



OPTIMAL SEQUENCING OF TREATMENT FOR ADVANCED GASTRIC AND ESOPHAGEAL CANCER

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Disclosures



- Grant/Research Support from Merck.
- Consultant for Amgen, Astellas, AstraZeneca, Bristol-Myers Squibb, Daiichi-Sankyo, Foundation Medicine, Macrogenics, Merck, Ono Pharmaceuticals, Turning Point Therapeutics, Yiviva.
- Speakers Bureau for Merck, BMS

Changing the Paradigm for First-Line Metastatic Gastric Cancer – Checkmate 649

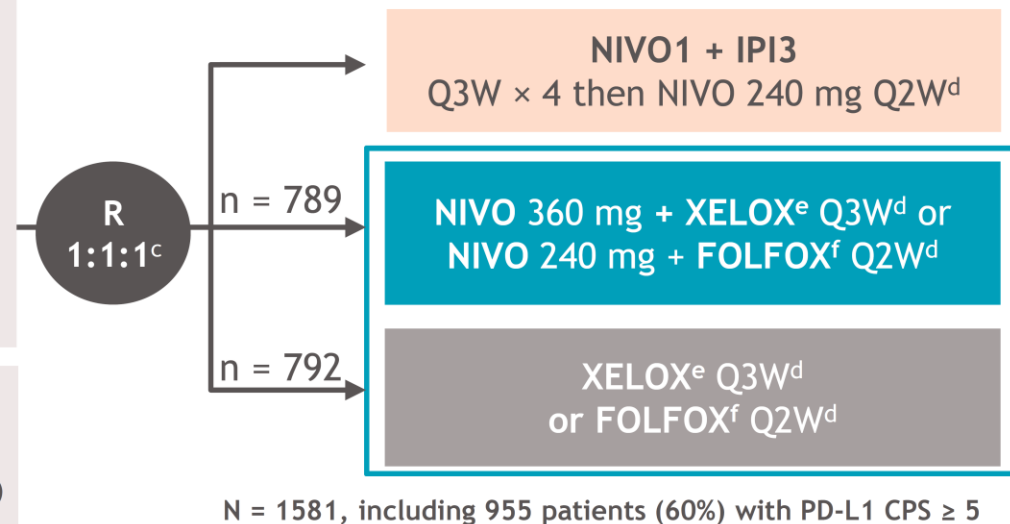


Key eligibility criteria

- 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 ($\geq 1\%$ 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 or all randomized)
- OS (PD-L1 CPS ≥ 10)
- PFS^g (PD-L1 CPS ≥ 10 , 1, or all randomized)
- ORR^g

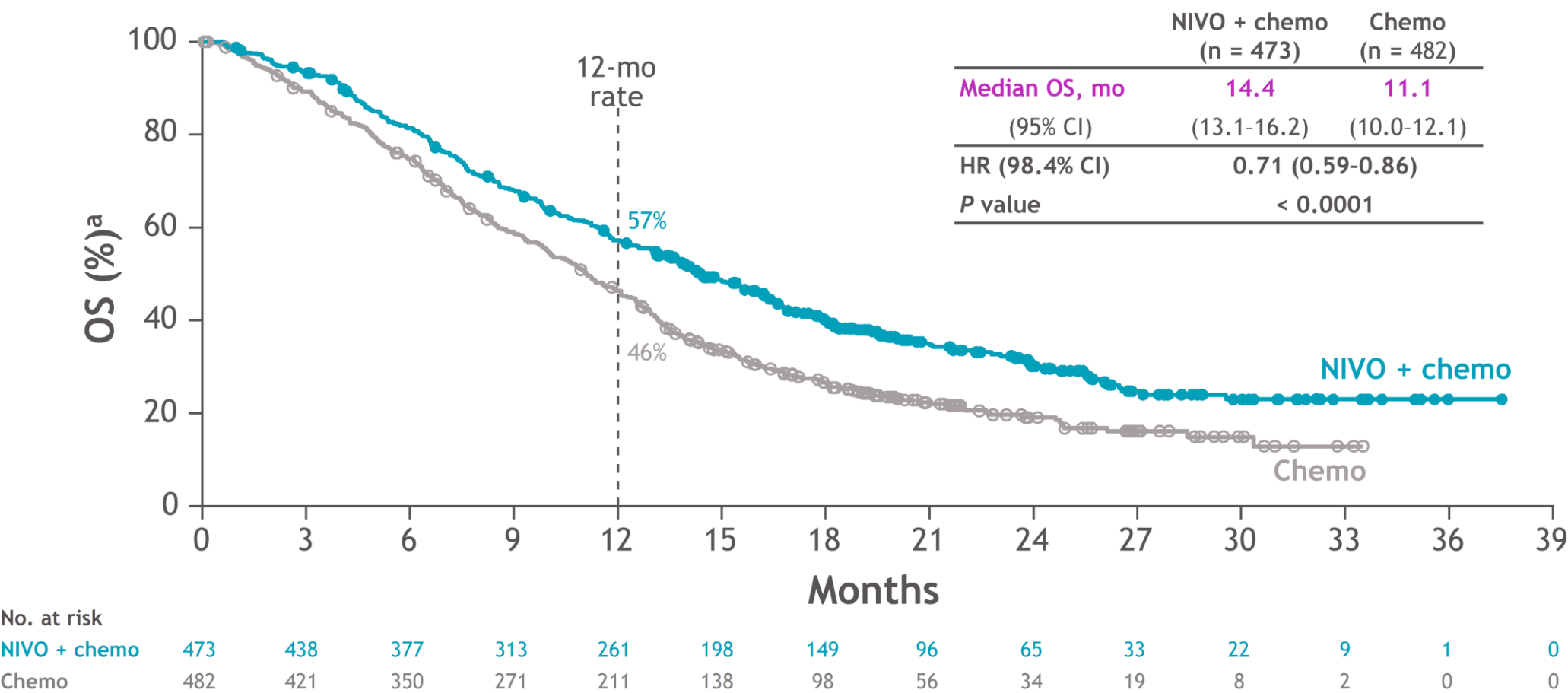
Checkmate 649 – Baseline Characteristics



	NIVO + chemo (n = 789)	Chemo (n = 792)
Median age (range), years	62 (18-88)	61 (21-90)
Male, %	68	71
Race, %		
Asian	24	24
Non-Asian	76	76
ECOG PS 1, %	59	57
Primary tumor location, %		
GC	70	70
GEJC	17	16
EAC	13	14
Metastatic disease, %	96	95
Liver metastases, %	38	40
Signet ring cell carcinoma, %	18	17
MSI status, ^a %		
MSS	88	86
MSI-H	3	3
FOLFOX/XELOX received on study, ^b %	54/46	53/47

^aMSI status was invalid/not available for 71 patients in the NIVO + chemo arm and 89 patients in the chemo arm; ^bPatients who received at least 1 dose of the assigned treatment; NIVO + chemo n = 782 and chemo n = 767.

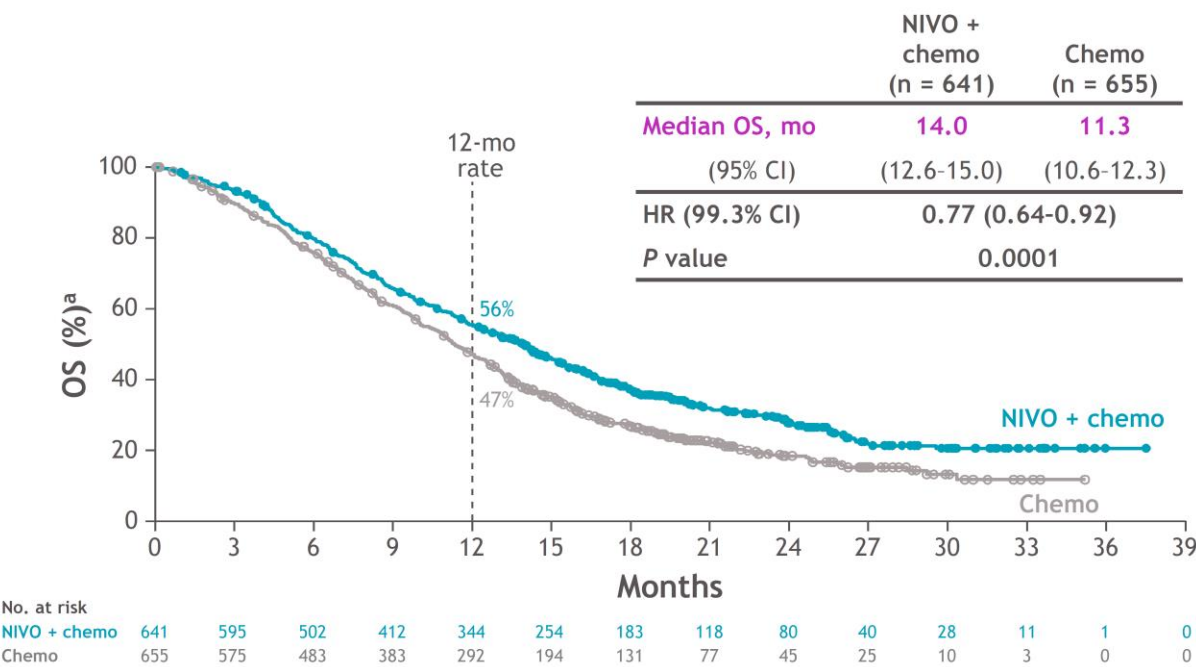
Checkmate 649 – Overall Survival in PD-L1 CPS ≥ 5 Population



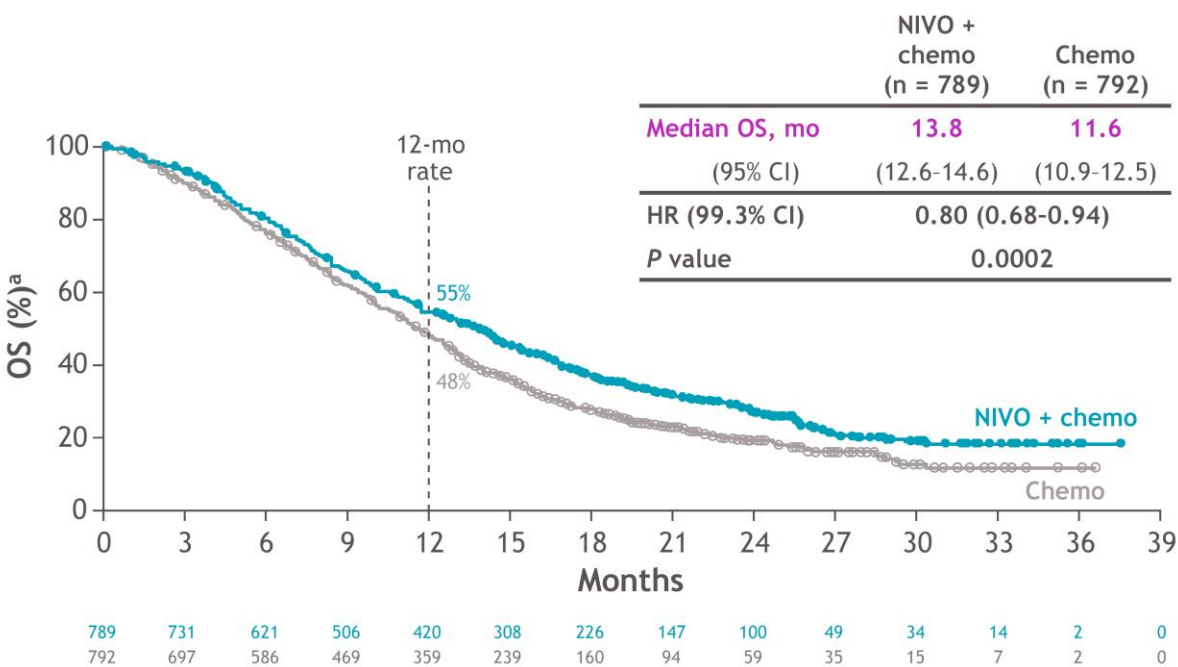
Checkmate 649 – Overall Survival in PD-L1 CPS ≥ 1 and All-Patients Population



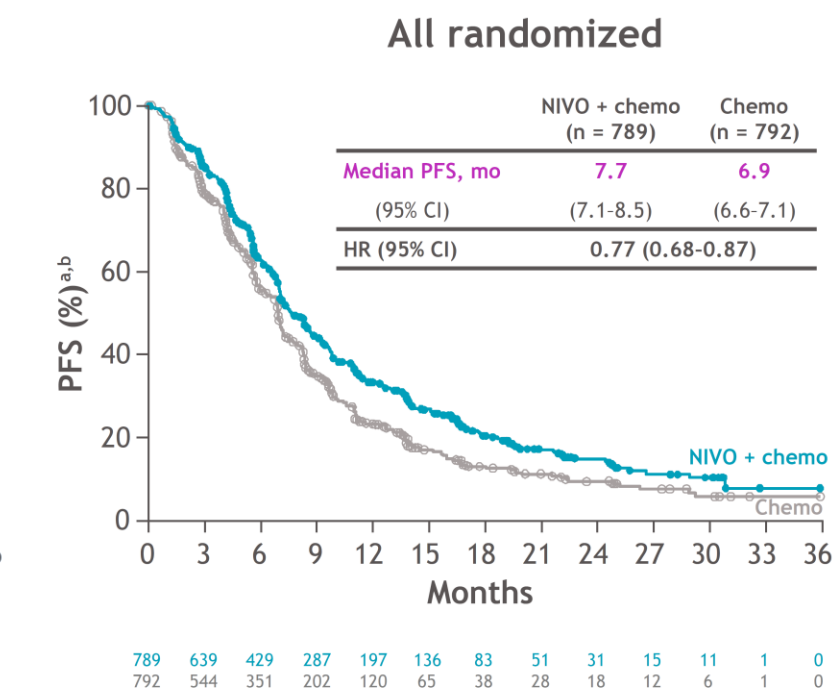
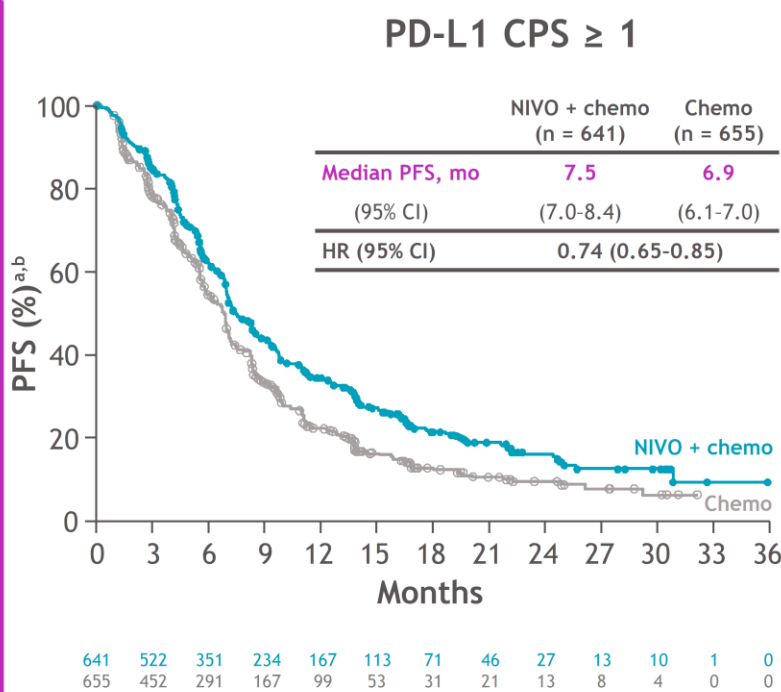
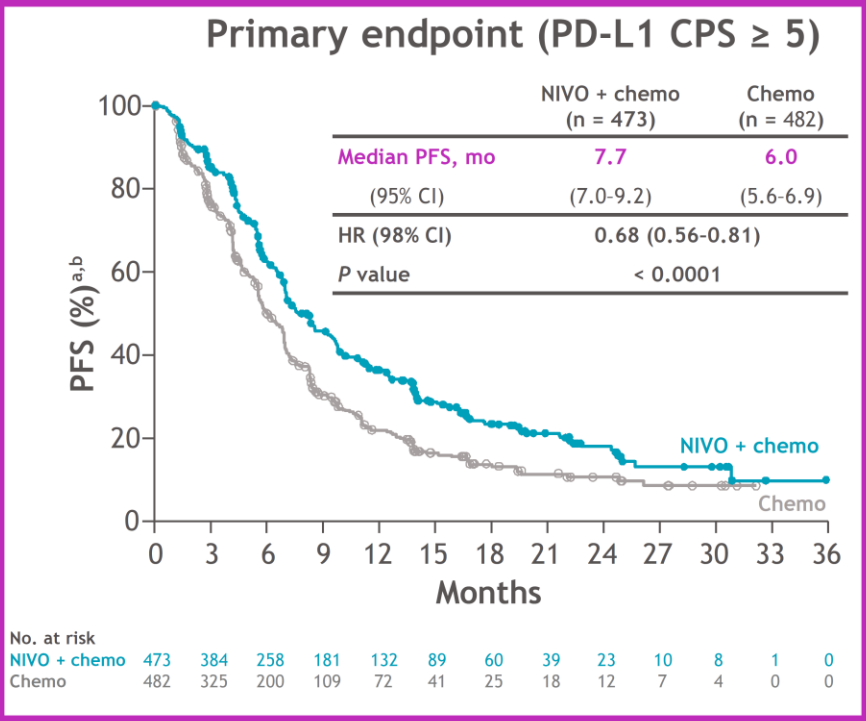
PD-L1 CPS ≥ 1



All randomized



Checkmate 649 – Progression-free Survival

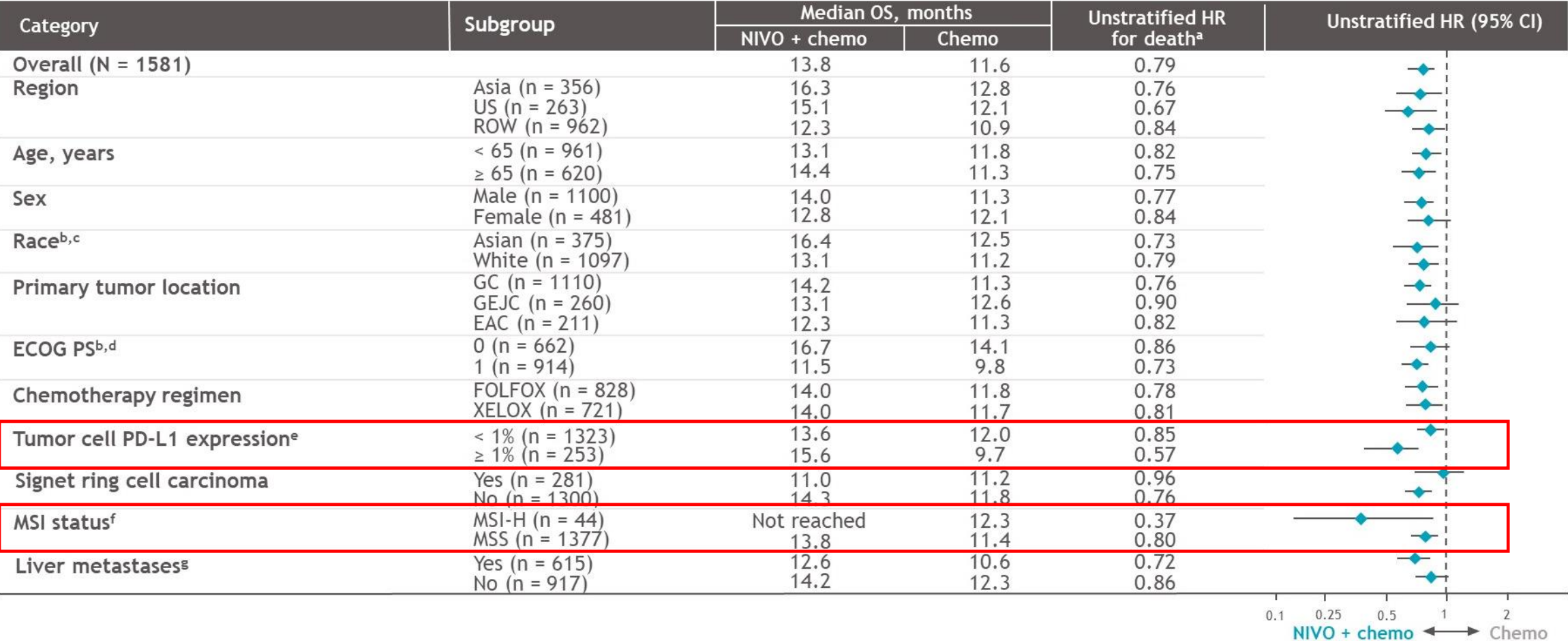


12-mo rate: NIVO + chemo, 36%; chemo, 22%

NIVO + chemo, 34%; chemo, 22%

NIVO + chemo, 33%; chemo, 23%

Checkmate 649 – OS Subgroup Analyses of All Randomized Patients



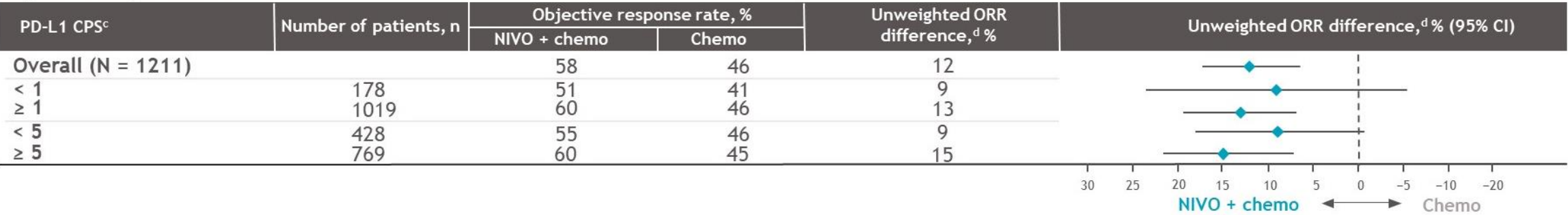
Checkmate 649 – PD-L1 CPS Subgroup Analyses



Survival



Objective response rate



Checkmate 649 – Rates of Adverse Adverts

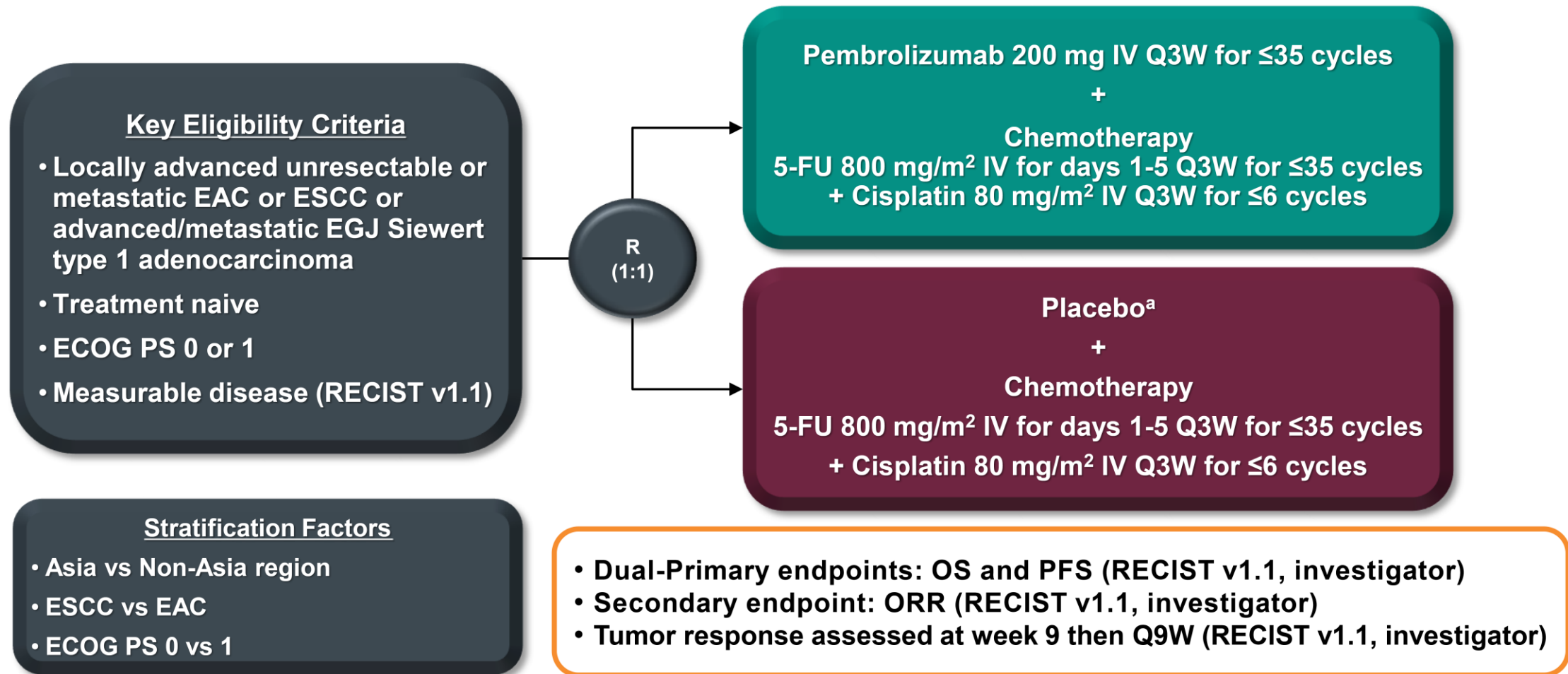


Patients, n (%)	All treated ^a			
	NIVO + chemo (n = 782) ^b		Chemo (n = 767) ^b	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Any TRAEs ^c	738 (94)	462 (59)	679 (89)	341 (44)
Serious TRAEs ^c	172 (22)	131 (17)	93 (12)	77 (10)
TRAEs leading to discontinuation ^c	284 (36)	132 (17)	181 (24)	67 (9)
Treatment-related deaths	12 ^d (2)		4 ^e (< 1)	

- The most common any-grade TRAEs ($\geq 25\%$) across both arms were nausea, diarrhea, and peripheral neuropathy
- The incidence of TRAEs in patients whose tumors expressed PD-L1 CPS ≥ 5 was consistent with all treated patients across both arms

^aPatients who received ≥ 1 dose of study drug; ^bAssessed in all treated patients during treatment and for up to 30 days after the last dose of study treatment; ^cThere were 4 grade 5 events in the NIVO + chemo arm, 1 case each of cerebrovascular accident, febrile neutropenia, gastrointestinal inflammation, and pneumonia. There were no grade 5 events in the chemo arm; ^dOne event each of febrile neutropenia, gastrointestinal bleeding, gastrointestinal toxicity, infection, interstitial lung disease, intestinal mucositis, neutropenic fever, pneumonia, pneumonitis, pulmonitis, septic shock (capecitabine-related), and stroke. ^eOne event each of diarrhea-associated toxicity, asthenia and severe hiporexy, pulmonary thromboembolism, and interstitial pneumonia.

Changing the Paradigm for First-Line Metastatic Esophageal/GEJ Cancer – KEYNOTE-590



KEYNOTE-590 – Baseline Characteristics



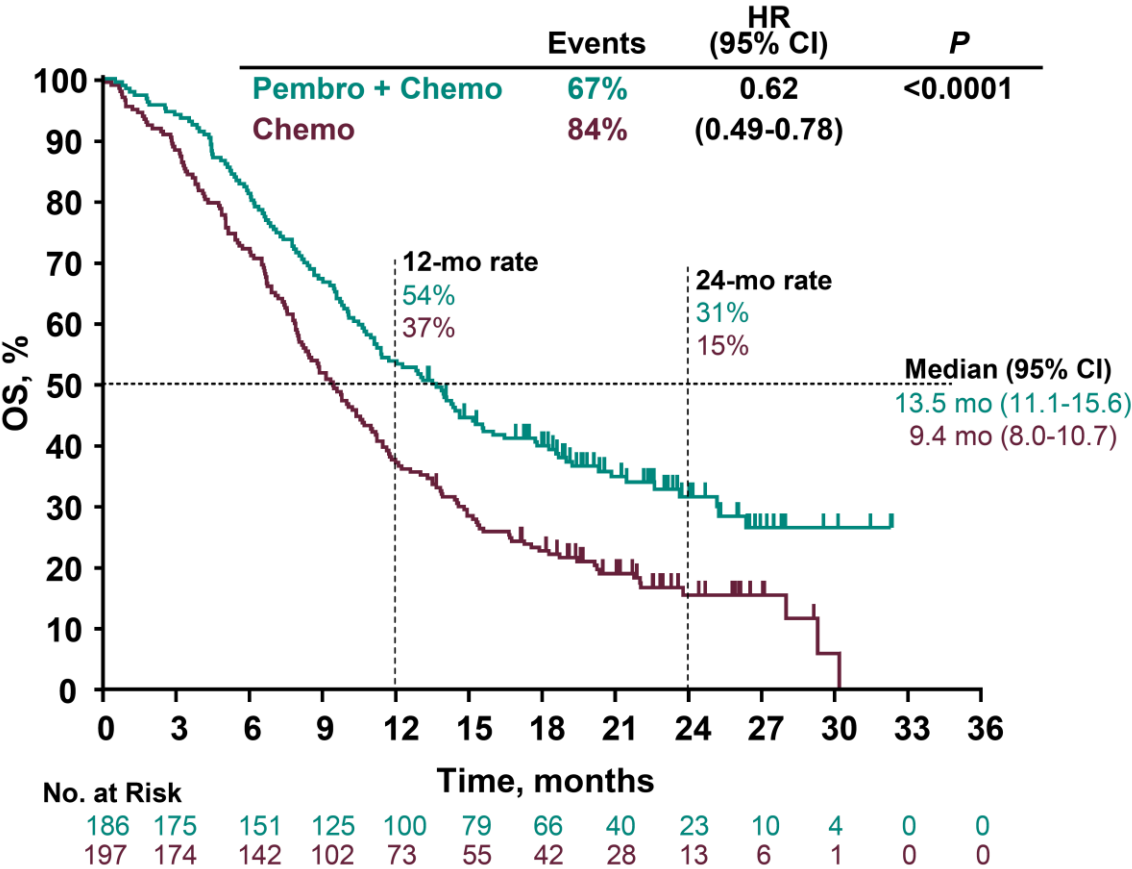
Characteristic, n (%)	Pembro + Chemo N = 373	Chemo N = 376
Median age, years (range)	64.0 (28-94)	62.0 (27-89)
≥65 years	172 (46)	150 (40)
Male	306 (82.0)	319 (84.8)
Asia Region	196 (52.5)	197 (52.4)
ECOG PS 1	223 (59.8)	225 (59.8)
Metastatic disease	344 (92.2)	339 (90.2)
Unresectable/locally-advanced	29 (7.8)	37 (9.8)
Squamous-cell carcinoma	274 (73.5)	274 (72.9)
Adenocarcinoma	99 (26.5)	102 (27.1)
Esophageal	58 (15.5)	52 (13.8)
EGJ	41 (11.0)	50 (13.3)
PD-L1 CPS ≥10 ^a	186 (49.9)	197 (52.4)

^aPD-L1 status was not evaluable or missing in 12 patients in the pembro + chemo group and 7 patients in the chemo group.
Data cut-off: July 2, 2020.

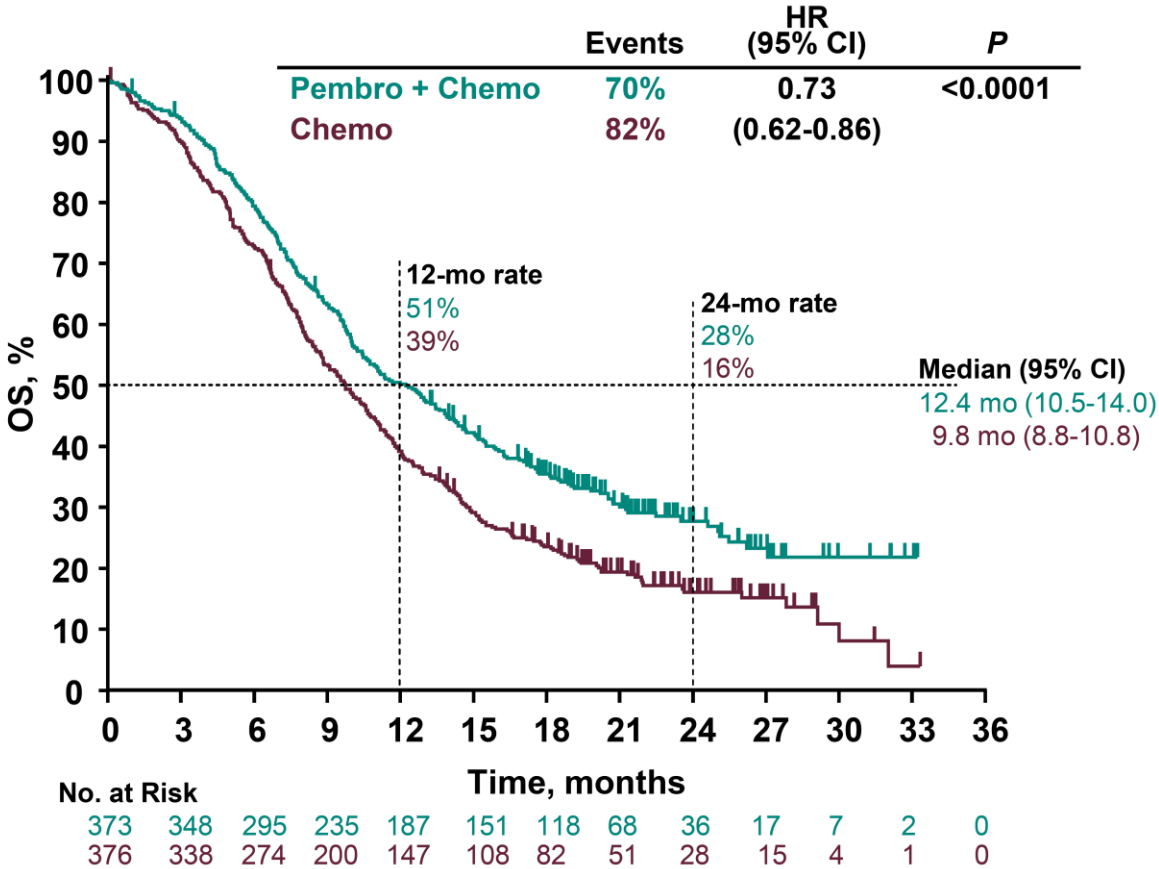
KEYNOTE-590 – Overall Survival in PD-L1 CPS ≥ 10 and All Patients



PD-L1 CPS ≥10



All Patients



KEYNOTE-590 – Exploratory Subgroup Analyses by Histology and PD-L1 Expression



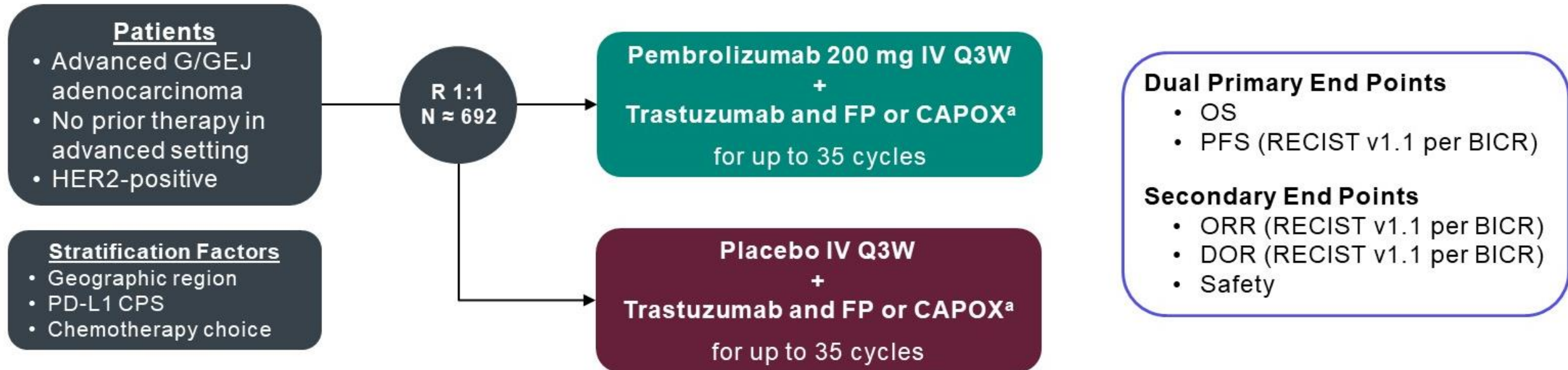
Subgroup	Overall Survival N, median OS* (95% CI), mo HR (95% CI) [†]		Progression-free Survival N, median PFS* (95% CI), mo HR (95% CI) [†]	
	P + C	C	P + C	C
ESCC CPS ≥10	N = 143 13.9 (11.1-17.7)	N = 143 8.8 (7.8-10.5)	N = 143 7.3 (6.2-8.2)	N = 143 5.4 (4.2-6.0)
	0.57 (0.43-0.75)		0.53 (0.40-0.69)	
Adenocarcinoma CPS ≥10	N = 43 12.1 (9.6-18.7)	N = 54 10.7 (8.2-15.3)	N = 43 8.0 (6.0-8.3)	N = 54 6.0 (4.1-6.2)
	0.83 (0.52-1.34)		0.49 (0.30-0.81)	
ESCC CPS <10	N = 121 10.5 (9.2-13.5)	N = 126 11.1 (9.1-12.4)	N = 121 6.2 (6.0-6.4)	N = 126 6.0 (5.3-6.2)
	0.99 (0.74-1.32)		0.83 (0.64-1.10)	
Adenocarcinoma CPS <10	N = 54 12.7 (8.1-16.1)	N = 46 8.4 (5.5-13.0)	N = 54 6.3 (5.6-8.3)	N = 46 5.7 (3.5-6.3)
	0.66 (0.42-1.04)		0.76 (0.49-1.19)	

*Based on Kaplan-Meier method for censored data.

[†]Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region and ECOG performance status.

Abbreviations; C, Chemotherapy; P, Pembrolizumab

Refining 1L Therapy in HER2+ Disease – KEYNOTE 811



Janjigian Y, et al. ASCO 2021. Abstract 4013

KEYNOTE 811 – Planned First Interim Analysis



Key Points

- Timing: to occur when first 260 participants enrolled had ≥8.5 mo of follow-up
- Objective: to assess whether adding pembrolizumab to trastuzumab and chemotherapy significantly improves ORR
- Superiority boundary: $P = 0.002$ (one-sided)
- Data cutoff date: June 17, 2020
 - 434 participants enrolled

Efficacy Population

- First 264 participants enrolled
- Follow-up duration^a
 - Median: 12.0 mo
 - Range: 8.5-19.4 mo
- Continuing any study treatment
 - Pembro arm: 40.6%
 - Placebo arm: 28.5%

Safety Population

- 433 participants who received ≥1 dose of study medication
- Follow-up duration^a
 - Median: 9.9 mo
 - Range: 0.1-19.4 mo
- Continuing any study treatment
 - Pembro arm: 58.5%
 - Placebo arm: 48.1%

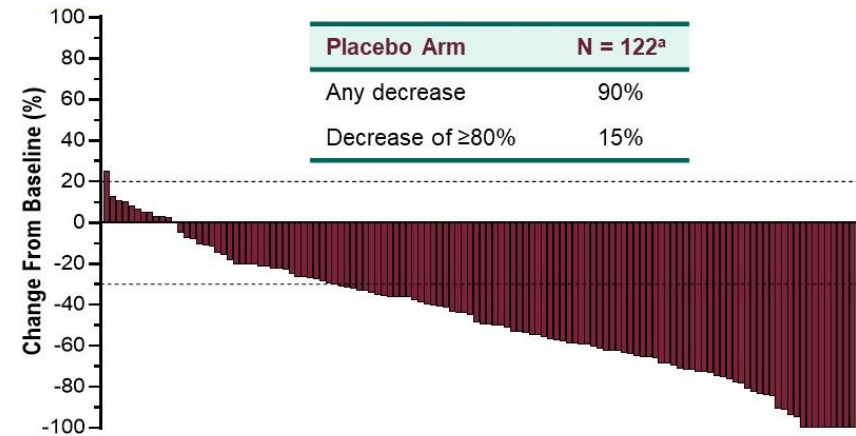
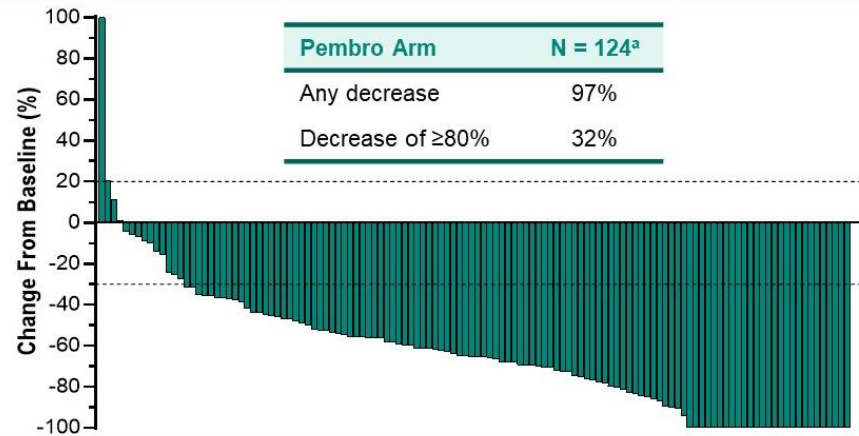
^aFollow-up duration was defined as the time from randomization to the data cutoff date.
Aus, Australia; EU, Europe; Isr, Israel; NAm, North America; ROW, rest of world.
The treatment regimen in both arms included trastuzumab and chemotherapy.

Baseline Characteristics – Efficacy Population

	Pembro Arm (N = 133)	Placebo Arm (N = 131)
Age, median (range)	62 y (19-84)	61 y (32-83)
Male sex	84%	79%
Region of enrollment		
Aus/EU/Isr/NAm	31%	34%
Asia	30%	30%
ROW	39%	37%
ECOG PS 1	51%	55%
Primary location of stomach	72%	68%
Histologic subtype		
Diffuse	21%	20%
Intestinal	61%	48%
Indeterminate	18%	32%
PD-L1 CPS ≥1	88%	85%
HER2 status		
IHC 2+, ISH positive	18%	21%
IHC 3+	82%	79%
Choice of chemotherapy		
CAPOX	86%	88%
FP	14%	12%

Janjigian Y, et al. ASCO 2021. Abstract 4013

KEYNOTE 811 – Response Rates



ORR and DCR, % (95% CI)	Pembro Arm (N = 133)	Placebo Arm (N = 131)
ORR	74.4% (66.2-81.6)	51.9% (43.0-60.7)
ORR difference ^b	22.7% (11.2-33.7) P = 0.00006	
DCR	96.2% (91.4-98.8)	89.3% (82.7-94.0)

Best Response, n (%)	Pembro Arm (N = 133)	Placebo Arm (N = 131)
CR	15 (11%)	4 (3%)
PR	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%

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KEYNOTE 811 – Adverse Events



All-Cause AEs

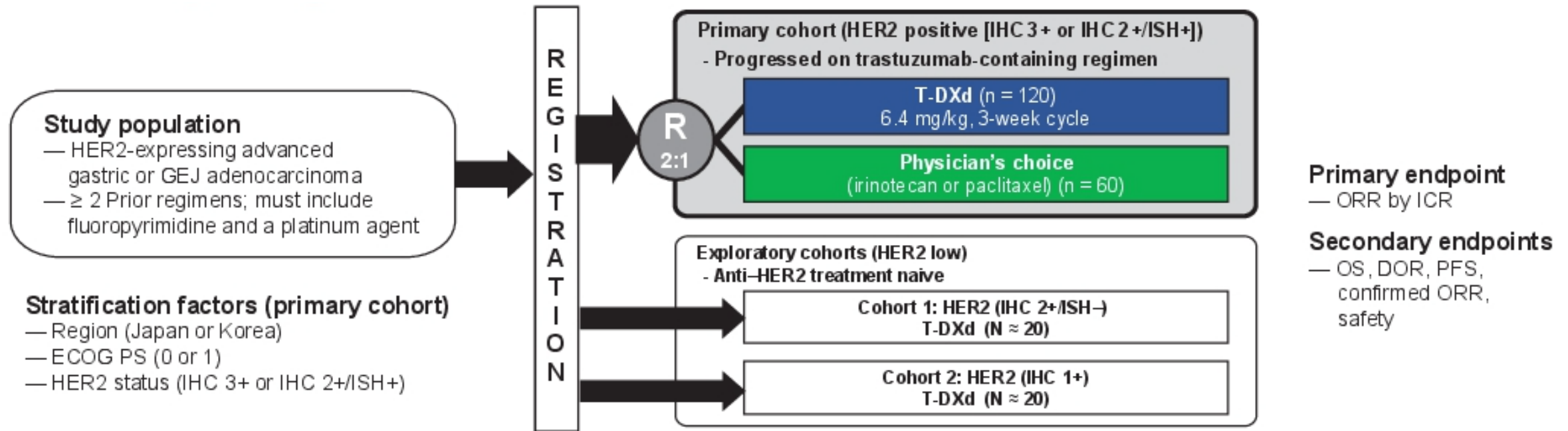
	Pembro Arm (N = 217)		Placebo Arm (N = 216)	
Summary				
Any grade	97%		98%	
Grade 3-5	57%		57%	
Serious	31%		38%	
Led to death	3%		5%	
Led to discon, any drug	24%		26%	
Incidence >20%	Any	Gr 3-5	Any	Gr 3-5
Diarrhea	53%	7%	44%	8%
Nausea	49%	5%	44%	6%
Anemia	41%	9%	44%	9%
↓ Appetite	31%	2%	32%	4%
Vomiting	31%	5%	27%	2%
↓ Platelet count	24%	8%	28%	7%
Fatigue	24%	4%	20%	3%
↓ Neutrophil count	24%	7%	25%	7%
Peripheral sensory neuropathy	23%	3%	19%	1%
↑ AST	21%	<1%	13%	<1%

Immune-Mediated AEs and Infusion Reactions^a

	Pembro Arm (N = 217)		Placebo Arm (N = 216)	
Summary				
Any grade	34%		21%	
Grade 3-5	10%		3%	
Serious	9%		3%	
Led to death	1%		<1%	
Led to discon, any drug	6%		2%	
Incidence ≥2 Participants	Any	Gr 3-5	Any	Gr 3-5
Infusion reactions	18%	3%	13%	1%
Pneumonitis	5%	1%	1%	0
Colitis	5%	3%	2%	2%
Hypothyroidism	5%	0	3%	0
Hyperthyroidism	4%	0	3%	0
Hypophysitis	1%	<1%	0	0
Hepatitis	1%	1%	1%	0
Severe skin reactions	1%	1%	0	0

Janjigian Y, et al. ASCO 2021. Abstract 4013

New Approach for HER2+ Disease in Later-line Therapy – DESTINY-Gastric01 Randomized Phase II



DESTINY-Gastric01 – Baseline Characteristics



Demographic Variable	T-DXd (n = 125)	PC Overall (n = 62)
Age, median (range), years ^a	65.0 (34.0-82.0)	66.0 (28.0-82.0)
Female, %	24.0	24.2
Region, %		
Japan/Korea	79.2/20.8	80.6/19.4
ECOG PS, %		
0/1	49.6/50.4	48.4/51.6
Histological subtype, %		
Intestinal	71.2	61.3
Diffuse	22.4	29.0
Other	6.4	9.7
HER2 expression, % ^b		
IHC 3+/IHC 2+, ISH+	76.8/23.2	75.8/24.2
Primary site, %		
Gastric/GEJ	86.4/13.6	88.7/11.3
Prior systemic therapies for advanced/metastatic disease, % ^e		
2	52.8	61.3
3	27.2	29.0
≥ 4	20.0	9.7
Prior treatment, %		
Containing trastuzumab	100.0	100.0
Containing ramucirumab	75.2	66.1
Containing taxane	84.0	88.7
Irinotecan or other topoisomerase I inhibitor	6.4	8.1
Immune checkpoint inhibitors	35.2	27.4

Shitara K, et al. ASCO 2020. Abstract 4513

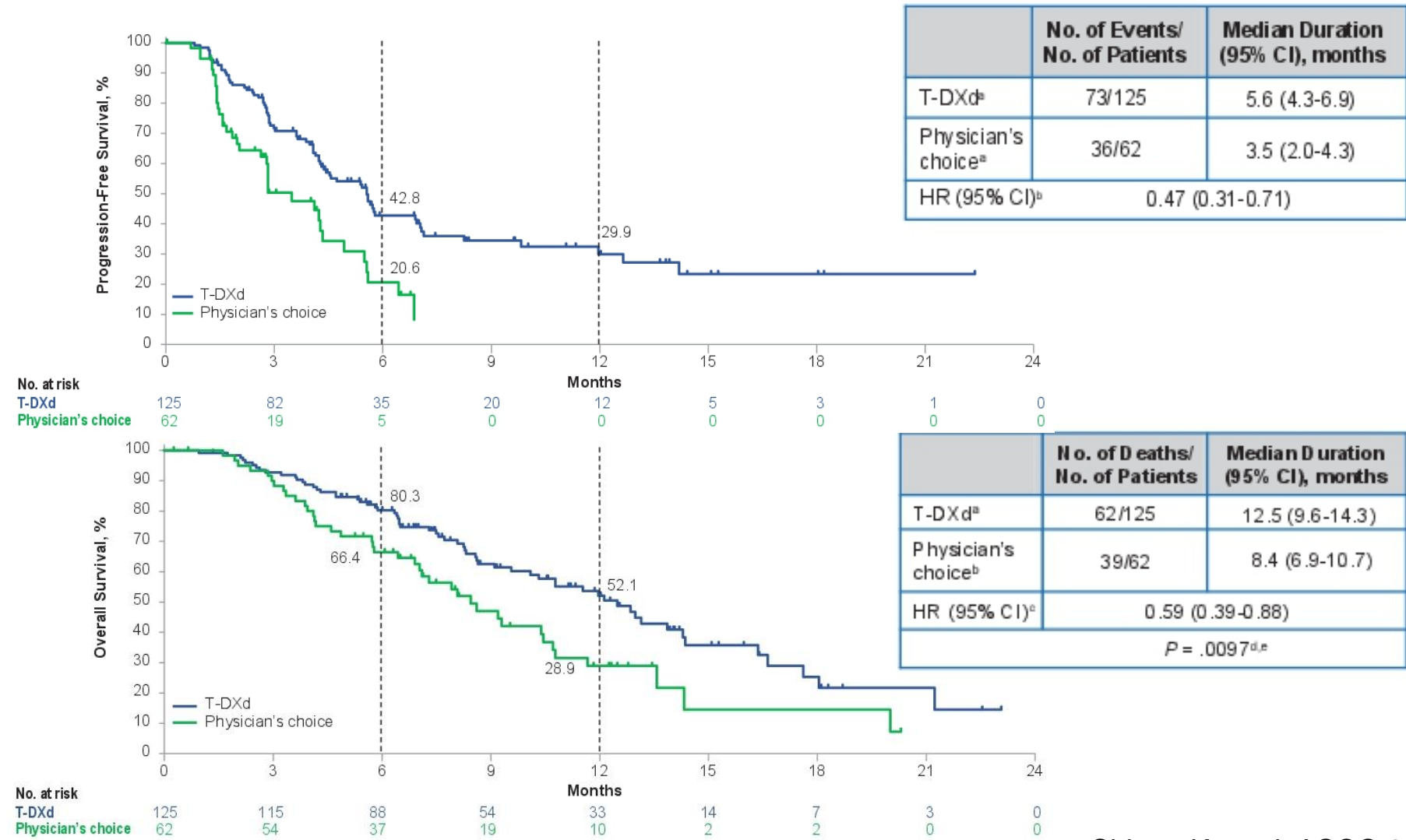
DESTINY-Gastric01 – Response Rates



	T-DXd (n = 119)	PC Overall (n = 56)
ORR (CR + PR) by ICR, n (%)^a	51.3% (n = 61) 95% CI, 41.9-60.5; <i>P</i> < .0001	14.3% (n = 8) 95% CI, 6.4-26.2
Confirmed ORR (CR + PR) by ICR, n (%)^a	42.9% (n = 51) 95% CI, 33.8-52.3	12.5% (n = 7) 95% CI, 5.2-24.1
CR	8.4% (n = 10)	0
PR	34.5% (n = 41)	12.5% (n = 7)
SD	42.9% (n = 51)	50.0% (n = 28)
PD	11.8% (n = 14)	30.4% (n = 17)
Not evaluable	2.5% (n = 3)	7.1% (n = 4)
Confirmed DCR (CR + PR + SD), n (%)^a	85.7% (n = 102) 95% CI, 78.1-91.5	62.5% (n = 35) 95% CI, 48.5-75.1
Confirmed DOR, median, months	11.3 95% CI, 5.6-NE	3.9 95% CI, 3.0-4.9
TTR, median, months	1.5 95% CI, 1.4-1.7	1.6 95% CI, 1.3-1.7

Shitara K, et al. ASCO 2020. Abstract 4513

DESTINY-Gastric01 – Progression-Free and Overall Survival



DESTINY-Gastric01 – Toxicities



Preferred Term, %	T-DXd (n = 125)			PC Overall (n = 62)		
	Grade			Grade		
	Any	3	4	Any	3	4
Any	100.0	60.8	8.4	98.4	41.9	11.3
Nausea	63.2	4.8	0	46.8	1.6	0
Neutrophil count decreased ^a	63.2	38.4	12.8	35.5	16.1	8.1
Decreased appetite	60.0	16.8	0	45.2	12.9	0
Anemia ^b	57.6	37.6	0	30.6	21.0	1.6
Platelet count decreased ^c	39.2	9.6	1.6	6.5	1.6	1.6
White blood cell count decreased ^d	37.6	20.8	0	35.5	8.1	3.2
Malaise	34.4	0.8	0	16.1	0	0
Diarrhea	32.0	2.4	0	32.3	1.6	0
Vomiting	26.4	0	0	8.1	0	0
Constipation	24.0	0	0	22.6	0	0
Pyrexia	24.0	0	0	16.1	0	0
Alopecia	22.4	0	0	14.5	0	0
Fatigue	21.6	7.2	0	24.2	3.2	0
Lymphocyte count decreased ^e	21.6	6.4	4.8	3.2	0	1.6

- 9.6% (12 pts) had T-DXd-related interstitial lung disease (ILD)/pneumonitis
- Median onset 84.5 days (36-638 days)
- 3 Grade 1, 6 Grade 2, 2 Grade 3, 1 Grade 4, 0 Grade 5
- 8 of 12 cases had resolved/were resolving (median time to resolution 57 days) at data analysis cut-off

Testing Trastuzumab Beyond Progression in Gastric Cancer – Japanese Second-Line T-ACT Trial



T-ACT study: Trial to Assess the Concept of TBP

HER2-positive advanced G/GEJ adenocarcinoma

refractory to first-line chemotherapy with fluoropyrimidine, platinum, and Tmab (≥ 3 doses and last dose within 6 wks of enrollment)

Stratification factor: Institution, ECOG PS 0–1/2, IHC3+ / IHC2+ & FISH+, Target lesion +/-

R 1:1

PTX

PTX 80 mg/m², on day 1, 8, 15, every 4 weeks

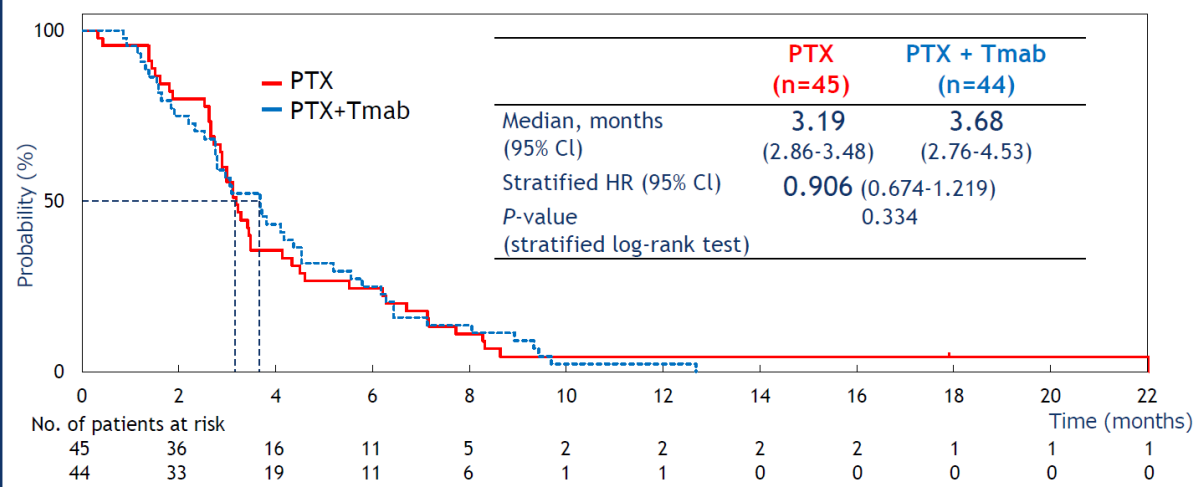
PTX + Tmab

Tmab 8 mg/kg loading dose and 6 mg/kg thereafter, on day 1, every 3 weeks
PTX 80 mg/m², on day 1, 8, 15, every 4 weeks

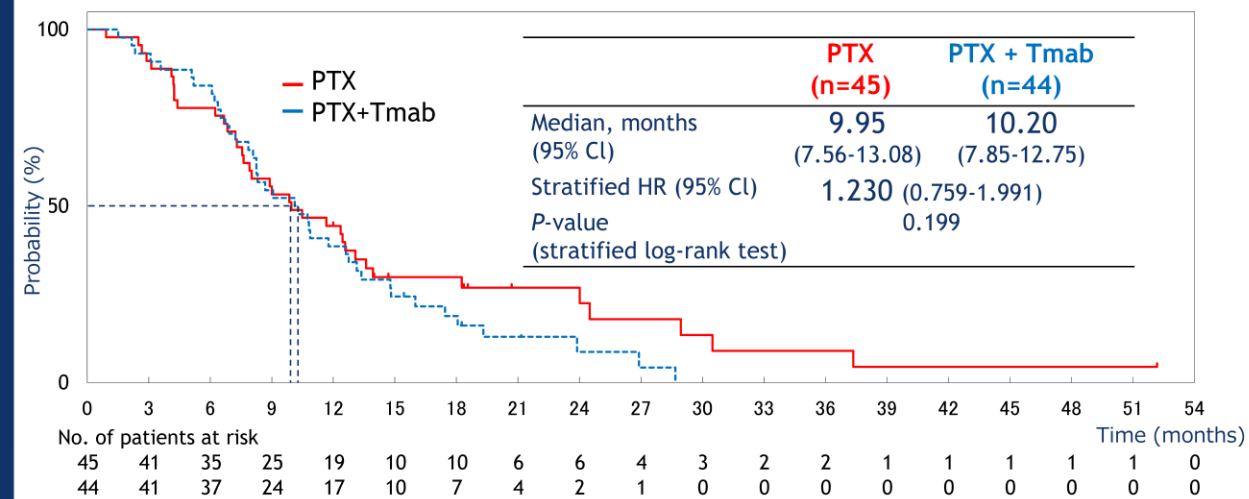
T-ACT – Progression-Free and Overall Survival



Progression-free Survival



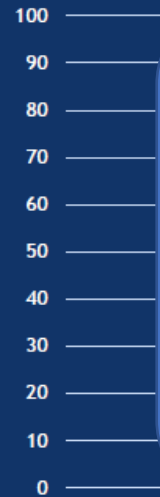
Overall Survival



HER2 Loss in T-ACT Trial



HER2-positive rates in available paired samples (n=16)



UPDATE: Phase 2 DESTINY-Gastric02 Trial – Single Arm T-DXd in Second-Line Therapy (N = 79)
Results: ORR 38%, Median PFS 5.5 months
Key Eligibility: Central Lab confirmation HER2+ on fresh biopsy

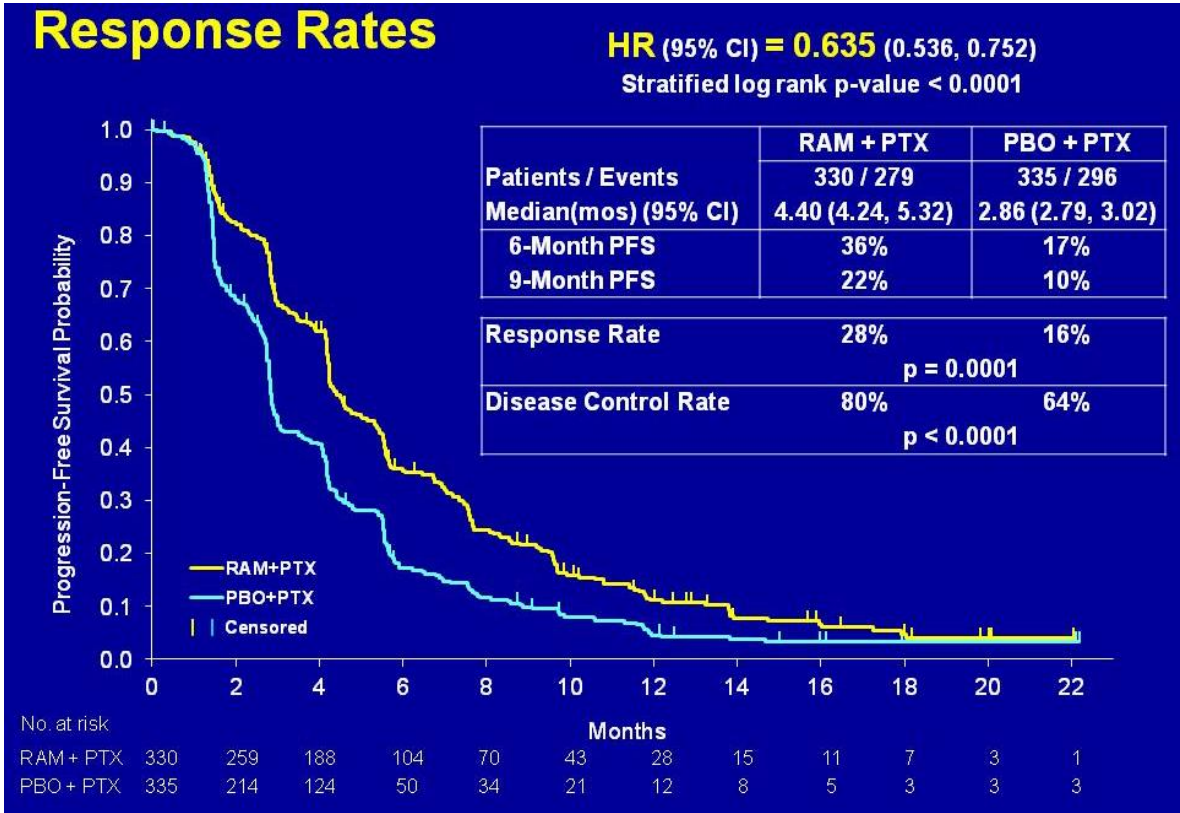
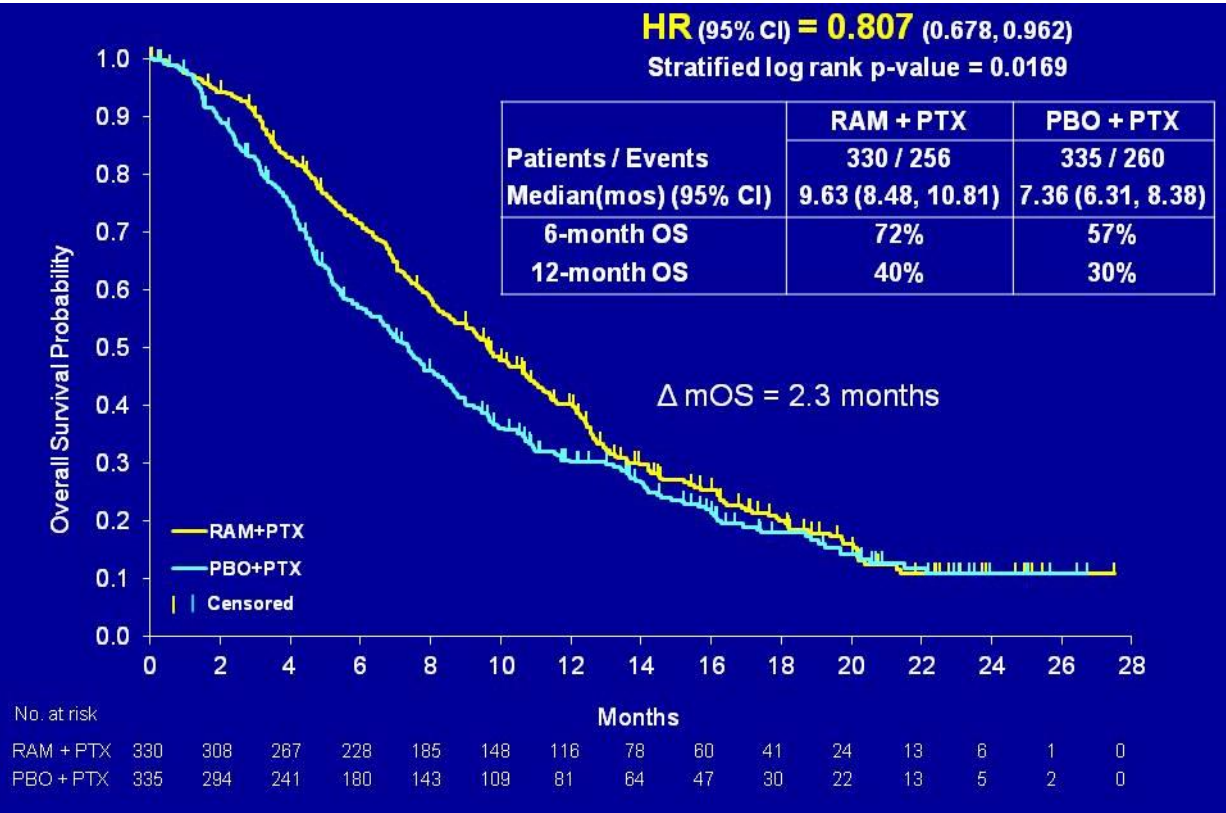
Before 1st line therapy			Before T-ACT trial		
HER2 status	IHC	FISH	HER2 status	IHC	FISH
+	3	-	+	3	+
+	3	-	+	3	+
+	2	+	+	3	+
+	2	+	+	3	+
+	0	-	+	3	+
+	0	-	+	3	+
+	0	-	+	3	+
+	0	-	+	3	+
+	0	-	+	3	+
+	0	-	+	3	+
+	0	-	+	3	+
+	0	-	+	3	+
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+	0	-	+	3	+
+	0	-	+	3	+

See Abstract 4029 Sukawa Y et al for more biomarker data

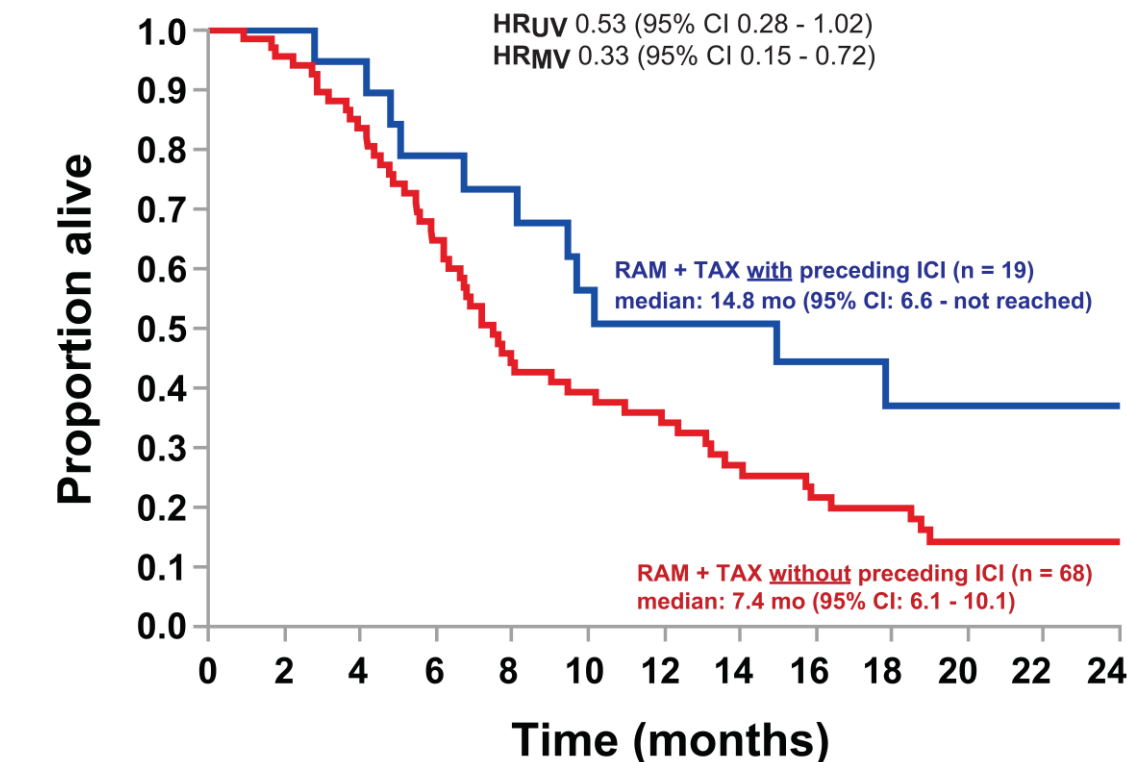
Definition of HER2 positive: IHC3+ or IHC2+ with FISH positive

The Reference Standard Second-Line Therapy

Paclitaxel + Ramucirumab – RAINBOW Trial

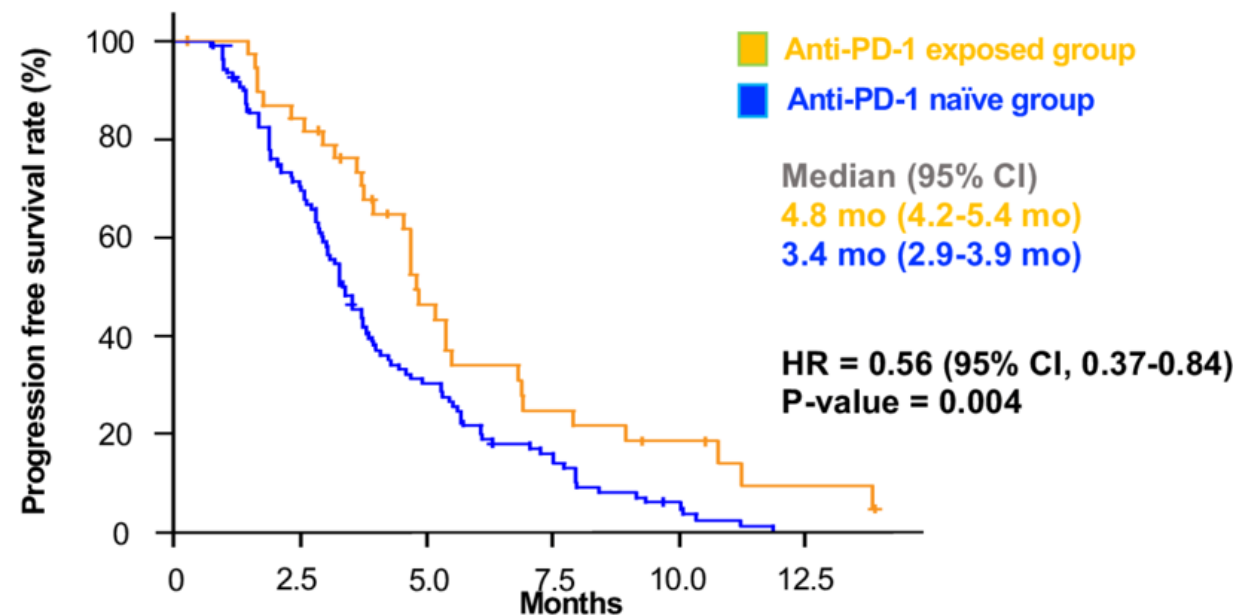


Retrospective Analyses of Paclitaxel + Ramucirumab Activity After Anti-PD-1 Exposure



Patients-at-risk

ICI-RAMTAX	19	19	18	14	13	10	9	8	6	4	4	3	3
RAMTAX	68	64	55	41	27	23	20	14	12	11	5	4	4



Trial in Progress – DESTINY-Gastric04



Primary Endpoint: OS (N = 490)

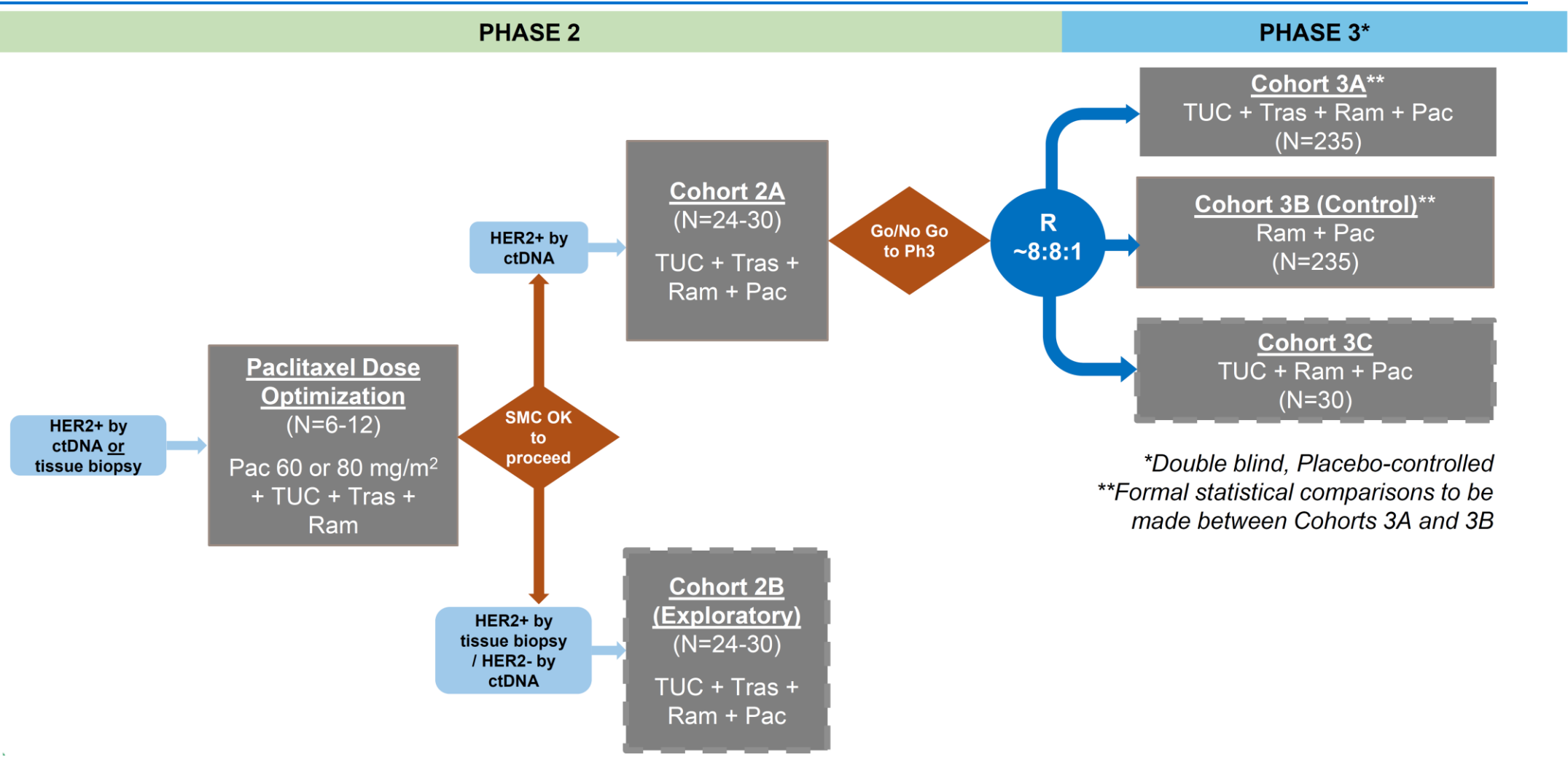
Enrollment:

- Metastatic gastric or GEJ adenocarcinoma
- Progressed on or after 1st-line trastuzumab-containing regimen
- Central lab confirmation HER2+ on fresh biopsy

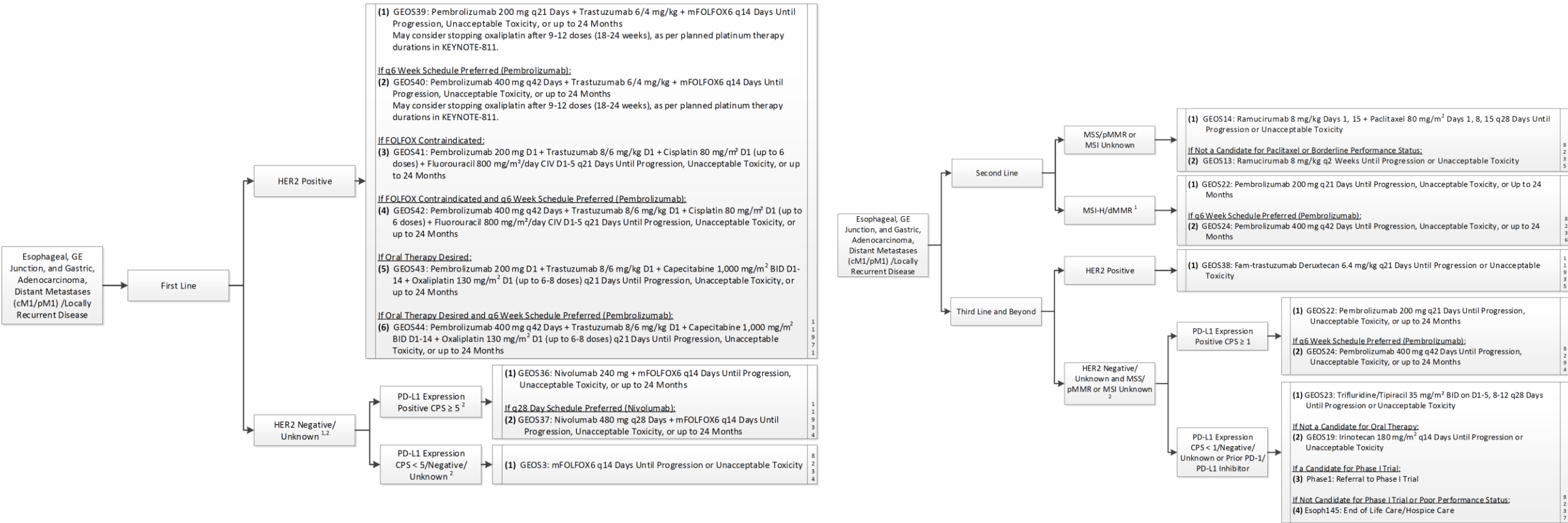
Trastuzumab deruxtecan

Paclitaxel + Ramucirumab

Trial in Progress – MOUNTAINEER-02



Practical Application of Sequencing Therapies - Pathways





THANK YOU!