Developments in Esophageal and Gastric Tumors

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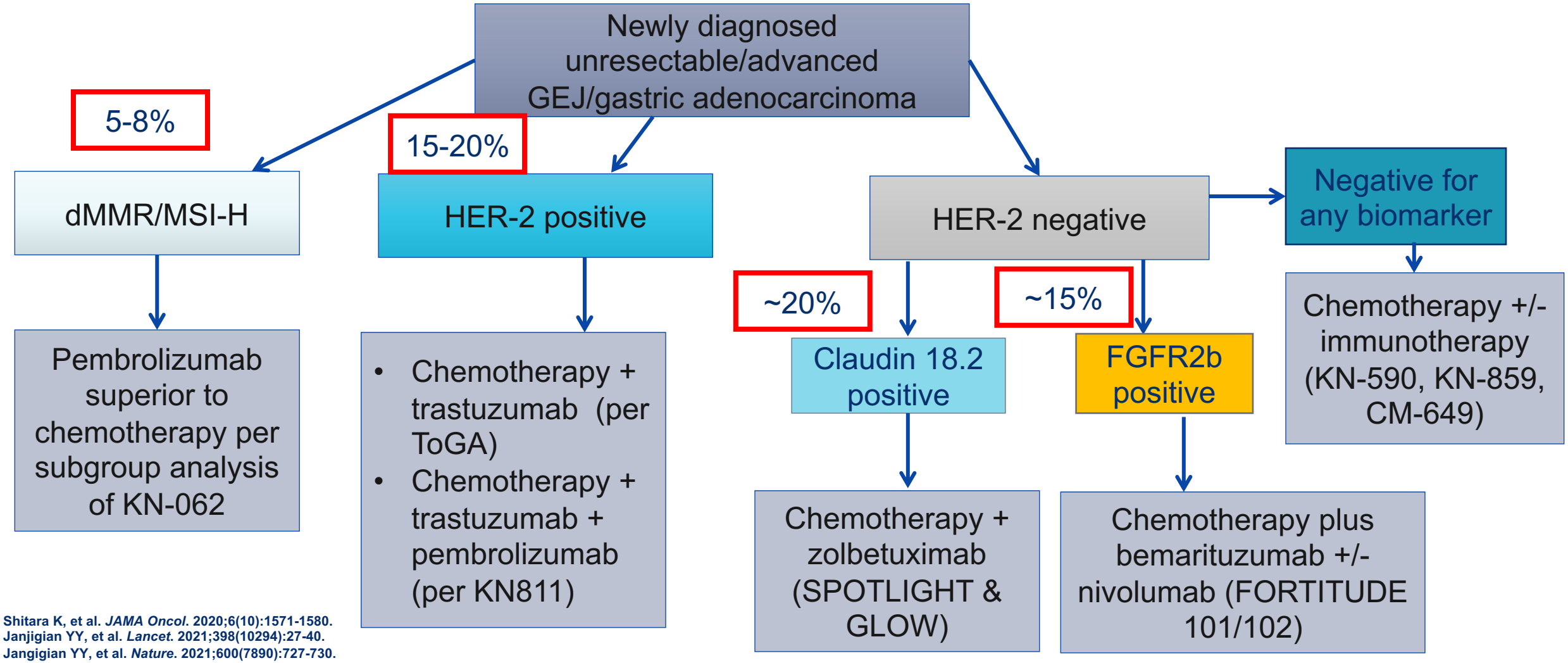
Agenda

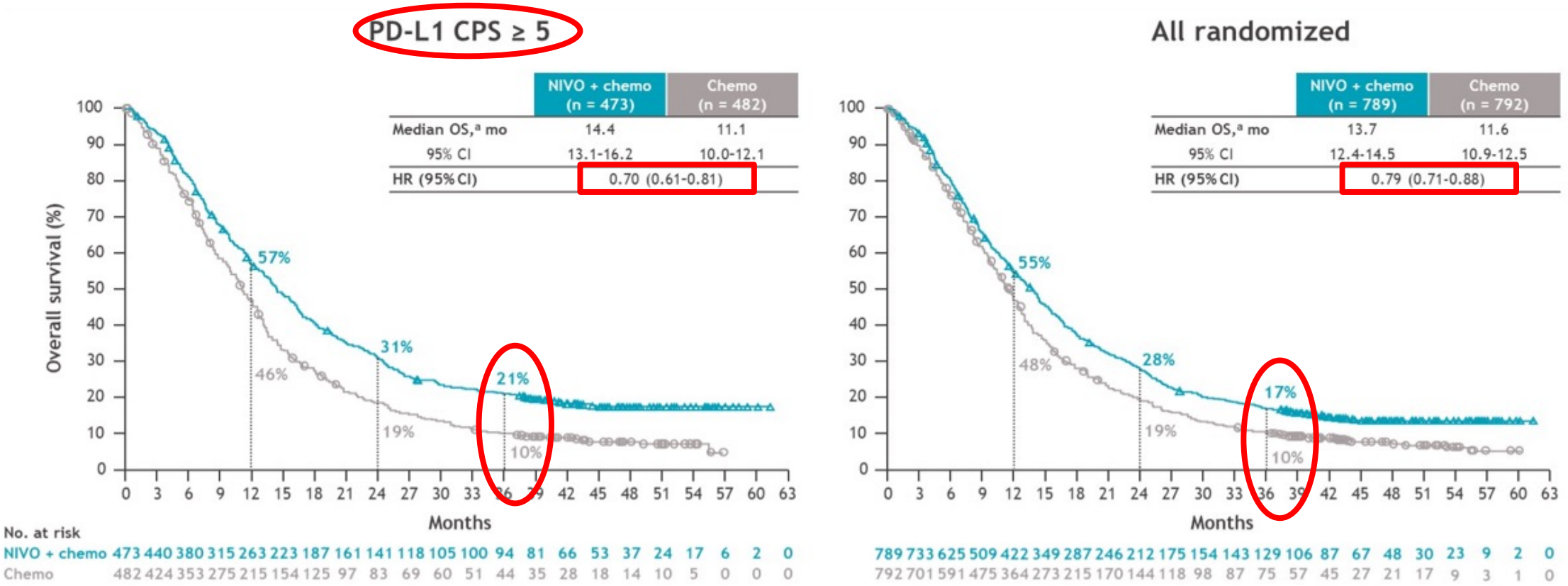
- Current state of art of 1st line treatment of gastroesophageal cancers- beyond HER2 and PD-L1
- Update from GI ASCO 2024 (Skyscraper, Keynote 585, Matterhorn)

Paradigm of treatment for treatment naïve stage IV GEJ/gastric cancer patients



Shitara K, et al. *JAMA Oncol*. 2020;6(10):1571-1580.
Janjigian YY, et al. *Lancet*. 2021;398(10294):27-40.
Jangigian YY, et al. *Nature*. 2021;600(7890):727-730.
Sun JM, et al. The Lancet. 2021; 398(10302): 759-771

CheckMate-649: Overall Survival at 36 Months



- 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

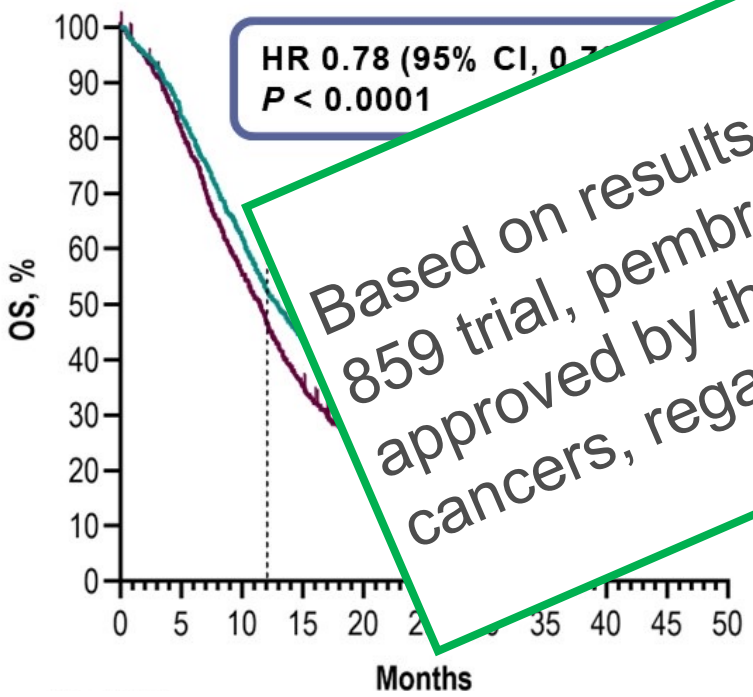
[a]Minimum follow-up, 36.2 months.

- Janjigian, Y., et al. GI ASCO (2023).

KEYNOTE-859 Primary Endpoint: Overall Survival

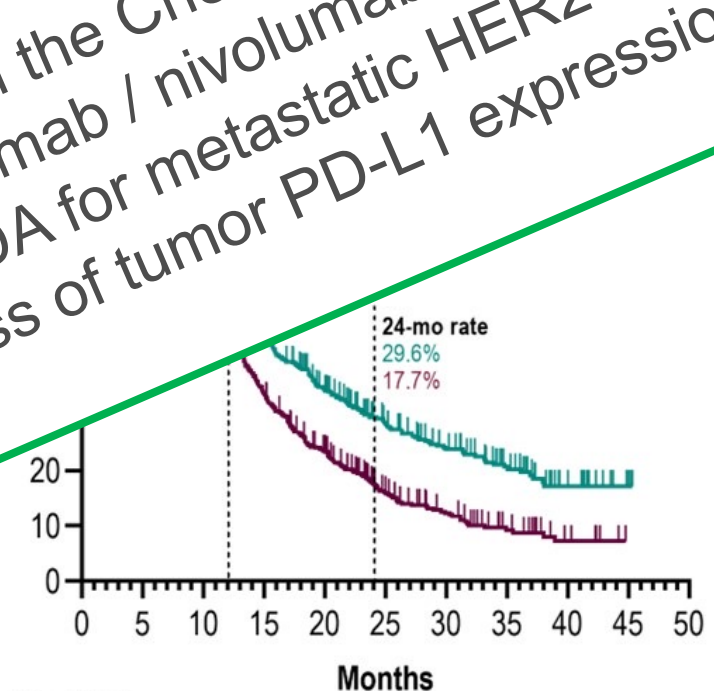
Overall

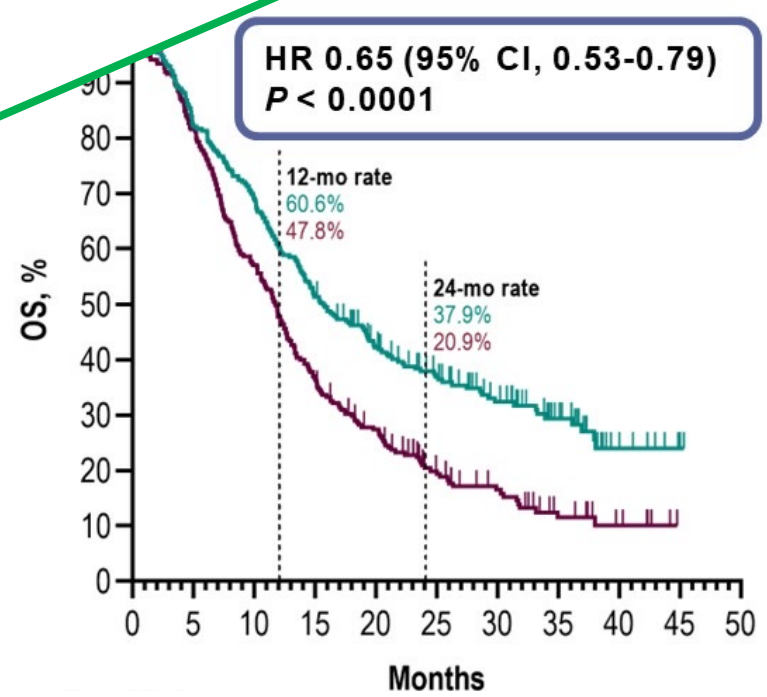
	Pts w/ Event	Median (95% CI), mo
Pembro + chemo	76.3%	12.9 (11.9-14.0)
Placebo + chemo	84.4%	11.5 (10.6-12.1)



PD-L1 CPS ≥10

	Pts w/ Event	Median (95% CI), mo
Pembro + chemo	4%	15.7 (13.8-19.3)
Placebo + chemo	%	11.8 (10.3-12.7)





Based on results from the CheckMate-649 and KEYNOTE-859 trial, pembrolizumab / nivolumab with chemotherapy was approved by the FDA for metastatic HER2-negative G/GEJ cancers, regardless of tumor PD-L1 expression

Pembro, pembrolizumab.

Rha ST, et al. *Ann Oncol*. 2023;34:319-20; Rha SY, et al. ASCO 2023. Abstract 4014.

KEYNOTE-811 Study Design (NCT03615326)
Phase 3 Randomized, Placebo-Controlled

Key Eligibility Criteria
- Advanced, unresectable G/GEJ adenocarcinoma
- No prior systemic therapy in advanced setting
- HER2+ by central review (IHC 3+ or IHC 2+ ISH+)
- ECOG PS 0 or 1

R 1:1
N=698

Pembrolizumab 200 mg IV Q3W + Trastuzumab and FP or CAPOX[a]
for up to 35 cycles

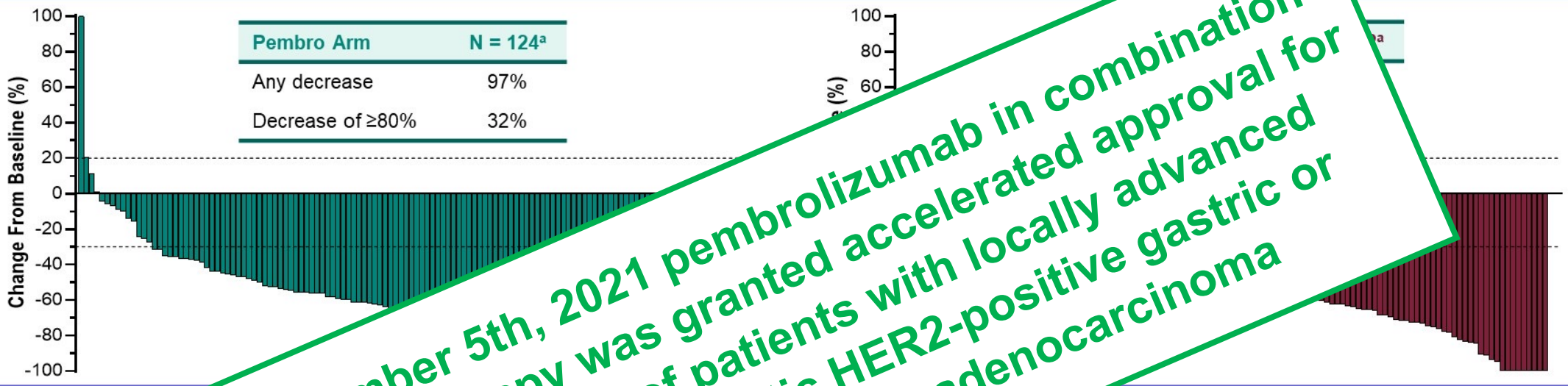
Placebo IV Q3W + Trastuzumab and FP or CAPOX[a]
for up to 35 cycles

Stratification Factors
- Geographic region
- PD-L1 CPS <1 vs CPS ≥1
- Chemotherapy choice

Endpoints
- Dual primary: OS, PFS
- Secondary: ORR, DOR , safety

[a]Trastuzumab: 6 mg/kg IV Q3W following an 8 mg/kg loading dose. FP: 5-fluorouracil 800 mg/m^2 IV on D1-5 Q3W + cisplatin 80 mg/m^2 IV Q3W. CAPOX: capecitabine 1000 mg/m^2 BID on D1-14 Q3W + oxaliplatin 130 mg/m2 IV Q3W. PFS, ORR, DOR per RECIST by BICR.
BICR, blinded independent central review; CPS, combined positive score; PD-L1, programmed death ligand 1.
Janjigian YY, et al. ESMO 2023. Abstract 15110.

KEYNOTE 811: Interim Analysis Results



Pembro Arm	N = 124[a]
Any decrease	97%
Decrease of ≥80%	32%

On November 5th, 2021 pembrolizumab in combination with chemotherapy was granted accelerated approval for first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma

ORR and DC % (95% CI)		
ORR		
ORR difference[b]		
DCR	(91.4-98.8)	89.3% (82.7-94.0)

	= 133)	lacebo Arm (N = 131)
ORR	**15 (11%)**	**4 (3%)**
	84 (63%)	**64 (49%)**
SD	29 (22%)	49 (37%)
PD	5 (4%)	7 (5%)
Not evaluable	0	2 (2%)
Not assessed	0	5 (4%)

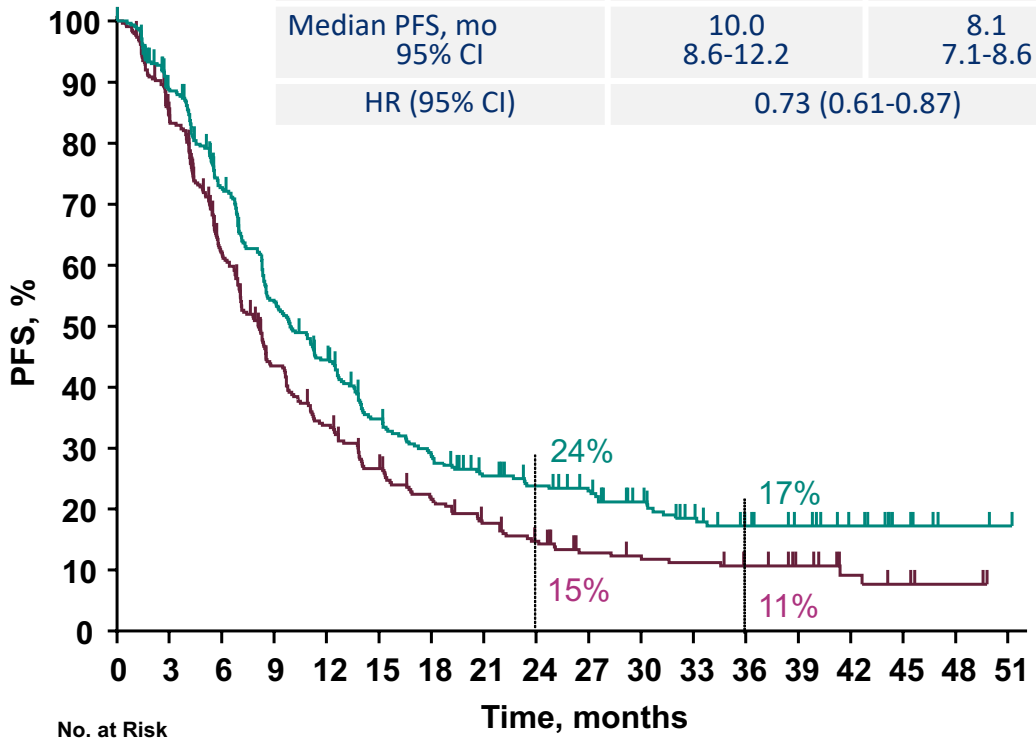
Duration of Response[c]	Pembro Arm (N = 99)	Placebo Arm (N = 68)
Median[d]	10.6 mo	9.5 mo
Range	1.1+ to 16.5+	1.4+ to 15.4+
≥6-mo duration[d]	70.3%	61.4%
≥9-mo duration[d]	58.4%	51.1%

Jangigian YY, et al. *J Clin Oncol*. 2021;39(15_suppl.):4013. Jangigian YY, et al. *Nature*. 2021;600(7890):727-730.

Progression-Free Survival at 38.5 Months of Follow-Up[a] RECIST V1.1, BICR

All patients

	Pembrolizuab	Placebo
Median PFS, mo 95% CI	10.0 8.6-12.2	8.1 7.1-8.6
HR (95% CI)	0.73 (0.61-0.87)	

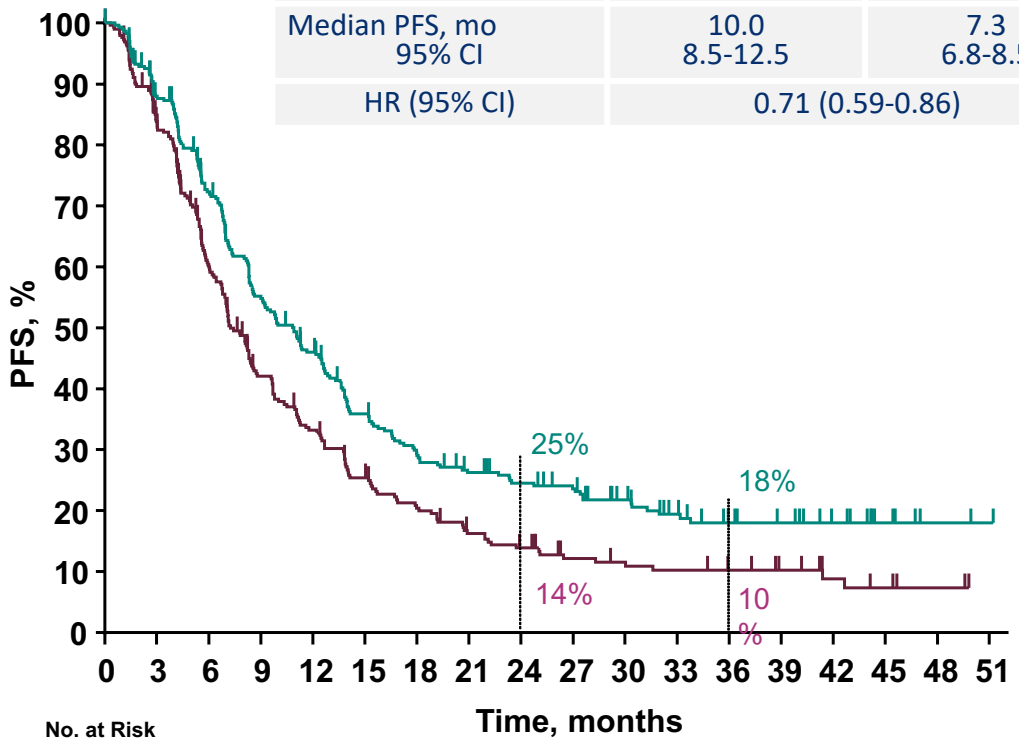


No. at Risk

Pembrolizumab gp	350	296	234	173	139	102	84	67	59	53	41	31	24	20	14	6	2	1
Placebo gp	348	274	184	121	93	71	55	43	34	25	23	21	17	11	6	4	2	0

PD-L1 CPS ≥1[b]

	Pembrolizuab	Placebo
Median PFS, mo 95% CI	10.0 8.5-12.5	7.3 6.8-8.5
HR (95% CI)	0.71 (0.59-0.86)	



No. at Risk

Pembrolizumab gp	298	250	200	151	123	91	74	63	56	51	39	30	23	20	14	6	2	1
Placebo gp	296	231	152	100	78	58	45	34	28	20	18	16	14	10	6	4	2	0

Data cut-off: March 29, 2023.

aMedian follow-up; bNot a prespecified endpoint.

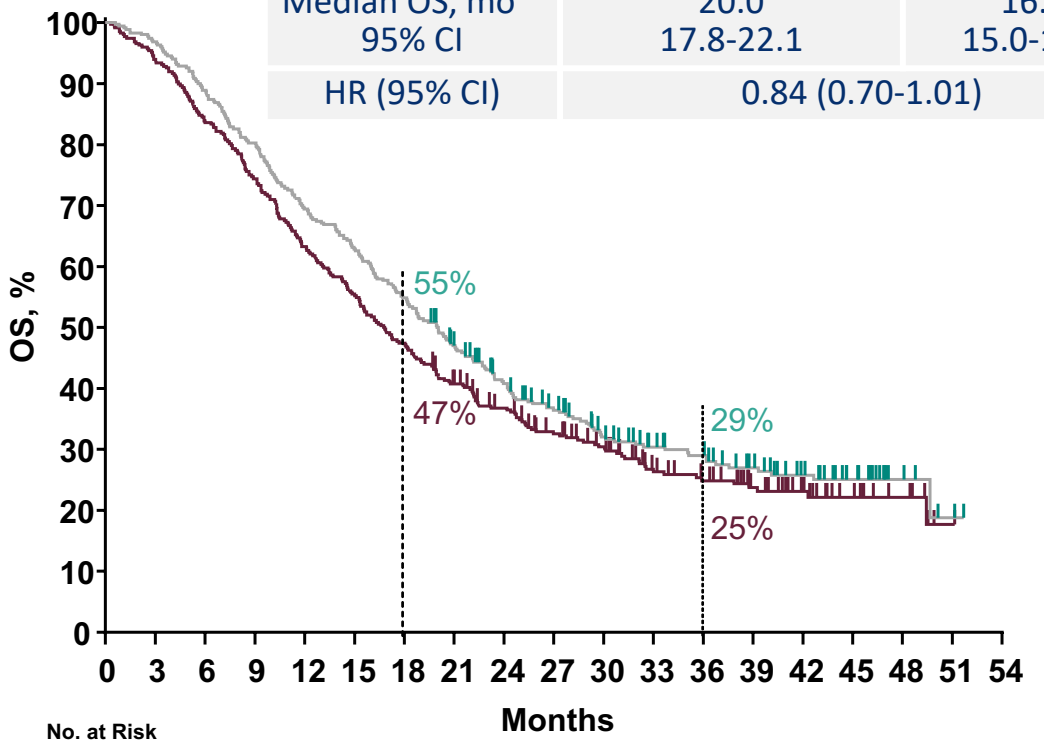
BICR, blinded independent central review; CI, confidence interval; PFS, progression-free survival; RECIST, response evaluation criteria in solid tumors.

Janjigian YY, et al. ESMO 2023. Abstract 15110.

Overall Survival at the Third Interim Analysis

All patients

	Pembrolizumab	Placebo
Median OS, mo 95% CI	20.0 17.8-22.1	16.8 15.0-18.7
HR (95% CI)	0.84 (0.70-1.01)	

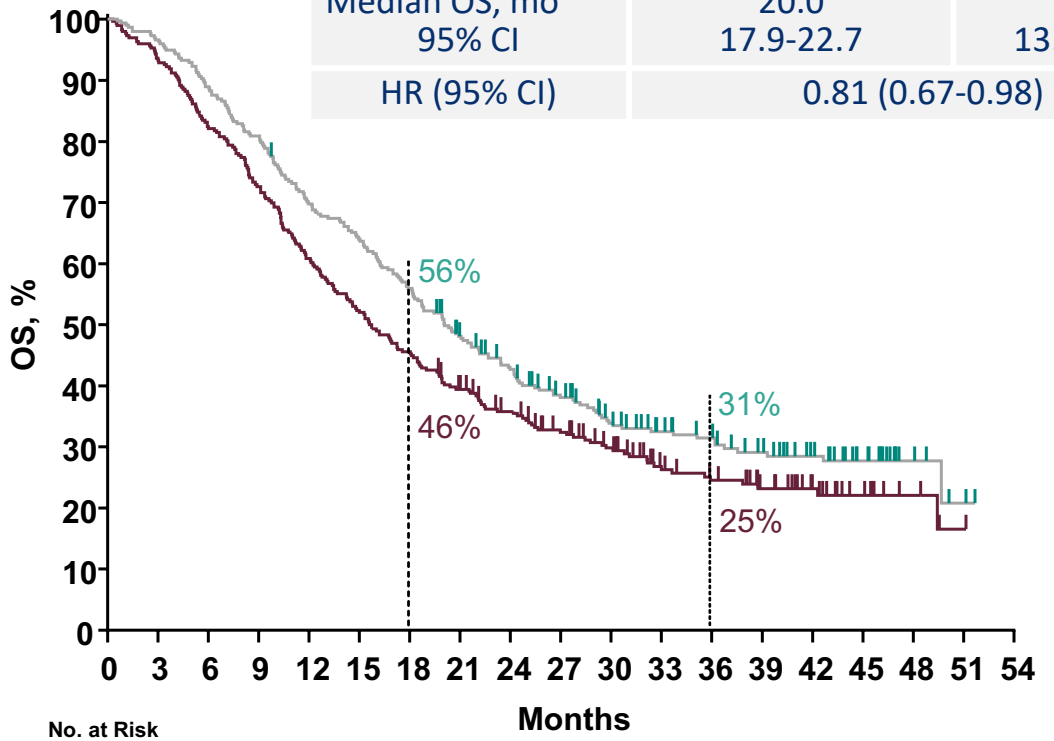


No. at Risk

Pembrolizumab gp	350	339	311	281	243	220	192	156	126	105	84	69	61	48	37	23	7	2	0
Placebo gp	348	327	292	259	220	193	165	138	116	96	83	58	51	37	25	15	8	1	0

PD-L1 CPS ≥1[a]

	Pembrolizumab	Placebo
Median OS, mo 95% CI	20.0 17.9-22.7	15.7 13.5-18.5
HR (95% CI)	0.81 (0.67-0.98)	



No. at Risk

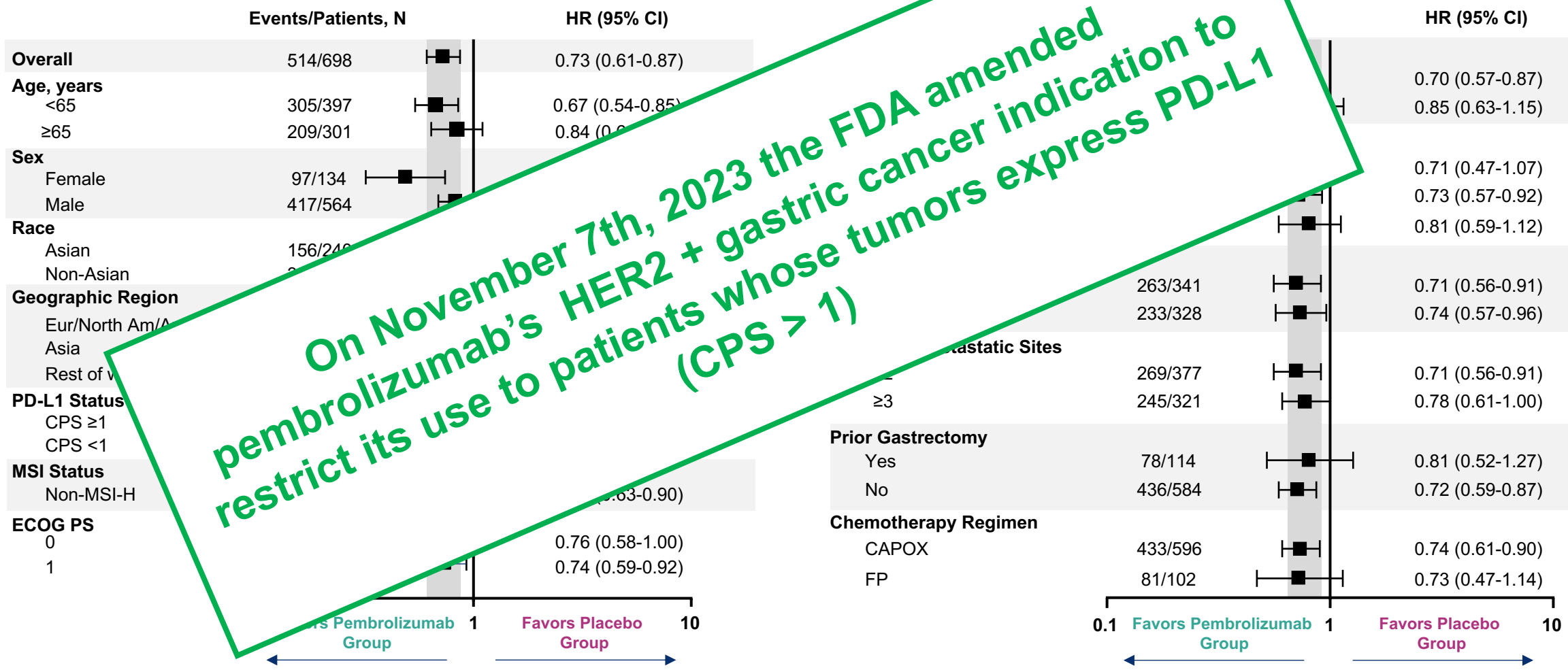
Pembrolizumab gp	298	288	265	241	207	190	166	136	115	96	78	64	58	47	37	23	7	2	0
Placebo gp	296	277	244	215	180	155	135	113	96	80	67	47	41	31	21	12	5	1	0

Data cut-off: March 29, 2023. OS did not meet the prespecified criteria for significance at IA3 and will be retested at final analysis.

[a]Not a prespecified endpoint.

Janjigian YY, et al. ESMO 2023. Abstract 15110.

Progression-Free Survival in Key Subgroup IA3



On November 7th, 2023 the FDA amended pembrolizumab's HER2 + gastric cancer indication to restrict its use to patients whose tumors express PD-L1 (CPS > 1)

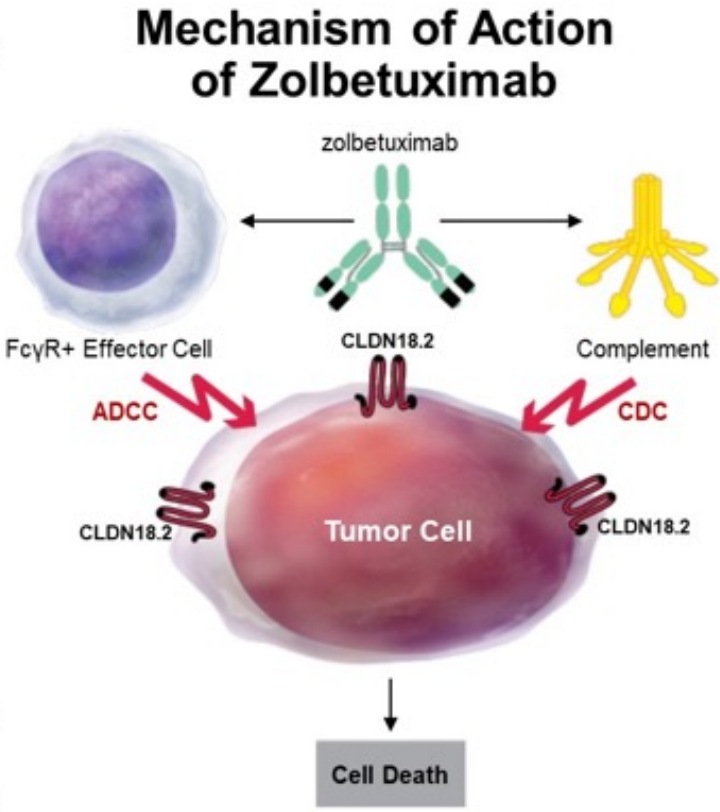
Data cut-off: March 29, 2023.

CAPOX, oxaliplatin + capecitabine; ECOG, Eastern Cooperative Oncology Group; FP, 5-fluorouracil + cisplatin; MSI, microsatellite instability; PS, performance status.

Janjigian YY, et al. ESMO 2023. Abstract 15110.

What is Zolbetuximab?

- CLDN18.2 is a tight junction protein normally expressed in gastric mucosa cells and retained in G/GEJ adenocarcinoma[1–8]
- CLDN18.2 may become exposed on the surface of G/GEJ adenocarcinoma cells, making it a promising target[2–8]
- Zolbetuximab is a first-in-class chimeric IgG1 monoclonal antibody that targets CLDN18.2 and induces ADCC/CDC[4–8]
- In the phase 2b FAST study, EOX ± zolbetuximab prolonged survival in a subgroup of patients with higher expression of CLDN18.2 in tumor cells[8]
  - mPFS: 9.0 vs 5.7 months with zolbetuximab + EOX vs EOX alone
  - mOS: 16.5 vs 8.9 months with zolbetuximab + EOX vs EOX alone

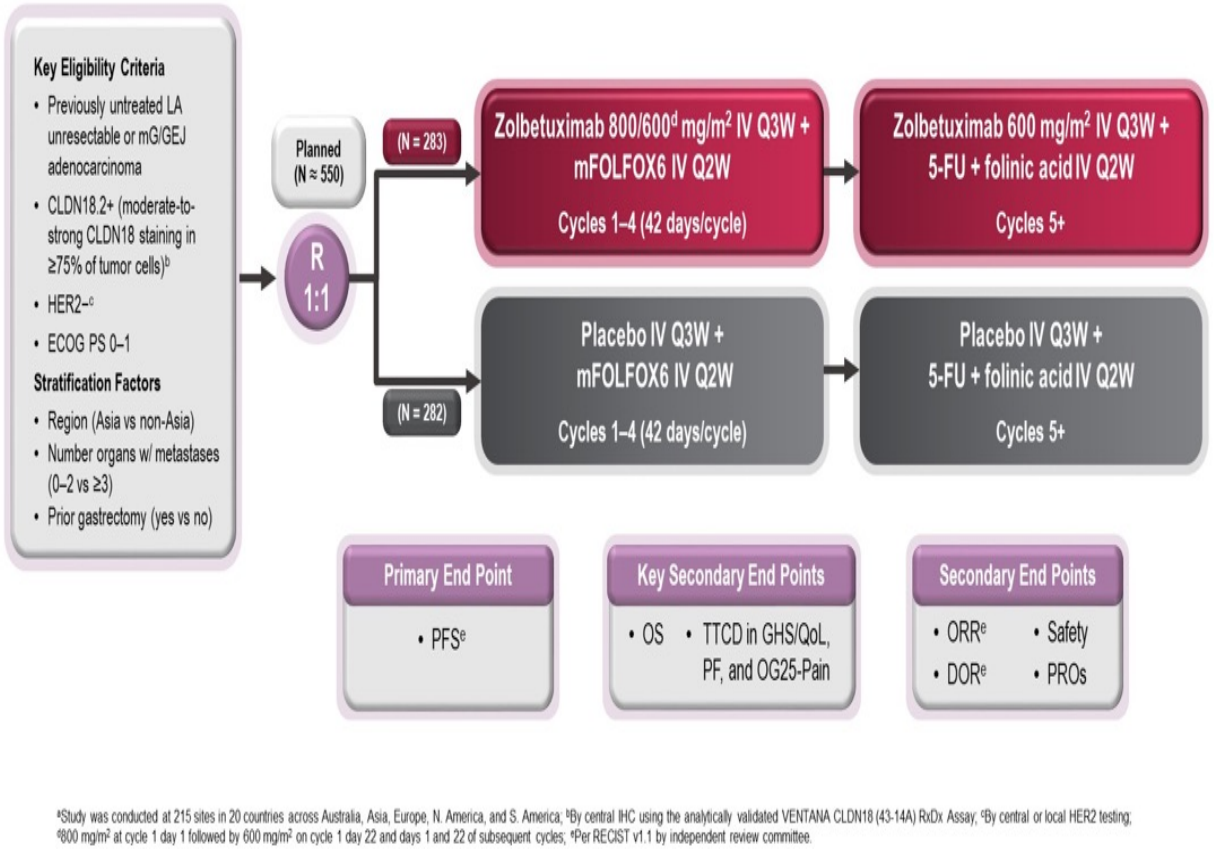


1. Niimi T et al. *Mol Cell Biol*. 2001;21:7380–90; 2. Sahin U et al. *Clin Cancer Res*. 2008;14:7624–34; 3. Moran D et al. *Ann Oncol*. 2018;29:viii14-viii57; 4. Sahin U et al. *Eur J Cancer*. 2018;100:17–26; 5. Rhode C et al. *Jpn J Clin Oncol*. 2019;49:870–6; 6. Türeci Ö et al. *Ann Oncol*. 2019;30:1487-95. 7. Pellino A et al. *J Pers Med*. 2021; 11(11):1095; 8. Sahin U et al. *Ann Oncol*. 2021;32:609–19.

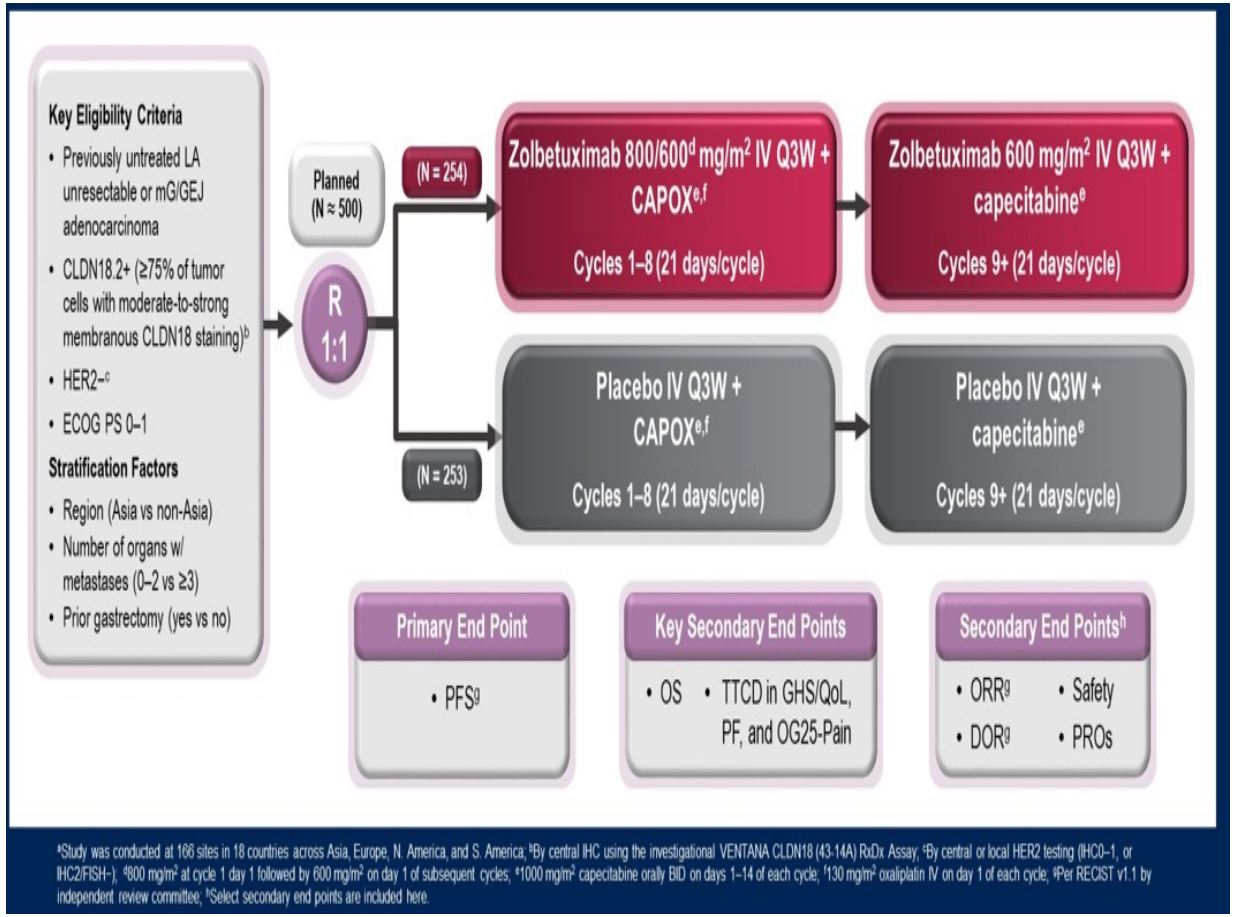
- Shitara, *et al. GI ASCO (*2023). LBA292

Two Studies
SPOTLIGHT and GLOW

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



[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.



[a]Study was conducted at 166 sites in 18 countries across Asia, Europe, N. America, and S. America; [b]By central IHC using the investigational VENTANA CLDN18 (43-14A) RxDx Assay; [c]By central or local HER2 testing (IHC0–1, or IHC2/FISH−); [d]800 mg/m² at cycle 1 day 1 followed by 600 mg/m² on day 1 of subsequent cycles; [e]1000 mg/m² capecitabine orally BID on days 1–14 of each cycle; [f]130 mg/m² oxaliplatin IV on day 1 of each cycle; [g]Per RECIST v1.1 by independent review committee; [h]Select secondary end points are included here.

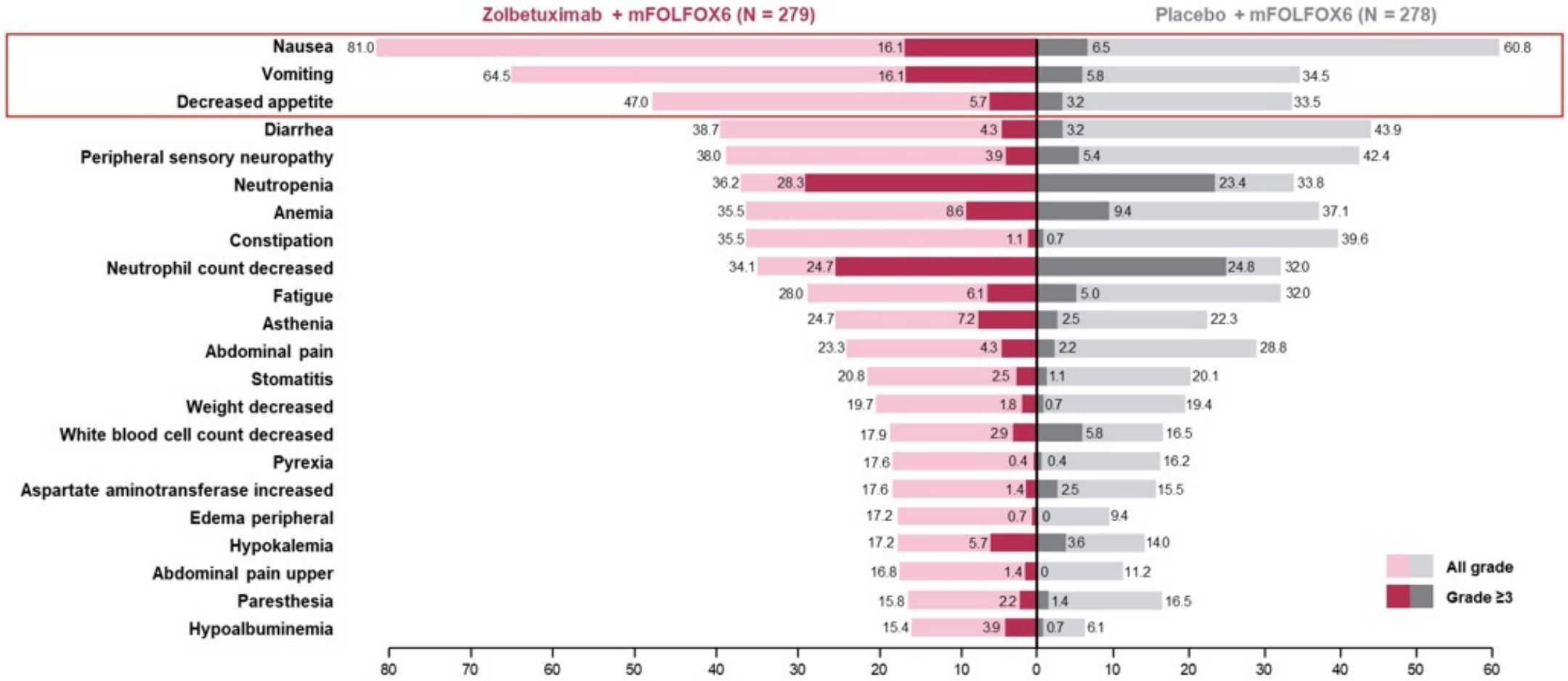
Shah et al. *Lancet*. 2023. (*GLOW*); Shitara et al. *Lancet*. 2023. (*SPOTLIGHT*);

GLOW and SPOTLIGHT – Efficacy Comparison

	GLOW CAPOX + zolbetuximab vs CAPOX + placebo Patients (N = 254 vs 253)	SPOTLIGHT mFOLFOX6 + zolbetuximab vs mFOLFOX 6 vs placebo Patients (N = 283 vs 282)
Median Progression-free Survival	8.28 vs 6.80 months HR 0.682 (95% CI 0.545 - 0.854; P = 0.0004)	11.04 vs 8.94 months HR 0.730 (95% CI, 0.587, 0.907; P = 0.0022)
Median Overall Survival	14.32 vs 12.16 months HR 0.771 (95% CI 0.624-0.952; P = 0.0079)	18.2 vs 15.6 months HR 0.778 (95% CI 0.637 - 0.949; P = 0.0067)
Objective Response Rate (CR + PR)	54.1% vs 48.5%	61.1% vs 62.4%

Shah et al. *Lancet*. 2023. (*GLOW*); Shitara et al. *Lancet*. 2023. (*SPOTLIGHT*);

TEAEs Occurring in ≥ 15% of Patients

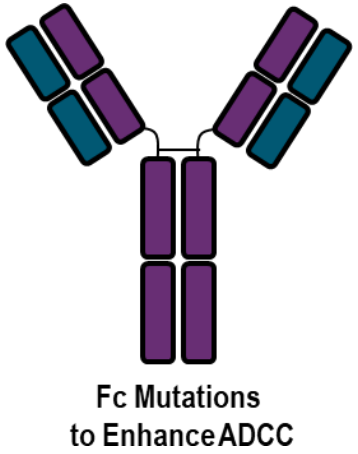


- The most common TEAEs with zolbetuximab + mFOLFOX6 were nausea and vomiting as on-target effects

CLDN18.2 Targeted treatments

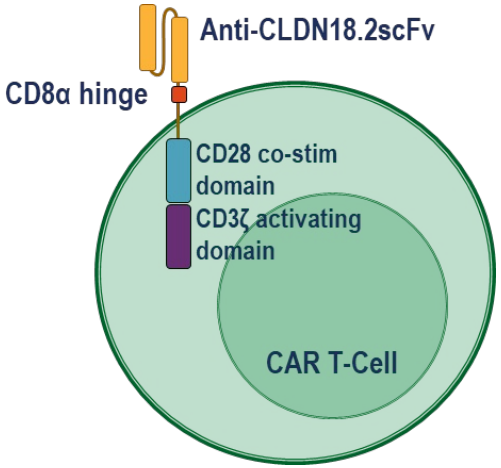
Monoclonal antibody

- Humanized mAb
- Engineered mAb



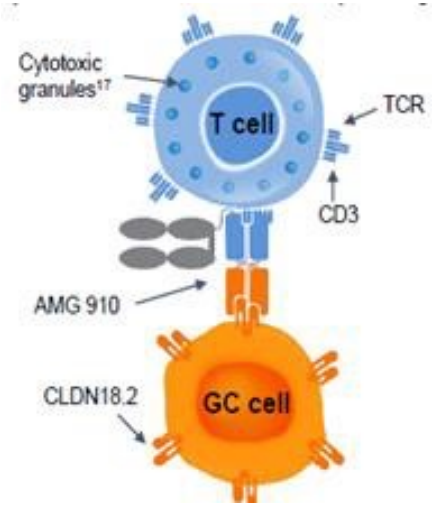
IMAB306/Zolbetuximab
TST-001
ABI011, MIL93, ZL1211 etc.

CAR-T



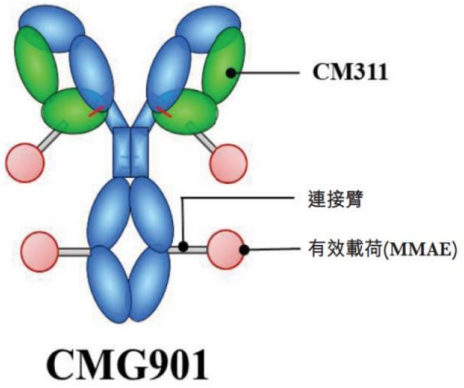
CT-041
LCAR-C18S
LY011

BITE Bispecific



AMG910/ASP2138 (CD3)
Q-1802 (PD-L1)
TJ-CD4B (4-1BB)
PT886 (CD47)

ADCs



CMG901
SYSA1801
TPX4589
RC118
LM302
SOT102
SKB315
JS107
IBI343

Summary

- In HER2 negative patients, there is now FDA approval of chemotherapy plus immunotherapy. The magnitude of benefit of adding immunotherapy increases with selection of high PD-L1 cases.
- The addition of pembrolizumab in the KEYNOTE-811 trial improved PFS and ORR, particularly in dual HER2 and PD-L1 overexpressed tumors (CPS > 1)
- Claudin 18.2 is a new biomarker and zolbetuximab is a monoclonal antibody targeting this. Two studies- SPOTLIGHT and GLOW have shown PFS and OS benefit with the addition of zolbetuximab to chemotherapy in the first line setting.
- However as of Jan 12, 2024 FDA has not approved zolbetuximab due to unresolved deficiencies following its pre-license inspection of a third-party manufacturing facility.

Moving on to GI ASCO 2024

MOFFITT CANCER CENTER

ASCO Gastrointestinal Cancers Symposium

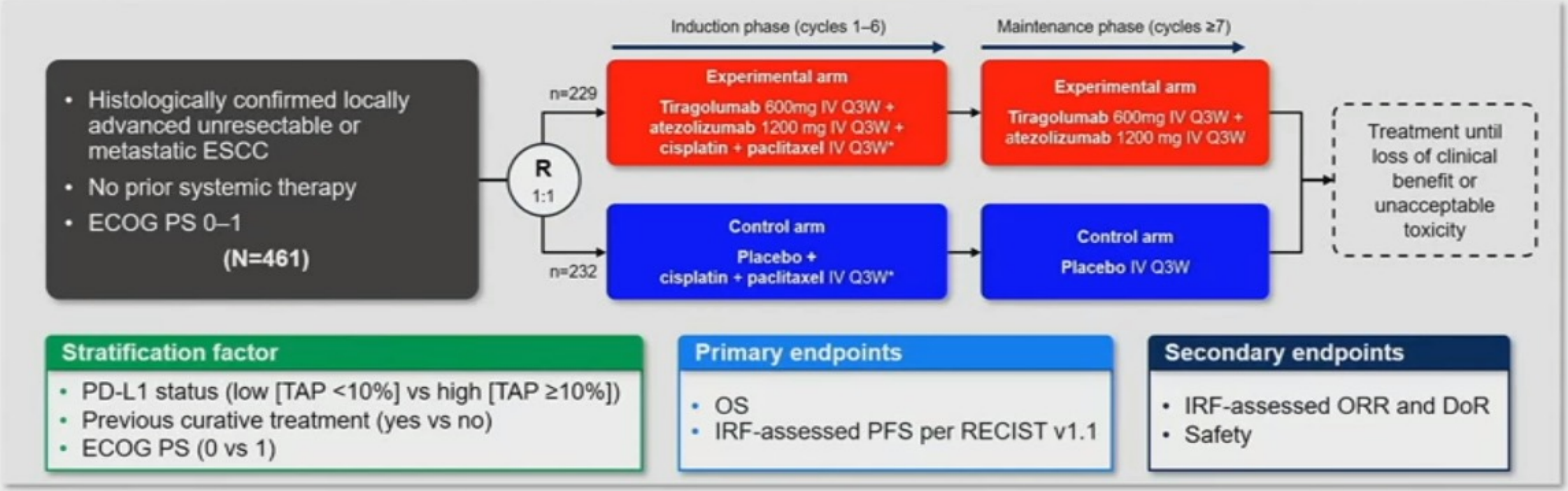
SKYSCRAPER-08: a phase III, randomized, double-blind, placebo-controlled study of first-line tiragolumab + atezolizumab and chemotherapy in patients with esophageal squamous cell carcinoma

Chih-Hung Hsu,[1] Zhihao Lu,[2] Shegan Gao,[3] Junye Wang,[4] Jong-Mu Sun,[5] Tianshu Liu,[6] Qingxia Fan,[7] Jun Cai,[8] Feijiao Ge,[9] Sijing Li,[8] Li Zhang,[9] Edward Cha,[10] Lin Shen,[2]

[1]National Taiwan University Hospital, Taipei City, Taiwan; [2]Peking University Cancer Hospital & Institute, Beijing, China; [3]The First Affiliated Hospital of University of Science and Technology, Lucyang, China; [4]Affiliated Hospital of Jining Medical University, Shandong, China; [5]Samsung Medical Center, Seoul, South Korea; [6]Department of Medical Oncology, Zhongshan Hospital, Fudan University, Shanghai, China; [7]The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; [8]F. Hoffmann-La Roche Ltd., Shanghai, China; [9]F. Hoffmann-La Roche Ltd., Beijing, China; [10]Genentech, Inc., South San Francisco, California, USA

SKYSCRAPER-08: a phase III, double-blind, multicenter, randomized study

- Patients were enrolled across Asia at 67 centers in mainland China, Hong Kong, Taiwan, South Korea, and Thailand



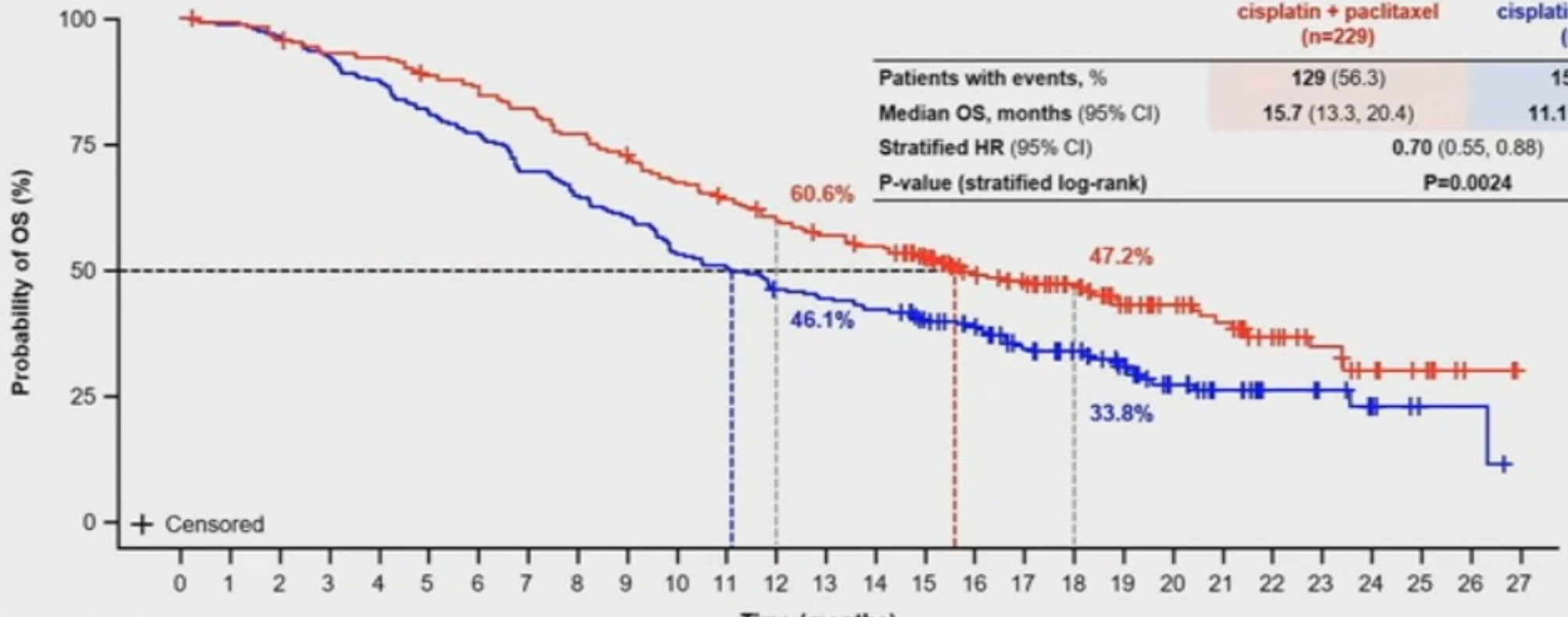
*Choice of chemotherapy reflects the current treatment paradigm in China (paclitaxel 175 mg/m² IV + cisplatin 60–80 mg/m²)
DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; INV, investigator
IRF, independent review facility; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival
Q3W, once every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TAP, tumor area positivity

NCT04540211

PRESENTED BY: DR CHIH-HUNG HSU

Final analysis of OS (primary endpoint)

	Tiragolumab + atezolizumab + cisplatin + paclitaxel (n=229)	Placebo + cisplatin + paclitaxel (n=232)
Patients with events, %	**129** (56.3)	**158** (68.1)
Median OS, months (95% CI)	**15.7** (13.3, 20.4)	**11.1** (9.6, 13.6)
Stratified HR (95% CI)	**0.70** (0.55, 0.88)	
P-value (stratified log-rank)	**P=0.0024**	



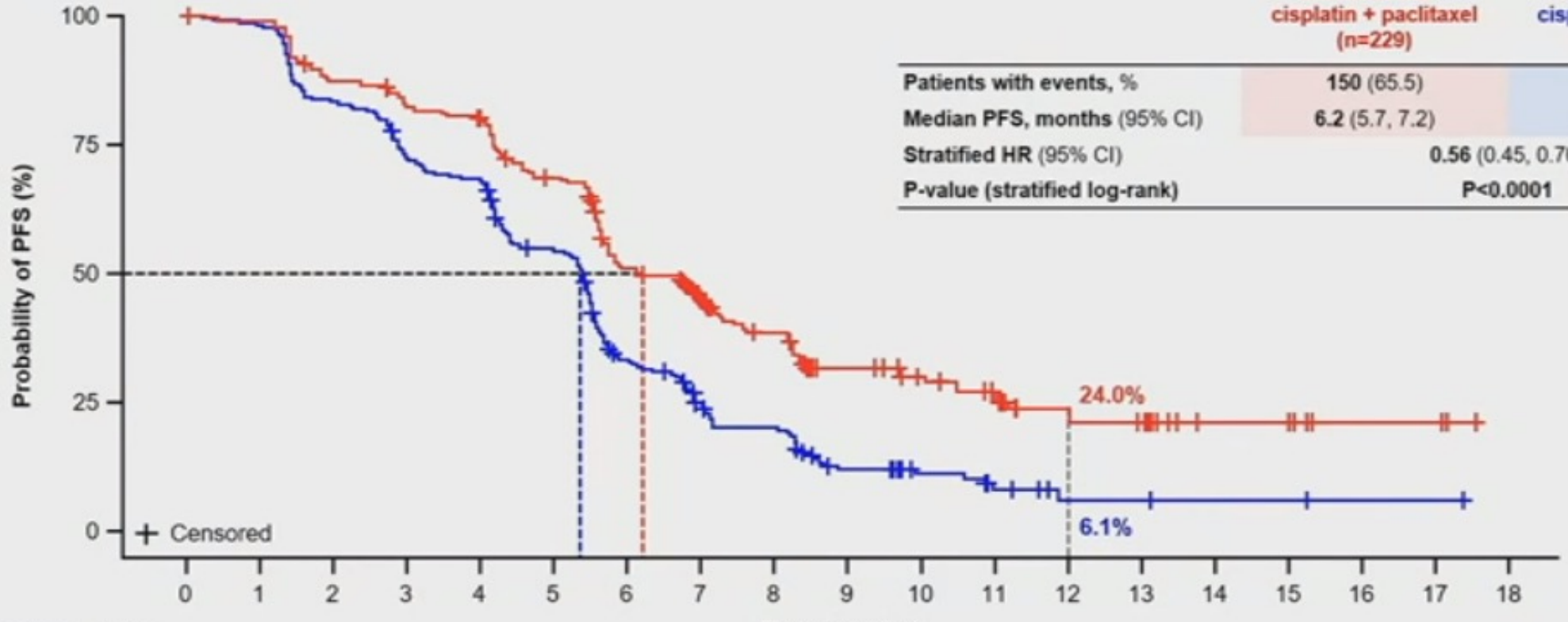
Patients at risk

Tira + atezo + cisplatin + paclitaxel	229	226	218	211	209	200	195	184	174	164	151	143	134	125	119	105	87	78	64	49	41	32	23	16	10	7	2	NE
Placebo + cisplatin + paclitaxel	232	225	219	210	200	183	174	157	146	137	120	115	103	99	94	83	75	59	52	39	26	18	11	9	7	3	2	NE

Intent-to-treat population. CCOD: 13 February 2023 (final analysis). Minimum survival follow-up time (LPI date to CCOD), 14.5 months
CCOD: clinical cut-off date; CI, confidence interval; HR, hazard ratio; LPI, last person in

IRF-assessed PFS per RECIST v1.1 (primary endpoint)

	Tiragolumab + atezolizumab + cisplatin + paclitaxel (n=229)	Placebo + cisplatin + paclitaxel (n=232)
Patients with events, %	**150** (65.5)	**193** (83.2)
Median PFS, months (95% CI)	**6.2** (5.7, 7.2)	**5.4** (4.4, 5.5)
Stratified HR (95% CI)	**0.56** (0.45, 0.70)	
P-value (stratified log-rank)	**P<0.0001**	



Patients at risk

Tira + atezo + cisplatin + paclitaxel	229	222	194	182	176	148	107	82	64	40	32	26	18	15	7	7	3	3	NE
Placebo + cisplatin + paclitaxel	232	224	190	164	155	119	69	48	38	18	12	7	3	3	2	2	1	1	NE

Intent-to-treat population. Clinical cut-off date: 15 June 2022 (primary analysis)

PRESENTED BY: DR CHIH-HUNG HSU

Key secondary endpoints: IRF-assessed ORR and DoR

	Tiragolumab + atezolizumab + cisplatin + paclitaxel (n=226)	Placebo + cisplatin + paclitaxel (n=222)
Responders	135 (**59.7**)	101 (**45.5**)
CR	26 (**11.5**)	7 (**3.2**)
PR	109 (**48.2**)	94 (**42.3**)
SD	43 (**19.0**)	58 (**26.1**)
PD	21 (**9.3**)	44 (**19.8**)
NE/missing	27 (**11.9**)	19 (**8.6**)
Patients with ongoing response	64 (**47.4**)	24 (**23.8**)
Median DoR, months (95% CI)	**7.1** (6.3, 9.5)	**4.3** (4.1, 5.5)

All data are n (%) unless otherwise stated. Data cut-off: 15 June 2022 (primary analysis)
ORR analysis set includes all patients with measurable disease at baseline per IRF. DoR analysis set includes all confirmed responders per IRF
CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease

Safety overview: summary of adverse events

	Tiragolumab + atezolizumab + cisplatin + paclitaxel (n=228)	Placebo + cisplatin + paclitaxel (n=227)
All grade AEs, any cause	**225 (98.7)**	**226 (99.6)**
Treatment-related	224 (98.2)	223 (98.2)
Grade 3–4 AEs	**155 (68.0)**	**139 (61.2)**
Treatment-related	136 (59.6)	128 (56.4)
Grade 5 AEs	**13 (5.7)**	**11 (4.8)**
Treatment-related*	6 (2.6)	2 (0.9)
SAEs	**94 (41.2)**	**89 (39.2)**
Treatment-related	60 (26.3)	56 (24.7)
AEs leading to treatment discontinuation	**45 (19.7)**	**24 (10.6)**
All treatments	11 (4.8)	8 (3.5)
Tiragolumab / atezolizumab / placebo	26 (11.4)	11 (4.8)
Chemotherapy	31 (13.6)	22 (9.7)
AEs leading to dose modification/interruption	**146 (64.0)**	**128 (56.4)**
All grade AESIs	173 (75.9)	113 (49.8)
Grade 3–4	29 (12.7)	11 (4.8)
Grade 5	3 (1.3)	0
Requiring systemic corticosteroids	77 (33.8)	22 (9.7)

Safety evaluable population. All data are n (%) unless otherwise stated. Data cut-off: 13 February 2023
Median duration of safety follow-up: placebo + chemotherapy, 7.6 months; tiragolumab + atezolizumab + chemotherapy, 8.3 months
*Grade 5 treatment-related AEs in the placebo + chemotherapy arm included gastrointestinal infection and death (n=1 each); in the tiragolumab + atezolizumab + chemotherapy arm included immune-mediated lung disease, pneumonitis, cardiac arrest, gastrointestinal hemorrhage, hepatic failure and pneumonia bacterial (n=1 each)
AEs, adverse events; AESIs, adverse events of special interest; SAEs, serious adverse events

Addition of immunotherapy to perioperative chemotherapy in GEJ/gastric cancer

MOFFITT CANCER CENTER

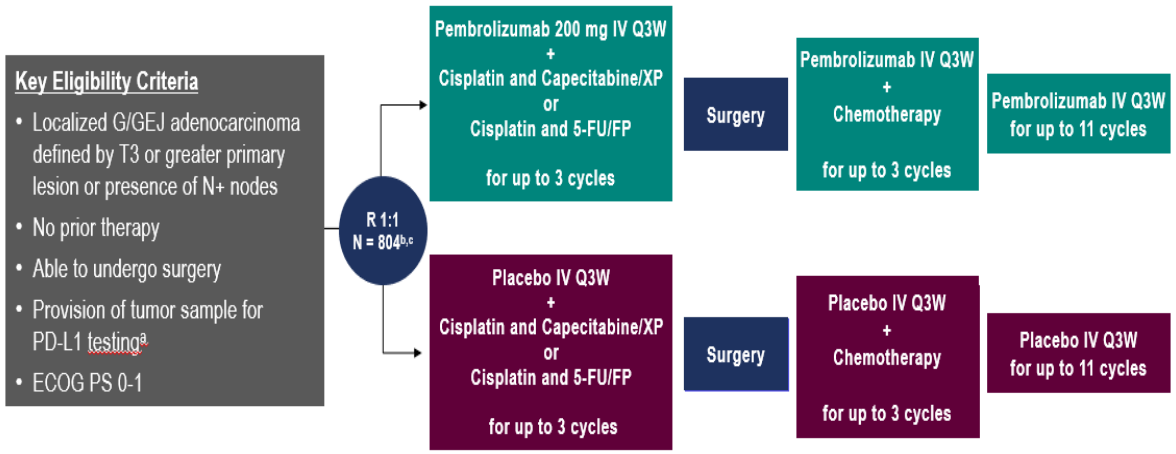
Goal of Therapy : perioperative chemotherapy

1. Shrink the tumor to achieve pCR / Increase downstage (Local control)
2. Eliminate micrometastases (distant control)
3. Ensure surgery is not compromised by treatment toxicity

KEYNOTE 585 & MATTERHORN

KEYNOTE-585 Study Design

Randomized, Double-Blind, Phase 3 Trial of Neoadjuvant and Adjuvant Pembrolizumab Plus Chemotherapy Versus Placebo Plus Chemotherapy in G/GEJ Adenocarcinoma (Main Cohort)



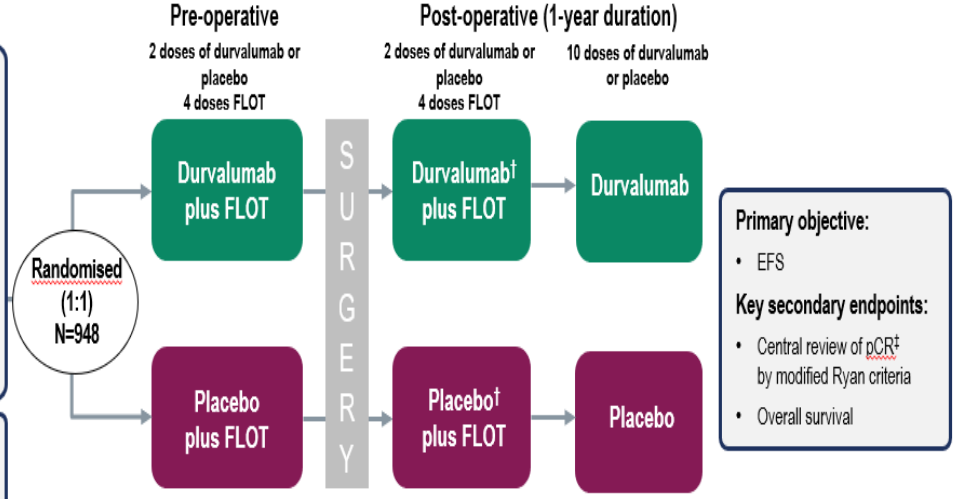
Stratification factors
- Geographic region (Asia versus non-Asia)
- Tumor staging (II vs III vs IVa)
- Chemotherapy backbone (XP/FP vs FLOT)

Endpoints:
- Primary: pathCR rate per BICR, EFS per investigator, OS (main cohort), safety (FLOT)
- Key secondary: safety (main cohort), safety, OS, EFS (main plus FLOT cohort)

MATTERHORN is a global, Phase 3, randomised, double-blind, placebo-controlled study

Study population
- Gastric and GEJ adenocarcinoma
- Stage II, III and IVA (>T2 N0-3 M0 or T0-4 N+ M0)
- No evidence of metastasis
- No prior therapy
- ECOG PS 0 or 1
- Global enrolment from Asia, Europe, North America and South America

Stratification factors
- Geographic region: Asia versus non-Asia
- Clinical lymph node status: positive versus negative
- PD-L1 status: TAP <1% versus TAP ≥1%*



Durvalumab 1500 mg or placebo Q4W (Day 1) plus FLOT Q2W (Days 1 and 15) for 4 cycles (2 doses of durvalumab or placebo plus 4 doses of FLOT pre- and post-operative) followed by durvalumab or placebo Q4W (Day 1) for 10 further cycles

KEYNOTE 585 & MATTERHORN

Study design

	KEYNOTE 585	MATTERHORN
Trial design	Global Phase III RCT	Global Phase III RCT Placebo
Sample size		
Chemotherap		
Immune che		th chemo nt
Region		
Primary endpoint	pathCR rate per BICR (Mandard), EFS per investigator, OS (main cohort), safety (FLOT) Complex statistical approach	EFS Key secondary endpoint pCR (modified Ryan) Simple statistical approach

Pathological complete response (pCR) improved in KN-585, but EFS and OS was not statistically superior

MATTERHORN reported superior pCR, with EFS data yet pending

Pathological complete response (pCR) improved in KN-585, but EFS and OS not statistically superior

MATTERHORN reported superior pCR, with EFS data yet pending

Pembrolizumab Plus FLOT Versus FLOT as Neoadjuvant and Adjuvant Therapy in Locally Advanced Gastric and Gastroesophageal Junction Cancer: Analysis of the FLOT Cohort from the Phase 3 KEYNOTE-585 Study

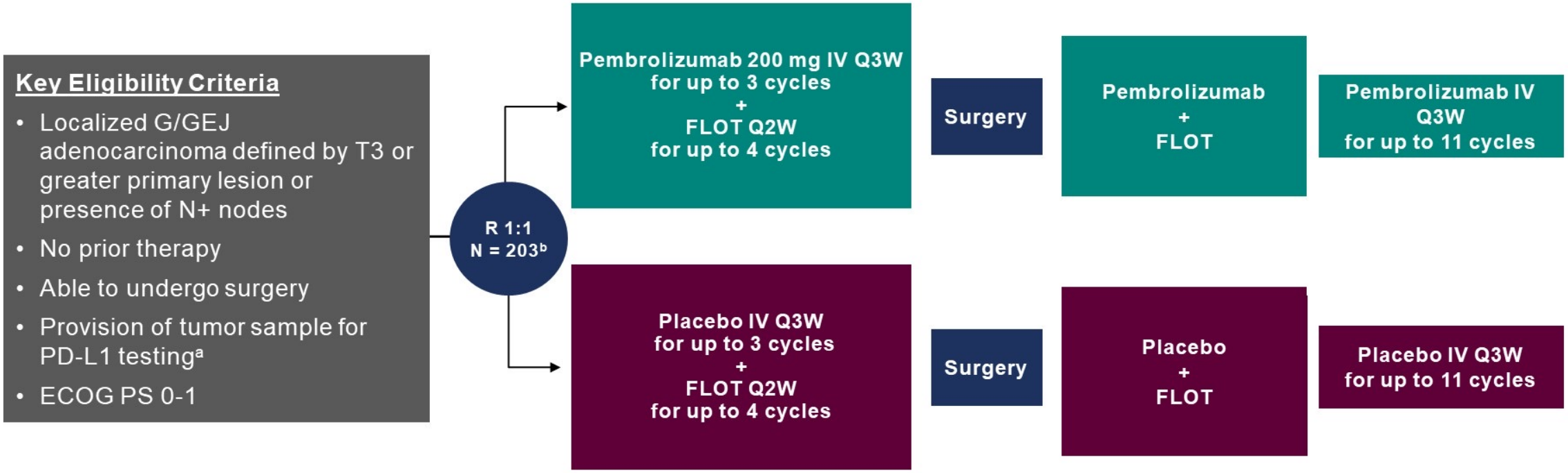
Salah-Eddin Al-Batran,[1,2] Kohei Shitara,[3*] Gunnar Folprecht,[4] Markus Moehler,[5] Eray Goekkurt,[6] Irit Ben-Aharon,[7] Sara Lonardi,[8] Stacey Stein,[9] Ayala Hubert,[10] Ian Chau,[11] Moshe Mishaeli,[12] Luis Villanueva,[13] Petr Kavan,[14] Xiao Fang,[15] Chie-Schin Shih,[15] Pooja Bhagia,[15] Lucjan Wyrwicz[16]

[1]Krankenhaus Nordwest, UCT-University Cancer Center, Frankfurt, Germany; [2]Frankfurter Institut für Klinische Krebsforschung IKF GmbH at Krankenhaus Nordwest, Frankfurt, Germany; [3]National Cancer Center Hospital East, Kashiwa, Japan; [4]University Hospital Carl Gustav Carus and Technische Universitat Dresden, Dresden, Germany; [5]Department of Medicine and Research Center for Immunotherapy Johannes Gutenberg University-Clinic, Mainz, Germany; [6]Practice of Hematology and Oncology (HOPE), Hamburg, Germany; [7]Division of Oncology, Rambam Health Care Center, Haifa, Israel; [8]Veneto Institute of Oncology IOV-IRCCS, Padua, Italy; [9]Yale Cancer Center, New Haven, Connecticut, USA; [10]Sharett Institute of Oncology, Hadassah-Hebrew Medical Center, Jerusalem, Israel; [11]Royal Marsden NHS Foundation Trust, London, United Kingdom; [12] Oncology Department, Meir Medical Center, Kfar Sava, Israel; [13]Fundacion Arturo Lopez Perez FALP, Santiago, Chile; [14]Segal Cancer Center, Jewish General Hospital, McGill University, Montreal, Canada; [15]Merck & Co., Inc., Rahway, NJ, USA; [16]Maria Sklodowska-Curie National Cancer Research Institute, Warsaw, Poland

*Presenting author

KEYNOTE-585 Study Design

Randomized, Double-Blind, Phase 3 Trial of Neoadjuvant and Adjuvant Pembrolizumab Plus Chemotherapy Versus Placebo Plus Chemotherapy in G/GEJ Adenocarcinoma (**FLOT Cohort**)



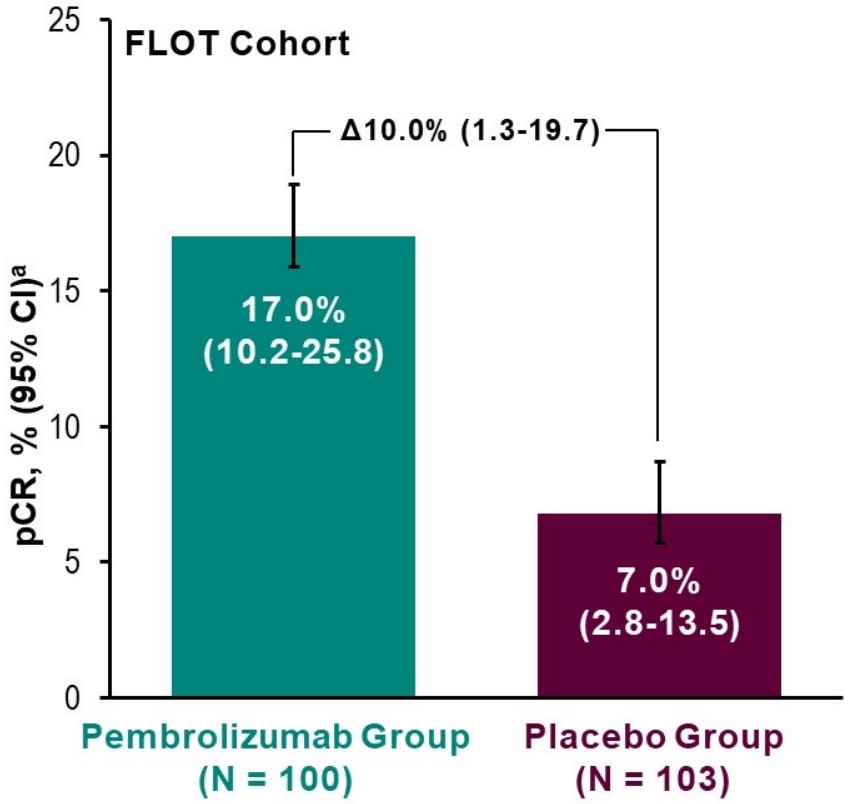
Stratification factors
- Geographic region (Asia versus non-Asia)
- Tumor staging (II vs III vs IVa)
- Chemotherapy backbone (XP/FP vs FLOT)

Endpoints:
- Primary: safety
- Key secondary: pathCR rate per BICR, EFS per investigator, OS

[a]PD-L1 status was centrally assessed; [b]203 patients were randomized 1:1 to a separate FLOT cohort evaluating pembrolizumab + FLOT vs placebo + FLOT (5-FU 2600 mg/m^2, leucovorin 200 mg/m^2, oxaliplatin 85 mg/m^2, docetaxel 50 mg/m^2) Q2W for up to 4 cycles in the neoadjuvant and adjuvant phases.

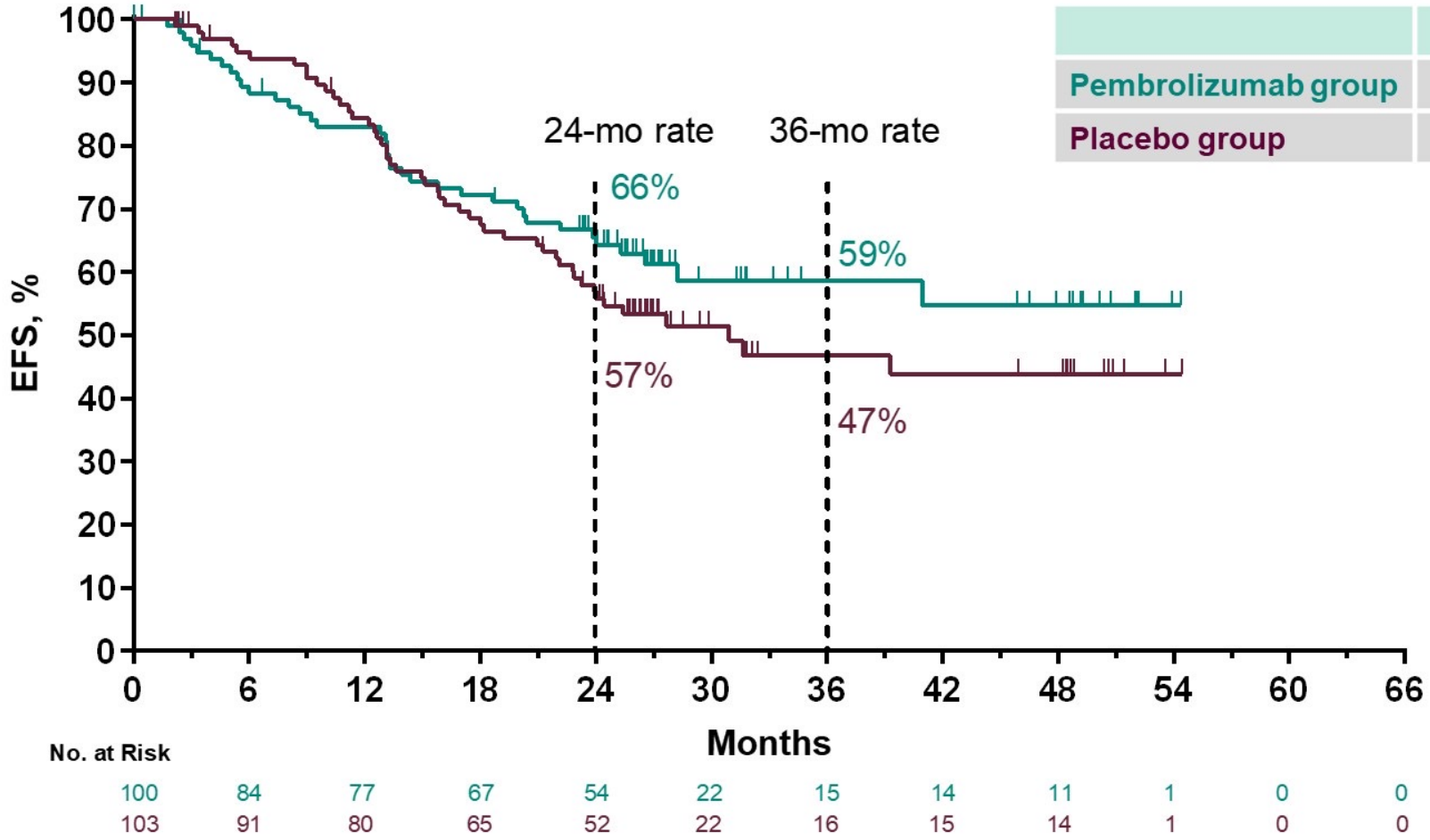
Pathological Complete Response[a]

Assessed by Blinded, Independent Central Review



Data cutoff date 09 Feb 2023. [a]Defined as no invasive disease within an entirely submitted and evaluated gross lesion and histologically defined nodes. Median Follow-Up: 31.6 months (range, 24.5-57.6).

Event-Free Survival: FLOT Cohort

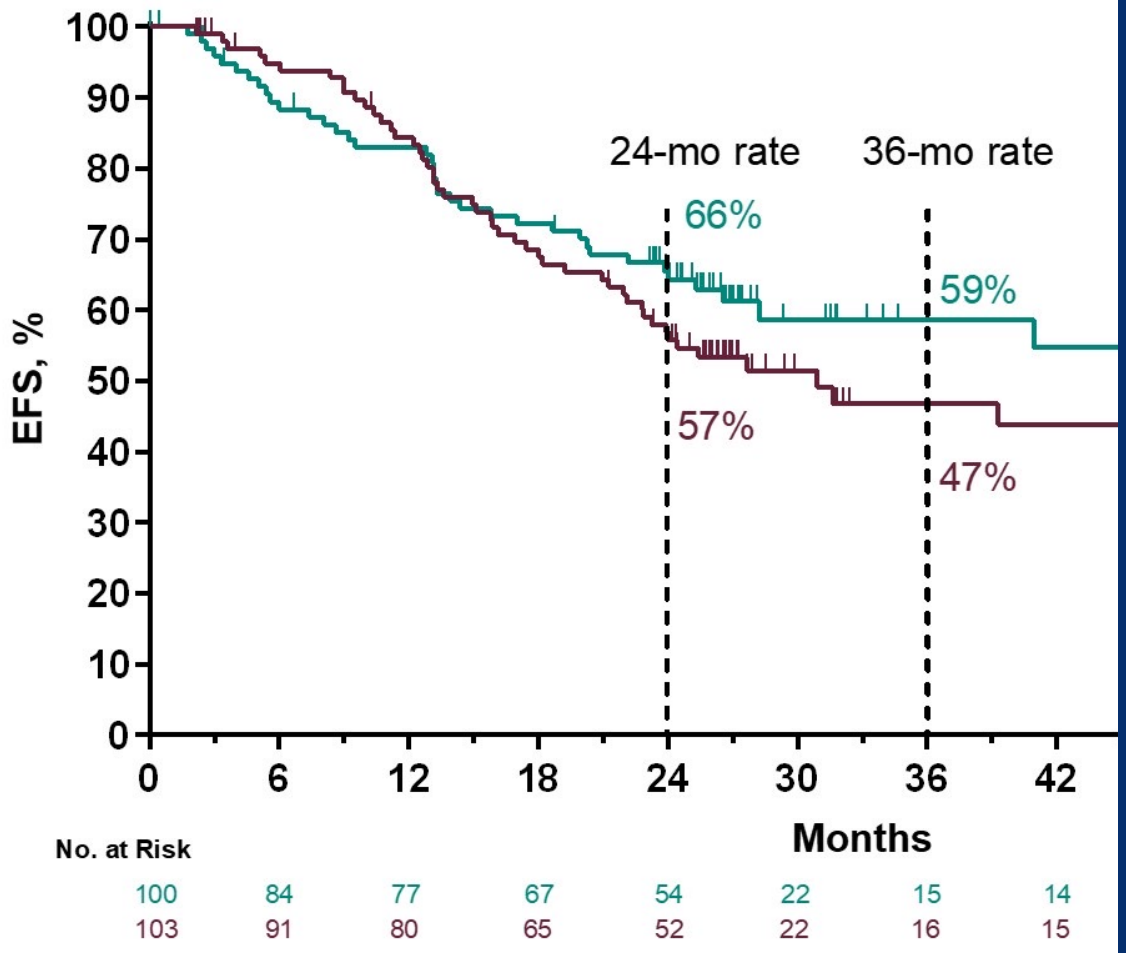


	Events	Median (95% CI), mo
Pembrolizumab group	37%	NR (28.2-NR)
Placebo group	47%	30.9 (22.8-NR)

HR 0.79 (95% CI, 0.52-1.22)

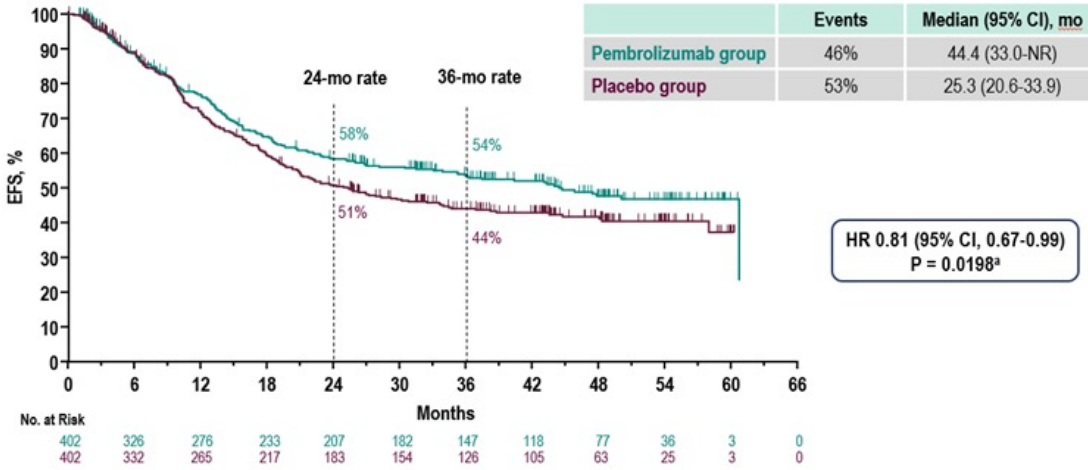
Data cutoff date: 09 Feb 2023. Median Follow-Up[a]: 31.6 months (range, 24.5-57.6). EFS defined as time from randomization to first occurrence of radiographic disease progression per RECIST v1.1, local or distant recurrence as assesses by CT scan or biopsy if indicated, clinical progression, or death due to any cause per investigator assessment. NR, not reached.

Event-Free Survival: FLOT



Data cutoff date: 09 Feb 2023. Median Follow-Up[a]: 31.6 months (range, 24.5-57.6). EFS defined as time from randomization to first indicated, clinical progression, or death due to any cause per investigator assessment. NR, not reached.

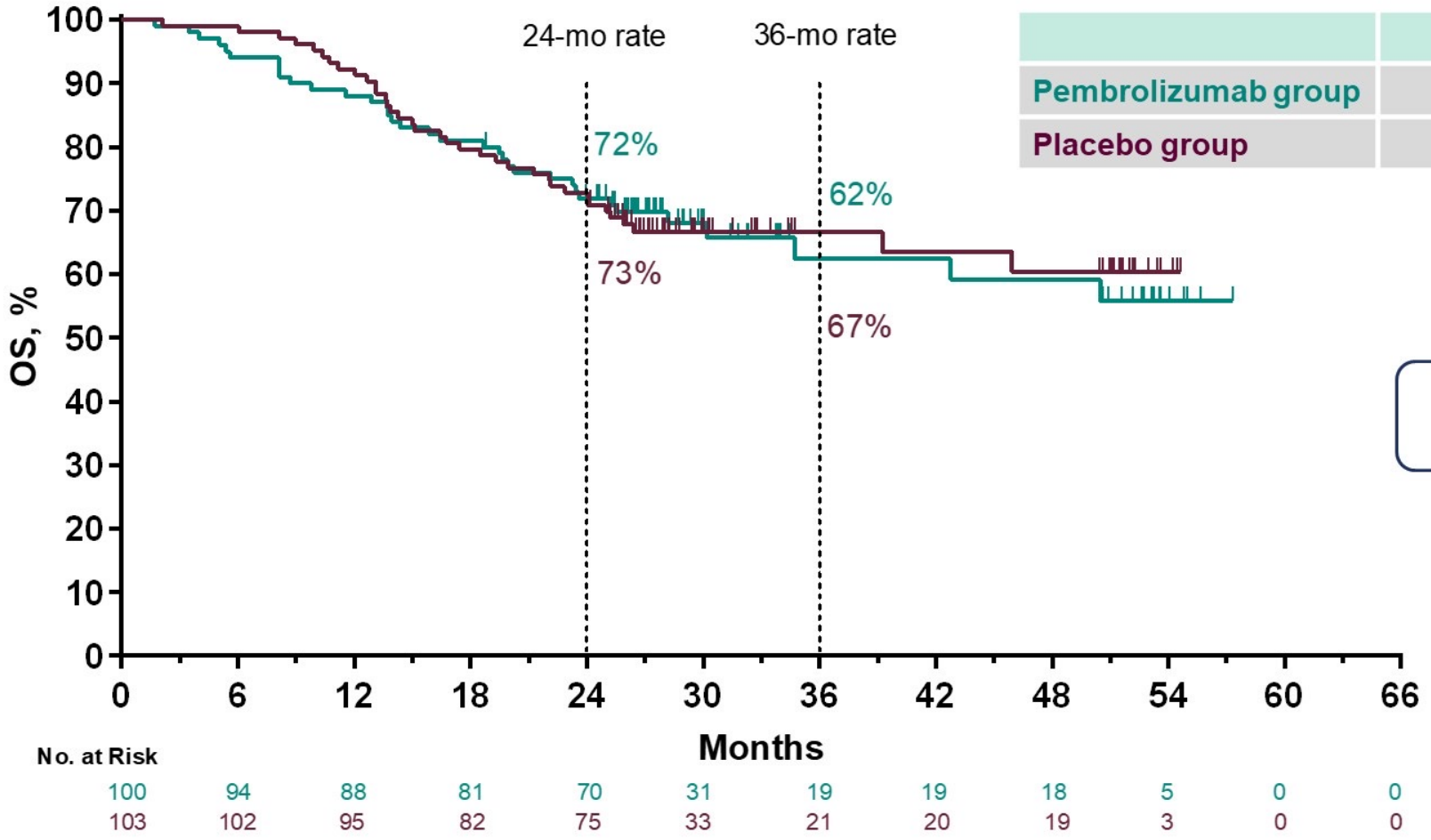
Event-Free Survival: Main Cohort



	Events	Median (95% CI), mo
Pembrolizumab group	46%	44.4 (33.0-NR)
Placebo group	53%	25.3 (20.6-33.9)

HR 0.81 (95% CI, 0.67-0.99)
P = 0.0198[a]

Overall Survival: FLOT Cohort

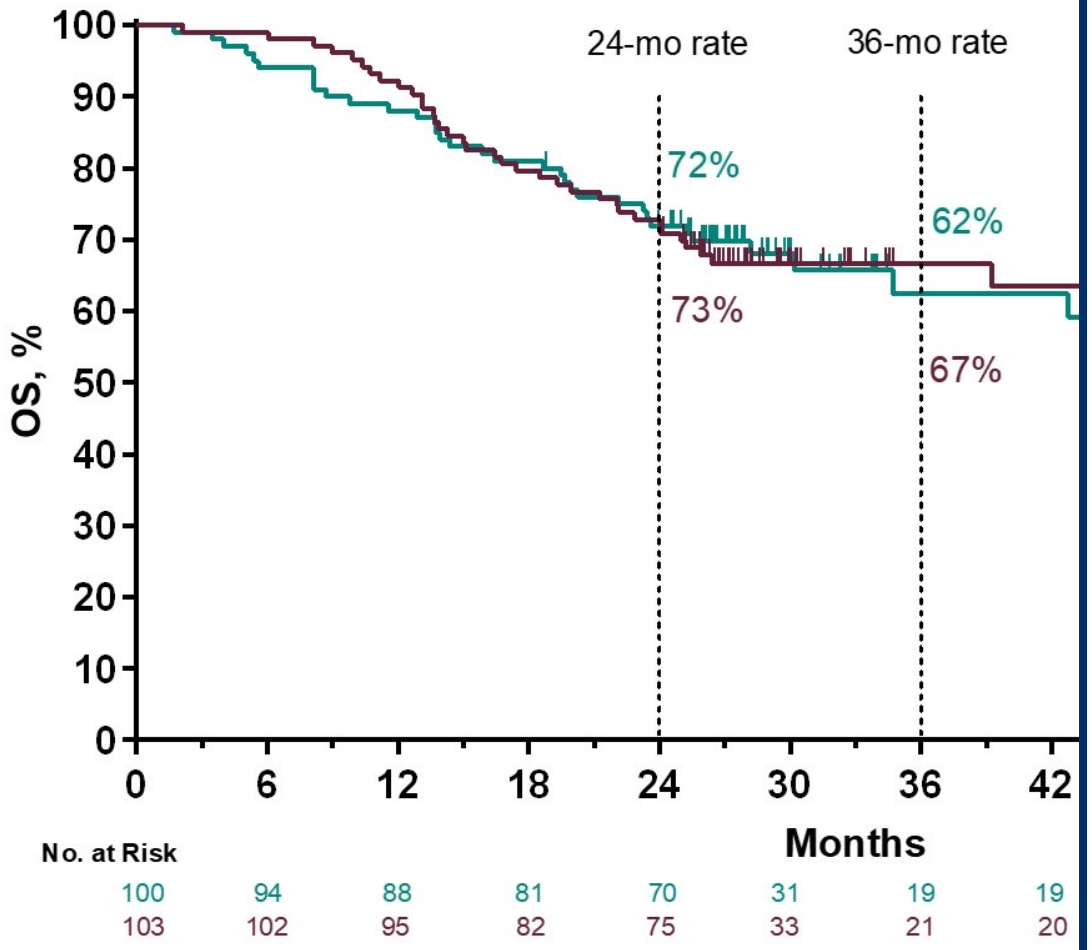


	Events	Median (95% CI), mo
Pembrolizumab group	35%	NR (34.7-NR)
Placebo group	35%	NR (45.9-NR)

HR 1.04 (95% CI, 0.66-1.66)

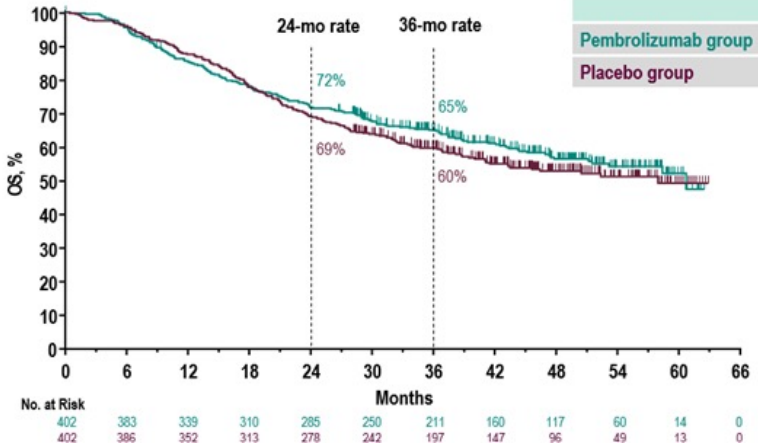
Data cutoff date: 09 Feb 2023. Median Follow-Up: 31.6 months (range, 24.5-57.6).

Overall Survival: FLOT Coh



Data cutoff date: 09 Feb 2023. Median Follow-Up: 31.6 months (range, 24.5-57.6).

Overall Survival: Main Cohort



	Events	Median (95% CI), mo
Pembrolizumab group	41%	60.7 (51.5-NR)
Placebo group	45%	58.0 (41.5-NR)

HR 0.90 (95% CI, 0.73-1.12)

ASCO Gastrointestinal Cancers Symposium

Pathological complete response to 5-fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT) with or without durvalumab in resectable gastric and gastroesophageal junction cancer: subgroup analysis by region from the Phase 3, randomized, double-blind MATTERHORN study

Yelena Y. Janjigian, MD

Yelena Y. Janjigian[1], Salah-Eddin Al-Batran[2], Zev A. Wainberg[3], Eric Van Cutsem[4], Daniela Molena[5], Kei Muro[6], Woo Jin Hyung[7], Lucjan Wyrwicz[8], Do-Youn Oh[9], Takeshi Omori[10], Markus Moehler[11], Marcelo Garrido[12], Sulene C.S. Oliveira[13], Moishe Liberman[14], Victor Castro Oliden[15], Mehmet Bilici[16], John F. Kurland[17], Ioannis Xynos[18], Helen Mann[18], Josep Tabernero[19]

[1]Gastrointestinal Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Institute of Clinical Cancer Research, Krankenhaus Nordwest, University Cancer Center, Frankfurt, Germany; [3]Department of Gastrointestinal Medical Oncology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [4]Department of Gastroenterology/Digestive Oncology, University Hospitals Leuven and KU Leuven, Leuven, Belgium; [5]Division of Thoracic Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [6]Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan; [7]Department of Surgery, Yonsei University College of Medicine, Seoul, Republic of Korea; [8]Department of Oncology and Radiotherapy, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [9]Division of Medical Oncology, Department of Internal Medicine, Seoul National University Hospital; Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea; [10]Department of Gastroenterological Surgery, Osaka International Cancer Institute, Osaka, Japan; [11]Research Center for Immunotherapy (FZI), Johannes Gutenberg-University Clinic, Mainz, Germany; [12]Hemato-Oncology Department, SAGA Clinical Trial Centre and Universidad Mayor, Santiago, Chile; [13]Clinical Oncology, The Clinical Research Center, Northern Riograndense League Against Cancer, Natal, Rio Grande do Norte, Brazil; [14]Division of Thoracic Surgery, Department of Surgery, Centre Hospitalier de l'Université de Montréal, Centre de Recherche du CHUM, Montréal, QC, Canada; [15]National Institute of Neoplastic Diseases (INEN), Lima, Peru; [16]Department of Medical Oncology, Atatürk University Faculty of Medicine, Erzurum, Turkey; [17]Oncology R&D, Late-Stage Development, AstraZeneca, Gaithersburg, MD, USA; [18]Oncology R&D, Late-Stage Development, AstraZeneca, Cambridge, UK; [19]Medical Oncology Department, Vall d'Hebron Hospital Campus & Institute of Oncology (VHIO), IOB-Quiron, UVic-UCC, Barcelona, Spain

Methods

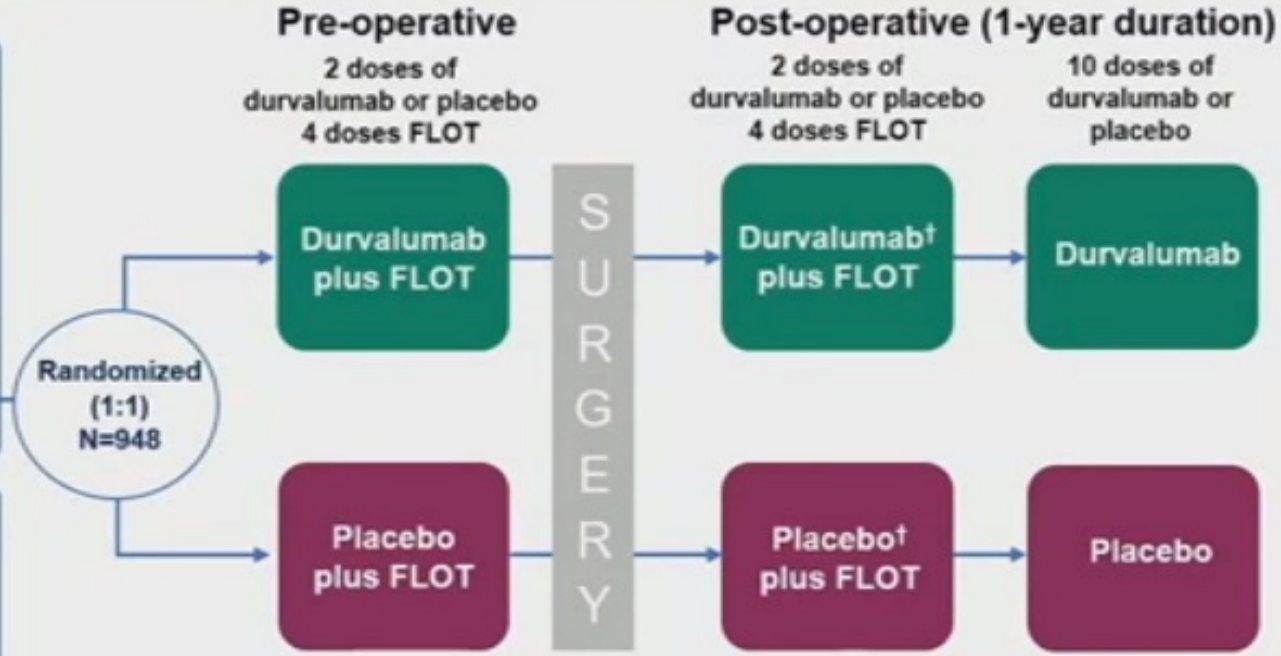
MATTERHORN is a global, Phase 3, randomized, double-blind, placebo-controlled study

Study population

- Gastric and GEJ adenocarcinoma
- Stage II, III and IVA (>T2 N0-3 M0 or T0-4 N1-3 M0)
- No evidence of metastasis
- No prior therapy
- ECOG PS 0 or 1
- Global enrolment from Asia, Europe, North America, and South America

Stratification factors

- Geographic region: Asia versus non-Asia
- Clinical lymph node status: positive versus negative
- PD-L1 status: TAP <1% versus TAP ≥1%*



Durvalumab 1500 mg or placebo Q4W (Day 1) plus FLOT Q2W (Days 1 and 15) for 4 cycles (2 doses of durvalumab or placebo plus 4 doses of FLOT pre- and post-operative), followed by durvalumab or placebo Q4W (Day 1) for 10 further cycles

Primary objective:

- EFS

Key secondary objectives:

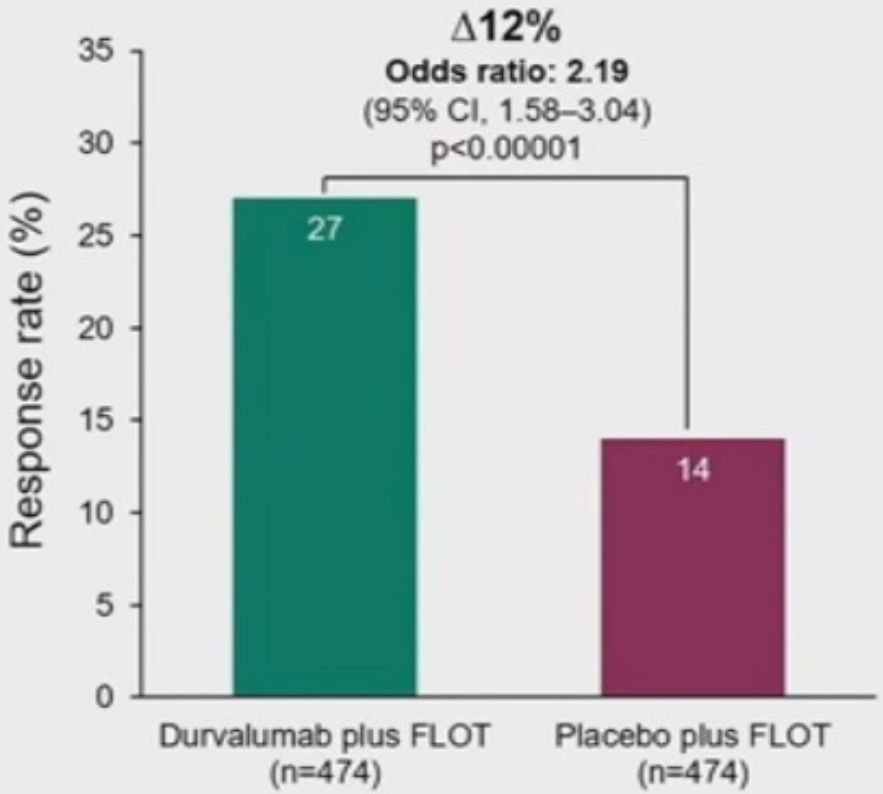
- Central review of pathological complete response by modified Ryan criteria
- OS

FLOT: 5-fluorouracil 2600 mg/m², oxaliplatin 85 mg/m², docetaxel 50 mg/m², leucovorin 200 mg/m² on Days 1 and 15 of a 4-week cycle for 2 cycles (4 doses) pre- and post-operative; durvalumab: 1500 mg on Day 1 of a 4-week cycle, 2 cycles (2 doses) of durvalumab or placebo pre- and post-operative, followed by 10 cycles (10 doses) of durvalumab or placebo on Day 1 of a 4-week cycle.
*Measured by VENTANA PD-L1 (SP263) assay. †Durvalumab or placebo monotherapy may be continued if post-operative FLOT is discontinued due to toxicity.
ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; GEJ, gastrooesophageal junction; OS, overall survival; PD-L1, programmed cell death ligand-1; PS, performance status; Q2W, every 2 weeks; Q4W, every 4 weeks; TAP, tumor area positivity.

PRESENTED BY: Yelena Y. Janjigian, MD

Combined complete and near-complete pathological response

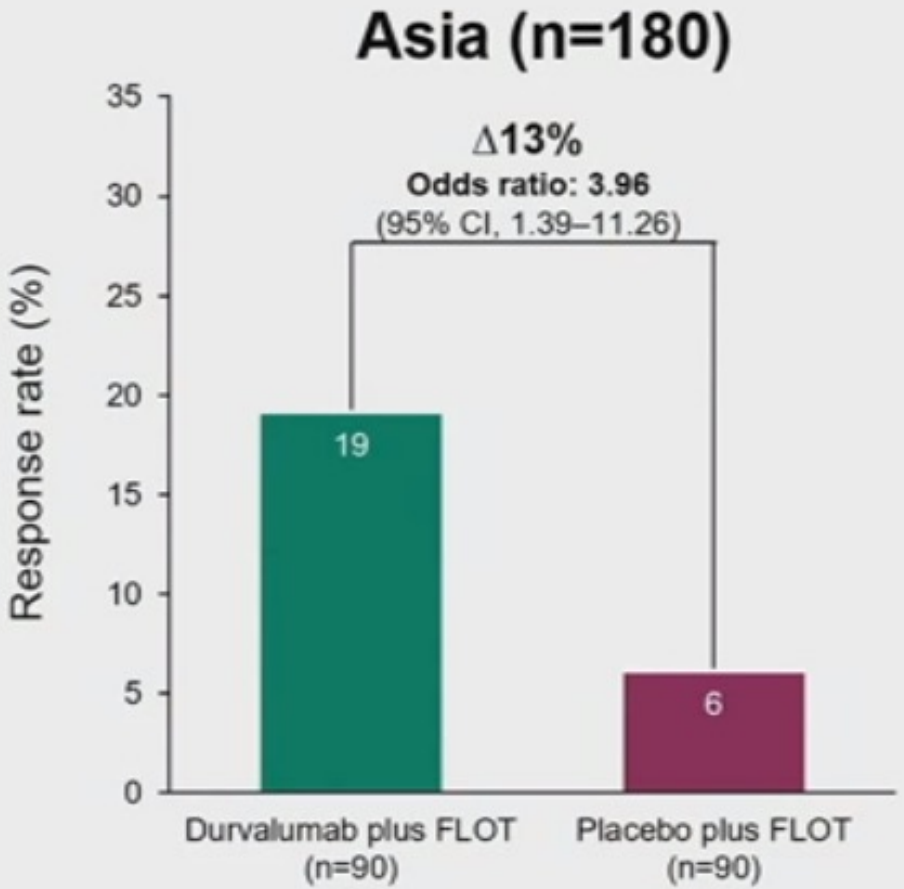
Durvalumab plus FLOT showed improvement in combined complete and near-complete pathological response

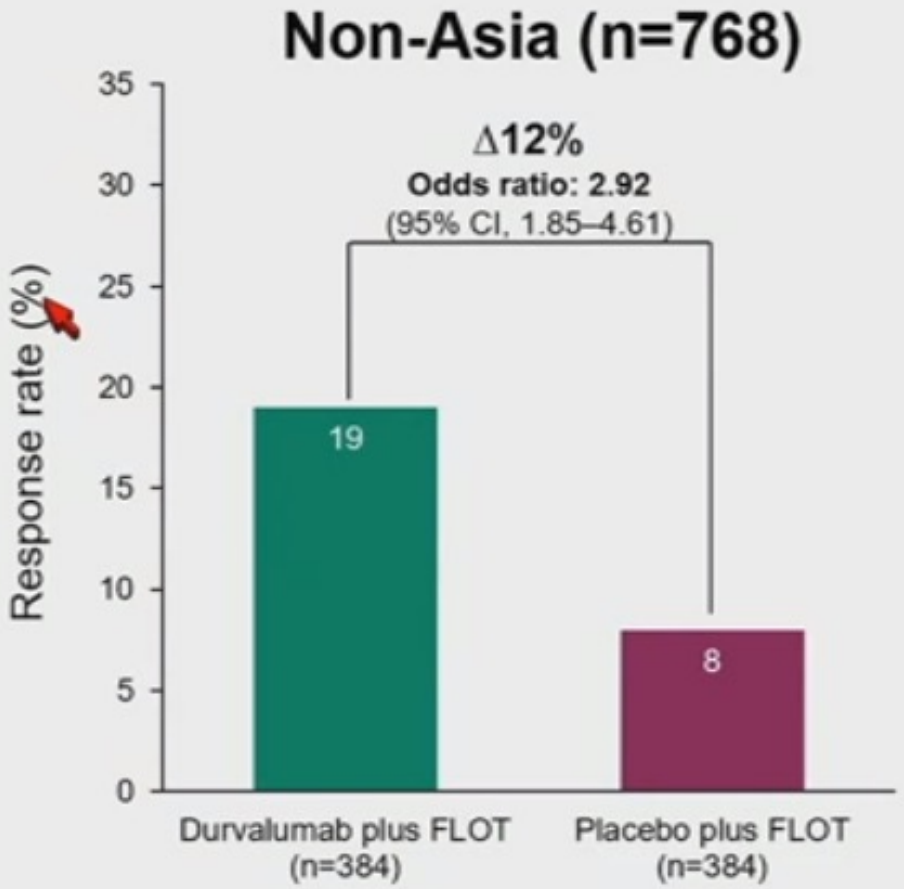


Near-complete pathological response = single cells or rare small groups of cancer cells at the time of resection, per modified Ryan criteria

Participants achieve pathological complete response if there is no residual viable tumor cells found at primary tumor and resected lymph nodes at the time of resection, meaning a pathological regression of 100%, based on central assessment. Participants achieve near-complete pathological response if there are single cells or rare small groups of cancer cells found at primary tumor and resected lymph nodes at the time of resection, based on central assessment. Central review of pathological complete response was scored using modified Ryan criteria.
CI, confidence interval; FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel.
Janjigian YY, et al. *Annal Oncol* 2023;34:S1315-S1316.

Pathological complete response in Asia and non-Asia

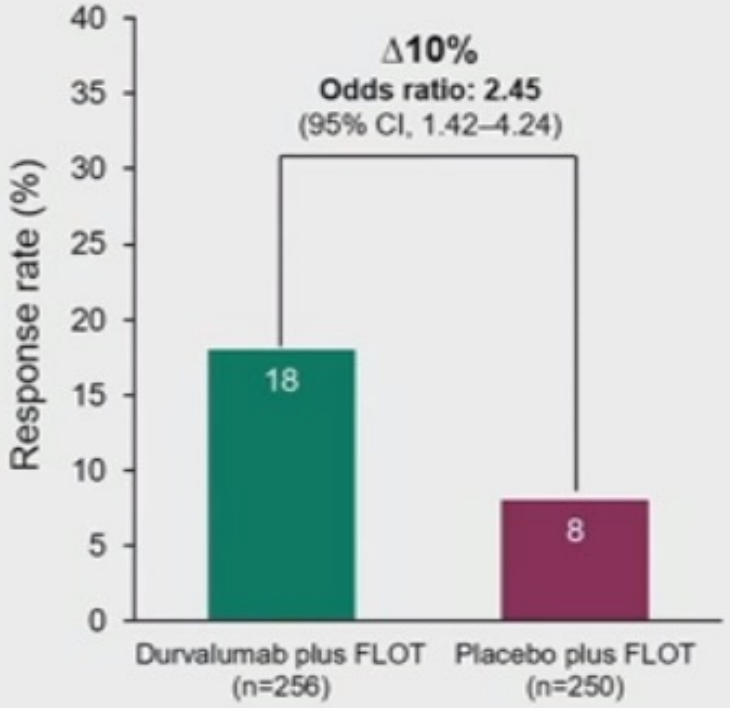




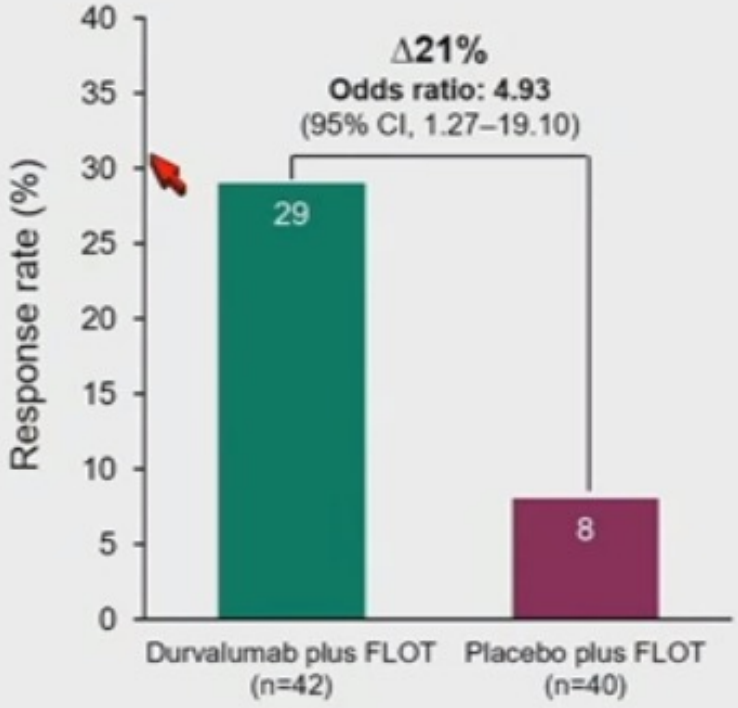
Participants achieve pathological complete response if there is no residual viable tumor cells found at primary tumor and resected lymph nodes at the time of resection, meaning a pathological regression of 100%, based on central assessment. Central review of pathological complete response was scored using modified Ryan criteria.
CI, confidence interval; FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel.

Pathological complete response by region (non-Asia)

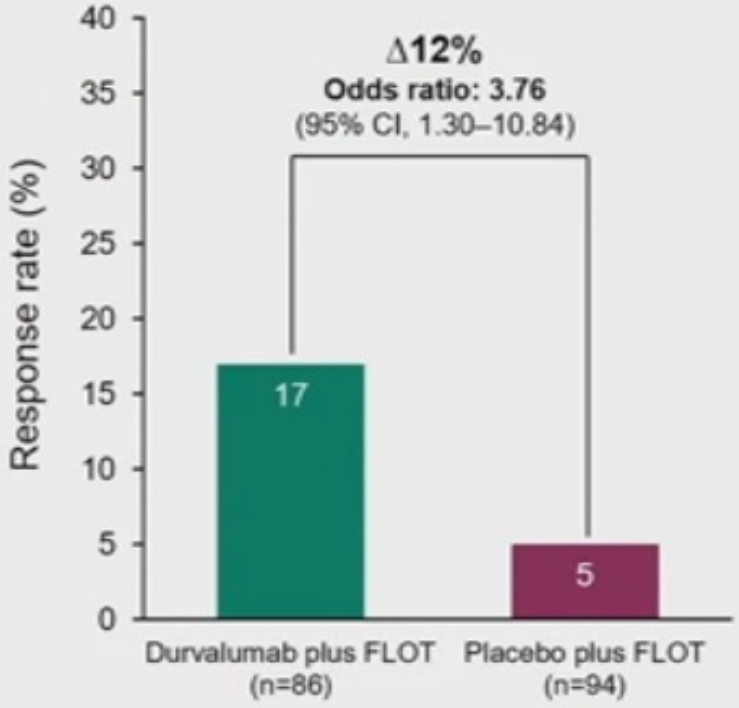
Europe (n=506)



North America (n=82)

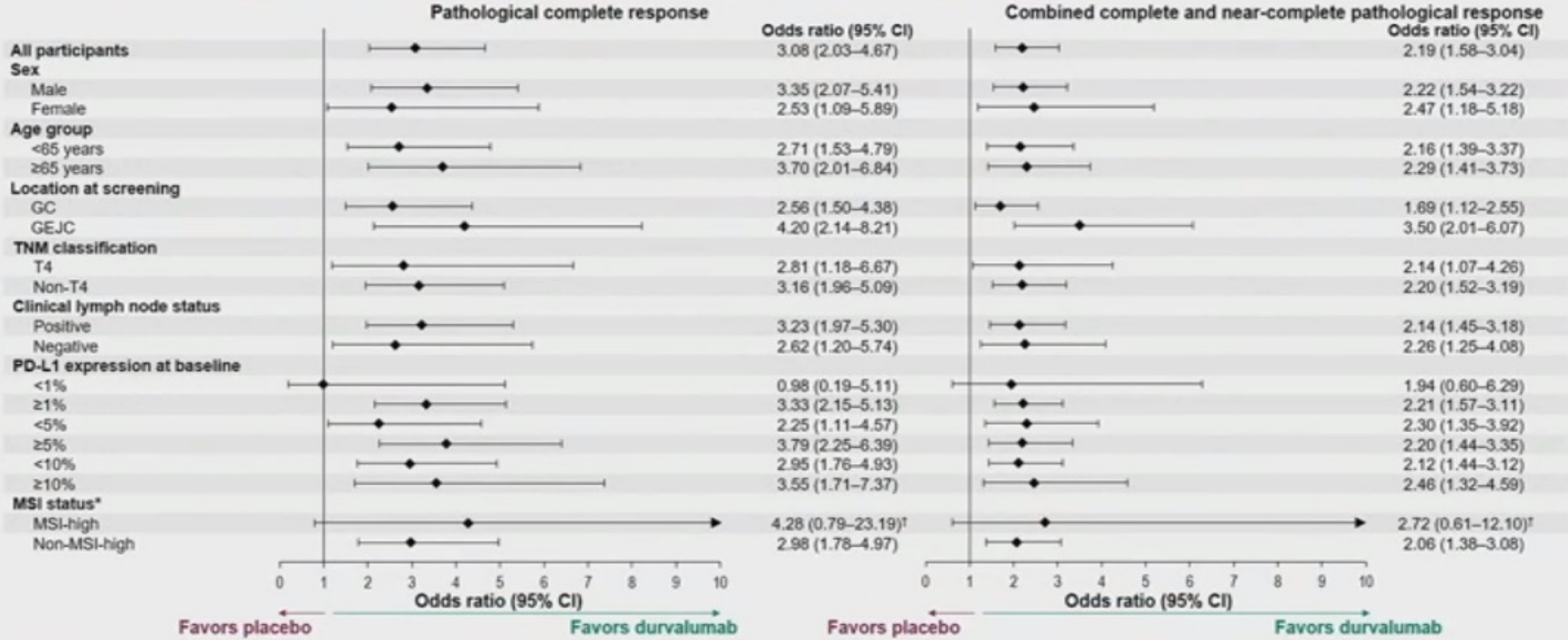


South America (n=180)



Participants achieve pathological complete response if there is no residual viable tumor cells found at primary tumor and resected lymph nodes at the time of resection, meaning a pathological regression of 100%, based on central assessment. Central review of pathological complete response was scored using modified Ryan criteria.
CI, confidence interval; FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel.

Pathological response by subgroups



Participants achieve pathological complete response if there is no residual viable tumor cells found at primary tumor and resected lymph nodes at the time of resection, meaning a pathological regression of 100%, based on central assessment. Participants achieve near-complete pathological response if there are single cells or rare small groups of cancer cells found at primary tumor and resected lymph nodes at the time of resection, based on central assessment. Central review of pathological complete response was scored using modified Ryan criteria. *Out of 948 participants randomized in MATTERHORN, 781 participants were eligible for MSI testing based on consent, local laws, and submission of sufficient tissue; 660 participants were evaluable per Foundation Medicine Inc criteria. MSI status could not be determined for samples from 250 participants. MSI-high = fraction unstable loci >0.0124. Non-MSI-high includes those with MSS, MSI-equivocal, and MSI-unknown. †Upper CIs exceeding a ratio of 10 are truncated for the figure.

CI, confidence interval; GC, gastric cancer; GEJC, gastroesophageal junction cancer; MSI, microsatellite instability; MSS, microsatellite stable; PD-L1, programmed cell death ligand-1.

Janjigian YY, et al. Presented at: European Society for Medical Oncology (ESMO) Congress 2023; October 20–24, 2023; Madrid, Spain. FPN (Final Publication Number): LBA73.

Baseline characteristics in Asia and non-Asia

A higher percentage of participants in Asia had an ECOG PS of 0, GC, lymph node positive, and T4 stage tumors

		Asia		Non-Asia	
		Durvalumab plus FLOT (n=90)	Placebo plus FLOT (n=90)	Durvalumab plus FLOT (n=384)	Placebo plus FLOT (n=384)
ECOG PS, n (%)	0	81 (90)	86 (96)	256 (67)	280 (73)
Primary tumor location, n (%)	Gastric GEJ	75 (83) 15 (17)	82 (91) 8 (9)	249 (65) 135 (35)	234 (61) 150 (39)
Primary tumor stage, n (%)	T0-T2 T3 T4	4 (4) 32 (36) 54 (60)	4 (4) 37 (41) 49 (54)	46 (12) 275 (72) 63 (16)	32 (8) 284 (74) 68 (18)
Clinical lymph node status,* n (%)	Positive	70 (78)	69 (77)	259 (67)	261 (68)

The Asia subgroup included participants enrolled in Japan, Republic of Korea, and Taiwan.
*Stratification factor data.
ECOG, Eastern Cooperative Oncology Group; FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; GC, gastric cancer; GEJ, gastroesophageal junction; PS, performance status.

Summary

- Combination of atezolizumab and tiragolumab with chemotherapy did result in improvement of OS, PFS and RR compared standard chemotherapy. However benefit of tiragolumab is unclear? Is more better?
- The addition of IO to chemotherapy increased pCR however does not translate to improved OS (at least not yet)
- We are eagerly awaiting OS result from MATTERHORN study.