Gastro-esophageal Cancer Update

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2023 ASCO ANNUAL MEETING

ATTRACTION-5: A Phase 3 study of nivolumab plus chemotherapy as postoperative adjuvant treatment for pathological stage III gastric or gastroesophageal junction cancer

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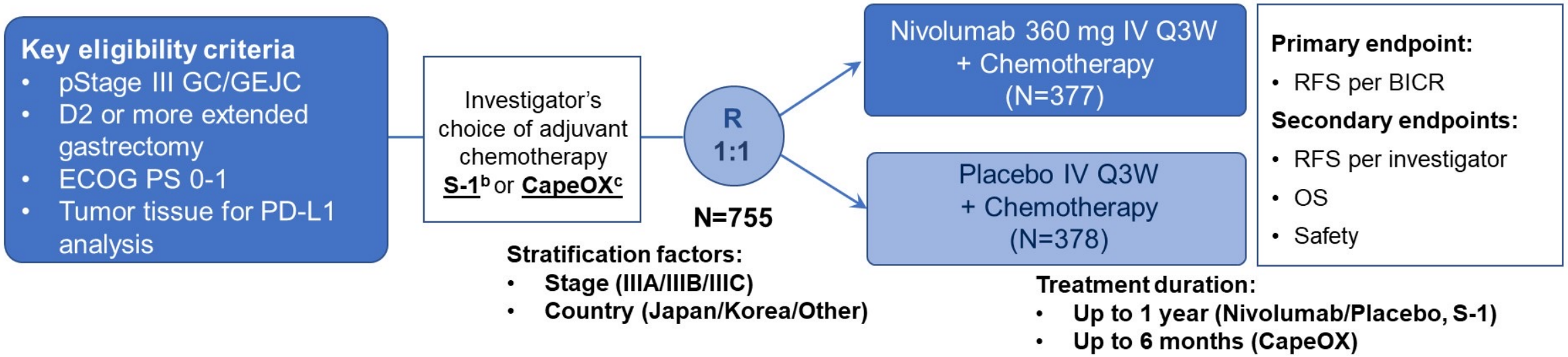
Study design

- Phase 3, double-blind, placebo-controlled study of Asian patients (Japan, Korea, Taiwan, China)[a]

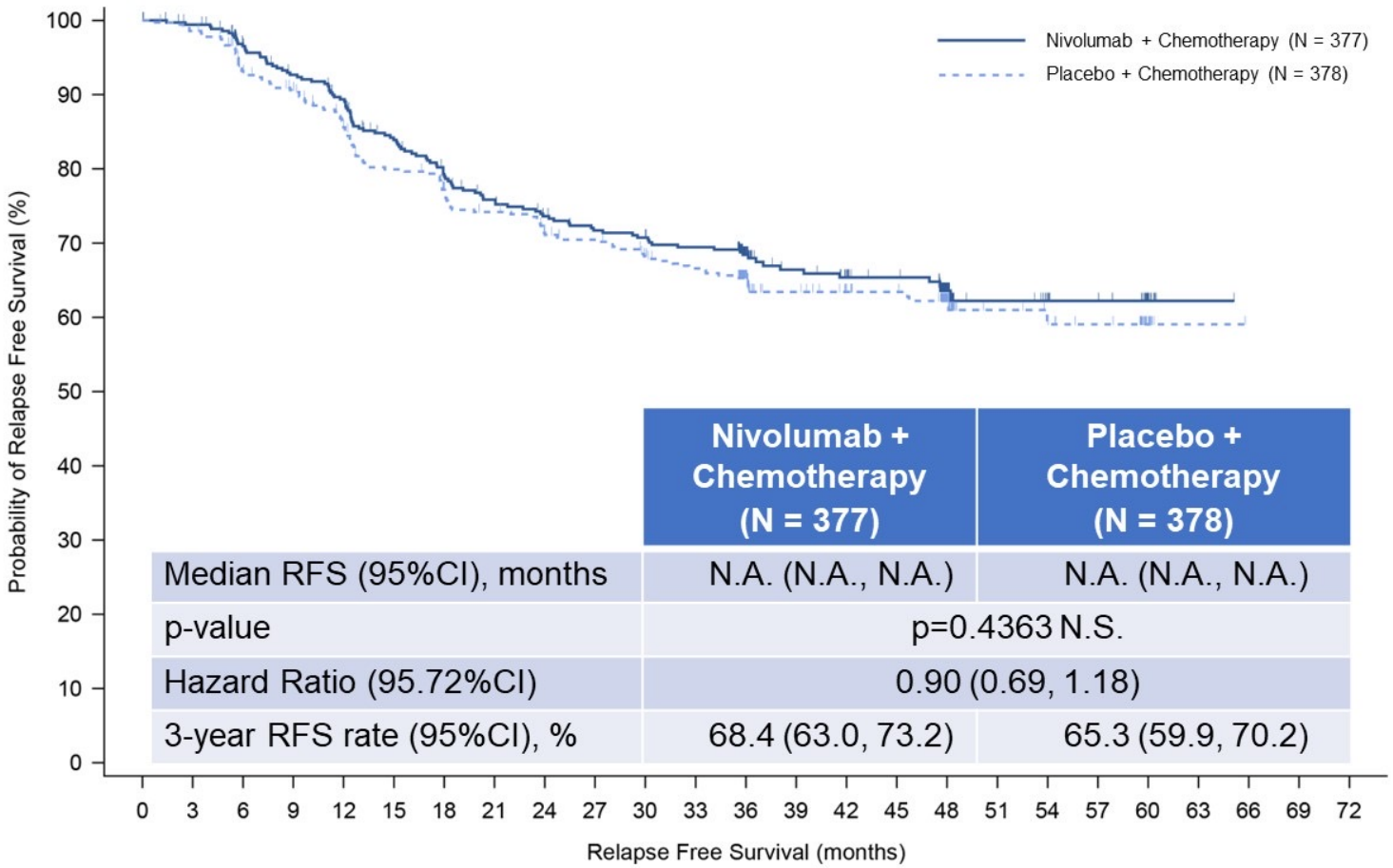


- Planned sample size: 700 patients (assuming HR=0.67; 3-year RFS, 71% vs 60%)
- Patients were randomized from February 2017 to August 2019
- All data are based on a clinical data cutoff of August 2022, at which point the minimum follow-up after the last patient randomized was 36 months

[a]ClinicalTrials.gov number, NCT03006705; [b]**S-1 therapy:** S-1 40 mg/m^2/dose orally twice daily (day1-28) , Q6W; [c]**CapeOX therapy:** Oxaliplatin 130 mg/m^2 IV once daily (day1), and Capecitabine 1000 mg/m^2/dose orally twice daily (day1-14), Q3W.

Abbreviations: BICR, blinded independent central review; CapeOX, capecitabine/oxaliplatin; GC, gastric cancer; GEJC, gastroesophageal junction cancer; IV, intravenous; OS, overall survival; pStage III, pathological stage III; Q3W, every 3 weeks; Q6W, every 6 weeks; RFS, relapse-free survival; S-1, tegafur/gimeracil/oteracil.

Primary endpoint: RFS per BICR



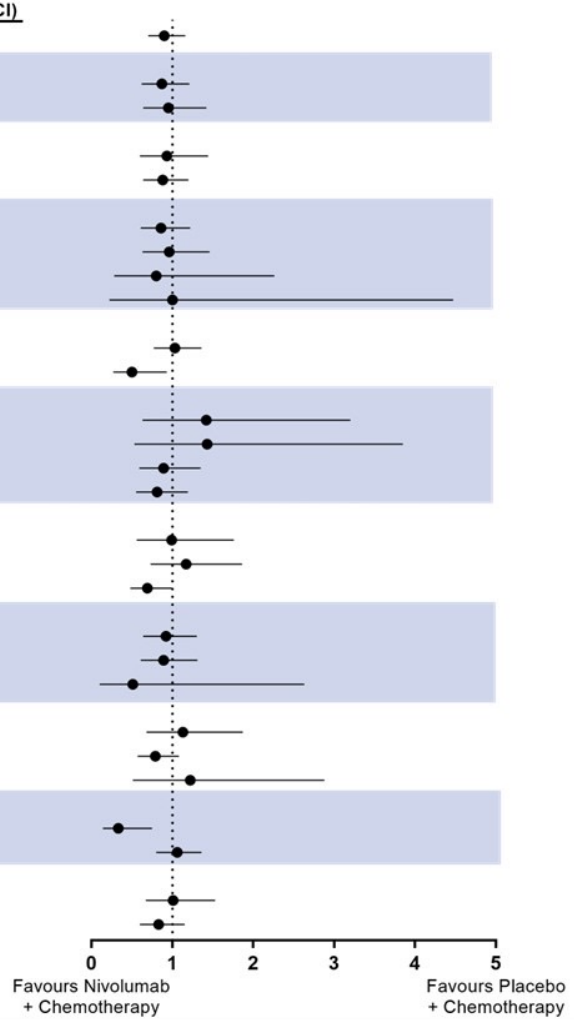
	Nivolumab + Chemotherapy (N = 377)	Placebo + Chemotherapy (N = 378)
Median RFS (95%CI), months	N.A. (N.A., N.A.)	N.A. (N.A., N.A.)
p-value	p=0.4363 N.S.	
Hazard Ratio (95.72%CI)	0.90 (0.69, 1.18)	
3-year RFS rate (95%CI), %	68.4 (63.0, 73.2)	65.3 (59.9, 70.2)

At Risk

Nivolumab + Chemotherapy	377	349	326	310	297	273	255	241	231	223	219	214	162	127	120	114	58	33	28	24	9	1	0	0	0
Placebo + Chemotherapy	378	353	324	311	288	267	254	242	228	223	212	204	148	118	110	107	57	33	30	26	10	1	0	0	0

RFS per BICR in subgroups

	Nivolumab + Chemotherapy Events/patients	Placebo + Chemotherapy Events/patients	Unstratified HR (95%CI)
Overall	113/377	124/378	0.90 (0.70-1.16)
Age			
<65 years	63/212	78/222	0.87 (0.62-1.21)
≥65years	50/165	46/156	0.95 (0.64-1.42)
Sex			
Female	39/110	43/115	0.93 (0.60-1.44)
Male	74/267	81/263	0.88 (0.64-1.20)
Country			
Japan	60/182	67/183	0.86 (0.61-1.22)
Korea	44/157	44/155	0.96 (0.63-1.46)
Taiwan	6/23	9/24	0.80 (0.28-2.26)
China	3/15	4/16	1.00 (0.22-4.47)
ECOG PS			
0	98/299	95/294	1.03 (0.77-1.36)
1	15/78	29/84	0.50 (0.27-0.93)
Primary sites			
GEJ	10/21	14/31	1.42 (0.63-3.20)
Gastric fundus	9/26	7/25	1.43 (0.53-3.85)
Gastric corpus	44/161	46/154	0.89 (0.59-1.35)
Gastric antrum and pylorus	50/169	57/168	0.81 (0.55-1.19)
Pathological stage			
IIIA	23/110	24/111	0.99 (0.56-1.76)
IIIB	37/127	33/129	1.17 (0.73-1.86)
IIIC	53/140	67/138	0.69 (0.48-0.99)
Type of surgery			
Total gastrectomy	61/164	64/164	0.92 (0.64-1.30)
Distal gastrectomy	50/204	55/199	0.89 (0.61-1.31)
Others	2/9	5/15	0.51 (0.10-2.63)
Histology			
Intestinal type	31/134	29/140	1.13 (0.68-1.87)
Diffuse type	71/213	83/209	0.79 (0.57-1.08)
Others	11/30	10/26	1.22 (0.51-2.88)
Tumor cell PD-L1 expression			
≥1%	9/52	15/34	0.33 (0.14-0.75)
<1%	103/309	106/333	1.06 (0.81-1.40)
Chemotherapy regimen			
S-1	46/132	45/135	1.01 (0.67-1.53)
CapeOX	67/245	79/243	0.83 (0.60-1.15)



Summary

- ATTRACTION-5, a phase 3 study that compared adjuvant nivolumab + chemotherapy with placebo + chemotherapy in patients with pStage III G/GEJ cancer, did not meet the primary endpoint of RFS

- Safety of nivolumab + chemotherapy was consistent with the known safety profile of nivolumab and each adjuvant chemotherapy

- Further analyses are necessary to understand the outcome of ATTRACTION-5, since relatively favorable results were observed in some subgroups

Demographic and Clinical Characteristics of the Patients at Baseline.*

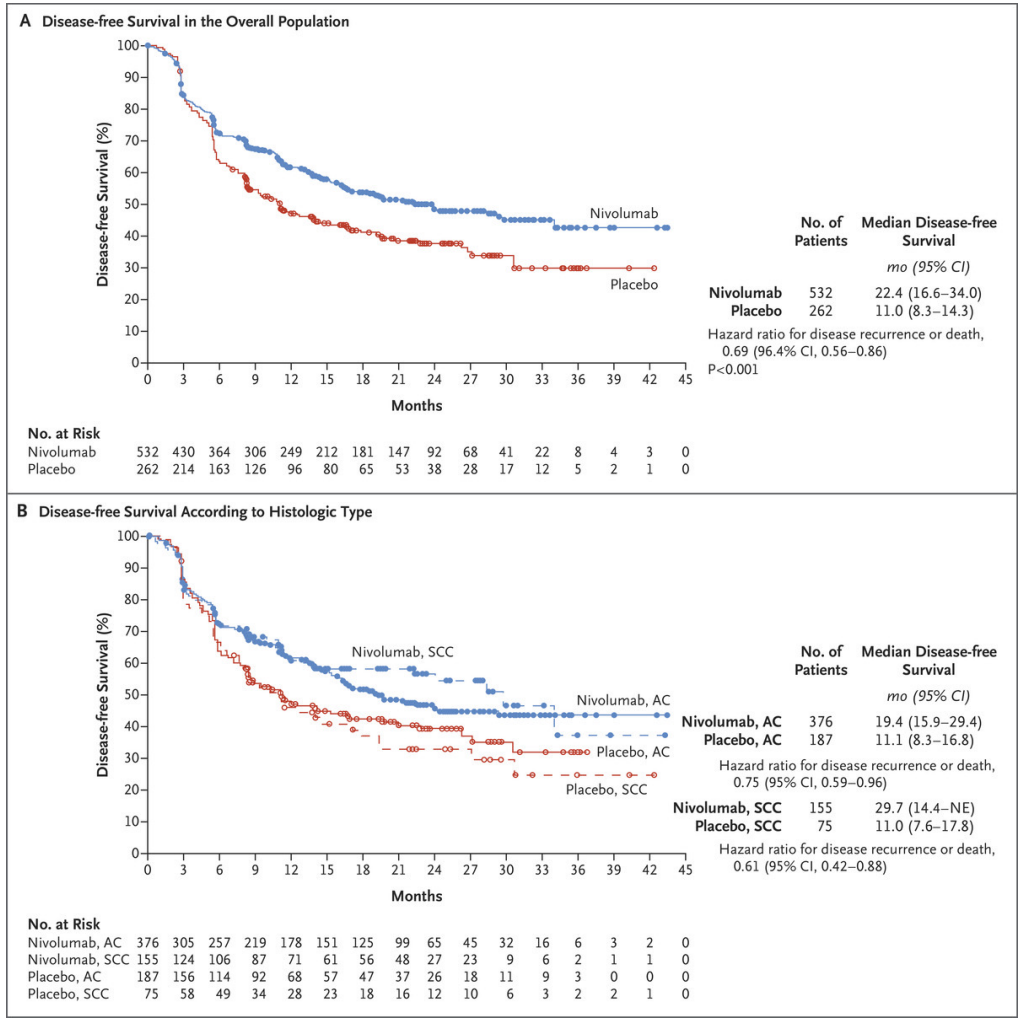
Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Nivolumab (N = 532)	Placebo (N = 262)
Median age (range) — yr	62 (26–82)	61 (26–86)
Male sex — no. (%)	449 (84)	222 (85)
Race — no. (%)†		
White	432 (81)	216 (82)
Asian	83 (16)	34 (13)
Black	7 (1)	2 (<1)
Other	10 (2)	9 (3)
Not reported	0	1 (<1)
Geographic region — no. (%)		
Europe	202 (38)	101 (39)
United States or Canada	167 (31)	88 (34)
Asia	77 (14)	29 (11)
Rest of the world‡	86 (16)	44 (17)
ECOG performance-status score — no. (%)§		
0	308 (58)	156 (60)
1	224 (42)	106 (40)
Disease stage at initial diagnosis — no. (%)		
II	179 (34)	99 (38)
III	351 (66)	163 (62)
Not reported	2 (<1)	0
Tumor location at trial entry — no. (%)		
Esophagus	311 (58)	151 (58)
Gastroesophageal junction	221 (42)	111 (42)
Histologic type — no. (%)¶		
Adenocarcinoma	376 (71)	187 (71)
Squamous-cell carcinoma	155 (29)	75 (29)
Other	1 (<1)	0
Tumor-cell PD-L1 expression at trial entry — no. (%)‖		
<1%	374 (70)	196 (75)
≥1%	89 (17)	40 (15)
Indeterminate or could not be evaluated	69 (13)	26 (10)
Pathological lymph-node status at trial entry — no. (%)**		
≥ypN1	305 (57)	152 (58)
ypN0	227 (43)	109 (42)
Not known	0	1 (<1)
Pathological tumor status at trial entry — no. (%)**		
ypT0	31 (6)	16 (6)
ypT1 or ypT2	202 (38)	106 (40)
ypT3 or ypT4	296 (56)	140 (53)
Not known	3 (<1)	0

* Percentages may not total 100 because of rounding. ECOG denotes Eastern Cooperative Oncology Group, and PD-L1 programmed death ligand 1.
† Race was reported by the patients.
‡ The "rest of the world" category comprised Argentina, Australia, Brazil, Israel, Mexico, and Turkey.
§ ECOG performance-status scores range from 0 to 5, with higher scores indicating greater disability.
¶ One patient in the nivolumab group had a histologic type of "other" (protocol deviation).
‖ In most patients, tumor-cell PD-L1 expression was determined with the use of the PD-L1 IHC 28-8 pharmDX assay (Dako, Agilent Technologies) from a tumor tissue specimen obtained from the patient after completion of chemoradiotherapy. However, tumor tissue from 40 patients was quantifiable only before chemoradiotherapy.
** Pathological lymph-node status and tumor status are classified according to the criteria of the seventh edition of the *Cancer Staging Manual* of the American Joint Committee on Cancer.

RJ Kelly et al. N Engl J Med 2021;384:1191-1203.

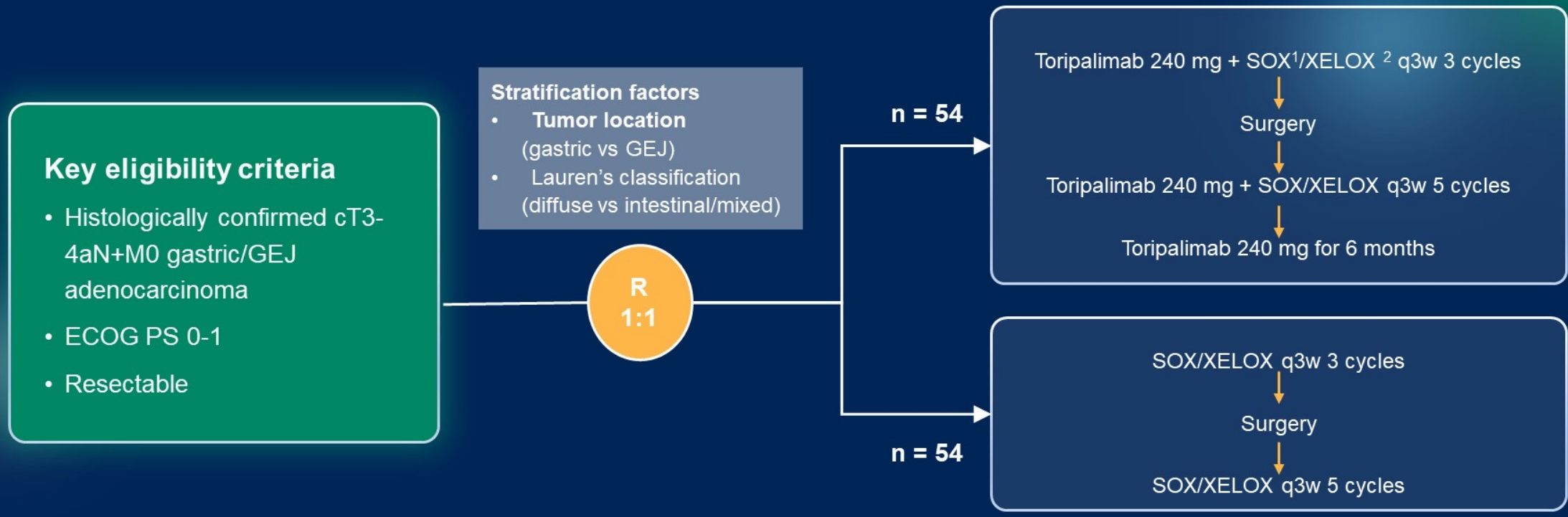
Disease-free Survival in the Intention-to-Treat Population.



RJ Kelly et al. N Engl J Med 2021;384:1191-1203.

Study design

This is a randomised, open-label, phase 2 trial



[1]S-1, 40-60 mg twice a day for 2 weeks followed by a rest of 1 week and oxaliplatin 130 mg/m^2, day 1, every 3 weeks; [2]Capecitabine 1000 mg/m2 twice a day for 2 weeks followed by a rest of 1 week and oxaliplatin 130 mg/m^2, day 1, every 3 weeks

Endpoints

Primary endpoint

TRG 0/1: rate of pathological complete response (TRG 0) or near complete response (TRG 1), according to NCCN guideline[1]

Tumor Regression Grade (TRG)	Microscopic findings
0 (complete response)	No viable cancer cells, including lymph nodes
1 (near complete response)	Single cells or rare small groups of cancer cells
2 (partial response)	Residual cancer cells with evident tumor regression but more than single cells or rare small groups of cancer cells
3 (poor or no response)	Extensive residual cancer with no evident tumor regression

[1] Shi C et al. College of American Pathologists 2005

Pathological outcomes-tumor regression grade

	Toripalimab + chemotherapy (n = 54)	Chemotherapy (n = 54)	P value
TRG			
TRG 0 (ypT0N0M0)	**12 (22%)**	**4 (7%)**	0.03
TRG 1	12 (22%)	7 (13%)	
TRG 2	16 (30%)	29 (54%)	
TRG 3	11 (20%)	12 (22%)	
Combined TRG 0-1	**24 (44%)**	**11 (20%)**	0.01
No surgery	3 (6%)	2 (4%)	

Primary endpoint

Pathological outcomes-tumor regression grade

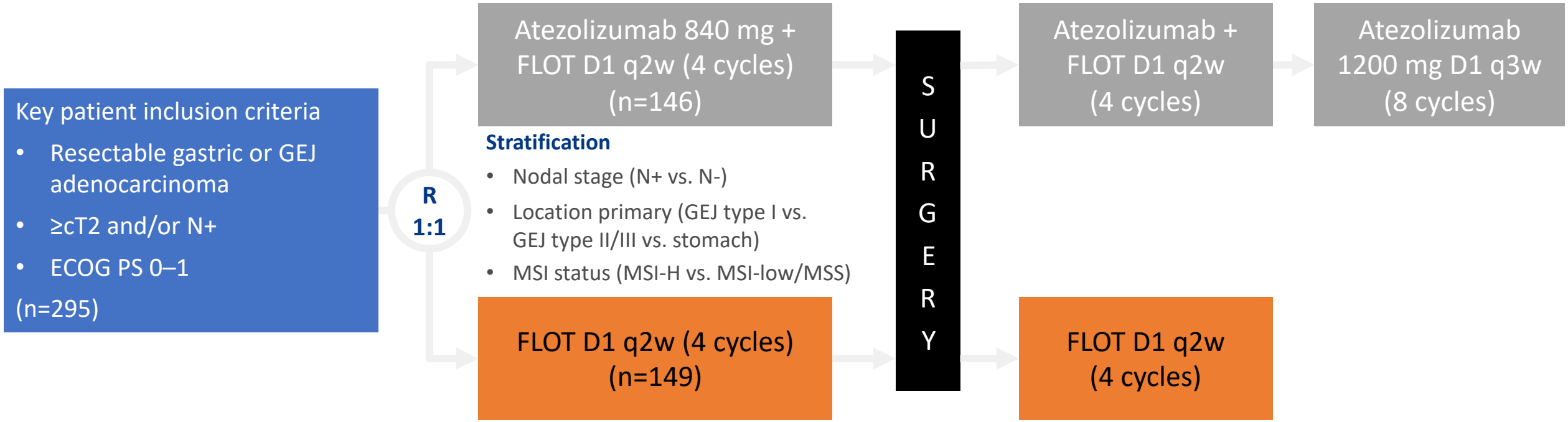
TRG 0/1 stratified by tumor location and Lauren's classification

	Toripalimab + chemotherapy (n = 54)	Chemotherapy (n = 54)
Tumor location		
Gastric	18/38 (49%)	9/34 (27%)
Gastro-oesophageal junction	6/17 (35%)	2/20 (10%)
Lauren's classification		
Diffuse	4/18 (22%)	3/20 (15%)
Intestinal/Mixed	20/36 (56%)	8/34 (24%)

4003: Surgical and pathological outcome, and pathological regression, in patients receiving perioperative atezolizumab in combination with FLOT chemotherapy versus FLOT alone for resectable esophagogastric adenocarcinoma: Interim results from DANTE, a randomized, multicenter, phase IIb trial of the FLOT-AIO German Gastric Cancer Group and Swiss SAKK – Al-Batran S-E, et al

Study objective

- To evaluate the efficacy and safety of atezolizumab + FLOT in patients with resectable esophagogastric adenocarcinoma in German and Swiss centers in the phase 2b DANTE study (interim analysis)



PRIMARY ENDPOINTS

- PFS, DFS

SECONDARY ENDPOINTS

- Surgical outcomes, OS, safety

FLOT, docetaxel 50 mg/m^2 + oxaliplatin 85 mg/m^2 + leucovorin 200 mg/m^2 + 5FU 2600 mg/m^2 D1 IV

Al-Batran S-E, et al. J Clin Oncol 2022;40(suppl):abstr 4003

4003: Surgical and pathological outcome, and pathological regression, in patients receiving perioperative atezolizumab in combination with FLOT chemotherapy versus FLOT alone for resectable esophagogastric adenocarcinoma: Interim results from DANTE, a randomized, multicenter, phase IIb trial of the FLOT-AIO German Gastric Cancer Group and Swiss SAKK – Al-Batran S-E, et al

Key results

Pathological regression*, n (%)	Local assessment				Central assessment			
	TRG1a		TRG1a/b		TRG1a		TRG1a/b	
	Atezo + FLOT	FLOT	Atezo + FLOT	FLOT	Atezo + FLOT	FLOT	Atezo + FLOT	FLOT
All patients (n=295; 146/149)	35 (24)	23 (15)	71 (49)	58 (39)	37 (25)	36 (24)	72 (49)	66 (44)
PD-L1 CPS ≥1 (n=170; 82/88)	20 (24)	13 (15)	42 (51)	40 (46)	21 (26)	20 (23)	43 (52)	41 (47)
PD-L1 CPS ≥5 (n=81; 40/41)	11 (28)	8 (20)	22 (55)	18 (44)	13 (33)	9 (22)	21 (53)	19 (46)
PD-L1 CPS ≥10 (n=53; 27/26)	9 (33)	3 (12)	18 (67)	10 (39)	11 (41)	5 (19)	19 (70)	13 (50)
MSI-H (n=23; 8/15)	5 (63)	4 (27)	6 (75)	7 (47)	5 (63)	4 (27)	6 (75)	7 (47)

Conclusions

- **In patients with resectable esophagogastric adenocarcinoma, perioperative atezolizumab + FLOT improved downstaging and pathological regression, particularly in those with higher PD-L1 expression or MSI-H tumors and was generally well-tolerated**

*Pathological complete and subtotal regression according to Becker criteria

Al-Batran S-E, et al. J Clin Oncol 2022;40(suppl):abstr 4003

2023 ASCO ANNUAL MEETING

EORTC European Organisation for Research and Treatment of Cancer

The future of cancer therapy

KCSG DUCG Dutch Upper GI Cancer Group

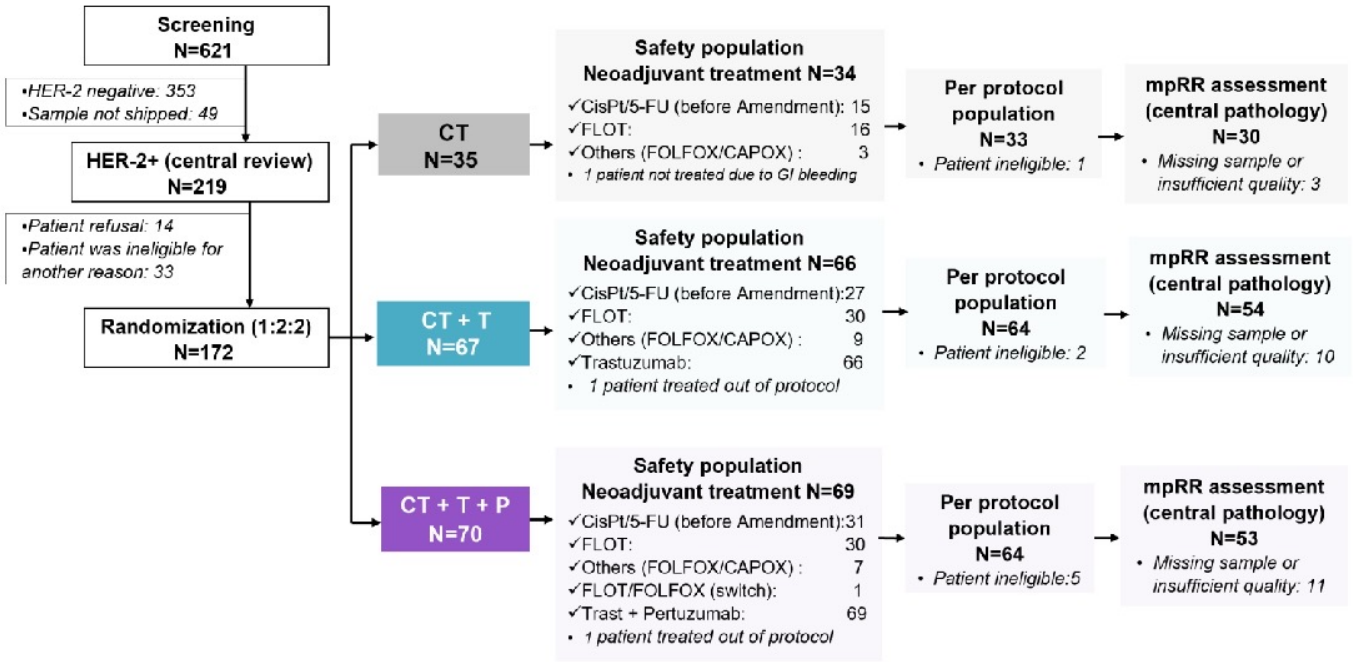
Integration of trastuzumab (T), with or without pertuzumab (P), into perioperative chemotherapy (CT) of HER-2 positive gastric (GC) and esophagogastric junction cancer (EGJC)

First results of the EORTC 1203 "INNOVATION" Study, in collaboration with the Korean Cancer Study Group (KCSG) and the Dutch Upper GI Cancer Group (DUCG)

A.D. Wagner, H.I. Grabsch, M.E. Mauer, R.U. Fumagalli, Y.-K Kang, O. Bouche, S. Lorenzen, M. Moehler, P. Thuss-Patience, A. Elme, G. Folprecht, U.M. Martens, D. Smith, M.d C. Galan Guzman, M. Ducreux, M. Diez Garcia, G. Piessen, S.Y. Rha, M. Collienne, F. Lordick

PRESENTED BY: Anna Dorothea Wagner, Lausanne University Hospital and University of Lausanne

Results:
Study population and patient characteristics

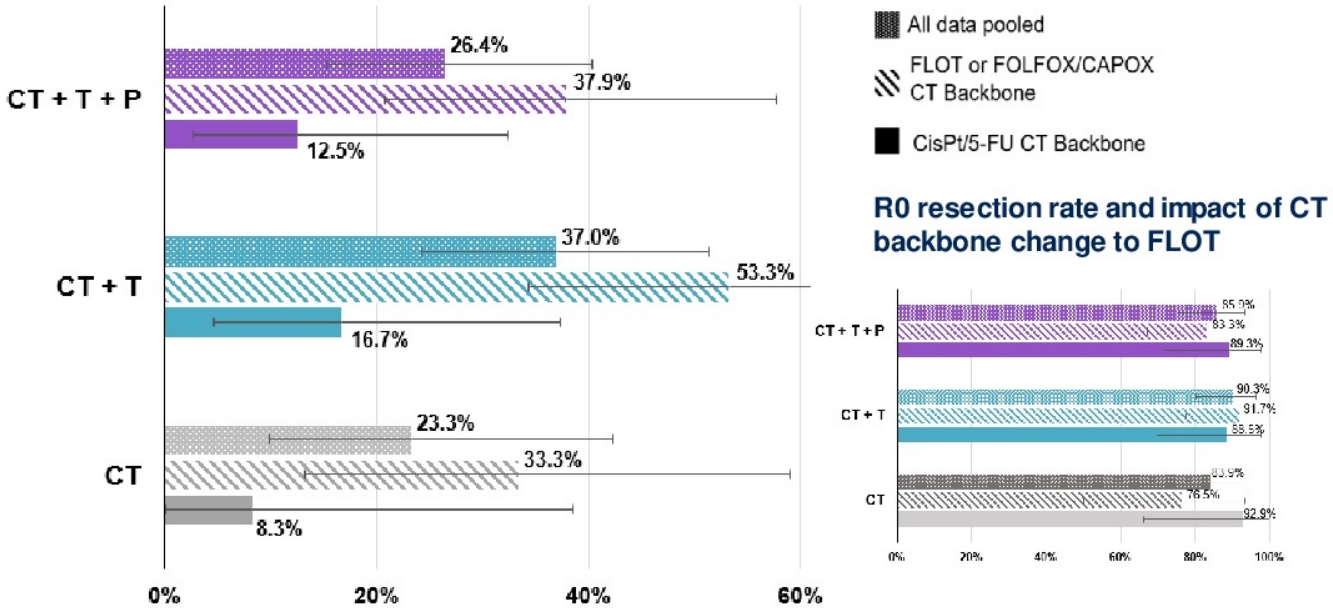


	Treatment arm (Per protocol population)		
	CT (N=33)	CT + T (N=64)	CT + T + P (N=64)
Age (years), Median (Range)	63 (32–79)	63 (36–84)	64 (42–78)
Sex, N (%)			
Male	31 (93.9)	43 (67.2)	57 (89.1)
Female	2 (6.1)	21 (32.8)	7 (10.9)
Tumor localization, N (%)			
Stomach	12 (36.4)	26 (40.6)	23 (35.9)
Esophagogastric junction	21 (63.6)	38 (59.4)	41 (64.1)
Histological subtype, N (%)			
Intestinal	25 (75.8)	45 (70.3)	46 (71.9)
Non-intestinal	8 (24.2)	19 (29.7)	18 (28.1)
Region, N (%)			
Asia	4 (12.1)	7 (10.9)	5 (7.8)
Europe	29 (87.9)	57 (89.1)	59 (92.2)
HER-2 status, N (%)			
IHC2+/FISH+	4 (12.1)	16 (25.0)	16 (25.0)
HER-2 IHC 3+	29 (87.9)	48 (75.0)	48 (75.0)

PRESENTED BY: Anna Dorothea Wagner, MD, Lausanne University Hospital and University of Lausanne

Results:

Primary endpoint analysis mpRR (%) and impact of CT backbone change to FLOT



R0 resection rate and impact of CT backbone change to FLOT

The increase of 3.1% (80% CI [-9.5%, 15.7%], one sided p=0.378) in CT+T+P arm *vs* CT arm was not statistically significant.
The increase in CT+T arm *vs* CT arm was of 13.7% (80% CI [0.7%, 26.7%], one sided p=0.099).

Adverse events

AEs with frequency > 15% in at least one arm, during neoadjuvant treatment, N (%)	Safety population					
	CT (n=34)		CT + T (n=66)		CT+ T + P (n=69)	
	Grade 3-5	All grades	Grade 3-5	All grades	Grade 3-5	All grades
Patients' worst grade	12 (35.3)	32 (94.1)	32 (48.5)	64 (97.0)	48 (69.6)	66 (95.7)
Anemia		1 (2.9)		3 (4.5)	2 (2.9)	11 (15.9)
Diarrhea	1 (2.9)	11 (32.4)	2 (3)	33 (50)	15 (21.7)	47 (68.1)
Mucositis oral	1 (2.9)	4 (11.8)	1 (1.5)	12 (18.2)	7 (10.1)	18 (26.1)
Nausea		14 (41.2)	2 (3)	28 (42.4)	8 (11.6)	33 (47.8)
Vomiting		1 (2.9)	1 (1.5)	6 (9.1)	2 (2.9)	18 (26.1)
Fatigue		10 (29.4)	3 (4.5)	19 (28.8)	3 (4.3)	23 (33.3)
Neutrophil count decreased	9 (26.5)	14 (41.2)	16 (24.2)	30 (45.5)	14 (20.3)	26 (37.7)
Weight loss				4 (6.1)		13 (18.8)
White blood cell decreased		1 (2.9)		6 (9.1)	3 (4.3)	13 (18.8)
Anorexia		9 (26.5)	1 (1.5)	13 (19.7)	3 (4.3)	15 (21.7)
Dysgeusia		6 (17.6)		7 (10.6)		8 (11.6)
Paresthesia		6 (17.6)		12 (18.2)		8 (11.6)
Peripheral sensory neuropathy		5 (14.7)		10 (15.2)		9 (13)
Epistaxis		1 (2.9)				11 (15.9)

Exposure to neoadjuvant treatment

Neoadjuvant treatment after FLOT CT backbone amendment	Safety population (FLOT CT Backbone only)		
	CT (N=16)	CT + T (N=30)	CT + T + P (N=31)
Number of cycles of FLOT, N (%)			
4	15 (93.8)	28 (93.3)	25 (80.6)
FLOT Relative Dose intensity* (%) – Median			
Oxaliplatin	99.0	93.9	87.9
Docetaxel	98.1	94.0	85.5
Folinic acid	99.1	94.6	93.2
5-FU	99.5	94.1	82.0
Trastuzumab		98.7	100.0
Pertuzumab			100.0

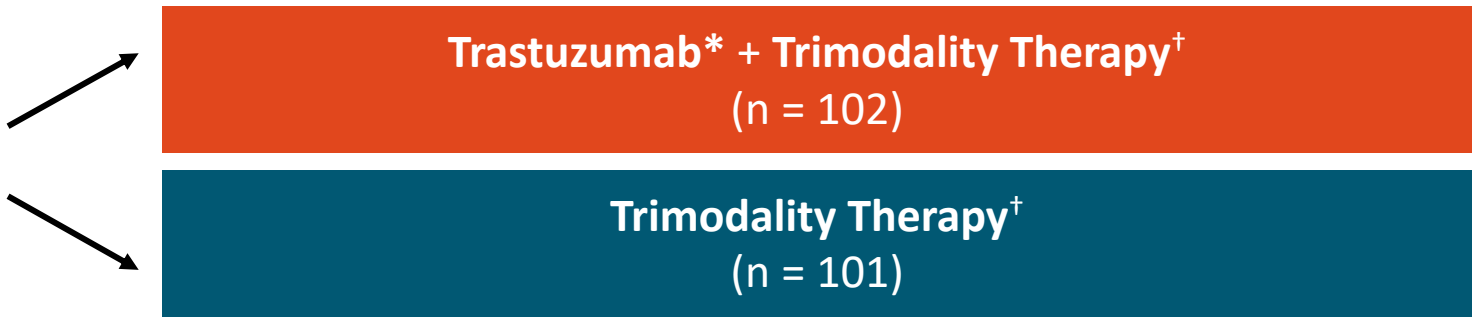
**calculated based on the number of cycles actually started by the patient*

PRESENTED BY: Anna Dorothea Wagner, MD, Lausanne University Hospital and University of Lausanne

RTOG 1010: Trastuzumab + Trimodality Treatment in Resectable HER2-Positive Esophageal Adenocarcinoma

- Randomized, open-label phase III trial

Patients with newly diagnosed stage T1N1-2, T2-3N0-2 esophageal adenocarcinoma involving mid (≤25 cm), distal, or esophagogastric junction and up to 5 cm of stomach; HER2 positive (IHC3+ or FISH+); candidate for potential curative resection; PS 0-2; LVEF ≥LLN (N = 203)



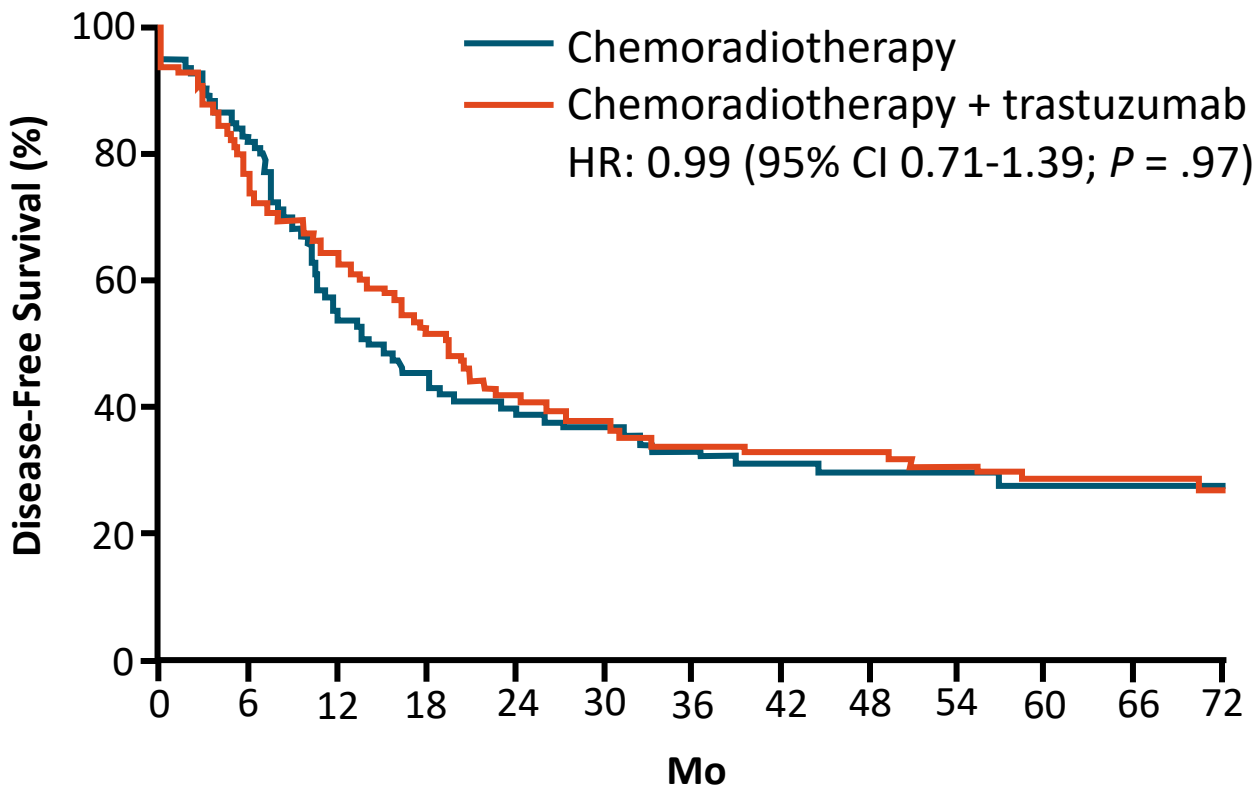
*Trastuzumab dosed at 4 mg/kg in Wk 1, 2 mg/kg/wk x 5 during chemoradiotherapy, 6 mg/kg for 1 dose prior to surgery; and 6 mg/kg Q3W for 13 treatments after surgery.

†Trimodality therapy consisted of paclitaxel 50 mg/m^2 plus carboplatin AUC 2 QW x 6 wk + concurrent radiation (50.4 Gy) over 5.5 wk, followed by surgery 5-8 wk after completion of radiation.

- Primary endpoint: DFS; key secondary endpoints: pCR, OS, safety, QoL

Safran. Lancet Oncol. 2022;23:259.

RTOG 1010: DFS (Primary Endpoint) and OS



- Median OS, trastuzumab + chemoRT vs chemoRT: 38.5 vs 38.9 mo (HR: 1.04; 95% CI: 0.71-1.50)

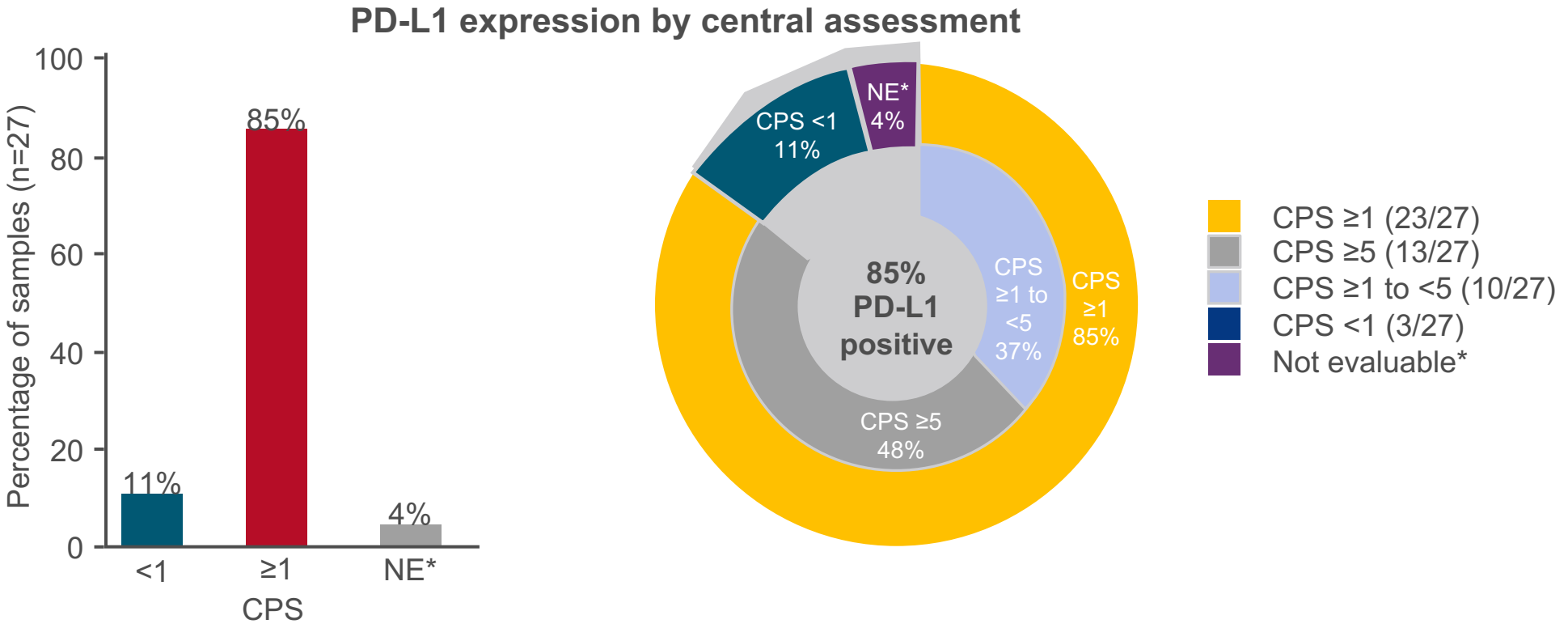
Safran. Lancet Oncol. 2022;23:259.

Slide credit: clinicaloptions.com

SO-7: Co-occurring HER2 and PD-L1 expression in patients with HER2-positive trastuzumab-refractory gastric cancer (GC)/gastroesophageal junction adenocarcinoma (GEJA): biomarker analysis from the trastuzumab deruxtecan (T-DXd) DESTINY-Gastric03 trial – Janjigian Y, et al

Key results

- There was 80% concordance between local and central testing for HER2 status



Conclusions

- **In patients with HER2+ trastuzumab-refractory gastric or GEJ adenocarcinoma, there was a substantial overlap between HER2 and PD-L1 positivity, which supports the use of dual therapy with an anti-HER2 and anti-PD-L1 agents**

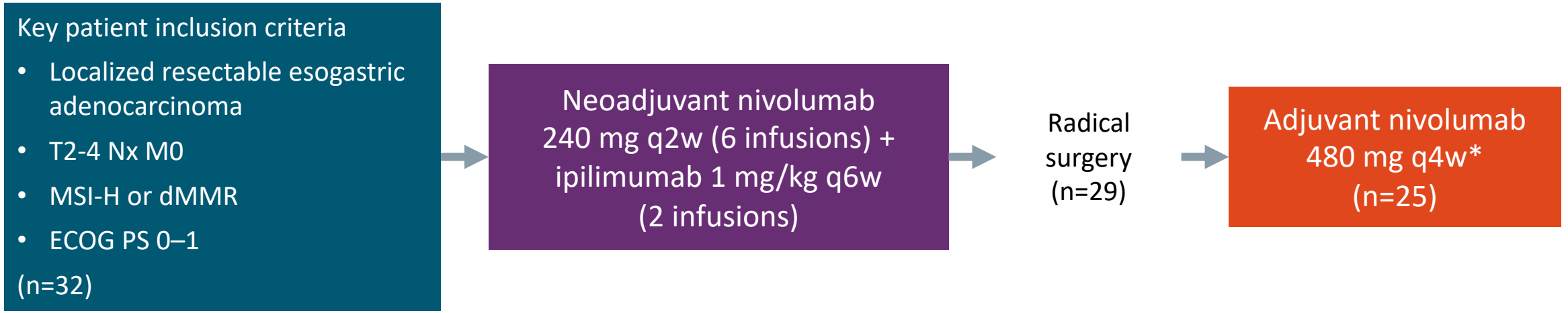
*Not evaluable, there was insufficient number of viable tumour cells (<100) present for PD-L1 testing

Janjigian Y, et al. Ann Oncol 2022;33(suppl):abstr SO-7

244: Neoadjuvant nivolumab plus ipilimumab and adjuvant nivolumab in patients (pts) with localized microsatellite instability-high (MSI)/mismatch repair deficient (dMMR) oeso-gastric adenocarcinoma (OGA): The GERCOR NEONIPIGA phase II study – André T, et al

Study objective

- To evaluate the efficacy and safety of neoadjuvant nivolumab + ipilimumab and adjuvant nivolumab in patients with localized MSI-H or dMMR esogastric adenocarcinoma in French centers in the phase 2 GERCOR NEONIPIGA study



PRIMARY ENDPOINT

- pCR

SECONDARY ENDPOINTS

- EFS, OS, safety

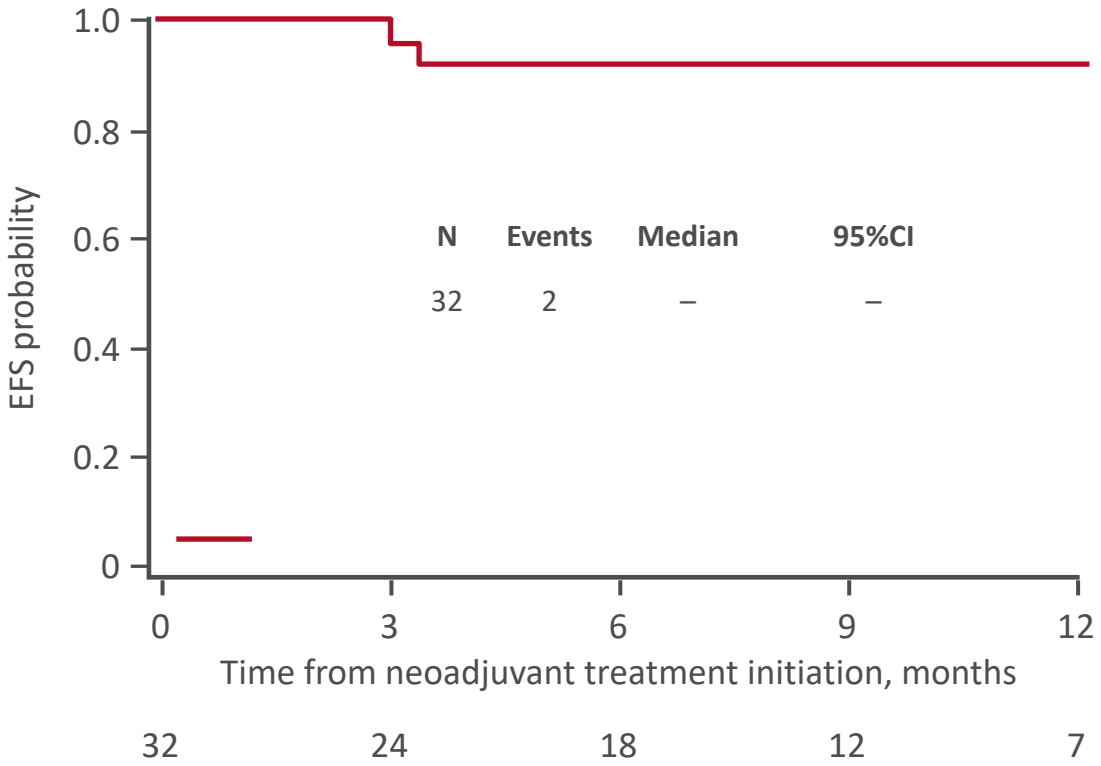
*Only patients with Becker tumor regression grade <3 received adjuvant nivolumab

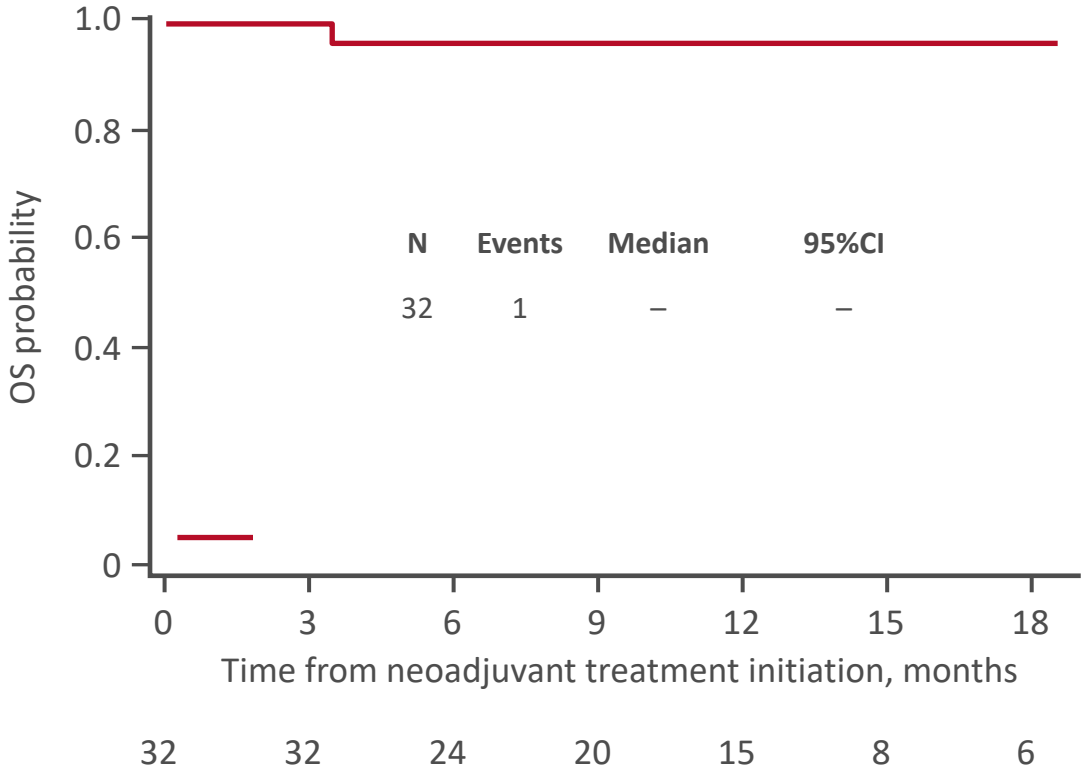
André T, et al. J Clin Oncol 2022;40(suppl):abstr 244

244: Neoadjuvant nivolumab plus ipilimumab and adjuvant nivolumab in patients (pts) with localized microsatellite instability-high (MSI)/mismatch repair deficient (dMMR) oeso-gastric adenocarcinoma (OGA): The GERCOR NEONIPIGA phase II study – André T, et al

Key results

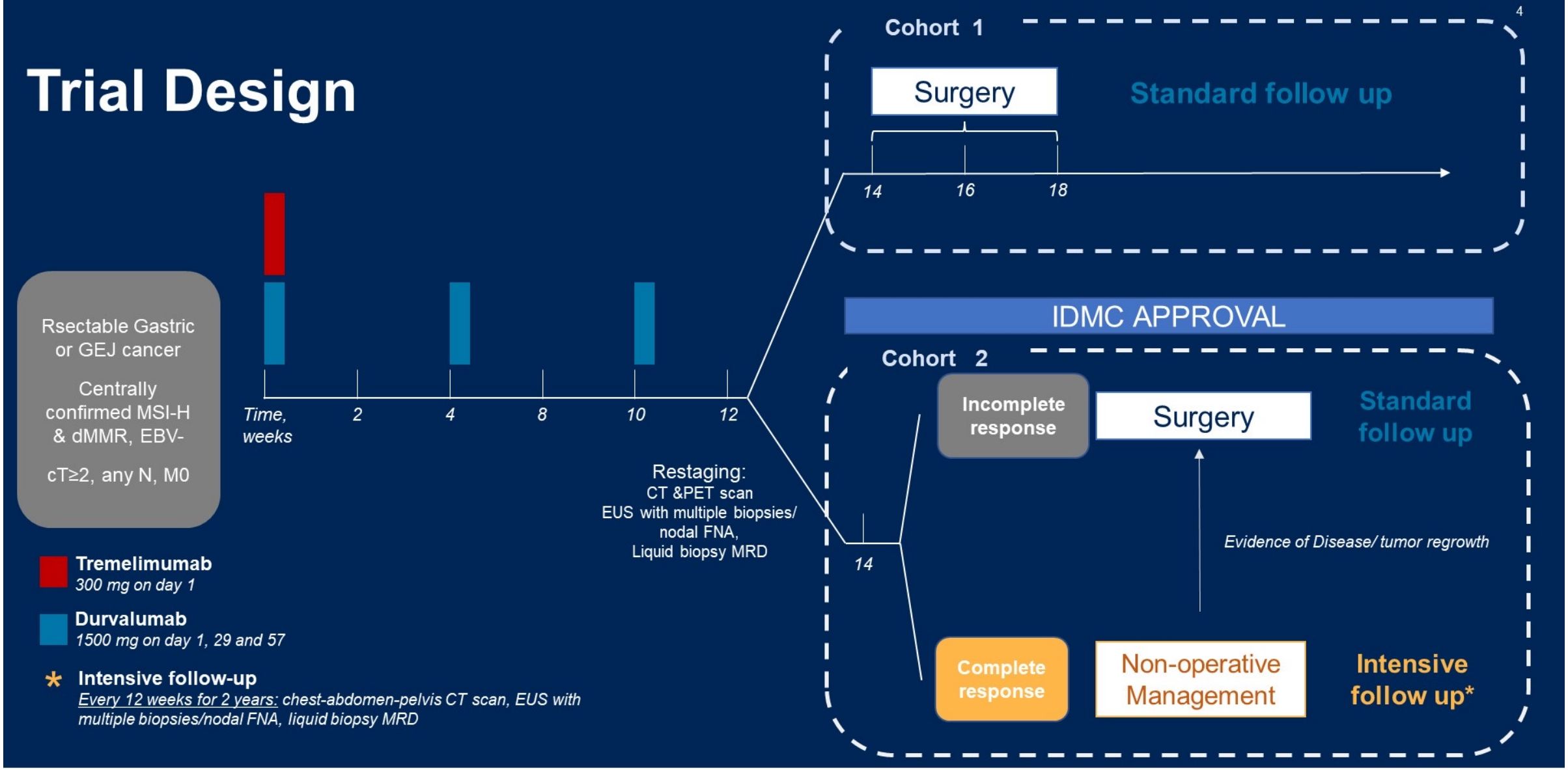
- pCR was achieved by 17 of 29 (58.6%) patients





André T, et al. J Clin Oncol 2022;40(suppl):abstr 244

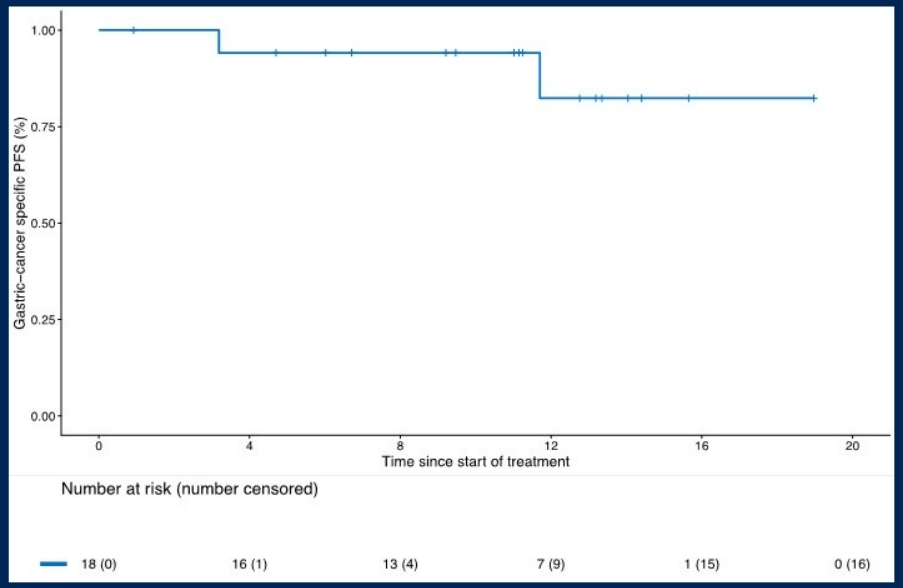
Trial Design



Survival endpoints

	PFS event	OS event	
01-020	Yes	No	CR to CAPOX
04-005	Yes	Yes	Heterogeneous pMMR/dMMR status
13-002	No	Yes	Late postoperative complications
01-009	No	Yes	Late postoperative complications
05-001	No	Yes	Second primary brain cancer

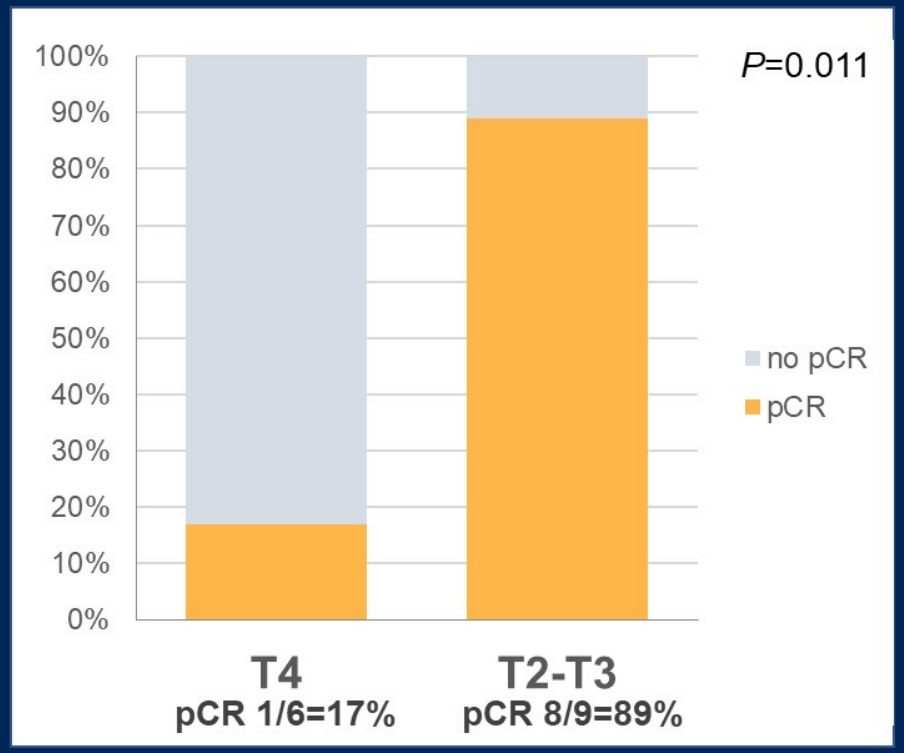
Gastric cancer-specific PFS



Data cutoff date: 16th December 2022, with a median follow up of 13.4 (IQR 9.7-14.2) months

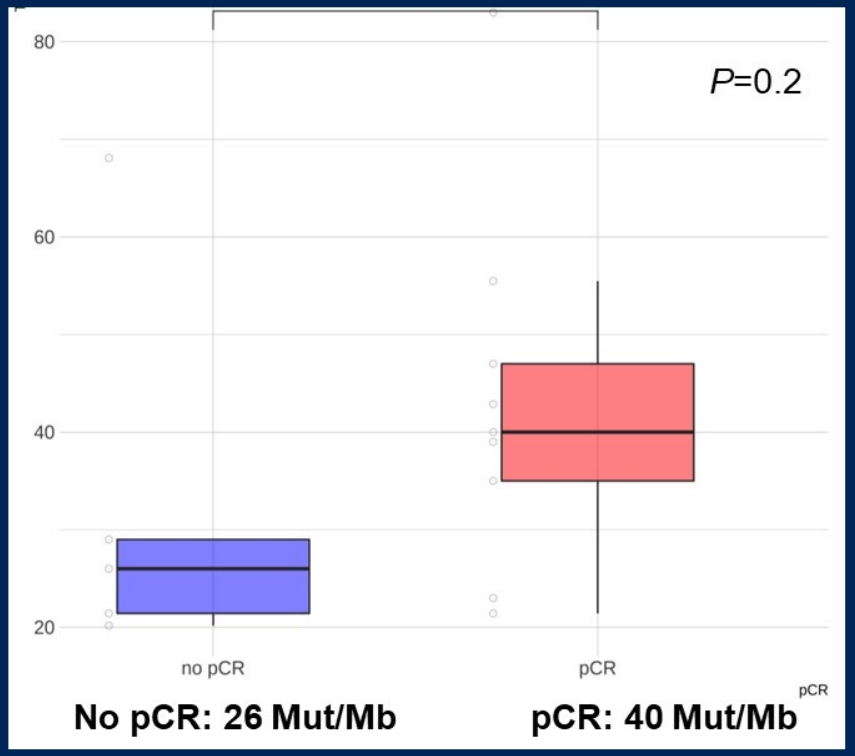
Exploratory analyses

Baseline clinical staging (EUS, CT +/- laparoscopy)



Significant correlation with pCR was found for baseline **cT stage**, but not for **cN stage**.

Baseline Tumor Mutational Burden



Numerical correlation with pCR was found for baseline **TMB**, but not for **PD-L1 CPS.**

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

[1]Yonsei Cancer Center, Yonsei University Health System, Seoul, Republic of Korea; [2]Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [3]Universidad de La Frontera, James Lind Cancer Research Center, Temuco, Chile; [4]Harbin Medical University Cancer Hospital, Harbin, China; [5]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [6]Samsung Medical Center, Seoul, Republic of Korea; [7]University Hospital Marqués de Valdecilla, IDIVAL, Santander, Spain; [8]Hospital Nossa Senhora da Conceição, Porto Alegre, Brazil; [9]Pontificia Universidad Católica de Chile, Santiago, Chile (currently at Universidad Mayor, Santiago, Chile); [10]University College Hospital, NHS Foundation Trust, London, UK; [11]IMAT-Oncomedica, Montería, Colombia; [12]Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China; [13]Trinity St. James Cancer Institute, Dublin, Ireland; [14]Health and Science University, Adana City Hospital, Adana, Turkey; [15]Nucleo de Pesquisa e Ensino da Rede São Camilo, São Paulo, Brazil; [16]Cancer Center of People's Liberation Army, Nanjing, China; [17]Merck & Co., Inc., Rahway, NJ, USA; [18]Seoul National University College of Medicine, Seoul, Republic of Korea

KEYNOTE-859 Study Design
Randomized, Double-Blind, Phase 3 Trial

Key Eligibility Criteria

- Histologically or cytologically confirmed adenocarcinoma of the stomach or GEJ
- Locally advanced unresectable or metastatic disease
- No prior treatment
- Known PD-L1 status (assessed centrally using PD-L1 IHC 22C3)
- HER2-negative status (assessed locally)
- ECOG PS 0 or 1

R 1:1

Pembrolizumab 200 mg IV Q3W for ≤35 cycles (~2 yr) + Chemotherapy[a] (FP or CAPOX)

Placebo IV Q3W for ≤35 cycles (~2 yr) + Chemotherapy[a] (FP or CAPOX)

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

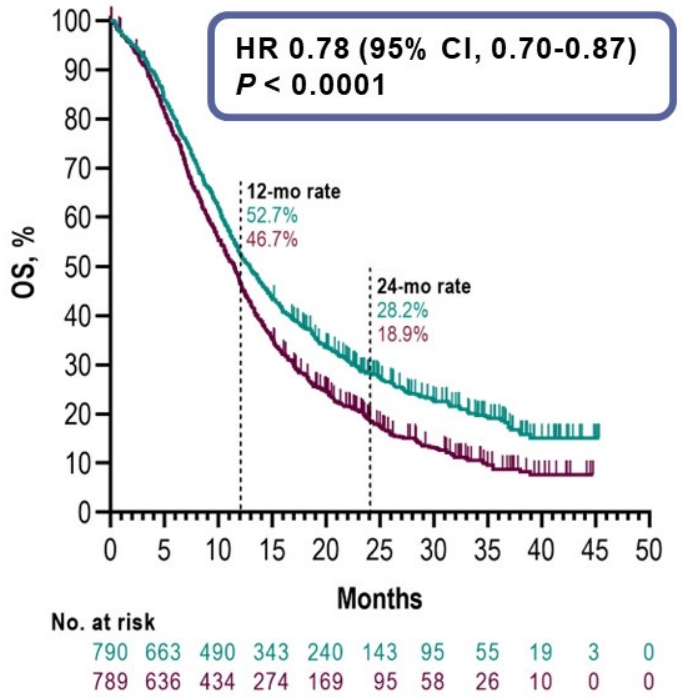
- **Alpha-controlled analyses:** OS, PFS, and ORR in the overall, PD-L1 CPS ≥1, and PD-L1 CPS ≥10 populations

[a] FP: 5-fluorouracil 800 mg/m^2/day IV continuous on days 1-5 Q3W + cisplatin 80 mg/m^2 IV Q3W. CAPOX: capecitabine 1000 mg/m^2 orally twice daily on days 1-14 Q3W + oxaliplatin 130 mg/m^2 IV Q3W. Cisplatin and oxaliplatin could have been limited to 6 cycles as per local country guidelines.
[b] Assessed per RECIST v1.1 by blinded, independent central review.
ClinicalTrials.gov number, NCT03675737.

Primary Endpoint: OS

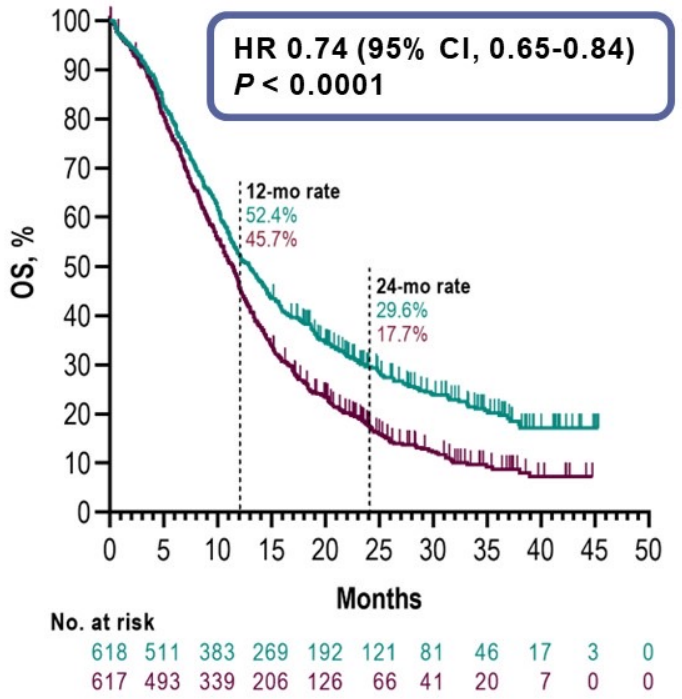
Overall[1]

	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)



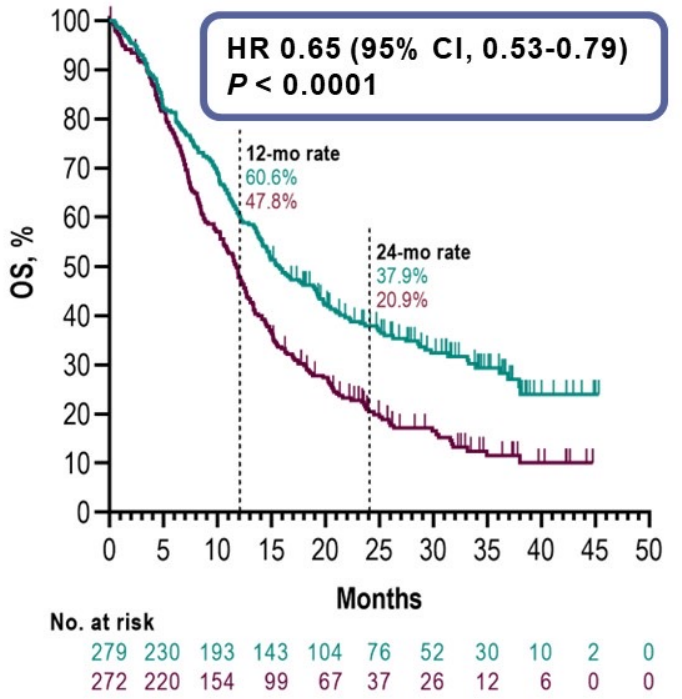
PD-L1 CPS ≥1

	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

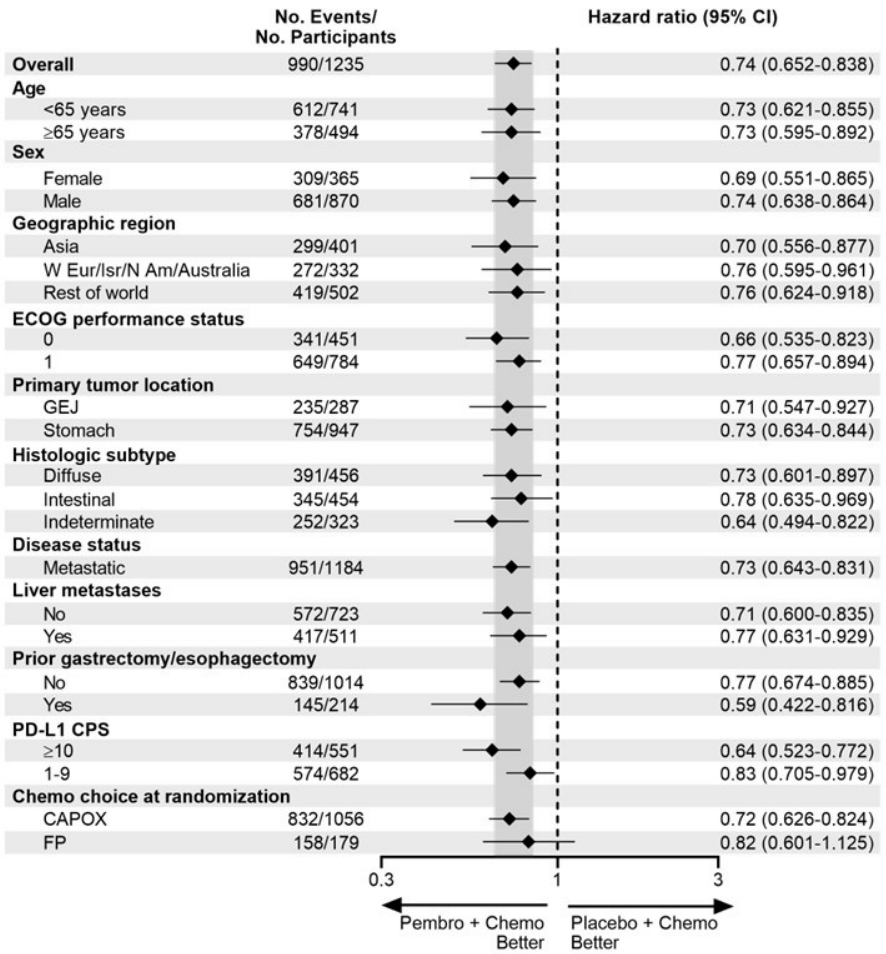
	Pts w/ Event	Median (95% CI), mo
Pembro + chemo	67.4%	15.7 (13.8-19.3)
Placebo + chemo	83.1%	11.8 (10.3-12.7)



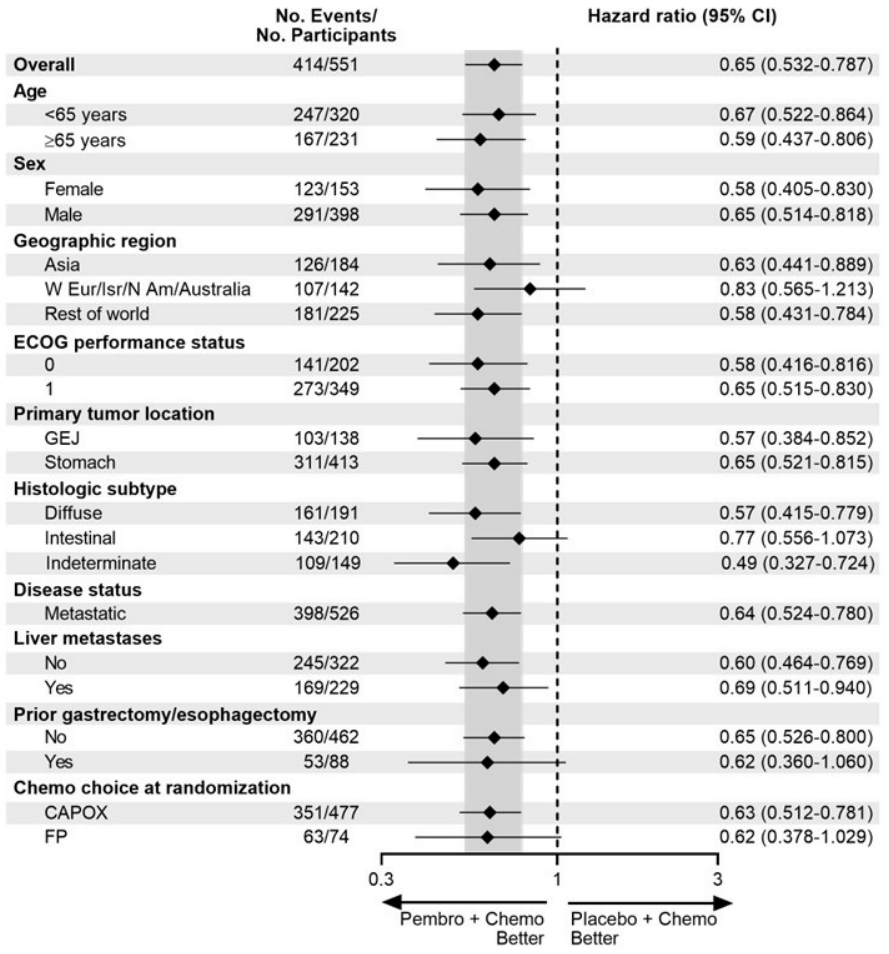
1. Rha SY et al. *Ann Oncol* 2023;34:319-320.
Data cutoff date: October 3, 2022.

Overall Survival in Subgroups

PD-L1 CPS ≥1



PD-L1 CPS ≥10

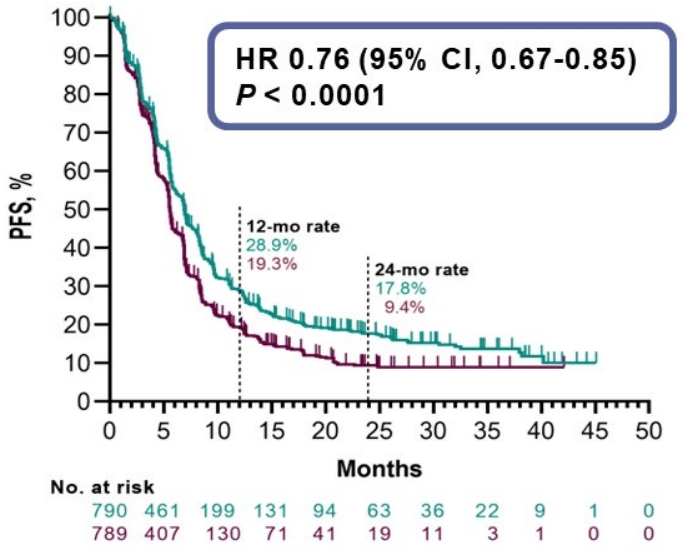


Data cutoff date: October 3, 2022.

Secondary Endpoints: PFS, ORR, and DOR

Overall[1]

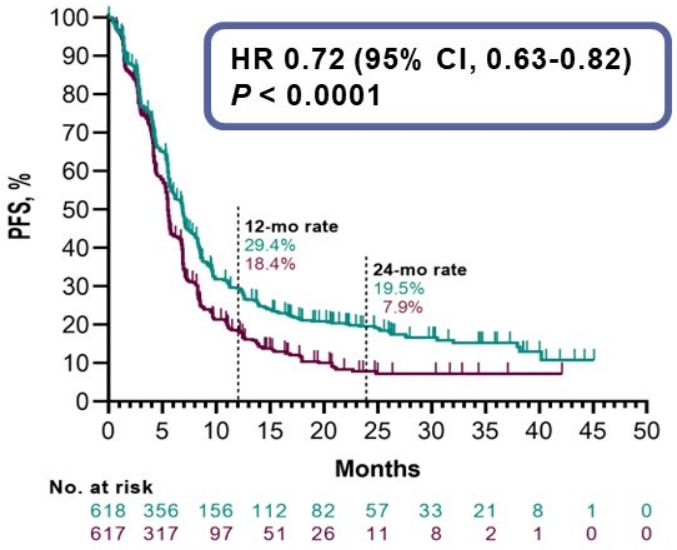
	Pts w/ Event	Median PFS (95% CI), mo
Pembro + chemo	72.4%	6.9 (6.3-7.2)
Placebo + chemo	77.1%	5.6 (5.5-5.7)



	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

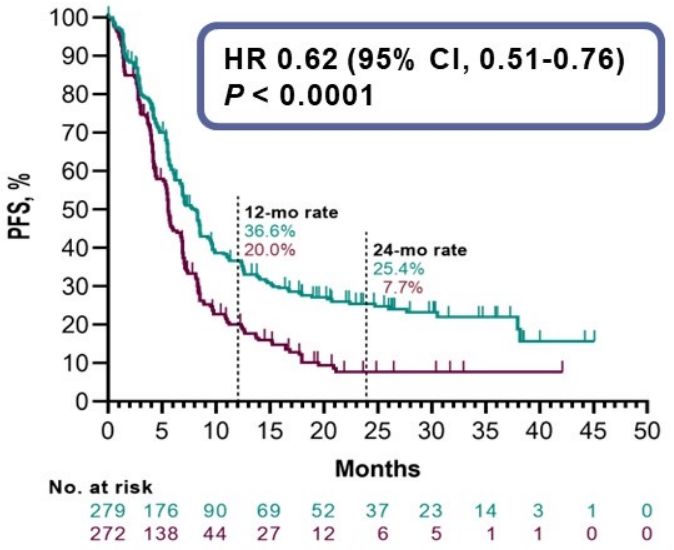
	Pts w/ Event	Median PFS (95% CI), mo
Pembro + chemo	71.7%	6.9 (6.0-7.2)
Placebo + chemo	78.3%	5.6 (5.4-5.7)



	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)

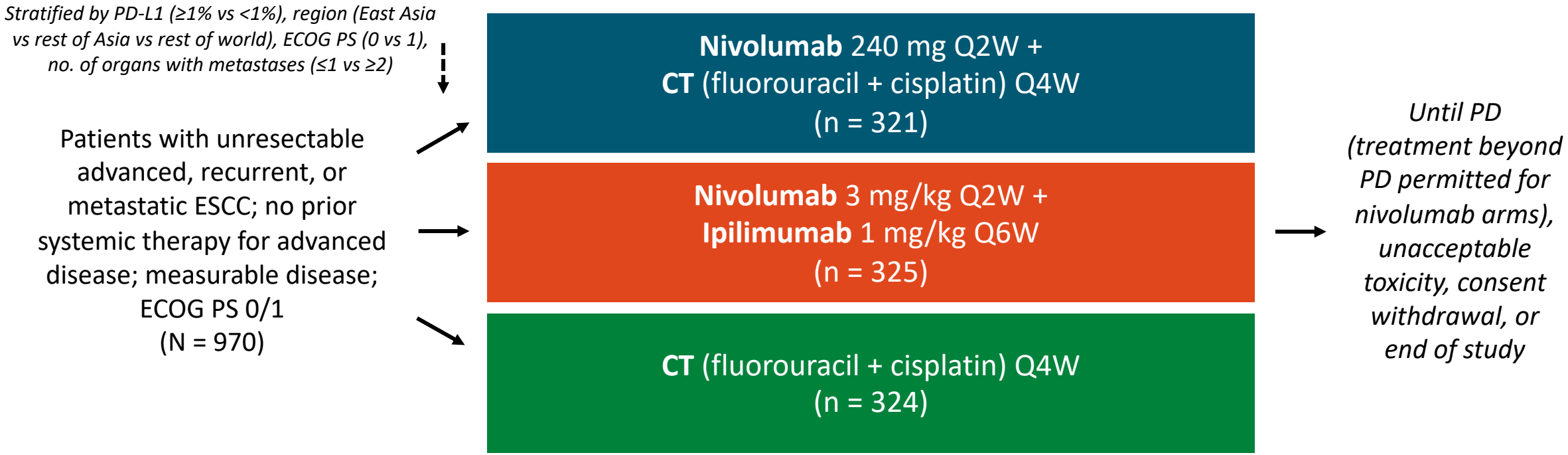


	Pembro + Chemo	Placebo + Chemo
ORR, % (95% CI)	60.6% (54.6-66.3)	43.0% (37.1-49.1)
Δ (95% CI)	17.5 (9.3-23.5); *P* = 0.00002	
mDOR (range)	10.9 mo (1.2+ - 41.5+)	5.8 mo (1.4+ - 31.2+)

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.

CheckMate 648: Study Design

- International, randomized, open-label phase III trial (28.8-mo follow-up; data cutoff: 2022-05-17)



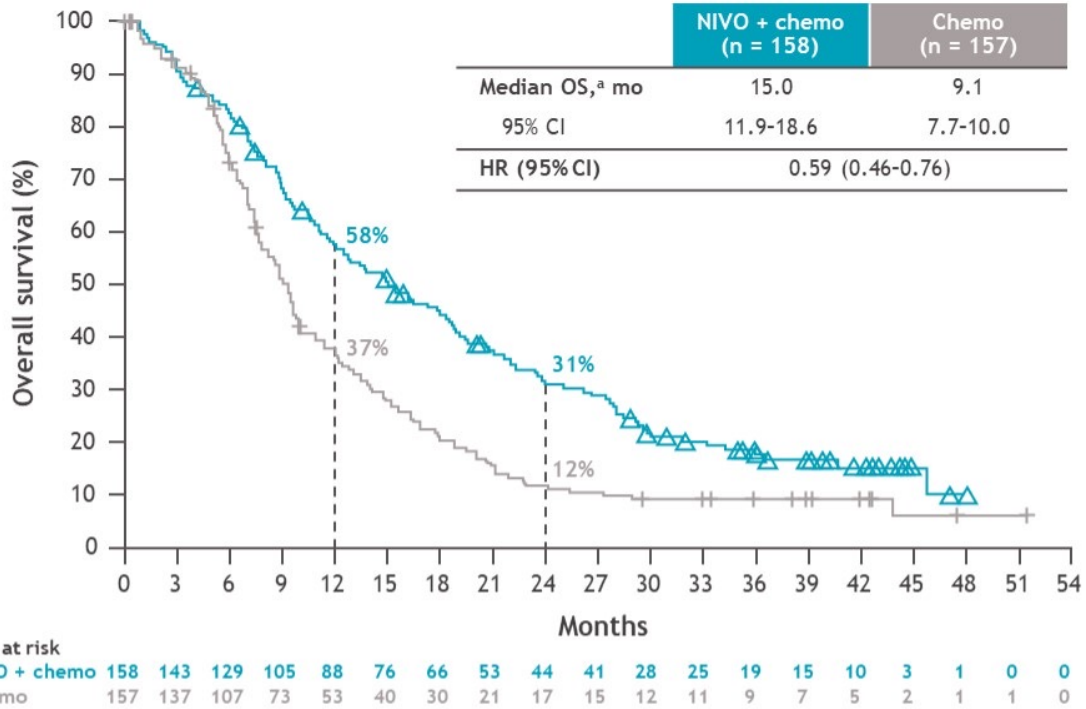
- **Coprimary endpoints:** OS and PFS per BICR in patients with tumor cell PD-L1 ≥1%
- **Secondary endpoints:** OS and PFS per BICR in all randomized patients, ORR per BICR in all randomized patients and those with tumor cell PD-L1 ≥1%

Kato. ASH 2022. Abstr 290.

Slide credit: clinicaloptions.com

OS with NIVO + chemo vs chemo: 29-month follow-up

Tumor cell PD-L1 ≥ 1%

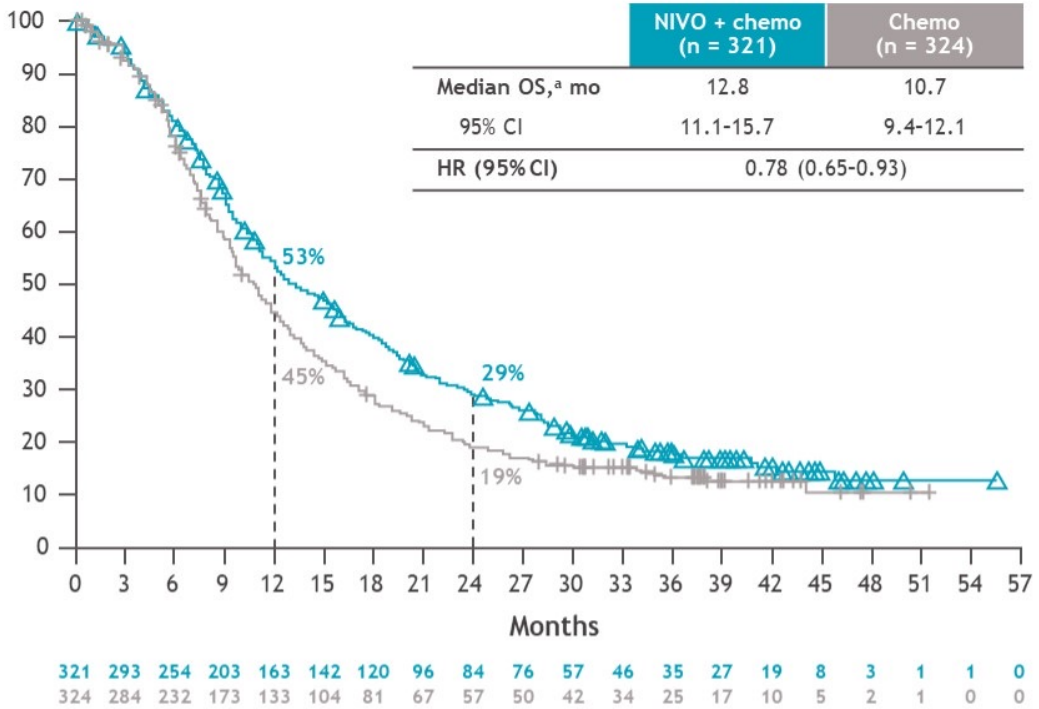


	NIVO + chemo (n = 158)	Chemo (n = 157)
Median OS,[a] mo	15.0	9.1
95% CI	11.9-18.6	7.7-10.0
HR (95% CI)	0.59 (0.46-0.76)	

No. at risk

NIVO + chemo	158	143	129	105	88	76	66	53	44	41	28	25	19	15	10	3	1	0	0
Chemo	157	137	107	73	53	40	30	21	17	15	12	11	9	7	5	2	1	1	0

All randomized



	NIVO + chemo (n = 321)	Chemo (n = 324)
Median OS,[a] mo	12.8	10.7
95% CI	11.1-15.7	9.4-12.1
HR (95% CI)	0.78 (0.65-0.93)	

NIVO + chemo	321	293	254	203	163	142	120	96	84	76	57	46	35	27	19	8	3	1	1	0
Chemo	324	284	232	173	133	104	81	67	57	50	42	34	25	17	10	5	2	1	0	0

- Clinically meaningful improvement in OS with NIVO + chemo vs chemo in the tumor cell PD-L1 ≥ 1% and all randomized populations was maintained with longer follow-up
  - Tumor cell PD-L1 ≥ 1%: 41% reduction in the risk of death and a 5.9-month improvement in median OS
  - All randomized: 22% reduction in the risk of death and a 2.1-month improvement in median OS

[a]Minimum follow-up, 28.8 months.

KEYNOTE-590: First-line Pembrolizumab + Chemotherapy vs Chemotherapy for Esophageal/GEJ Cancer

- Randomized phase III trial of **pembrolizumab + chemo*** vs **chemo*** for previously untreated patients with locally advanced unresectable or metastatic EAC, ESCC, or GEJA (N = 749)

Outcome	All Patients			All Patients PD-L1 CPS ≥10			ESCC			ESCC PD-L1 CPS ≥10		
	Pembro + CT (n = 373)	CT (n = 376)	HR/ *P* Val	Pembro + CT (n = 186)	CT (n = 197)	HR/ *P* Val	Pembro + CT (n = 274)	CT (n = 274)	HR/ *P* Val	Pembro + CT (n = 143)	CT (n = 143)	HR/ *P* Val
Median OS,† mo	12.4	9.8	0.73/ <.0001	13.5	9.4	0.62/ <.0001	12.6	9.8	0.72/ .0006	13.9	8.8	0.57/ <.0001
Median PFS,† mo	6.3	5.8	0.65/ <.0001	7.5	5.5	0.51/ <.0001	6.3	5.8	0.65/ <.0001	--	--	--

	CPS ≥10 (n = 383)	All Randomized	CPS <10 (n = 347)
HR for OS	0.62	0.73	0.86

*5-FU + cisplatin. †Primary endpoint.

Sun. Lancet. 2021;398:759.

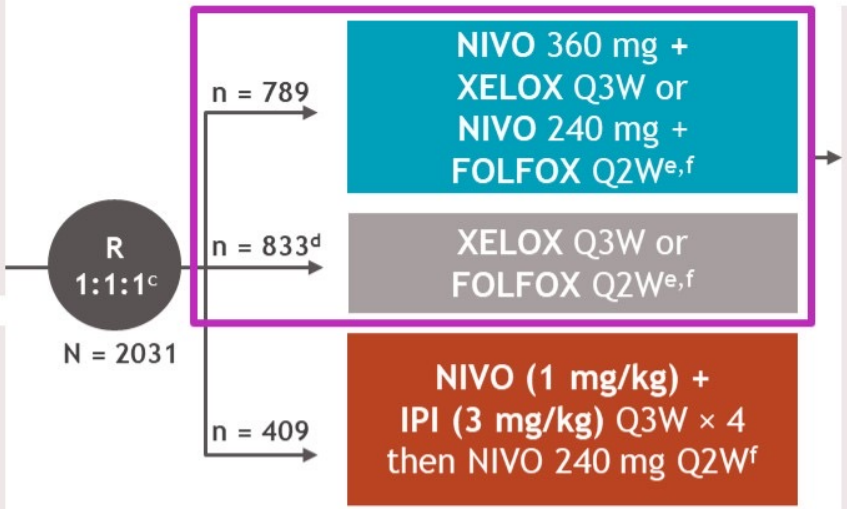
Slide credit: clinicaloptions.com

CheckMate 649 study design

- CheckMate 649 is a randomized, open-label, global phase 3 study[1,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**

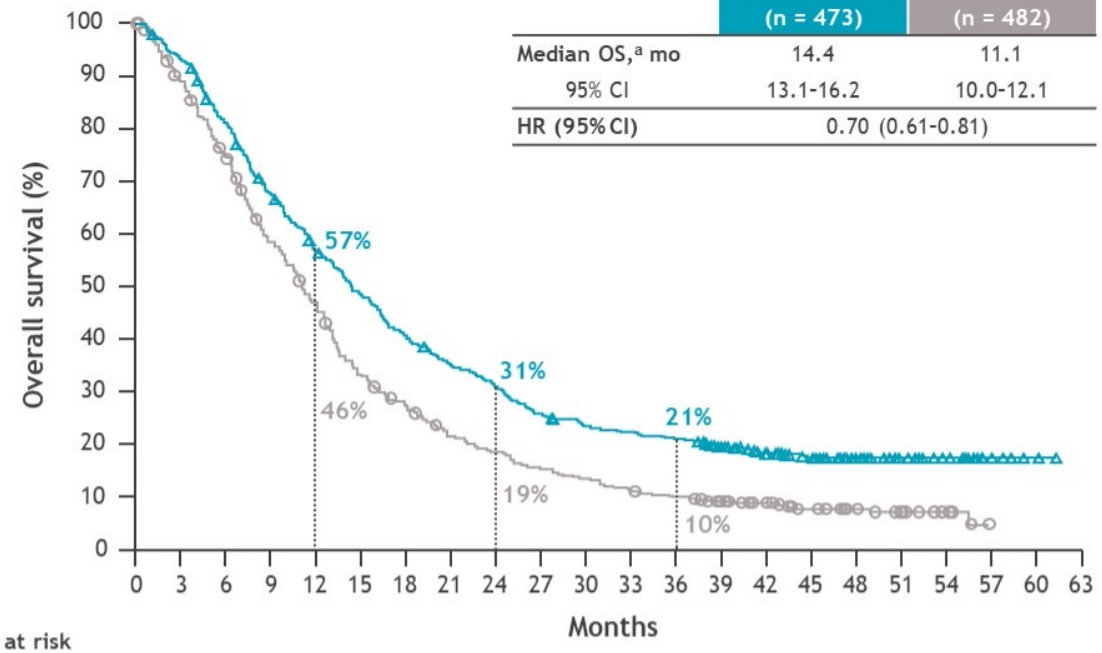
- Patients were enrolled from 175 hospitals and cancer centers in 29 countries
- At data cutoff (May 31, 2022), the minimum follow-up[h] was 36.2 months

[a]ClinicalTrials.gov. NCT02872116; [b]Less than 1% includes indeterminate tumor cell PD-L1 expression; [c]During concurrent randomization period; [d]Includes patients concurrently randomized to chemo vs NIVO + IPI (October 2016-June 2018) and to NIVO + chemo (April 2017-April 2019); [e]XELOX: oxaliplatin 130 mg/m^2 IV (day 1) and capecitabine 1000 mg/m^2 orally twice daily (days 1-14); FOLFOX: oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and FU 400 mg/m^2 IV (day 1) and FU 1200 mg/m^2 IV daily (days 1-2); [f]Until documented disease progression (unless consented to treatment beyond progression for NIVO + chemo or NIVO + IPI), discontinuation due to toxicity, withdrawal of consent, or study end. NIVO is given for a maximum of 2 years; [g]BICR assessed; [h]Time from concurrent randomization of the last patient to clinical data cutoff. 1. Janjigian YY, et al. *Lancet* 2021;398:27-40.

Overall survival: 36-month follow-up

PD-L1 CPS ≥ 5

	NIVO + chemo (n = 473)	Chemo (n = 482)
Median OS,[a] mo	14.4	11.1
95% CI	13.1-16.2	10.0-12.1
HR (95% CI)	0.70 (0.61-0.81)	

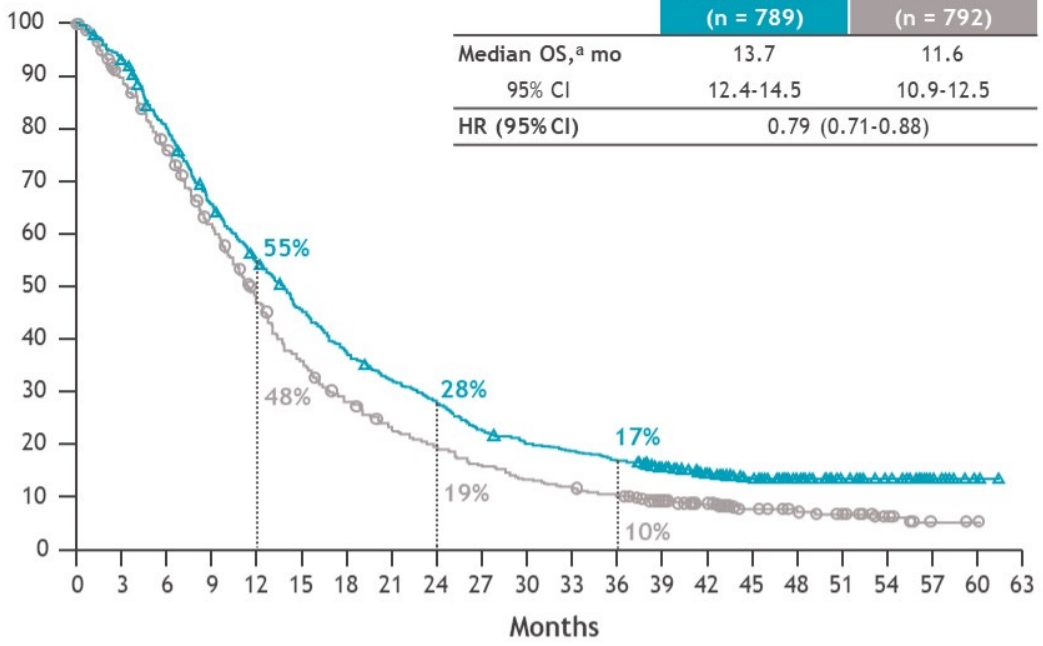


No. at risk

NIVO + chemo	473	440	380	315	263	223	187	161	141	118	105	100	94	81	66	53	37	24	17	6	2	0
Chemo	482	424	353	275	215	154	125	97	83	69	60	51	44	35	28	18	14	10	5	0	0	0

All randomized

	NIVO + chemo (n = 789)	Chemo (n = 792)
Median OS,[a] mo	13.7	11.6
95% CI	12.4-14.5	10.9-12.5
HR (95% CI)	0.79 (0.71-0.88)	



NIVO + chemo	789	733	625	509	422	349	287	246	212	175	154	143	129	106	87	67	48	30	23	9	2	0
Chemo	792	701	591	475	364	273	215	170	144	118	98	87	75	57	45	27	21	17	9	3	1	0

- Clinically meaningful improvement in OS with NIVO + chemo vs chemo was maintained with longer follow-up in PD-L1 CPS ≥ 5 and all randomized populations

[a]Minimum follow-up, 36.2 months.

1203O: FOLFOX plus nivolumab and ipilimumab versus FOLFOX induction followed by nivolumab and ipilimumab in patients with previously untreated advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction – results from the randomized phase 2 Moonlight trial of the AIO – Lorenzen S, et al

Study objective

- To evaluate the efficacy and safety of mFOLFOX induction therapy followed by nivolumab + ipilimumab in previously untreated patients with advanced or metastatic gastric or GEJ adenocarcinoma in the Moonlight study

Key patient inclusion criteria

- Locally advanced or metastatic gastric or GEJ adenocarcinoma
- HER2 negative
- No prior therapy
- ECOG PS 0–1

(n=90)

R 2:1

Sequential

mFOLFOX 3 cycles (n=59) → Nivolumab 240 mg q2w (4 cycles) + ipilimumab 1 mg/kg q6w (2 cycles) → Nivolumab q2w + ipilimumab q6w

Parallel

mFOLFOX + nivolumab 240 mg q2w + ipilimumab 1 mg/kg q6w (n=30)

Stratification

- ECOG PS (0 vs. 1)
- Tumour status (prior resection – yes vs. no)

PRIMARY ENDPOINT

- 6-mo PFS rate

SECONDARY ENDPOINTS

- OS, ORR, safety

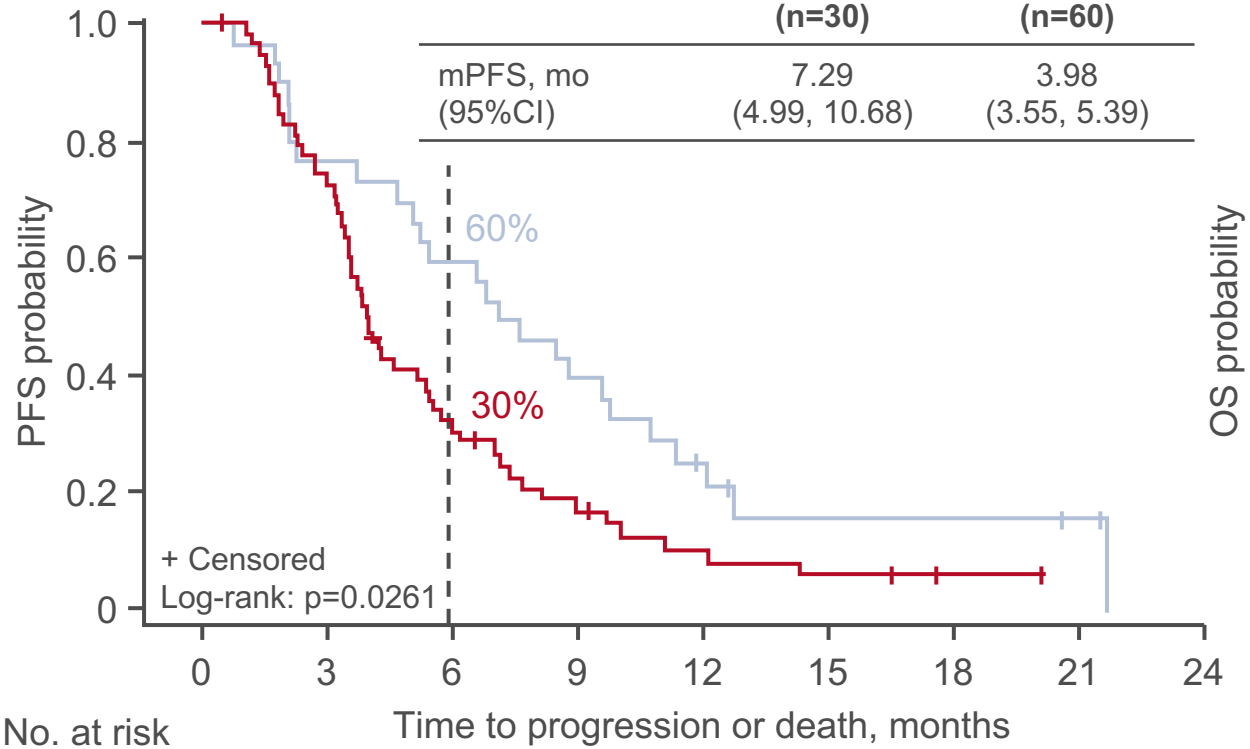
Presented at ESMO Congress 2022
Lorenzen S, et al. Ann Oncol 2022;33(suppl):abstr 1203O

1203O: FOLFOX plus nivolumab and ipilimumab versus FOLFOX induction followed by nivolumab and ipilimumab in patients with previously untreated advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction – results from the randomized phase 2 Moonlight trial of the AIO – Lorenzen S, et al

Key results

Progression-free survival

	Parallel (n=30)	Sequential (n=60)
mPFS, mo (95%CI)	7.29 (4.99, 10.68)	3.98 (3.55, 5.39)

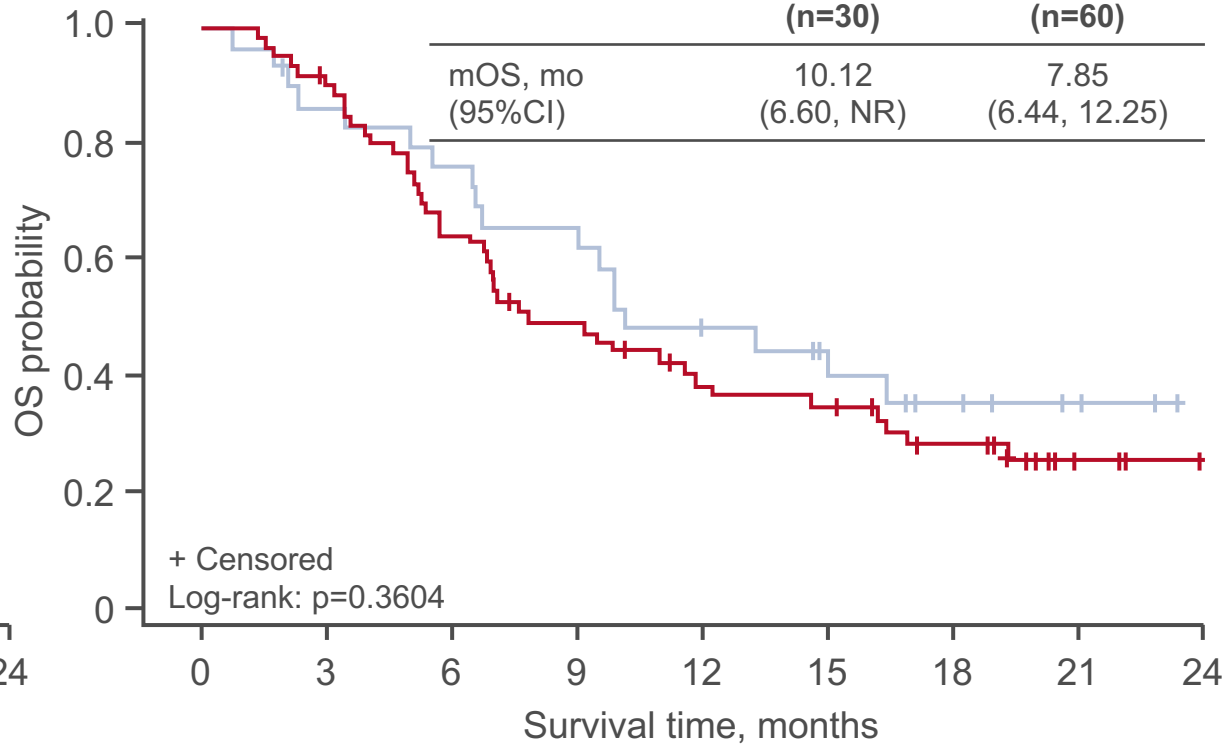


No. at risk

Parallel 30	23	18	12	5	3	3	2	0	
Sequential 60	43	18	10	5	3	1	0		

Overall survival

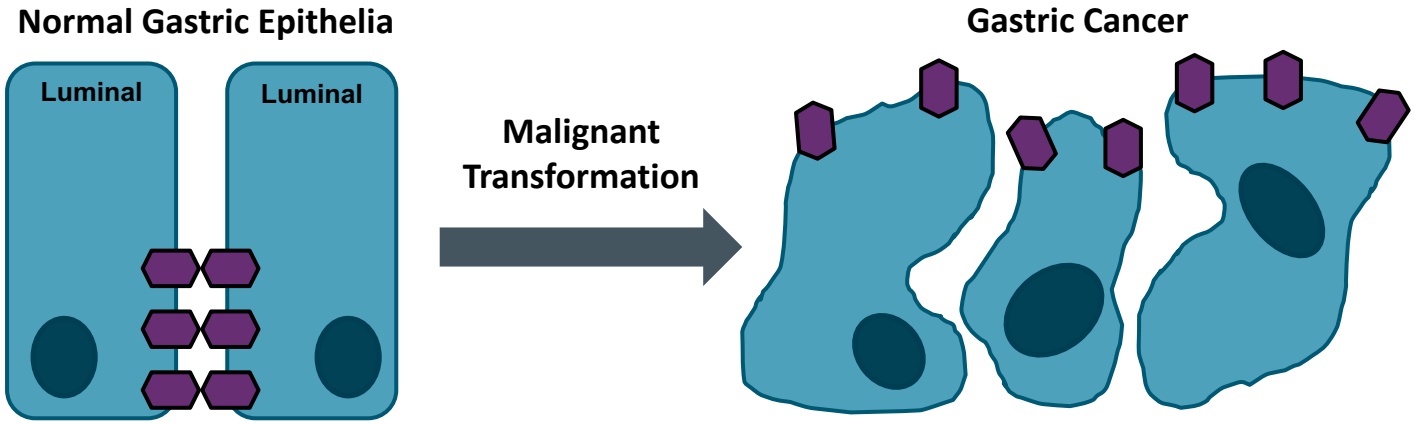
	Parallel (n=30)	Sequential (n=60)
mOS, mo (95%CI)	10.12 (6.60, NR)	7.85 (6.44, 12.25)

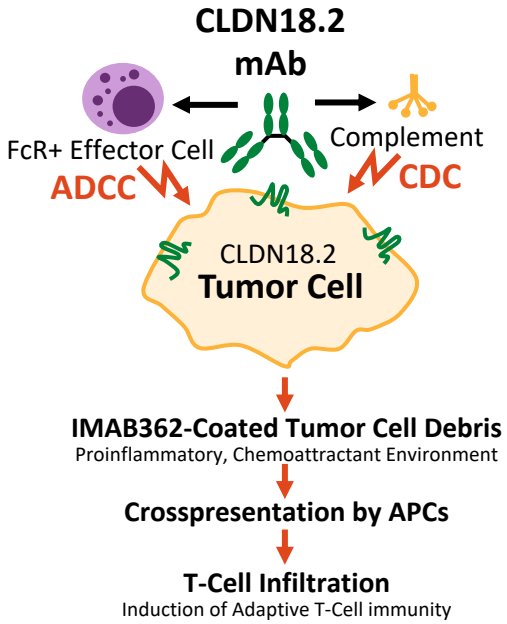


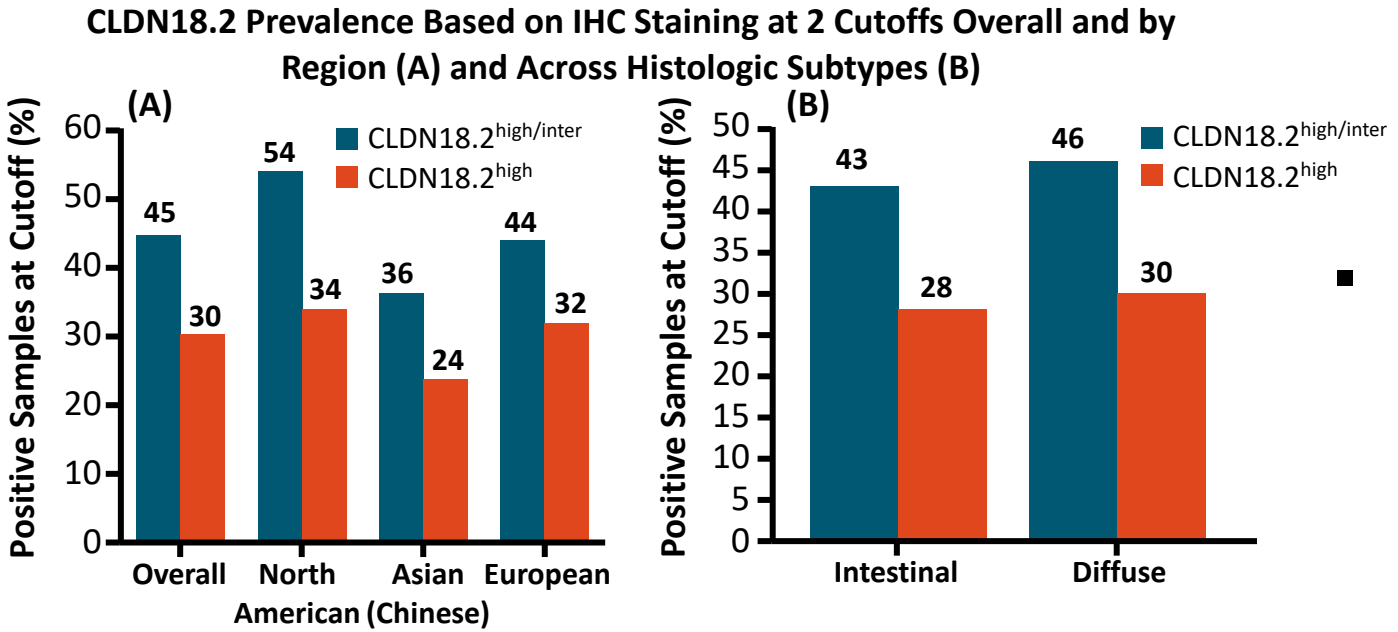
Parallel 30	30	25	22	19	13	10	7	4	0
Sequential 60	60	54	38	28	20	18	12	3	0

Lorenzen S, et al. Ann Oncol 2022;33(suppl):abstr 1203O

Claudin18.2—Leveraging Biology







- Claudin18.2 is a major structural component of intercellular tight junctions
- Not routinely expressed in any normal tissue outside gastric mucosa (cancer-restricted antigen)
- Broadly expressed in several tumor types including gastric, GEJ, biliary, and pancreatic

Baek. Anticancer Res. 2019;39:6973.

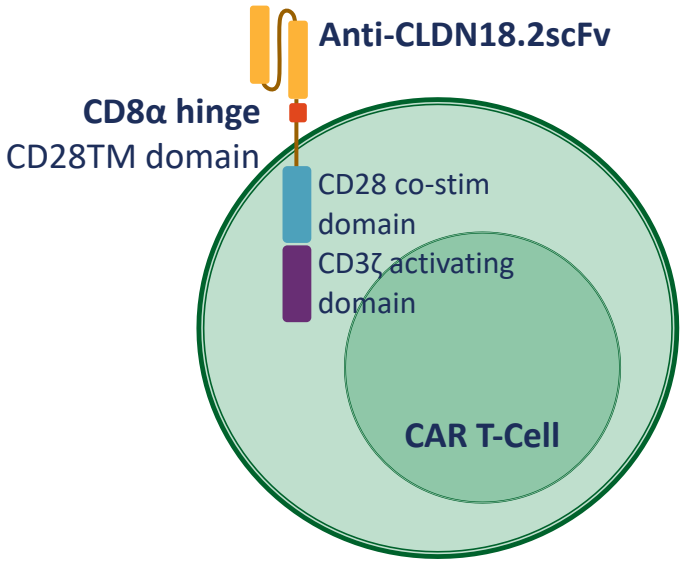
Slide credit: clinicaloptions.com

Major Claudin18.2 Strategies

Zolbetuximab (CLDN18.2 IgG1 mAb) is the most advanced CLDN18.2-directed agent, awaiting phase III 1L trial readouts (SPOTLIGHT and GLOW)

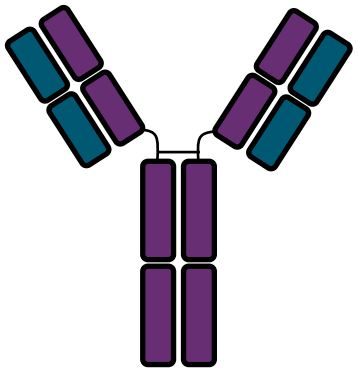
CAR T-Cell

CT041[1]



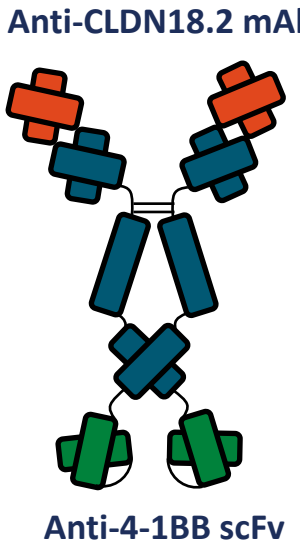
Engineered mAb

ZL-1211[2]
(Humanized IgG1)



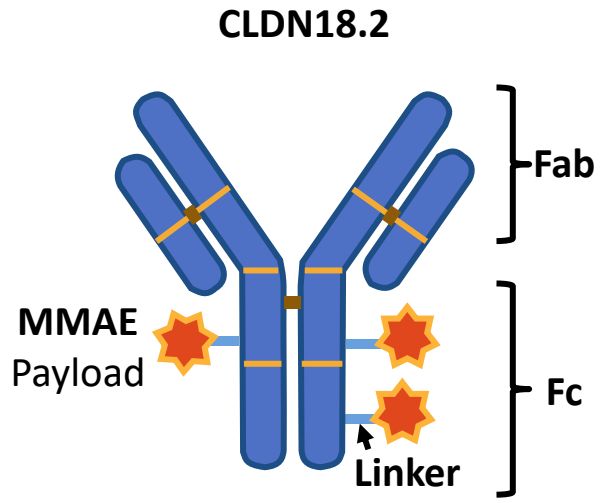
Bispecific Ab

TJ-CD4B[3]



Antibody–Drug Conjugate

CMG901[1]



1. Cao. Biomark Res. 2022;10:38. 2. Konno. AACR 2021. Abstr 1203. 3. Jiang. AACR 2020. Abstr 5644.

Slide credit: clinicaloptions.com

2023 ASCO® ANNUAL MEETING

Abstract 4046:

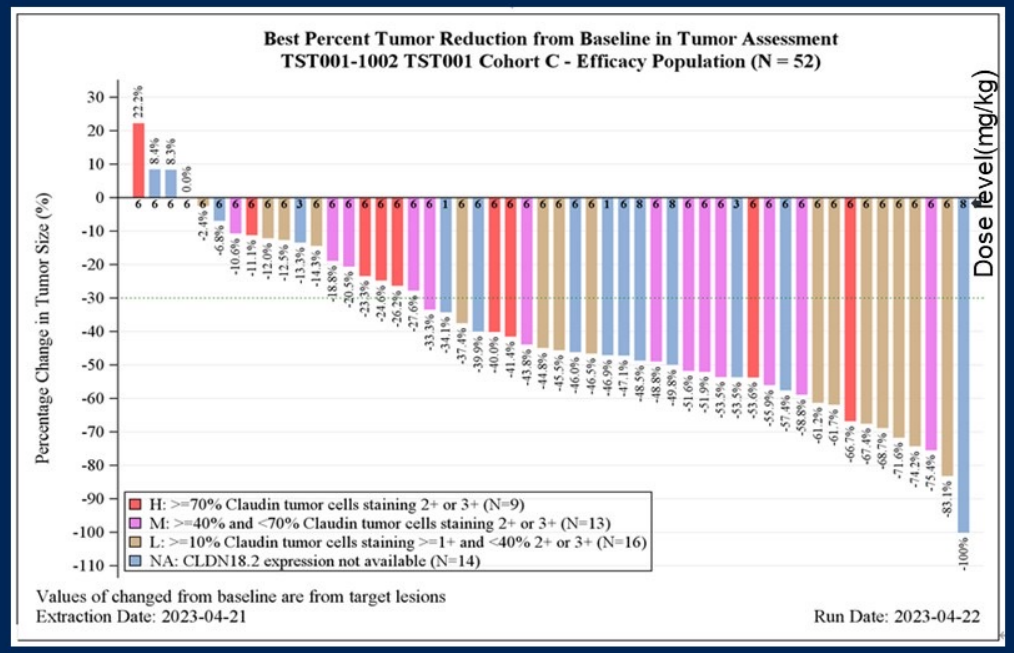
TST001 in Combination with Capecitabine and Oxaliplatin (CAPOX) as a First-Line Treatment of Advanced G/GEJ Cancer

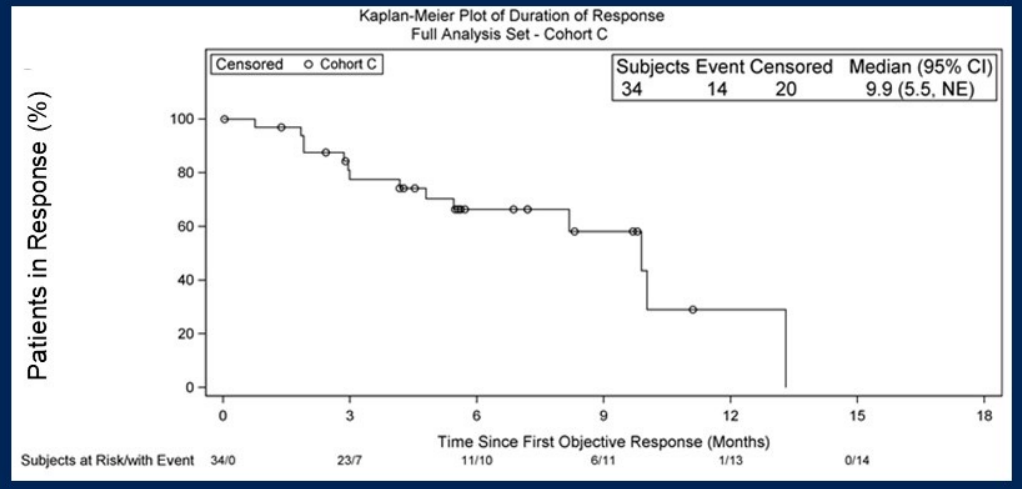
-updated data of Cohort C from a Phase I/IIa, Multi-center Study (TranStar102/TST001-1002)

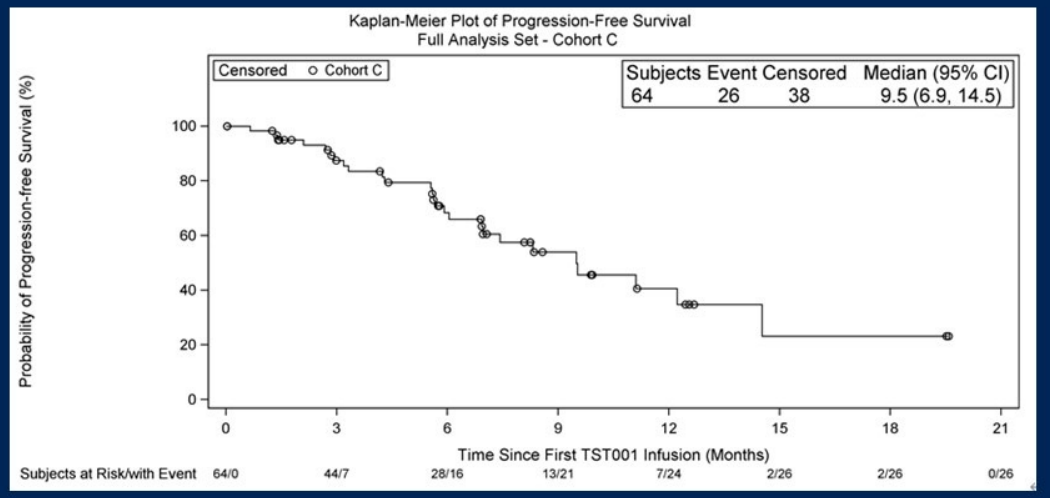
Authors: Lin Shen, Dan Liu, Ning Li, Weijian Guo, Tianshu Liu, Hongli Li, Jiayi Li, Yuxian Bai, Yanhong Deng, Zhi-xiang Zhuang, Meili Sun, Qingxia Fan, Fuyou Zhao, Liang Han, Zhenzhong Xia, Jianming Wang, Chuan Qi, Li Xu, Xueming Qian, Caroline Germa

Results – Efficacy

- As of April 21, 2023, among the 49 patients of 6mg/kg dose expansion group, 42 patients had measurable lesions and at least one post treatment tumor assessment, 28 (66.7%) achieved partial response.
- Estimated median duration of response was 9.9 months in 34 responders from all dose groups.
- Estimated median progression-free survival was 9.5 months from all dose groups.



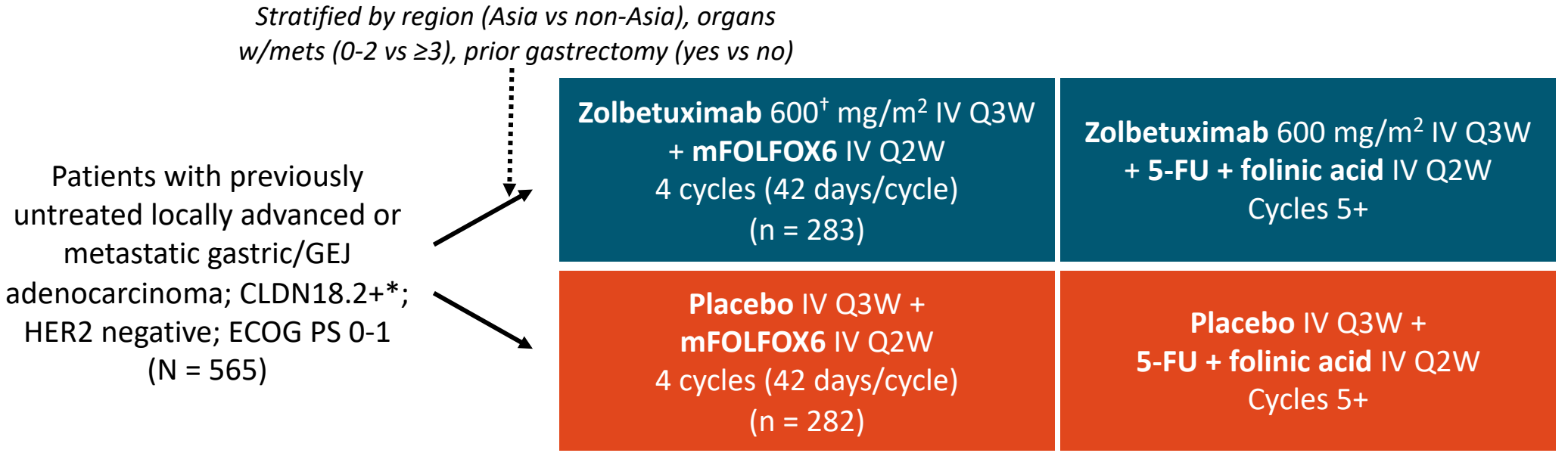




PRESENTED BY:
Lin, Shen. Peking University Cancer Hospital

SPOTLIGHT: Study Design

- Global, randomized, double-blind phase III trial



*Moderate-to-strong CLDN18 staining in ≥75% of tumor cells. †First dose only: 800 mg/m².

- **Primary endpoint:** PFS
- **Secondary endpoints:** OS, TTCD (GHS/QoL, PF, and QLQ-OG25-Pain score)
- **Additional endpoints:** ORR, DoR, safety, PROs

Shitara. ASCO GI 2023. Abstr LBA292.

Slide credit: clinicaloptions.com

SPOTLIGHT: Baseline Characteristics

Characteristic	Zolbetuximab + mFOLFOX6 (n = 283)	Placebo + mFOLFOX6 (n = 282)
Median age, yr (range)	62.0 (27-83)	60.0 (20-86)
Male, n (%)	176 (62.2)	175 (62.1)
Region: Asia/Non-Asia, n (%)	88 (31.1)/ 195 (68.9)	89 (31.6)/ 193 (68.4)
0-2 organs with metastases, n (%) ▪ ≥3	219 (77.4) 64 (22.6)	219 (77.7) 63 (22.3)
Prior gastrectomy, n (%) ▪ Yes ▪ No	84 (29.7) 199 (70.3)	82 (29.1) 200 (70.9)
Primary site, n (%) ▪ Stomach ▪ GEJ	219 (77.4) 64 (22.6)	210 (74.5) 72 (25.5)

Characteristic	Zolbetuximab + mFOLFOX6 (n = 283)	Placebo + mFOLFOX6 (n = 282)
Lauren classification, n (%) ▪ Diffuse ▪ Intestinal ▪ Mixed/others	 82 (29.1) 70 (24.8) 130 (45.9)	 117 (42.1) 66 (23.7) 95 (33.7)
ECOG PS 0/1, n (%)	125 (44.8)/ 153 (54.8)	115 (41.4)/ 163 (58.6)
Subsequent anticancer therapy, %	48	53

- PD-L1 CPS ≥5: 41/311 (13.2%) (ad hoc analysis using 28-8 pharmDx IHC assay)

Shitara. ASCO GI 2023. Abstr LBA292.

Slide credit: clinicaloptions.com

SPOTLIGHT: PFS and OS

PFS	Zolbetuximab + mFOLFOX6 (n = 283)	Placebo + mFOLFOX6 (n = 282)
Median PFS, mo (95% CI)	10.61 (8.90-12.48)	8.67 (8.21-10.28)
	HR: 0.751 (95% CI: 0.589-0.94) *P* = .0066	
12-mo PFS, %	49	35
24-mo PFS, %	24	15
Median F/U, mo	12.94	12.65

OS	Zolbetuximab + mFOLFOX6 (n = 283)	Placebo + mFOLFOX6 n = 282)
Median OS, mo (95% CI)	18.23 (16.43-22.90)	15.54 (13.47-16.53)
	HR: 0.75 (95% CI: 0.601-0.936) *P* = .0053	
12-mo OS, %	68	60
24-mo OS, %	39	28
Median F/U, mo	22.14	20.93

- Both PFS and OS longer with zolbetuximab + mFOLFOX6 across most subgroups

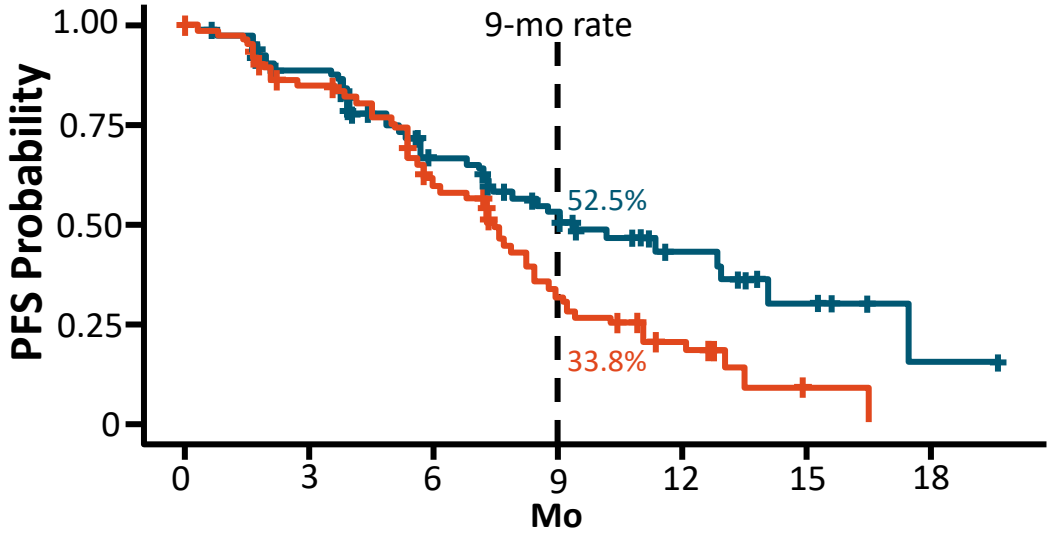
Data cutoff: 2022-09-09.

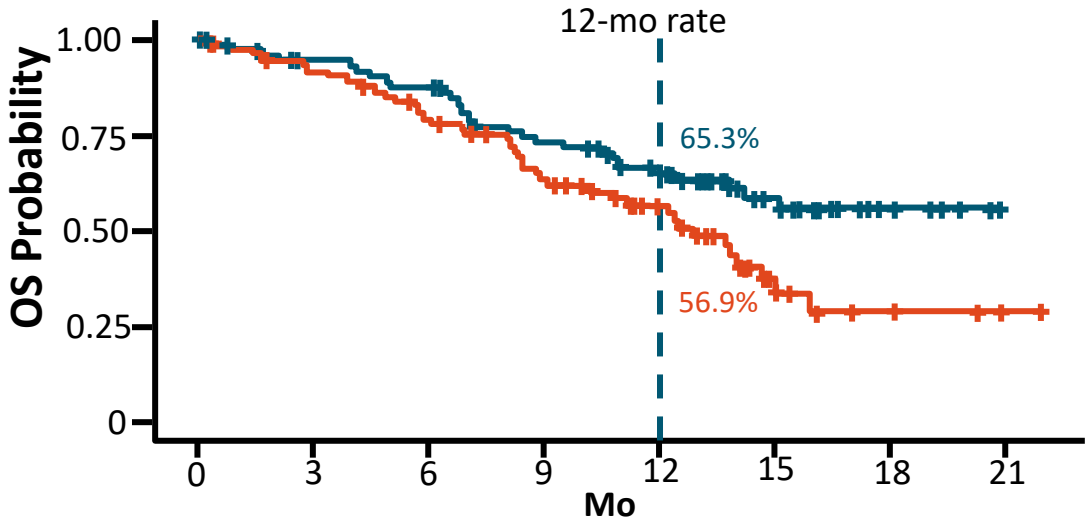
Shitara. ASCO GI 2023. Abstr LBA292.

Slide credit: clinicaloptions.com

FIGHT: First-line Bemarituzumab + mFOLFOX6 vs Placebo + mFOLFOX6 in Advanced Gastric/GEJ Cancer

- Randomized phase II trial of bemarituzumab (anti-FGFR2b antibody) or placebo + (both + mFOLFOX6) for patients with no prior therapy and unresectable locally advanced or metastatic gastric/GEJ adenocarcinoma with *FGFR2b* overexpression/amplification (N = 155)





	Bema + mFOLFOX6 (n = 77)	Placebo + mFOLFOX6 (n = 78)	
Median PFS, mo	9.5	7.4	HR 0.68; *P* = .0727)
Median OS, mo	Not reached	12.9	HR 0.58; *P* = .0268)

- Ongoing phase III: FORTITUDE-101 (bemarituzumab + mFOLFOX6, NCT05052801)

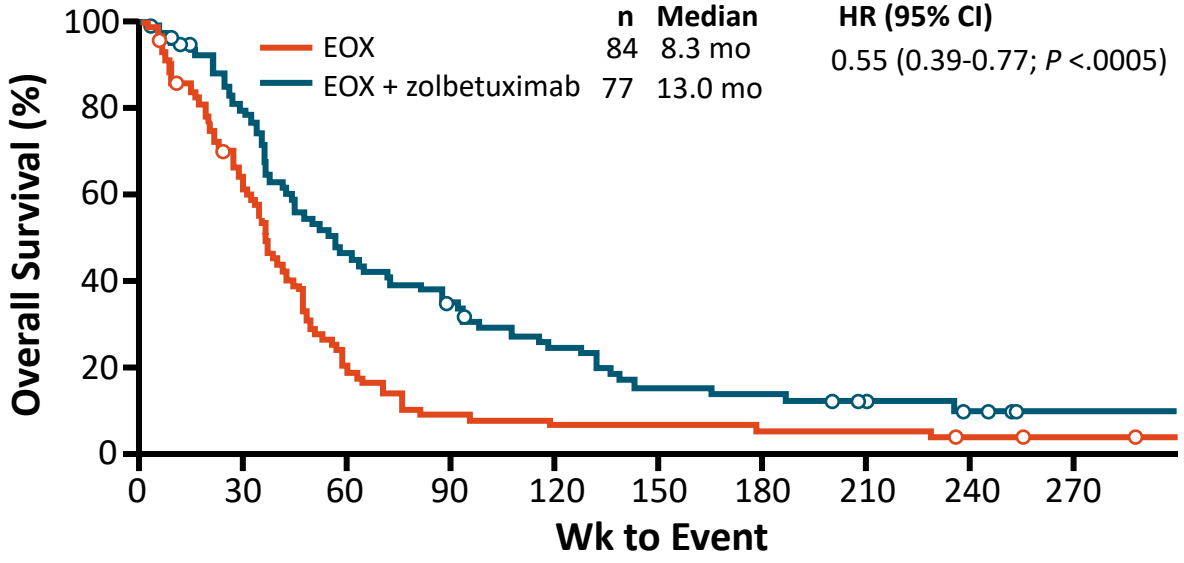
Wainberg. ASCO GI 2021. Abstr LBA160.

Slide credit: clinicaloptions.com

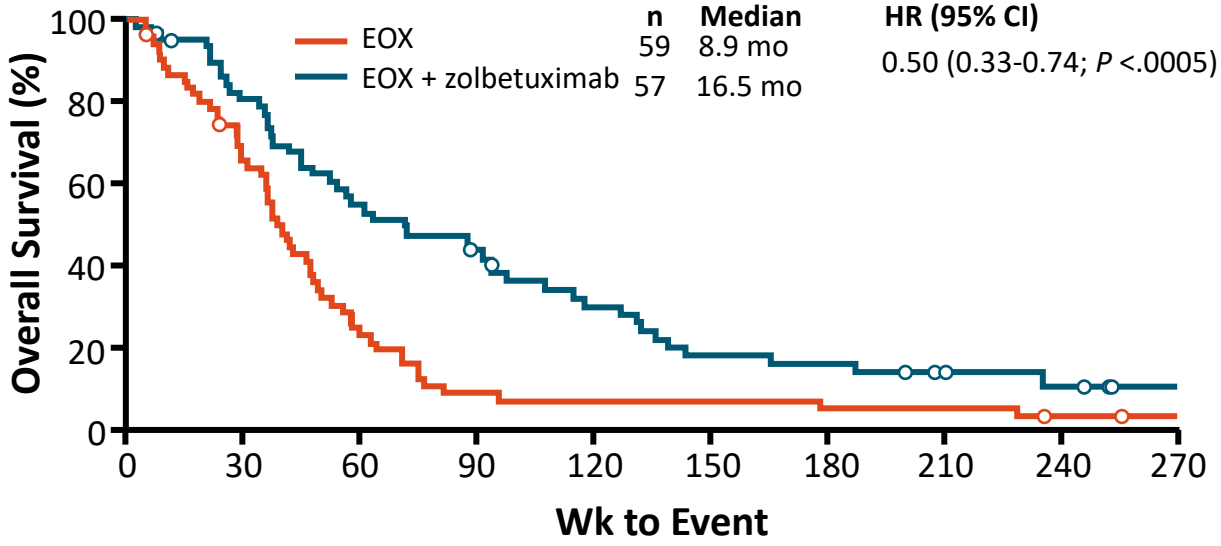
FAST: First-line Zolbetuximab (IMAB362) + EOX for Advanced CLDN18.2+ Gastric/GEJ Adenocarcinoma

- Randomized phase II study of first-line zolbetuximab + EOX vs EOX for patients with locally advanced, inoperable, recurrent, or metastatic CLDN18.2+ gastric or GEJ adenocarcinoma (N = 252)

OS in Overall Population*



OS in High CLDN18.2 Expressors†



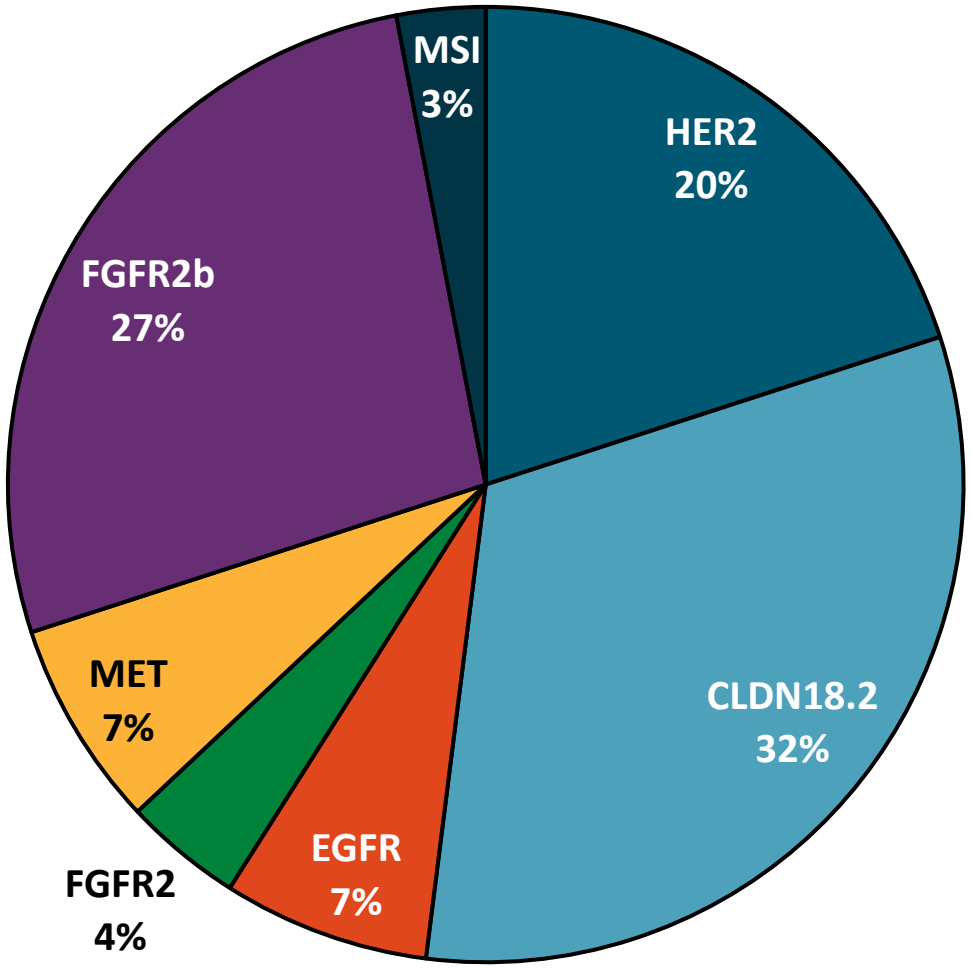
*Patients with ≥40% of tumor cells positive for CLDN18.2. †Patients with ≥70% of tumor cells positive for CLDN18.2.

- Ongoing: Spotlight (FOLFOX6 ± zolbetuximab, NCT03504397); GLOW (CapeOx ± zolbetuximab, NCT03653507)

Sahin. Ann Oncol. 2021;32:609.

Slide credit: clinicaloptions.com

NGS—the Right Tool for the Job



- HER2 status: NGS, FISH, IHC
- MSI status: NGS, PCR, IHC
- PD-L1 score: IHC

- NTRK status: NGS, IHC, FISH
- TMB level: NGS
- CLDN18.2 expression: IHC
- FGFR2 status: NGS, FISH, IHC
- $EGFR_{amp}$ status: NGS, FISH
- MET_{amp} status: NGS, FISH

Lee. J Pathol Transl Med. 2017;51:103. Schoemig-Markieffka. Gastric Cancer. 2021;24:1115.
Cai. J Transl Med. 2019;17:189. Baek. Anticancer Res. 2019;39:6973. Ahn. Mod Pathol. 2016;29:1095.

Slide credit: clinicaloptions.com