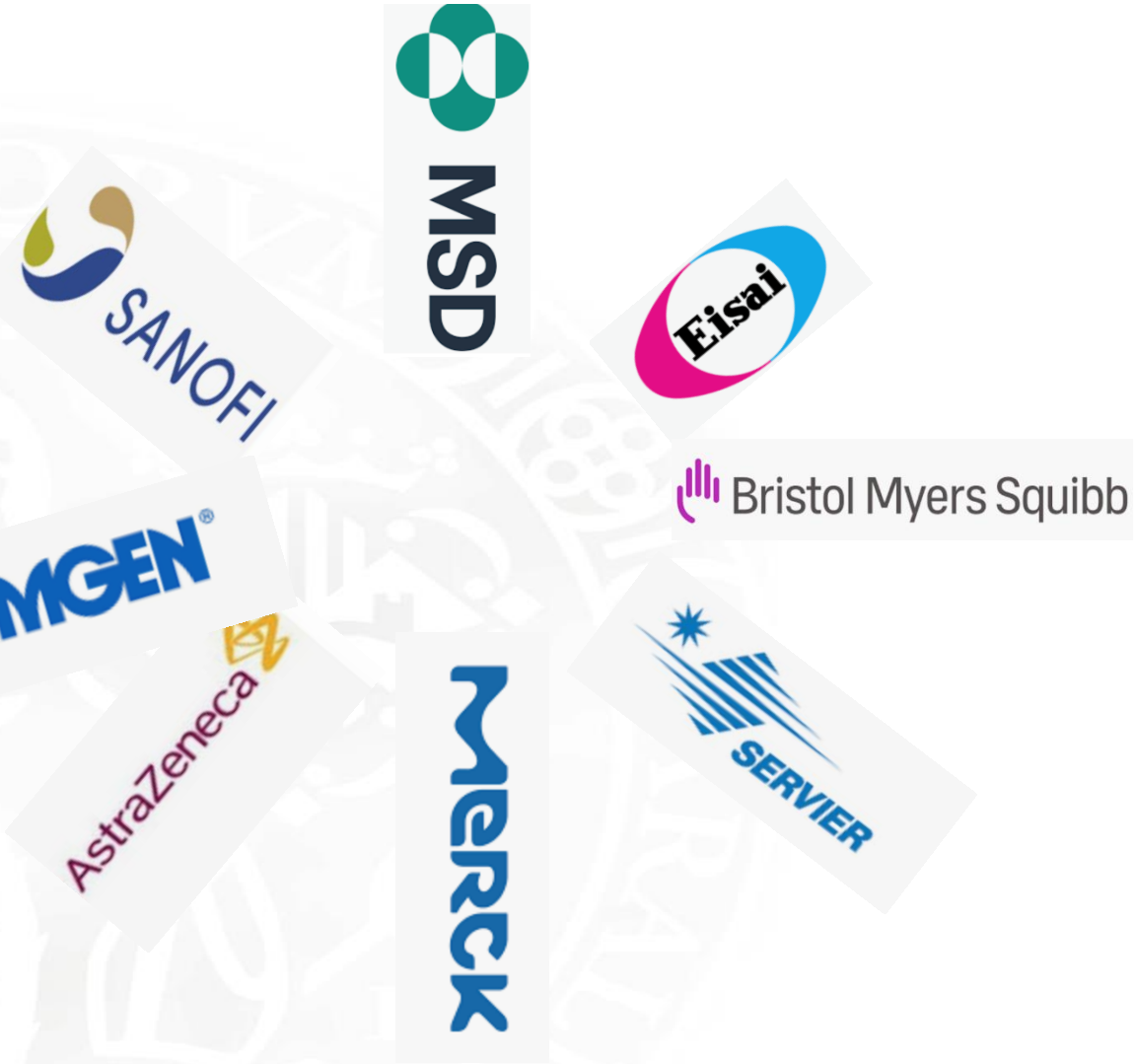
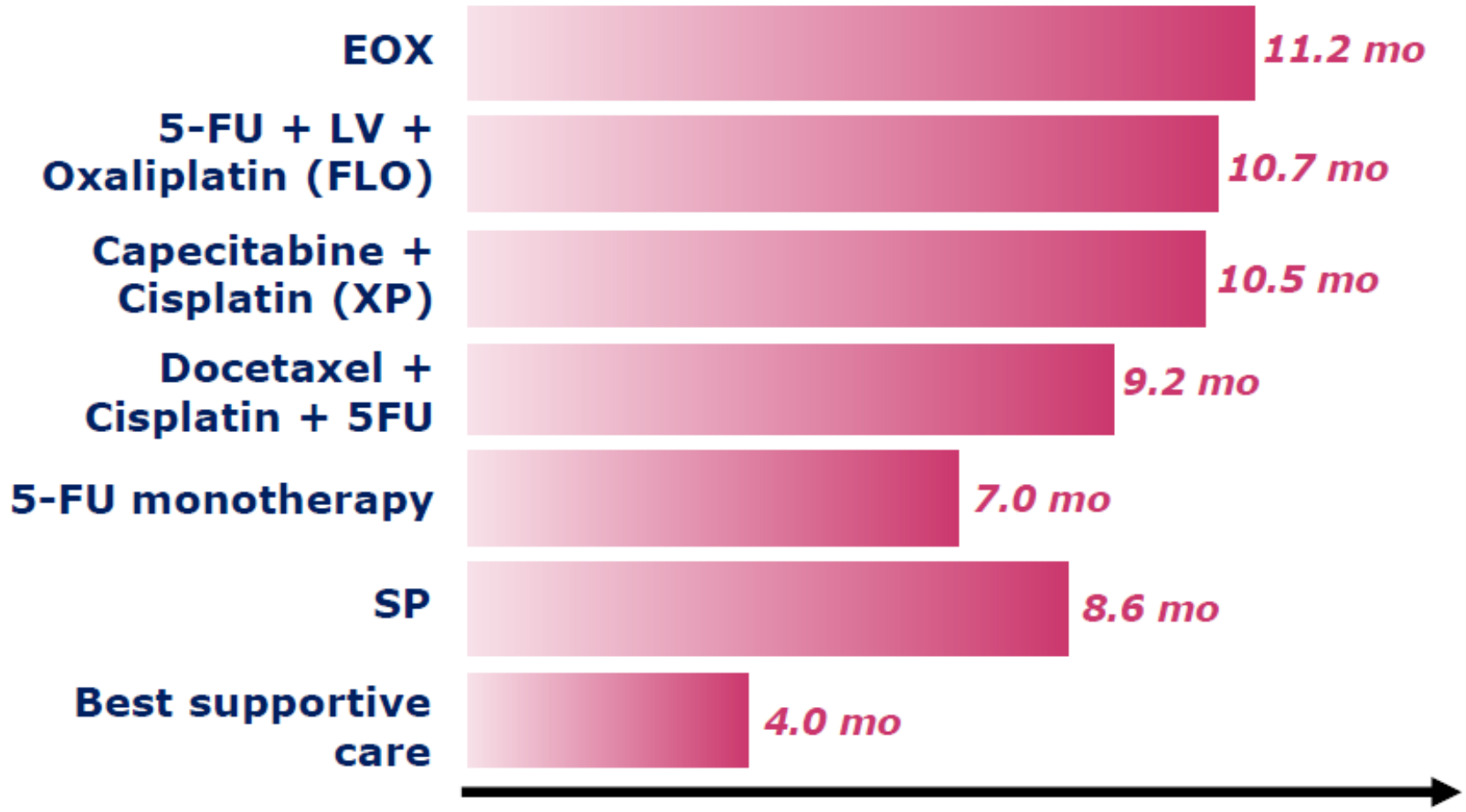
Advisory board, speakers' bureau, investigator's grant



I LINEA per Malattia METASTATICA



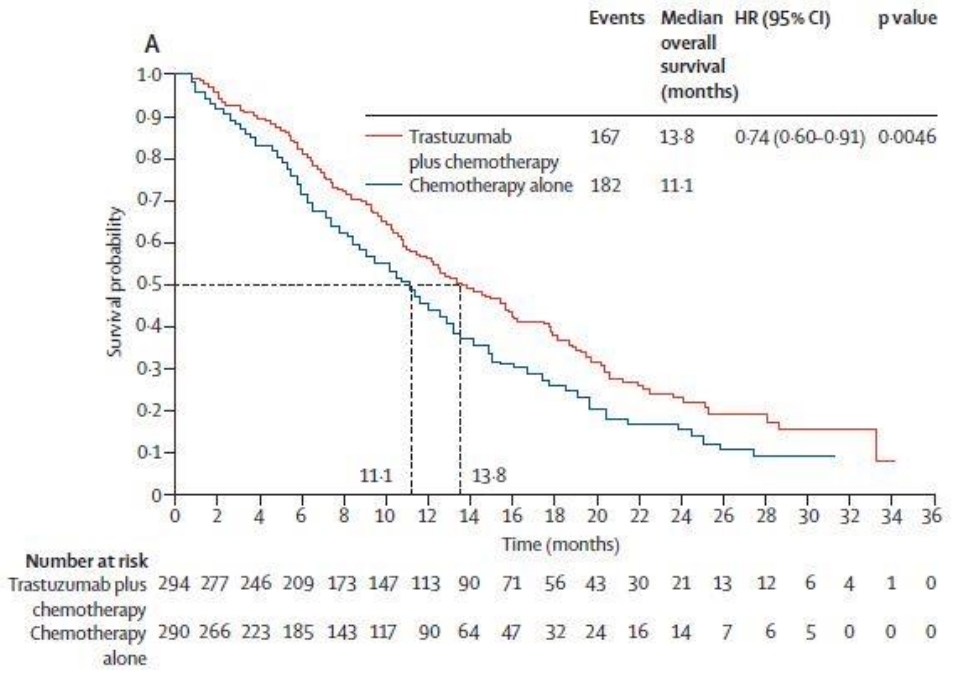
MALATTIA AVANZATA: I LINEA - HER2+

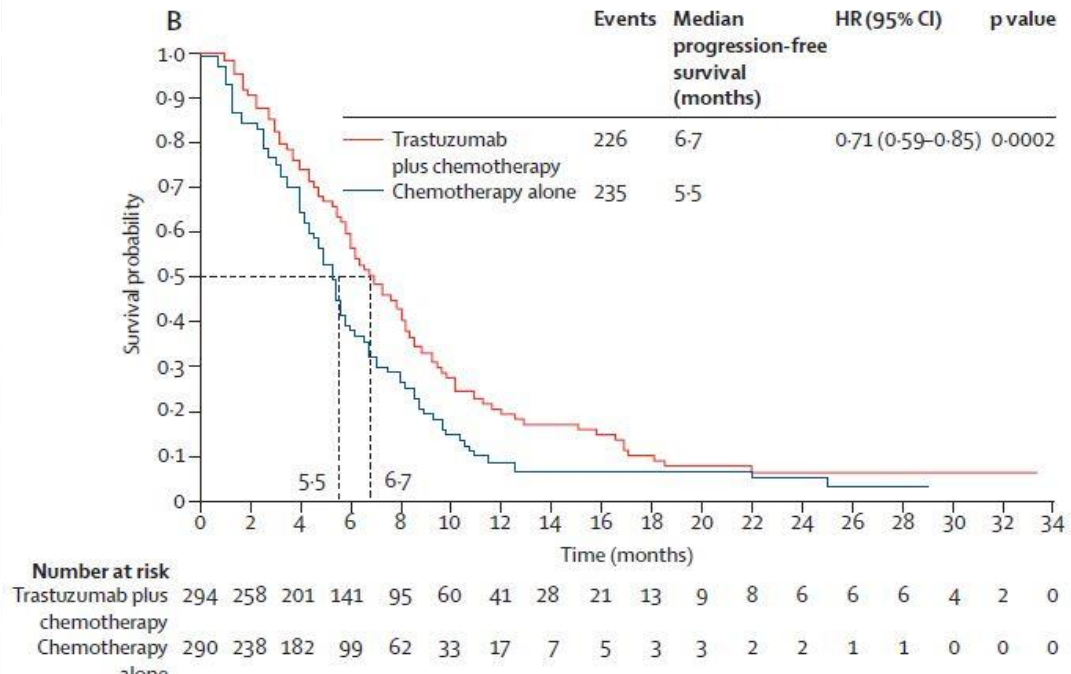
ARTICLES | VOLUME 376, ISSUE 9742, P687-697, AUGUST 28, 2010

Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial

Prof Yung-Jue Bang, MD * • Prof Eric Van Cutsem, MD * • Andrea Feyereislova, MD • Prof Hyun C Chung, MD • Prof Lin Shen, MD • Akira Sawaki, MD • et al. Show all authors • Show footnotes

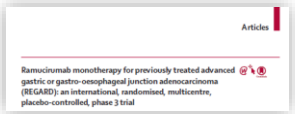
Published: August 20, 2010 • DOI: https://doi.org/10.1016/S0140-6736(10)61121-X





LA TERAPIA DI II LINEA: RUOLO DEL RAMUCIRUMAB

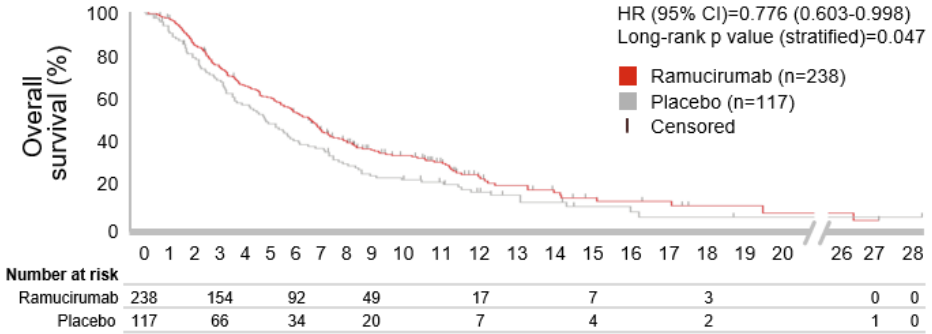
REGARD trials


Articles

Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial

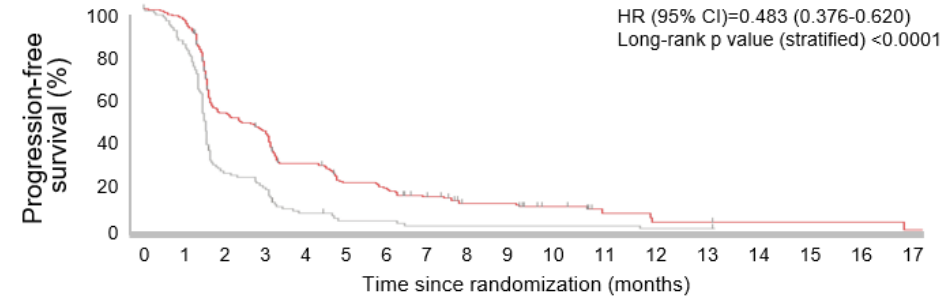
mOS:
5.2 months vs 3.8 months

Overall Survival



Number at risk									
Ramucirumab	238	154	92	49	17	7	3	0	0
Placebo	117	66	34	20	7	4	2	1	0

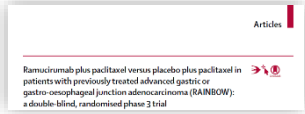
Progression Free Survival



Number at risk																	
Ramucirumab	238	213	113	65	61	45	30	18	18	11	5	4	2	1	1	1	1	0
Placebo	117	92	27	11	7	4	2	2	2	2	2	1	1	0	0	0	0	0

*Statistically significant

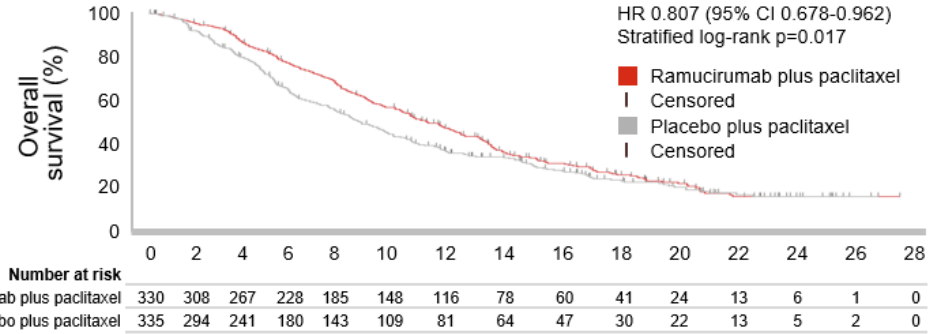
RAINBOW trials


Articles

Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial

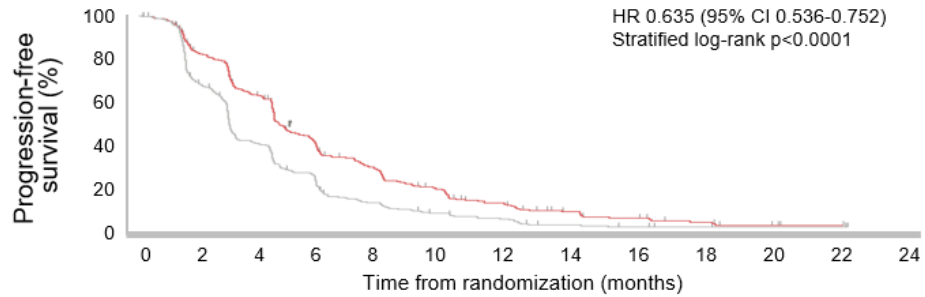
mOS:
9.6 months vs 7.4 months

Overall Survival



Number at risk														
Ramucirumab plus paclitaxel	330	308	267	228	185	148	116	78	60	41	24	13	6	1	0
Placebo plus paclitaxel	335	294	241	180	143	109	81	64	47	30	22	13	5	2	0

Progression Free Survival



Number at risk													
Ramucirumab plus paclitaxel	330	259	188	104	70	43	28	15	11	7	3	1	-
Placebo plus paclitaxel	335	214	124	50	34	21	12	8	5	3	3	3	-

Wilke H, Lancet Oncol 2014; Fuchs CS, Lancet Oncol 2014

TAGS: Phase 3 Trial of TAS-102 in advanced GC

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

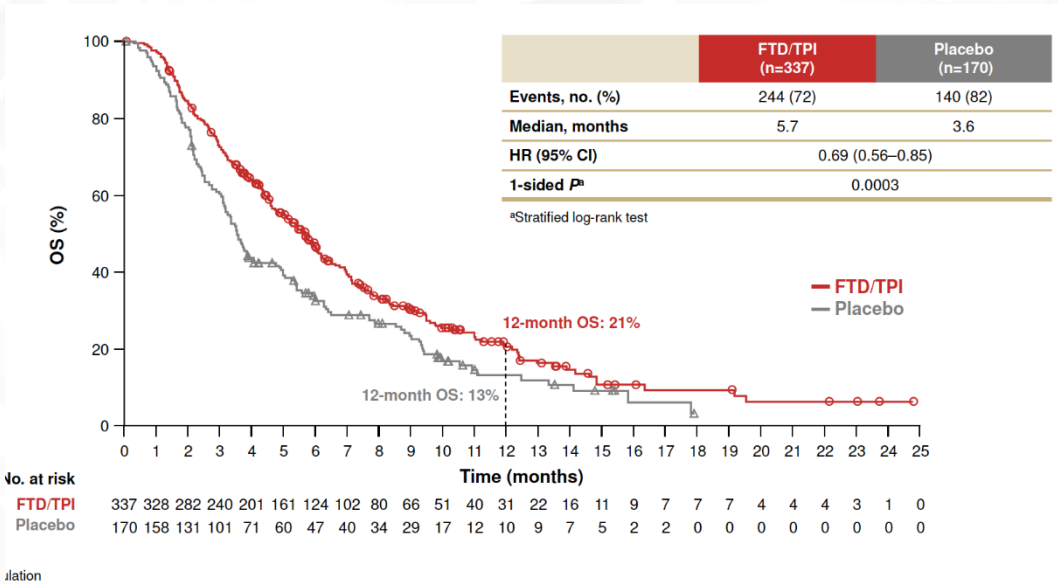
R 2:1

FTD/TPI (TAS-102) + BSC (n=337)
35 mg/m² 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

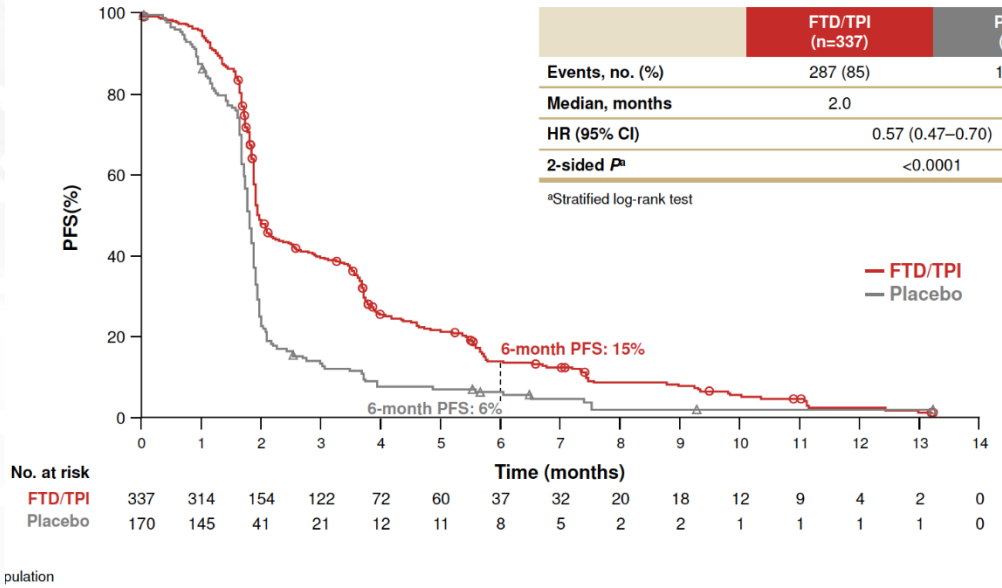
End points
- Primary:
  - OS
- Key secondary:
  - PFS, safety
- Other secondary:
  - ORR
  - DCR
  - QOL
  - Time to ECOG PS ≥2

RR 4 vs 2%
DCR 44% vs. 14% $p < 0.0001$
Time to deterioration of PS HR0.69 $p = 0.0001$



	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	

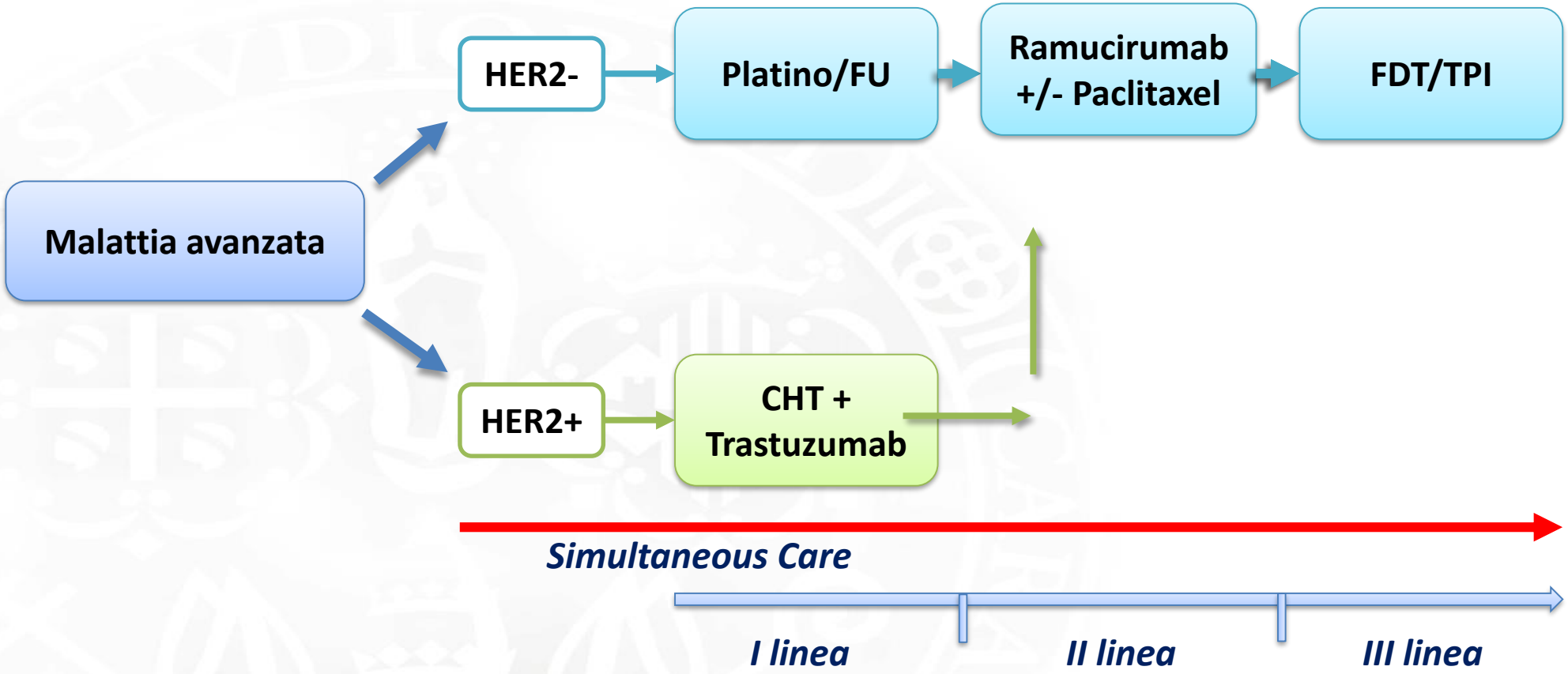
[a]Stratified log-rank test



	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

Tabernero et Al, ESMO GI 2018 & Arkenau et Al, ESMO 2018, Shitara et Al Lancet Oncolol 2018

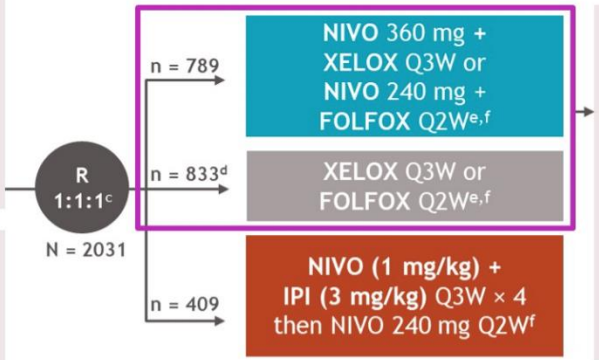

HER2-
Platino/FU
Ramucirumab
+/- Paclitaxel
FDT/TPI
Malattia avanzata
HER2+
CHT +
Trastuzumab
Simultaneous Care
I linea
II linea
III linea

First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial

- CheckMate 649 is a randomized, open-label, global phase 3 study[a]

Key eligibility criteria
- Previously untreated, unresectable, advanced or metastatic gastric/GEJ/esophageal adenocarcinoma
- No known HER2-positive status
- ECOG PS 0-1

Stratification factors
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[b])
- Region (Asia vs United States/Canada vs ROW)
- ECOG PS (0 vs 1)
- Chemo (XELOX vs FOLFOX)



Dual primary endpoints:
- OS and PFS[g] (PD-L1 CPS ≥ 5)

Secondary endpoints:
- OS (PD-L1 CPS ≥ 1, all randomized)
- OS (PD-L1 CPS ≥ 10)
- PFS[g] (PD-L1 CPS ≥ 10, ≥ 1, all randomized)
- ORR[g]

Exploratory endpoints:
- Safety
- QoL

	Patients with a PD-L1 CPS of five or more		All randomly assigned patients	
	Nivolumab plus chemotherapy (n=473)	Chemotherapy alone (n=482)	Nivolumab plus chemotherapy (n=789)	Chemotherapy alone (n=792)
(Continued from previous page)				
Site of metastases				
Liver	191 (40%)	217 (45%)	301 (38%)	314 (40%)
Peritoneum	101 (21%)	96 (20%)	188 (24%)	188 (24%)
CNS	1 (<1%)	0	1 (<1%)	0
Signet ring cell carcinoma‡				
Yes	72 (15%)	69 (14%)	145 (18%)	136 (17%)
No	401 (85%)	413 (86%)	644 (82%)	656 (83%)
Lauren classification				
Intestinal type	171 (36%)	176 (37%)	272 (34%)	267 (34%)
Diffuse type	137 (29%)	141 (29%)	254 (32%)	273 (34%)
Mixed	37 (8%)	30 (6%)	58 (7%)	48 (6%)
Unknown	128 (27%)	135 (28%)	205 (26%)	204 (26%)
Microsatellite instability status				
Microsatellite stable	423 (89%)	423 (88%)	695 (88%)	682 (86%)
Microsatellite instability-high	18 (4%)	16 (3%)	23 (3%)	21 (3%)
Not reported or invalid	32 (7%)	43 (9%)	71 (9%)	89 (11%)
Chemotherapy regimen§				
FOLFOX	237/468 (51%)	242/465 (52%)	422/782 (54%)	406/767 (53%)
XELOX	231/468 (49%)	223/465 (48%)	360/782 (46%)	361/767 (47%)

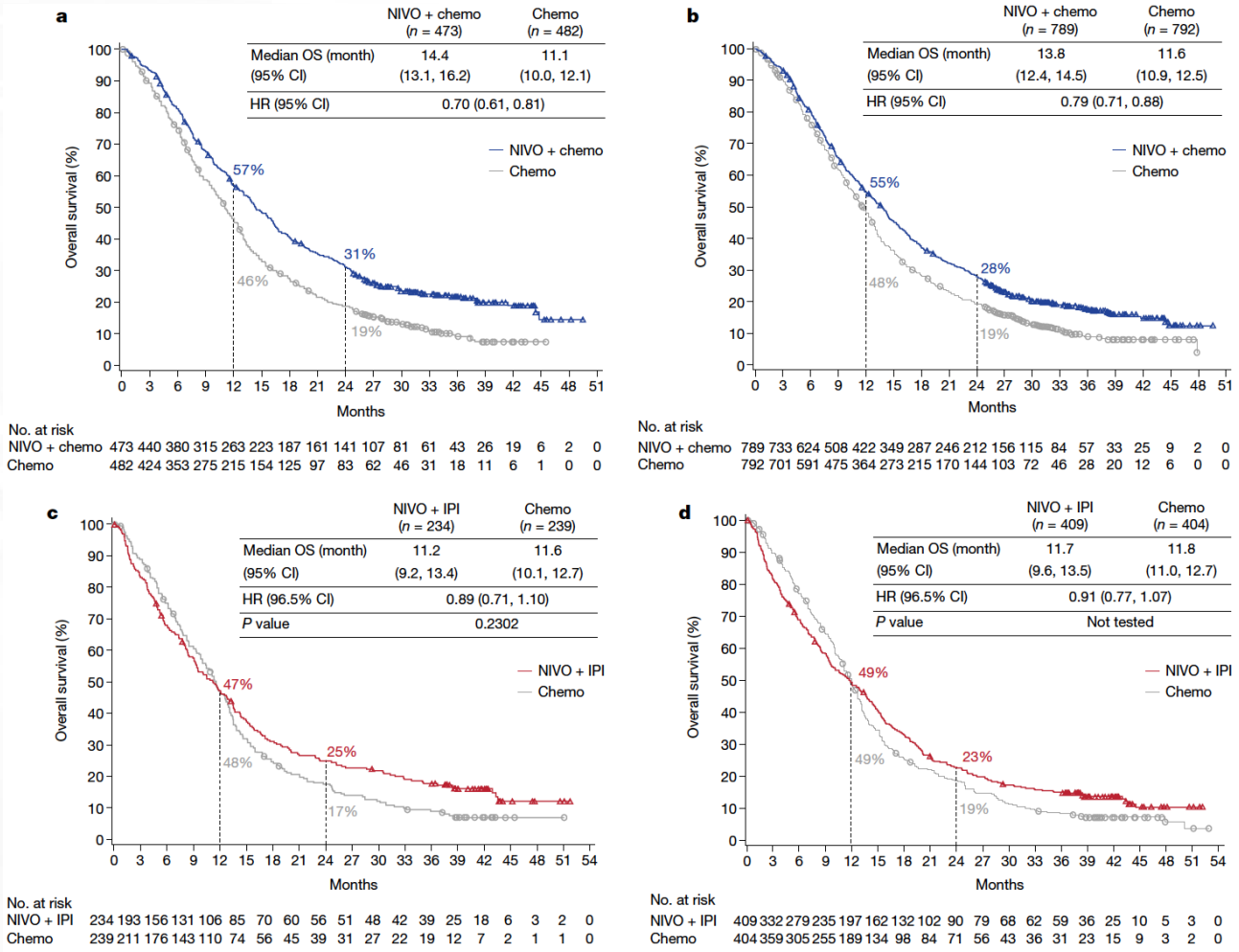
Data are median (IQR) or n (%). PD-L1=programmed cell death ligand 1. CPS=combined positive score. ECOG=Eastern Cooperative Oncology Group. FOLFOX=leucovorin, fluorouracil, and oxaliplatin. XELOX=capecitabine and oxaliplatin. *Based on case report form. All randomly assigned patients had ECOG performance status of 0 or 1 based on interactive response technology. †Includes indeterminate tumour cell PD-L1 expression. ‡Per WHO histological classification. §Patients who received at least one dose of the assigned treatment.

Table 1: **Baseline characteristics**

Janjigian & Shitara, Lancet 2021

Nivolumab plus chemotherapy or ipilimumab in gastro-oesophageal cancer

Overall Survival



Shitara, Nature 2022

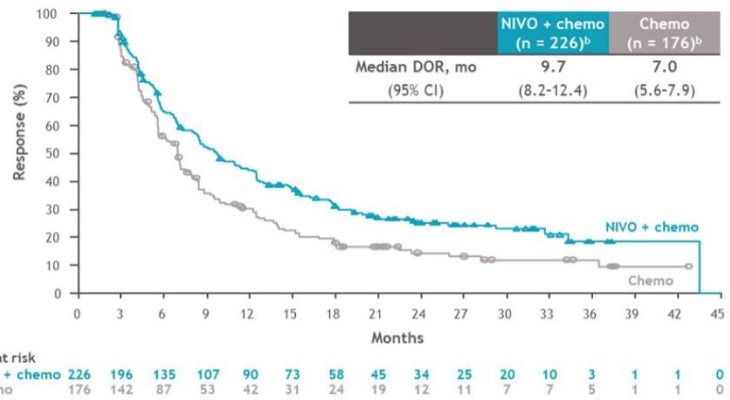
Nivolumab plus chemotherapy versus chemotherapy as first-line treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma: expanded analyses from 24-month follow-up of CheckMate 649

Response and Duration of Response

PD-L1 CPS ≥ 5[1]

Response per BICR	NIVO + chemo (n = 378)[a]	Chemo (n = 390)[a]
ORR, % (95% CI)	60 (55-65)	45 (40-50)
CR	13	7
PR	47	38
SD	28	34
PD	7	11

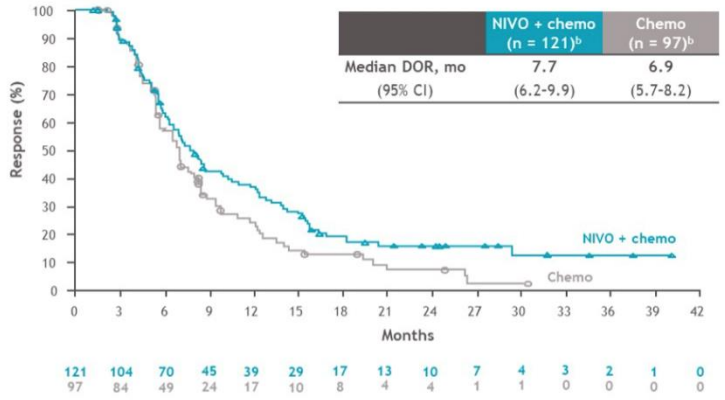
	NIVO + chemo (n = 226)[b]	Chemo (n = 176)[b]
Median DOR, mo	9.7	7.0
(95% CI)	(8.2-12.4)	(5.6-7.9)



PD-L1 CPS < 5

Response per BICR	NIVO + chemo (n = 219)[a]	Chemo (n = 209)[a]
ORR, % (95% CI)	55 (48-62)	46 (40-53)
CR	7	4
PR	48	42
SD	30	32
PD	7	10

	NIVO + chemo (n = 121)[b]	Chemo (n = 97)[b]
Median DOR, mo	7.7	6.9
(95% CI)	(6.2-9.9)	(5.7-8.2)



- ORR was higher and responses were more durable with NIVO + chemo vs chemo regardless of PD-L1 CPS ≥ 5 or < 5

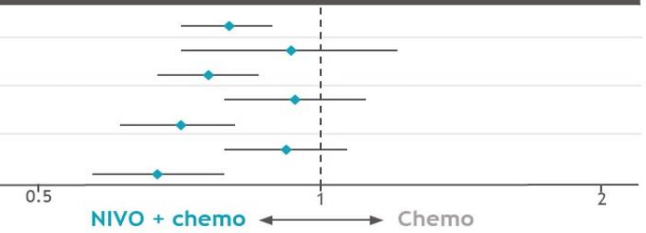
Shitara, ASCO Gastrointestinal Cancers Symposium 2022 & Lancet 2022

Nivolumab plus chemotherapy versus chemotherapy as first-line treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma: expanded analyses from 24-month follow-up of CheckMate 649

Efficacy subgroup analysis by PD-L1 CPS excluding MSI-H

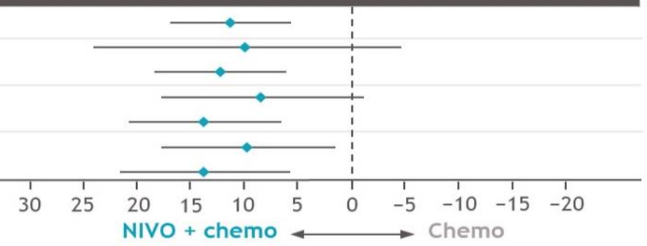
Overall survival

PD-L1 CPS[a]	Number of patients	Median, months		Unstratified HR[b]	Unstratified HR (95% CI)
		NIVO + chemo	Chemo		
Overall (N = 1537)		13.5	11.6	0.80	
< 1	262	13.4	12.5	0.93	
≥ 1	1256	13.6	11.4	0.76	
< 5	597	12.4	12.1	0.94	
≥ 5	921	14.2	11.1	0.71	
< 10	779	12.4	12.6	0.92	
≥ 10	739	14.4	10.9	0.67	



Objective response rate

PD-L1 CPS[c]	Number of patients	Objective response rate, %		Unweighted ORR difference,[d] %	Unweighted ORR difference, % (95% CI)
		NIVO + chemo	Chemo		
Overall (n = 1172)		58	46	12	
< 1	176	52	41	11	
≥ 1	982	60	47	13	
< 5	418	55	46	9	
≥ 5	740	60	46	14	
< 10	563	57	47	10	
≥ 10	595	59	45	14	



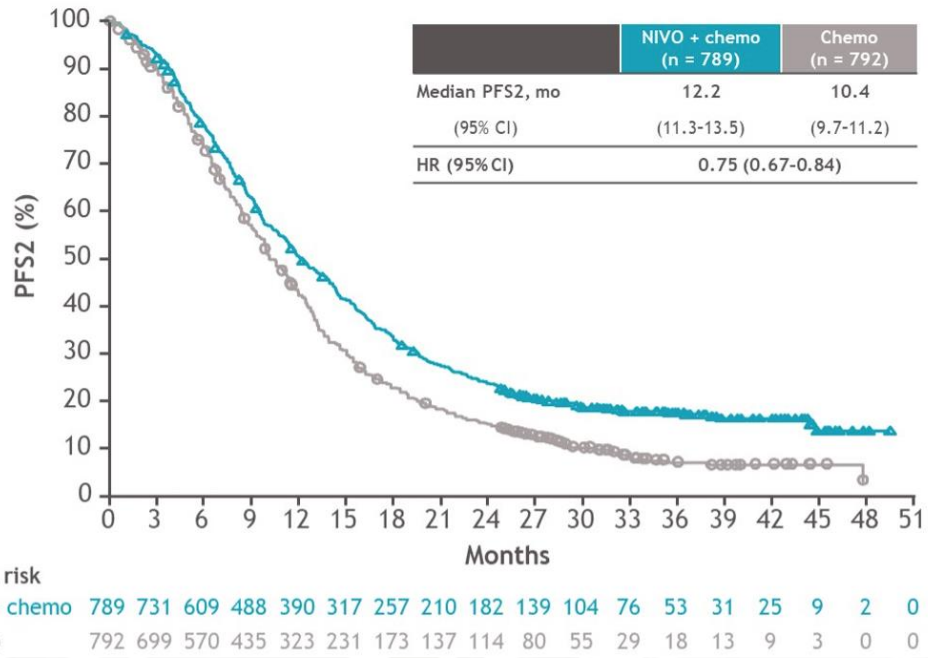
- OS and ORR benefits were consistent with the all randomized population when excluding patients with MSI-H tumors[e]

Shitara, ASCO Gastrointestinal Cancers Symposium 2022 & Lancet 2022

Nivolumab plus chemotherapy versus chemotherapy as first-line treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma: expanded analyses from 24-month follow-up of CheckMate 649

Progression Free Survival 2

All randomized patients



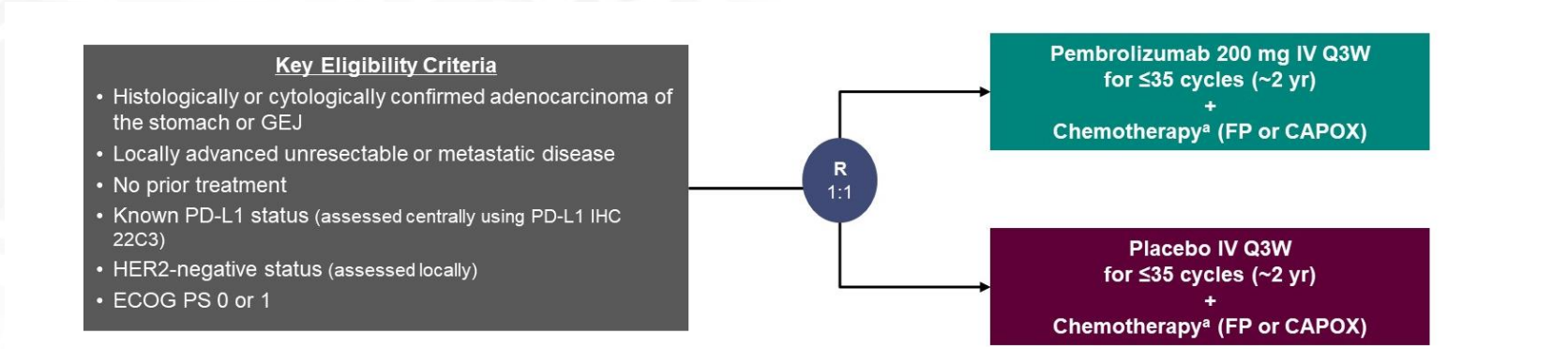
	NIVO + chemo (n = 789)	Chemo (n = 792)
Median PFS2, mo	12.2	10.4
(95% CI)	(11.3-13.5)	(9.7-11.2)
HR (95% CI)	0.75 (0.67-0.84)	

First subsequent therapy,[a] n (%)	NIVO + chemo (n = 789)	Chemo (n = 792)
Any subsequent therapy	325 (41)	346 (44)
Radiotherapy	32 (4)	28 (4)
Surgery	19 (2)	23 (3)
Systemic anticancer therapy[b]	290 (37)	329 (42)
Chemotherapy	267 (34)	297 (38)
Targeted therapy	92 (12)	76 (10)
Immunotherapy	8 (1)	27 (3)

Shitara, ASCO Gastrointestinal Cancers Symposium 2022 & Lancet 2022

KEYNOTE-859 Study of Pembrolizumab plus Chemotherapy for Advanced HER2-Negative Gastric or Gastroesophageal Junction Cancer: Outcomes in the Protocol-Specified PD-L1–Selected Populations

Sun Young Rha[1]; Lucjan S. Wyrwicz[2]; Patricio E. Yañez[3]; Yuxian Bai[4]; Min-Hee Ryu[5]; Jeeyun Lee[6]; Fernando Rivera[7]; Gustavo V. Alves[8]; Marcelo Garrido[9]; Kai-Keen Shiu[10]; Manuel González Fernández[11]; Jin Li[12]; Maeve A. Lowery[13]; Timuçin Çil[14]; Felipe J.S. Melo Curz[15]; Shukui Qin[16]; Lina Yin[17]; Sonal Bordia[17]; Pooja Bhagia[17]; Do-Youn Oh[18] on behalf the KEYNOTE-859 Investigators



Stratification Factors
- Geographic region (Europe/Israel/North America/ Australia vs Asia vs rest of world)
- PD-L1 CPS (<1 vs ≥1)
- Choice of chemotherapy[a] (FP vs CAPOX)

- **Primary End Point:** OS
- **Secondary End Points:** PFS,[b] ORR,[b] DOR,[b] and safety

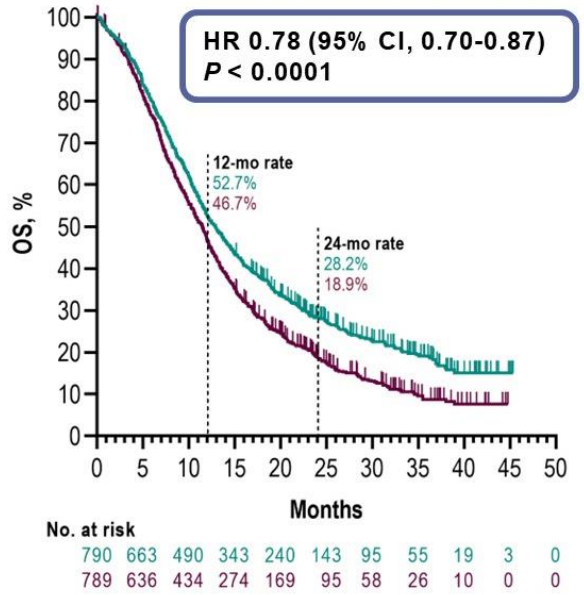
- **Alpha-controlled analyses:** OS, PFS, and ORR in the overall, PD-L1 CPS ≥1, and PD-L1 CPS ≥10 populations

Sun Young Rha et Al, ASCO23

Primary Endpoint: OS

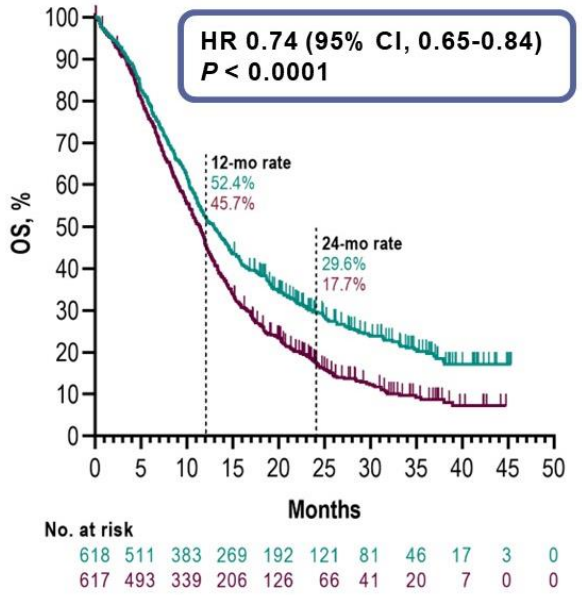
Overall[1]

	Pts w/ Event	Median (95% CI), mo
Pembro + chemo	76.3%	12.9 (11.9-14.0)
Placebo + chemo	84.4%	11.5 (10.6-12.1)



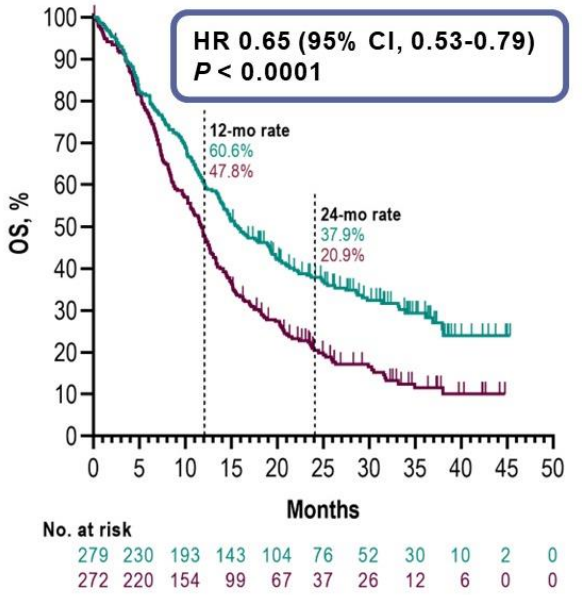
PD-L1 CPS ≥1

	Pts w/ Event	Median (95% CI), mo
Pembro + chemo	75.1%	13.0 (11.6-14.2)
Placebo + chemo	85.3%	11.4 (10.5-12.0)



PD-L1 CPS ≥10

	Pts w/ Event	Median (95% CI), mo
Pembro + chemo	67.4%	15.7 (13.8-19.3)
Placebo + chemo	83.1%	11.8 (10.3-12.7)



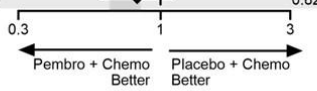
1. Rha SY et al. *Ann Oncol* 2023;34:319-320.
Data cutoff date: October 3, 2022.

Sun Young Rha et Al, ASCO23

Overall Survival in Subgroups

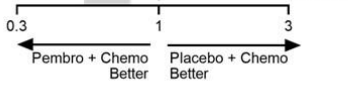
PD-L1 CPS ≥1

	No. Events/ No. Participants	Hazard ratio (95% CI)
Overall	990/1235	0.74 (0.652-0.838)
Age		
<65 years	612/741	0.73 (0.621-0.855)
≥65 years	378/494	0.73 (0.595-0.892)
Sex		
Female	309/365	0.69 (0.551-0.865)
Male	681/870	0.74 (0.638-0.864)
Geographic region		
Asia	299/401	0.70 (0.556-0.877)
W Eur/Isr/N Am/Australia	272/332	0.76 (0.595-0.961)
Rest of world	419/502	0.76 (0.624-0.918)
ECOG performance status		
0	341/451	0.66 (0.535-0.823)
1	649/784	0.77 (0.657-0.894)
Primary tumor location		
GEJ	235/287	0.71 (0.547-0.927)
Stomach	754/947	0.73 (0.634-0.844)
Histologic subtype		
Diffuse	391/456	0.73 (0.601-0.897)
Intestinal	345/454	0.78 (0.635-0.969)
Indeterminate	252/323	0.64 (0.494-0.822)
Disease status		
Metastatic	951/1184	0.73 (0.643-0.831)
Liver metastases		
No	572/723	0.71 (0.600-0.835)
Yes	417/511	0.77 (0.631-0.929)
Prior gastrectomy/esophagectomy		
No	839/1014	0.77 (0.674-0.885)
Yes	145/214	0.59 (0.422-0.816)
PD-L1 CPS		
≥10	414/551	0.64 (0.523-0.772)
1-9	574/682	0.83 (0.705-0.979)
Chemo choice at randomization		
CAPOX	832/1056	0.72 (0.626-0.824)
FP	158/179	0.82 (0.601-1.125)



PD-L1 CPS ≥10

	No. Events/ No. Participants	Hazard ratio (95% CI)
Overall	414/551	0.65 (0.532-0.787)
Age		
<65 years	247/320	0.67 (0.522-0.864)
≥65 years	167/231	0.59 (0.437-0.806)
Sex		
Female	123/153	0.58 (0.405-0.830)
Male	291/398	0.65 (0.514-0.818)
Geographic region		
Asia	126/184	0.63 (0.441-0.889)
W Eur/Isr/N Am/Australia	107/142	0.83 (0.565-1.213)
Rest of world	181/225	0.58 (0.431-0.784)
ECOG performance status		
0	141/202	0.58 (0.416-0.816)
1	273/349	0.65 (0.515-0.830)
Primary tumor location		
GEJ	103/138	0.57 (0.384-0.852)
Stomach	311/413	0.65 (0.521-0.815)
Histologic subtype		
Diffuse	161/191	0.57 (0.415-0.779)
Intestinal	143/210	0.77 (0.556-1.073)
Indeterminate	109/149	0.49 (0.327-0.724)
Disease status		
Metastatic	398/526	0.64 (0.524-0.780)
Liver metastases		
No	245/322	0.60 (0.464-0.769)
Yes	169/229	0.69 (0.511-0.940)
Prior gastrectomy/esophagectomy		
No	360/462	0.65 (0.526-0.800)
Yes	53/88	0.62 (0.360-1.060)
Chemo choice at randomization		
CAPOX	351/477	0.63 (0.512-0.781)
FP	63/74	0.62 (0.378-1.029)



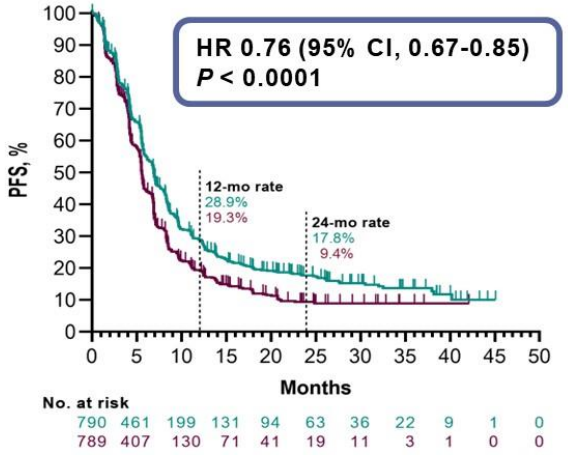
Data cutoff date: October 3, 2022.

Sun Young Rha et Al, ASCO23

Secondary Endpoints: PFS, ORR, and DOR

Overall[1]

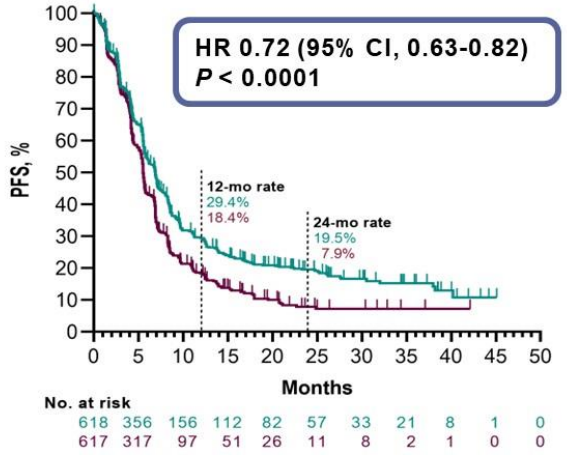
	Pts w/ Event	Median PFS (95% CI), mo
Pembro + chemo	72.4%	6.9 (6.3-7.2)
Placebo + chemo	77.1%	5.6 (5.5-5.7)



	Pembro + Chemo	Placebo + Chemo
ORR, % (95% CI)	51.3% (47.7-54.8)	42.0% (38.5-45.5)
Δ (95% CI)	9.3 (4.4-14.1); *P* = 0.00009	
mDOR (range)	8.0 mo (1.2+ - 41.5+)	5.7 mo (1.3+ - 34.7+)

PD-L1 CPS ≥1

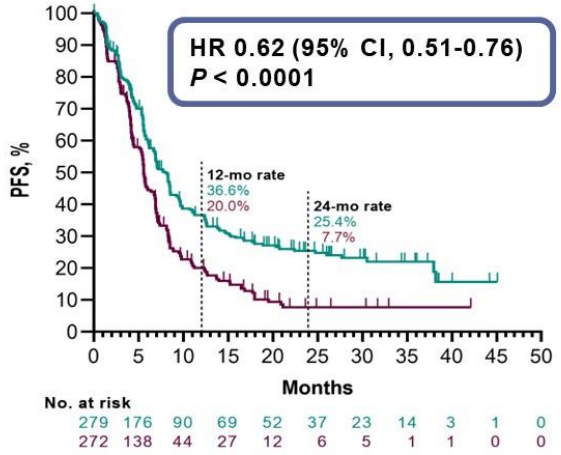
	Pts w/ Event	Median PFS (95% CI), mo
Pembro + chemo	71.7%	6.9 (6.0-7.2)
Placebo + chemo	78.3%	5.6 (5.4-5.7)



	Pembro + Chemo	Placebo + Chemo
ORR, % (95% CI)	52.1% (48.1-56.1)	42.6% (38.7-46.6)
Δ (95% CI)	9.5 (3.9-15.0); *P* = 0.00041	
mDOR (range)	8.3 mo (1.2+ - 41.5+)	5.6 mo (1.3+ - 34.2+)

PD-L1 CPS ≥10

	Pts w/ Event	Median PFS (95% CI), mo
Pembro + chemo	68.1%	8.1 (6.8-8.5)
Placebo + chemo	77.2%	5.6 (5.4-6.7)



	Pembro + Chemo	Placebo + Chemo
ORR, % (95% CI)	60.6% (54.6-66.3)	43.0% (37.1-49.1)
Δ (95% CI)	17.5 (9.3-23.5); *P* = 0.00002	
mDOR (range)	10.9 mo (1.2+ - 41.5+)	5.8 mo (1.4+ - 31.2+)

1. Rha SY et al. *Ann Oncol* 2023;34:319-320. Response was assessed per RECIST v1.1 by blinded, independent central review. Data cutoff date: October 3, 2022.

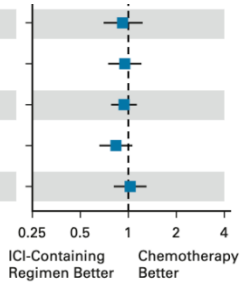
Sun Young Rha et Al, ASCO23

	Keynote 859	Checkmate 649
	n=1579 double-blind, pembrolizumab vs. placebo + chemo	n= 1581 open-label, nivolumab vs. placebo + chemo
Inclusion criteria	▪ Known PD-L1-status (centrally determined IHC 22C3)	▪ Regardless PD-L1-status (Dako IHC 28-8 pharm Dx assay)
Endpoints	Primary: OS Secondary: PFS/ ORR both in CPS ≥ 10 and CPS ≥ 1	Dual primary: OS and PFS in CPS ≥ 5
Results Overall survival	All pts: HR 0.78 (95% CI 0.70-0.87), *P* < 0.0001	All pts: HR 0.80 (99.3% CI 0.68-0.94) P = 0.0002

Low Programmed Death-Ligand 1–Expressing Subgroup Outcomes of First-Line Immune Checkpoint Inhibitors in Gastric or Esophageal Adenocarcinoma

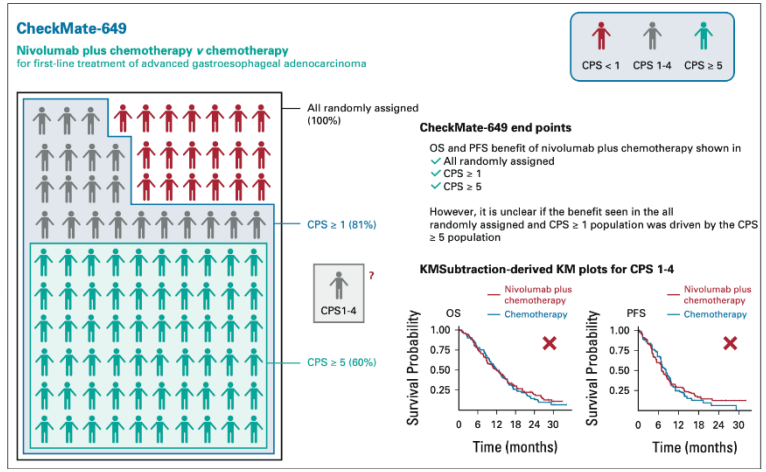
PD-L1 CPS 1-4 in CHECKMATE-649 and PD-L1 1-9 KEYNOTE-062 subgroups were identified with data unreported in the primary manuscript.

Trial	Comparison	No.	Location	PD-L1 Expression	HR (95% CI)
CheckMate-649	Nivolumab plus chemotherapy *v* chemotherapy	137 *v* 148	Gastric	CPS < 1	0.92 (0.70 to 1.23)
CheckMate-649	Nivolumab plus chemotherapy *v* chemotherapy	168 *v* 173	Gastric	CPS 1–4	0.95 (0.75 to 1.21)[a]
CheckMate-649	Nivolumab plus chemotherapy *v* chemotherapy	316 *v* 310	Gastric	CPS < 5	0.94 (0.78 to 1.13)
KEYNOTE-062	Pembrolizumab plus chemotherapy *v* chemotherapy	158 *v* 160	Gastric	CPS 1–9	0.84 (0.66 to 1.06)[a]
KEYNOTE-062	Pembrolizumab *v* chemotherapy	164 *v* 160	Gastric	CPS 1–9	1.03 (0.81 to 1.30)[a]

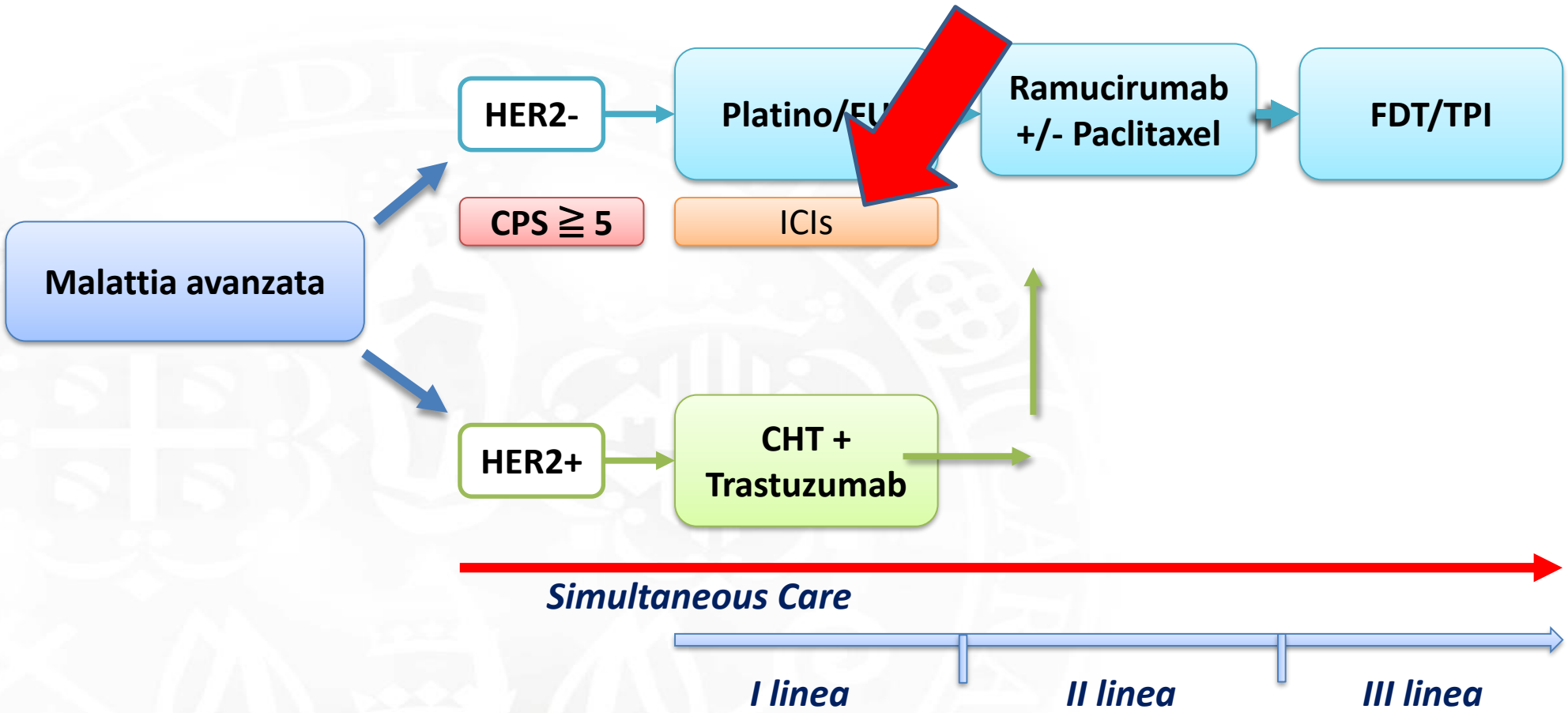


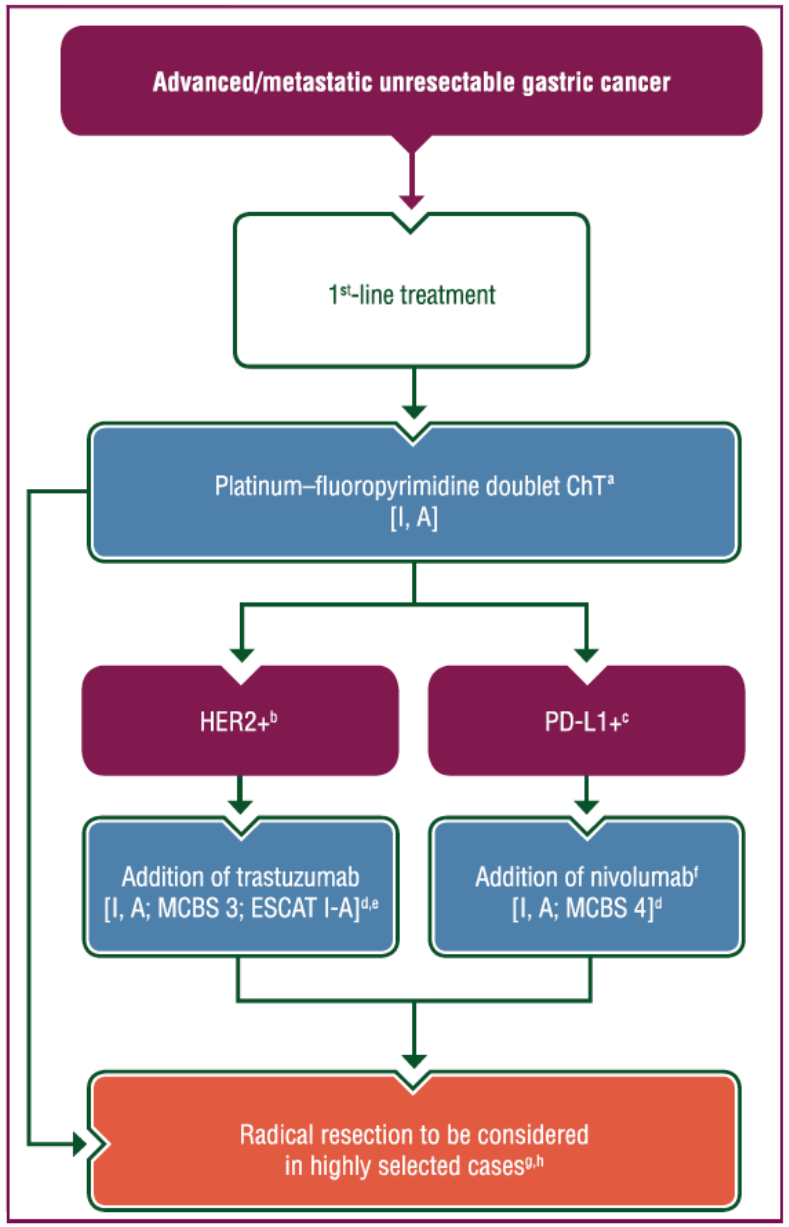
These data seem to suggest the lack of benefit in low PD-L1 expressing GEAC tumors.

KMSubtraction approach allows to reconstruct unreported Kaplan-Meier plots



Zhan JJ JCO 2022 & Cascinu S, ASCO GI 2022


HER2-
Platino/FU
Ramucirumab
+/- Paclitaxel
FDT/TPI
CPS ≧ 5
ICIs
Malattia avanzata
HER2+
CHT +
Trastuzumab
Simultaneous Care
I linea
II linea
III linea



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

F. Lordick[1], F. Carneiro[2,3,4], S. Cascinu[5], T. Fleitas[6], K. Haustermans[7], G. Piessen[8,9,10,11], A. Vogel[12] & E. C. Smyth[13], on behalf of the ESMO Guidelines Committee*

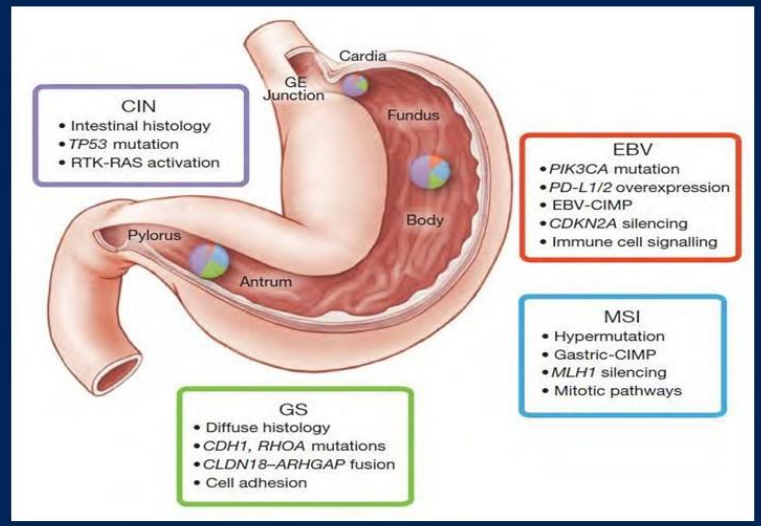
Surgery for metastatic gastric cancer

- Gastrectomy is not recommended in metastatic gastric cancer unless required for palliation of symptoms [I, D].
- Resection of metastases cannot be recommended in general, but might be considered as an individual approach in highly selected cases with oligometastatic disease and response to ChT [V, C].

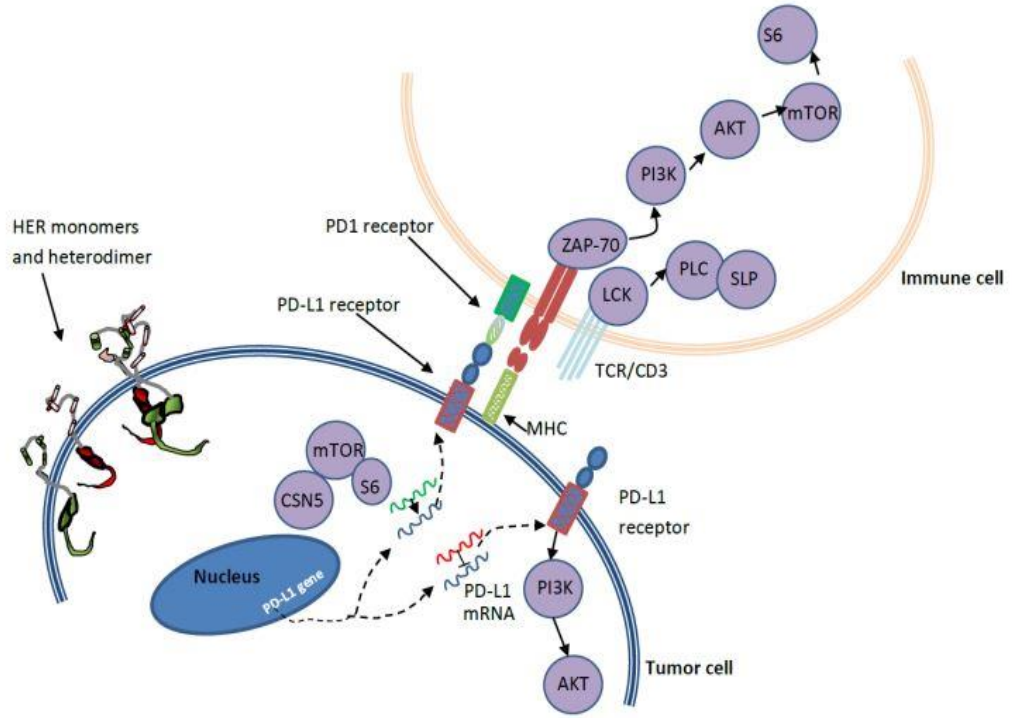
Lordick F et Al, Ann Oncol 2022

To be discussed – other targets, other therapies

- GS subtype: Claudin 18.2
- CIN/GS subtype: FGFR
- CIN subtype: HER2
- Other targets: the tumor microenvironment …



Combining anti-HER2 and Immunotherapy

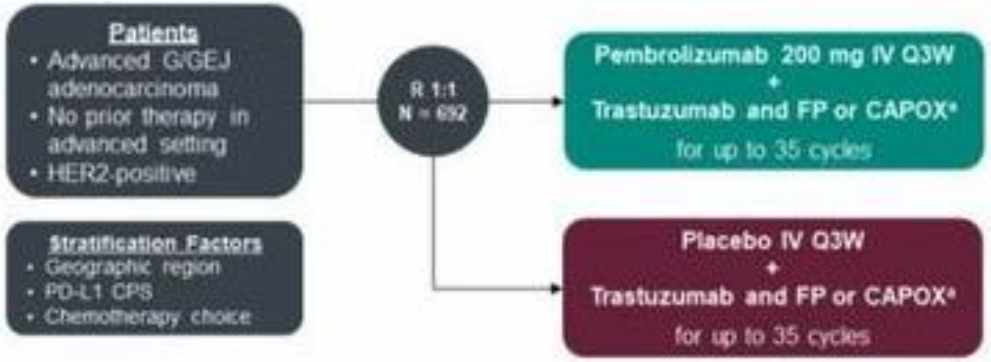


Trastuzumab **induces antibody-dependent cellular phagocytosis (ADCP) allowing uptake of tumor antigens by APC (dendritic cells)**

Oxaliplatin **induces immunogenic cell death of tumor cells, which activates APCs via calreticulin, HMGB1, and other damage-associated molecular patterns**

- R. Padmanabhan et al. Crosstalk between HER2 and PD-1/PD-L1 in Breast Cancer: From Clinical Applications to Mathematical Models. Cancers, 10 March 2020
- Krasniqi E, Barchiesi G, Pizzuti L et al. Immunotherapy in HER2-positive breast cancer: state of the art and future perspectives. J. Hematol. Oncol. 12(1), 111 (2019).
- Chaganty BKR, Qiu S, Gest A et al. Trastuzumab upregulates PD-L1 as a potential mechanism of trastuzumab resistance through engagement of immune effector cells and stimulation of IFNgamma secretion. Cancer Lett. 430, 47–56 (2018).

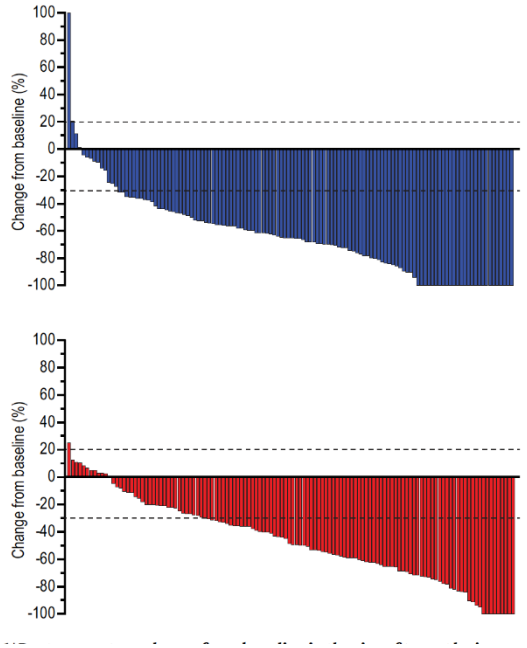
The KEYNOTE-811 trial of dual PD-1 and HER2 blockade in HER2-positive gastric cancer



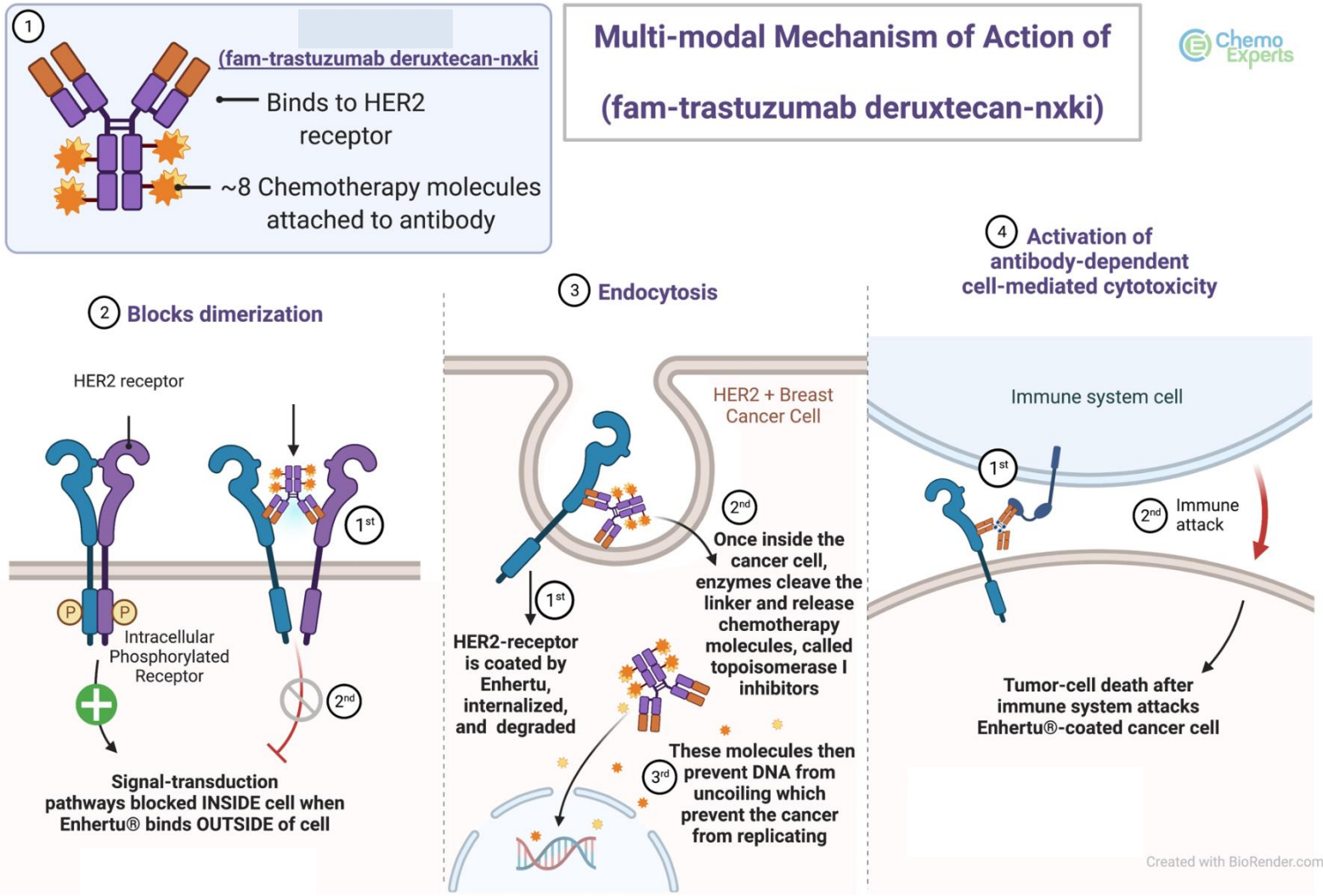
Dual Primary End Points
- OS
- PFS (RECIST v1.1 per BICR)

Secondary End Points
- ORR (RECIST v1.1 per BICR)
- DOR (RECIST v1.1 per BICR)
- Safety

Variable	Pembrolizumab group (*n* = 133)	Placebo group (*n* = 131)
Objective response (% (95% confidence interval))[a]	74.4 (66.2–81.6)	51.9 (43.0–60.7)
Disease control (% (95% confidence interval))[b]	96.2 (91.4–98.8)	89.3 (82.7–94.0)
Best overall response (number (%))		
Complete response	15 (11.3)	4 (3.1)
Partial response	84 (63.2)	64 (48.9)
Stable disease	29 (21.8)	49 (37.4)
Progressive disease	5 (3.8)	7 (5.3)
Not evaluable[c]	0 (0.0)	2 (1.5)
Not assessed[c]	0 (0.0)	5 (3.8)



Janjigian, Lancet 2021



https://www.chemoexperts.com/fam-trastuzumab-deruxtecan-nxki-enhertu.html

Updated Analysis of DESTINY-Gastric02: a Phase 2 Single-Arm Trial of Trastuzumab Deruxtecan (T-DXd) in Western Patients with HER2-Positive Unresectable/Metastatic Gastric/Gastroesophageal Junction (GEJ) Cancer Who Progressed on or After Trastuzumab-Containing Regimen

Key eligibility criteria

- Pathologically documented, unresectable or metastatic gastric or GEJ cancer
- Centrally confirmed HER2 positive disease (defined as IHC 3+ or IHC 2+/ISH+) on biopsy after progression on first-line trastuzumab-containing regimen
- ECOG PS 0 or 1

→ T-DXd 6.4 mg/kg Q3W N = 79[a] →

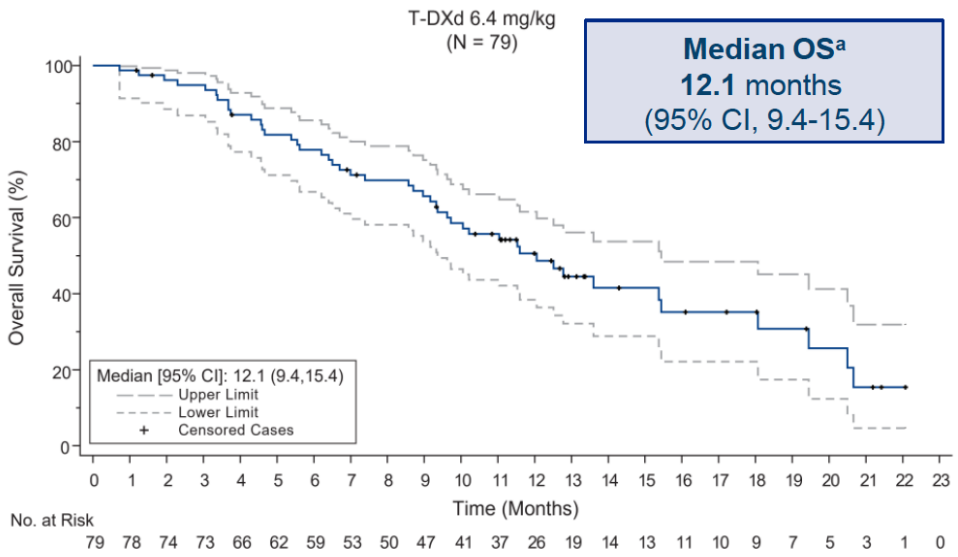
Primary endpoint

- Confirmed ORR by ICR

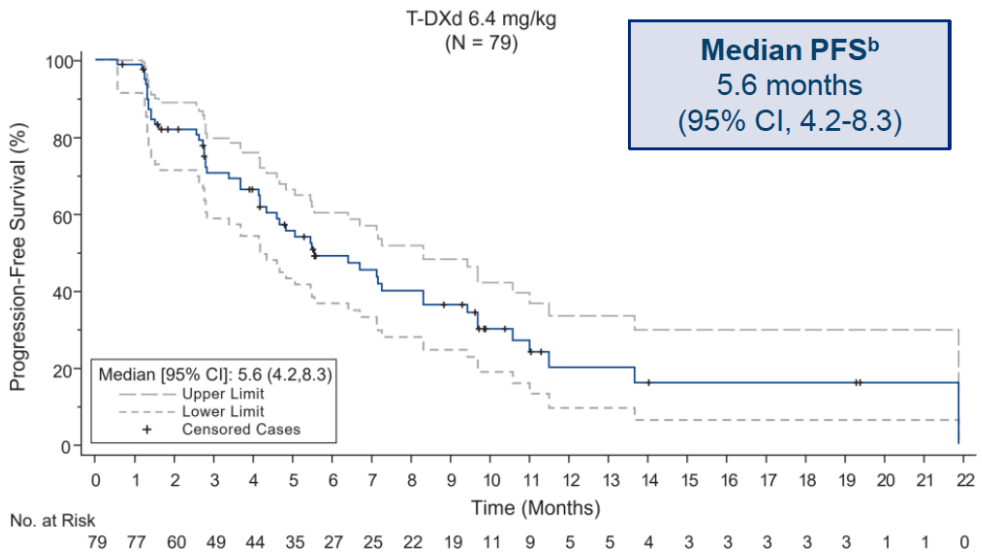
Secondary endpoints[b]

- PFS by ICR
- OS
- DoR
- Safety
- Patient-reported outcomes

Kaplan-Meier Plot of OS

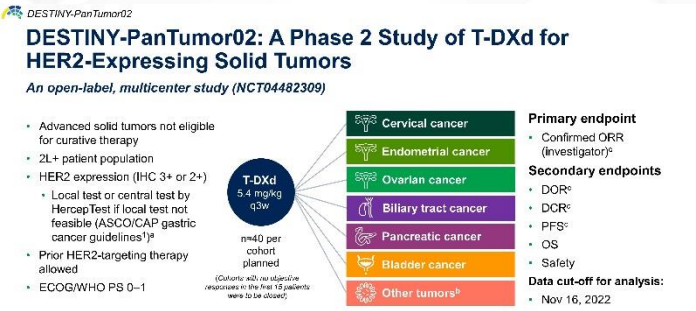


Kaplan-Meier Plot of PFS by ICR



Ku, ESMO 2022

DESTINY PanTumor02: Phase 2

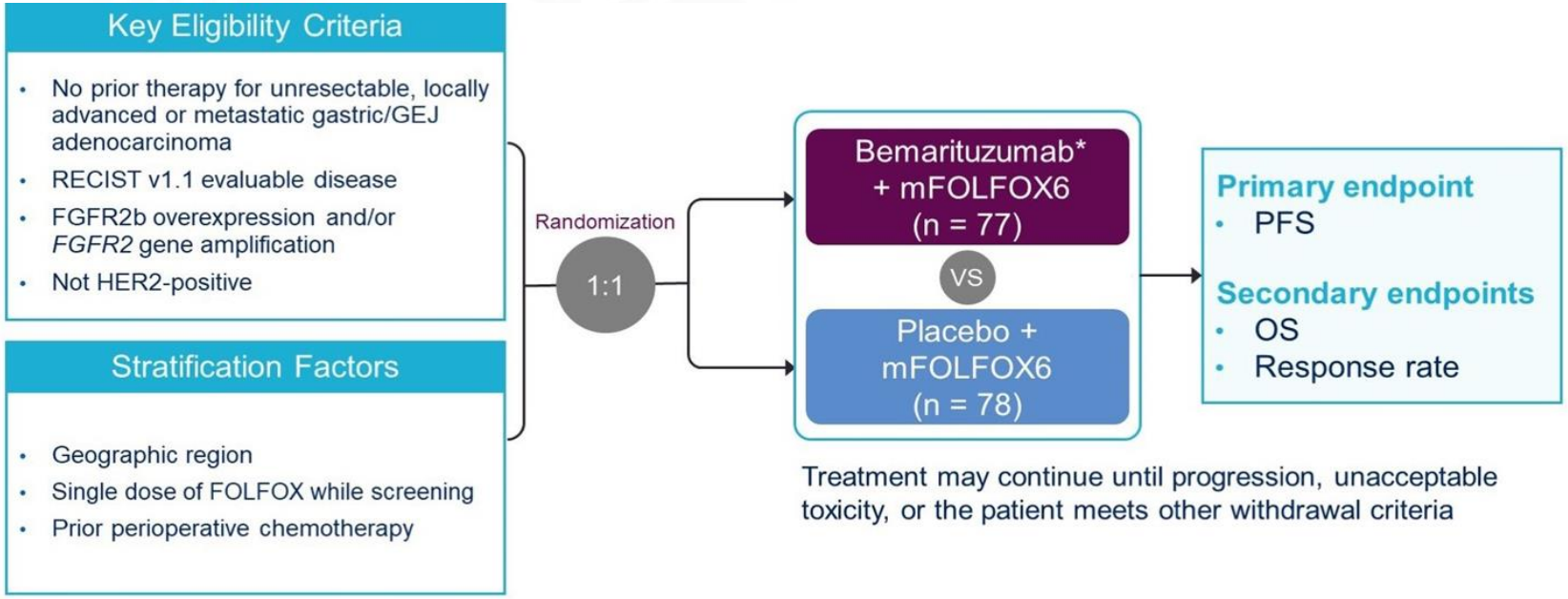


		Cervical (n=40)	Endometrial (n=40)	Ovarian (n=40)	BTC (n=41)	Pancreatic (n=25)	Bladder (n=41)	Other (n=40)	All patients (N=267)
Investigator assessment									
ORR, n (%)		**20 (50.0)**	**23 (57.5)**	**18 (45.0)**	**9 (22.0)**	**1 (4.0)**	**16 (39.0)**	**12 (30.0)**	**99 (37.1)**
Best overall response, n (%)	Complete response	2 (5.0)	7 (17.5)	4 (10.0)	1 (2.4)	0	1 (2.4)	0	15 (5.6)
	Partial response	18 (45.0)	16 (40.0)	14 (35.0)	8 (19.5)	1 (4.0)	15 (36.6)	12 (30.0)	84 (31.5)
	Stable disease	12 (30.0)	13 (32.5)	14 (35.0)	25 (61.0)	17 (68.0)	18 (43.9)	24 (60.0)	123 (46.1)
	PD	7 (17.5)	4 (10.0)	7 (17.5)	7 (17.1)	7 (28.0)	7 (17.1)	3 (7.5)	42 (15.7)
	Not evaluable	1 (2.5)	0	1 (2.5)	0	0	0	1 (2.5)	3 (1.1)
DCR[a] at 12 weeks, n (%)		27 (67.5)	32 (80.0)	28 (70.0)	27 (65.9)	9 (36.0)	29 (70.7)	30 (75.0)	182 (68.2)
Median DOR, months (95% CI)		9.8 (4.2–NE)	NR (9.9–NE)	11.3 (4.1–NE)	8.6 (2.1–NE)	NR	8.7 (4.3–11.8)	NR (4.1–NE)	11.8 (9.8–NE)
Independent central review: ORR, n (%)		16 (40.0)	21 (52.5)	17 (42.5)	11 (26.8)	3 (12.0)	17 (41.5)	13 (32.5)	98 (36.7)

Funda Meric-Berstam, ASCO 2023

FGFR-2 Amplification: 15%

Bemarituzumab is a first-in-class, humanized IgG1 monoclonal antibody that selectively binds to FGFR2b, inhibits ligand binding, and mediates antibody-dependent cell-mediated cytotoxicity

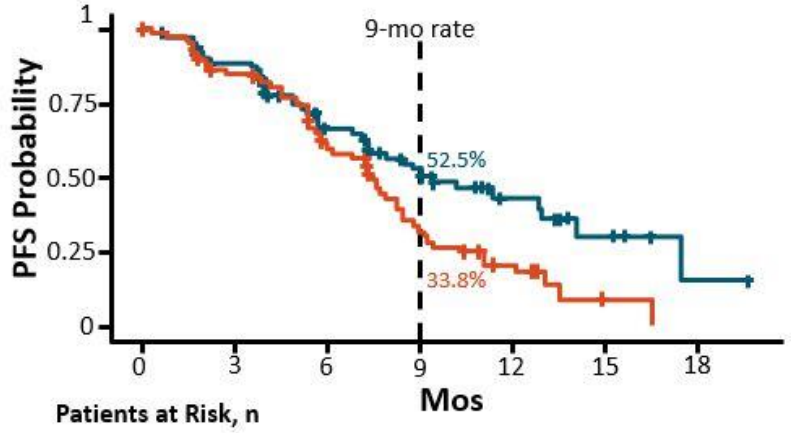


*Bemarituzumab dosing: 15 mg/kg Q2W beginning cycle 1 day 1 (plus 1 dose of 7.5 mg/kg on day 8 of cycle 1 only). FOLFOX6 dosing: standard fixed doses Q2W.
FGFR2b, fibroblast growth factor receptor 2b.

Wainberg et Al, ASCO GI 2021 & Lancet Oncol 2022

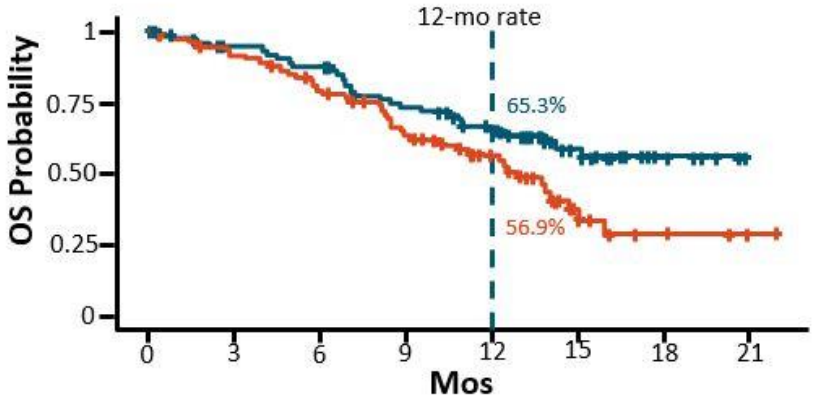
Biomarkers: Fibroblast Growth Factor Receptor 2 (FGFR-2)

FIGHT: PFS and OS



Patients at Risk, n

Bema + mFOLFOX6	77	62	40	28	12	5	1
Placebo + mFOLFOX6	78	59	37	19	9	1	0



	77	68	63	50	38	21	6	0
	78	68	57	42	27	10	4	1

	Bema + mFOLFOX6 (n = 77)	Placebo + mFOLFOX6 (n = 78)
Median PFS, mos	9.5	7.4
HR (95% CI)	0.68 (0.44-1.04; *P* = .0727)	

	Bema + mFOLFOX6 (n = 77)	Placebo + mFOLFOX6 (n = 78)
Median OS, mos	Not reached	12.9
HR (95% CI)	0.58 (0.35-0.95; *P* = .0268)	

Wainberg et Al, ASCO GI 2021 & Lancet Oncol 2022

Study Design: SPOTLIGHT

Global[a], randomized, double-blinded, placebo-controlled, phase 3 trial

Key Eligibility Criteria

- Previously untreated LA unresectable or mG/GEJ adenocarcinoma
- CLDN18.2+ (moderate-to-strong CLDN18 staining in ≥75% of tumor cells)[b]
- HER2–[c]
- ECOG PS 0–1

Stratification Factors

- Region (Asia vs non-Asia)
- Number organs w/ metastases (0–2 vs ≥3)
- Prior gastrectomy (yes vs no)

Planned (N ≈ 550)

R 1:1

(N = 283)

Zolbetuximab 800/600[d] mg/m² IV Q3W + mFOLFOX6 IV Q2W

Cycles 1–4 (42 days/cycle)

Zolbetuximab 600 mg/m² IV Q3W + 5-FU + folinic acid IV Q2W

Cycles 5+

(N = 282)

Placebo IV Q3W + mFOLFOX6 IV Q2W

Cycles 1–4 (42 days/cycle)

Placebo IV Q3W + 5-FU + folinic acid IV Q2W

Cycles 5+

Primary End Point

- PFS[e]

Key Secondary End Points

- OS
- TTCD in GHS/QoL, PF, and OG25-Pain

Secondary End Points

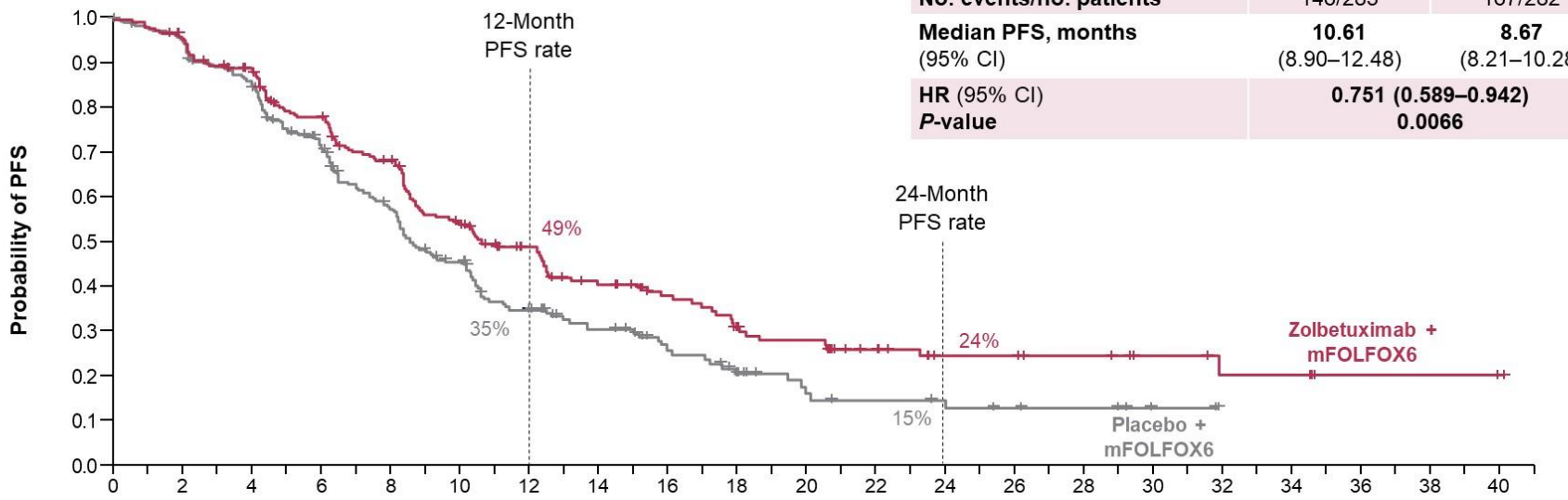
- ORR[e]
- DOR[e]
- Safety
- PROs

[a]Study was conducted at 215 sites in 20 countries across Australia, Asia, Europe, N. America, and S. America; [b]By central IHC using the analytically validated VENTANA CLDN18 (43-14A) RxDx Assay; [c]By central or local HER2 testing; [d]800 mg/m² at cycle 1 day 1 followed by 600 mg/m² on cycle 1 day 22 and days 1 and 22 of subsequent cycles; [e]Per RECIST v1.1 by independent review committee.

PRESENTED BY: Dr. Kohei Shitara

Primary End Point: PFS by Independent Review Committee[a]

	Zolbetuximab + mFOLFOX6	Placebo + mFOLFOX6
No. events/no. patients	146/283	167/282
Median PFS, months (95% CI)	**10.61** (8.90–12.48)	**8.67** (8.21–10.28)
HR (95% CI)	**0.751 (0.589–0.942)**	
***P*-value**	**0.0066**	



No. at Risk

Zolbetuximab + mFOLFOX6	283	263	254	232	226	190	187	148	143	108	102	84	78	59	56	53	43	40	33	28	28	21	19	17	12	12	12	10	10	9	7	7	5	5	5	2	2	2	2	2	1	0
Placebo + mFOLFOX6	282	273	260	237	226	183	168	136	122	91	83	60	56	43	40	38	26	25	19	14	12	9	9	9	8	7	6	5	5	4	2	2	0	0	0	0	0	0	0	0	0	0

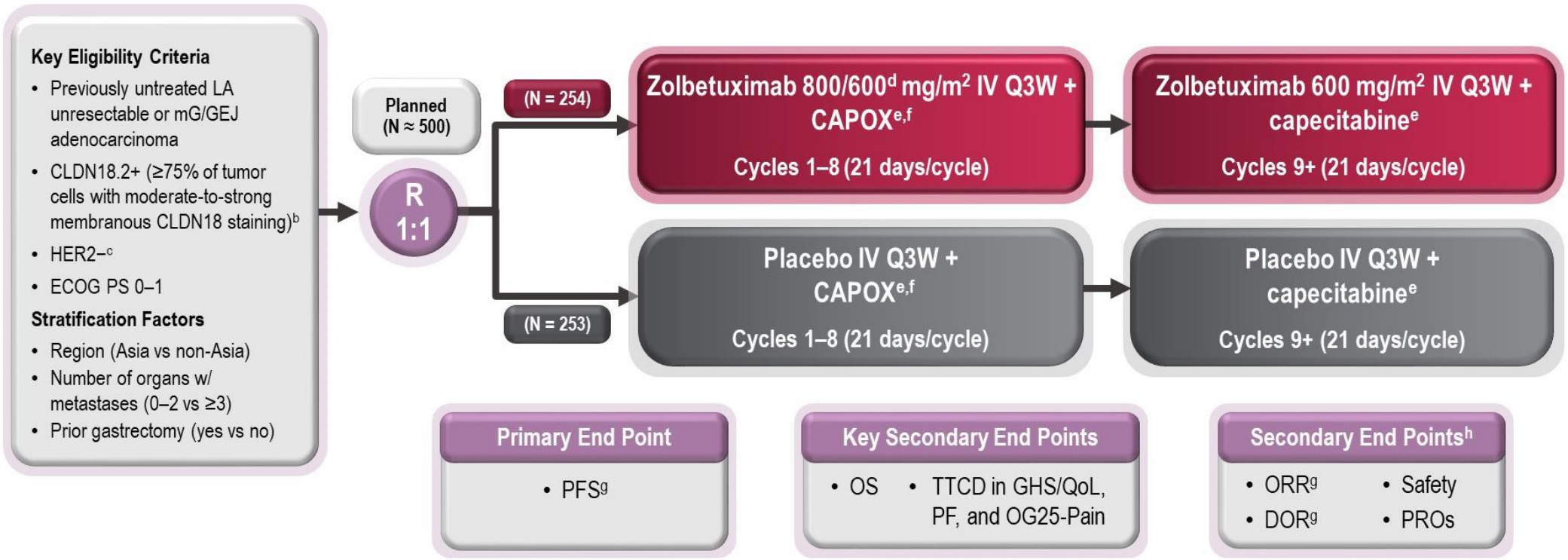
- PFS was significantly longer in patients treated with zolbetuximab + mFOLFOX6 vs placebo + mFOLFOX6

Data cutoff: September 9, 2022; Median follow-up = 12.94 months (zolbetuximab + mFOLFOX6) vs 12.65 months (placebo + mFOLFOX6).

[a]Per RECIST version 1.1.

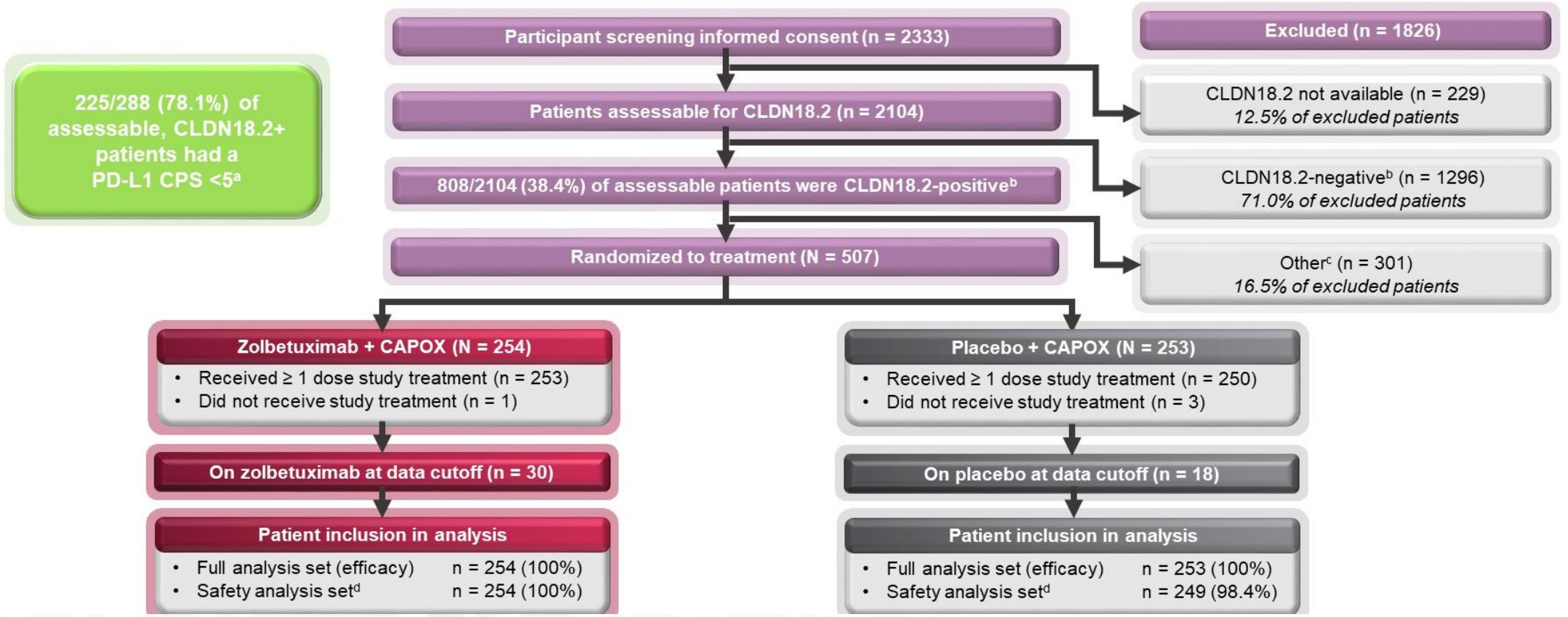
PRESENTED BY: Dr. Kohei Shitara

The GLOW trial



Rui-Hua Xu et Al, ASCO 2023

The GLOW trial



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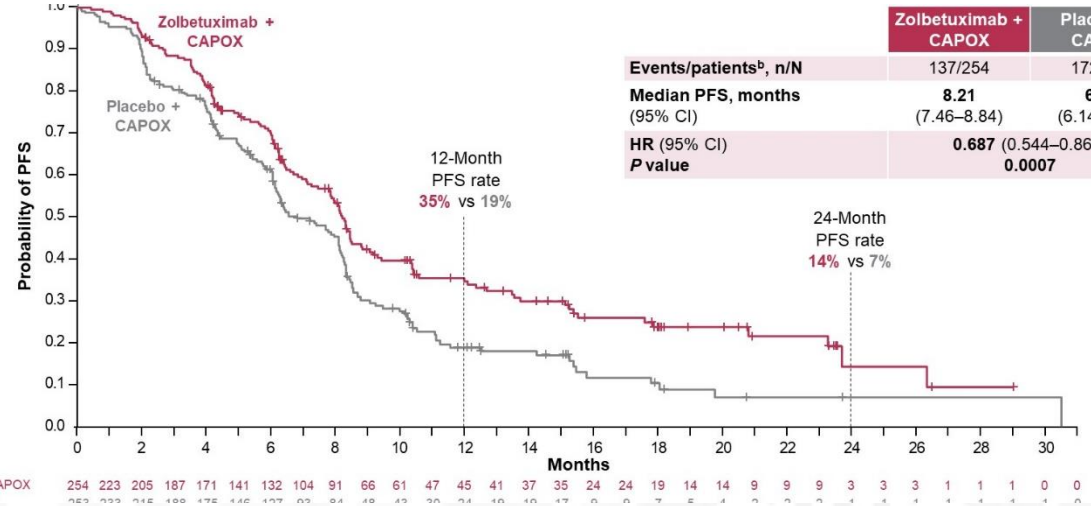
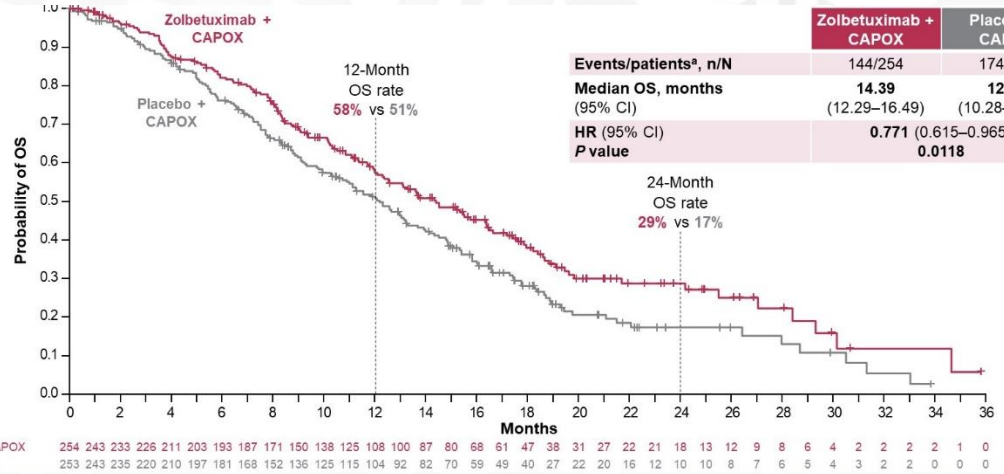
PFS (Primary)



	Zolbetuximab + CAPOX	Placebo + CAPOX
Events/patients[b], n/N	137/254	172/253
Median PFS, months (95% CI)	**8.21** (7.46–8.84)	**6.80** (6.14–8.08)
HR (95% CI)	**0.687** (0.544–0.866)	
***P* value**	**0.0007**	

OS (Secondary)



	Zolbetuximab + CAPOX	Placebo + CAPOX
Events/patients[a], n/N	144/254	174/253
Median OS, months (95% CI)	**14.39** (12.29–16.49)	**12.16** (10.28–13.67)
HR (95% CI)	**0.771** (0.615–0.965)	
***P* value**	**0.0118**	

RR (Secondary)

	Zolbetuximab + CAPOX (N = 195)	Placebo + CAPOX (N = 205)
ORR[b], n (%)	105 (53.8)	100 (48.8)
95% CI	46.58–60.99	41.76–55.84
BOR[c,d], n (%)		
CR	6 (3.1)	3 (1.5)
PR	99 (50.8)	97 (47.3)
SD	46 (23.6)	57 (27.8)
PD	10 (5.1)	25 (12.2)
Median DOR[b,e], months (95% CI)	6.28 (5.39–8.28)	6.18 (4.53–6.41)

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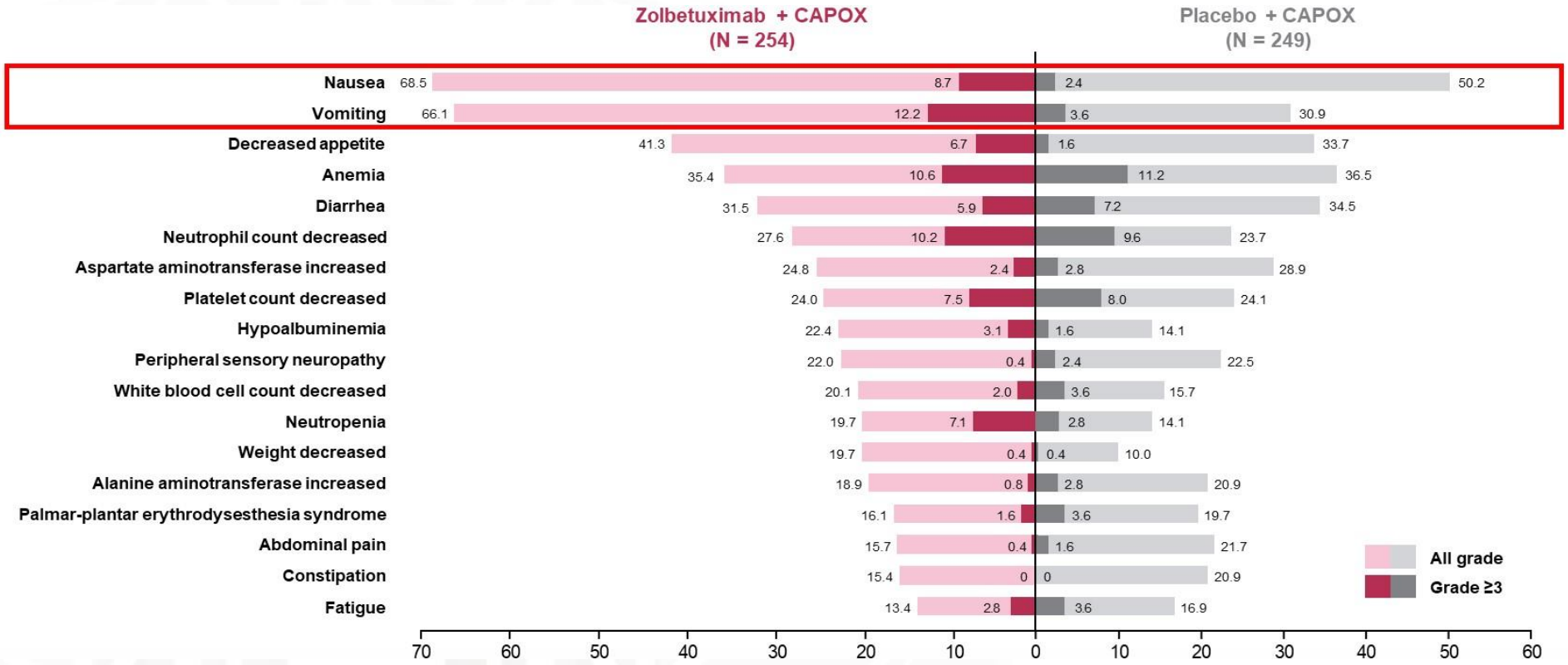
TEAEs[a] Occurring in ≥15% of All Treated Patients



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FLOW CHART carcinoma gastrico metastatico