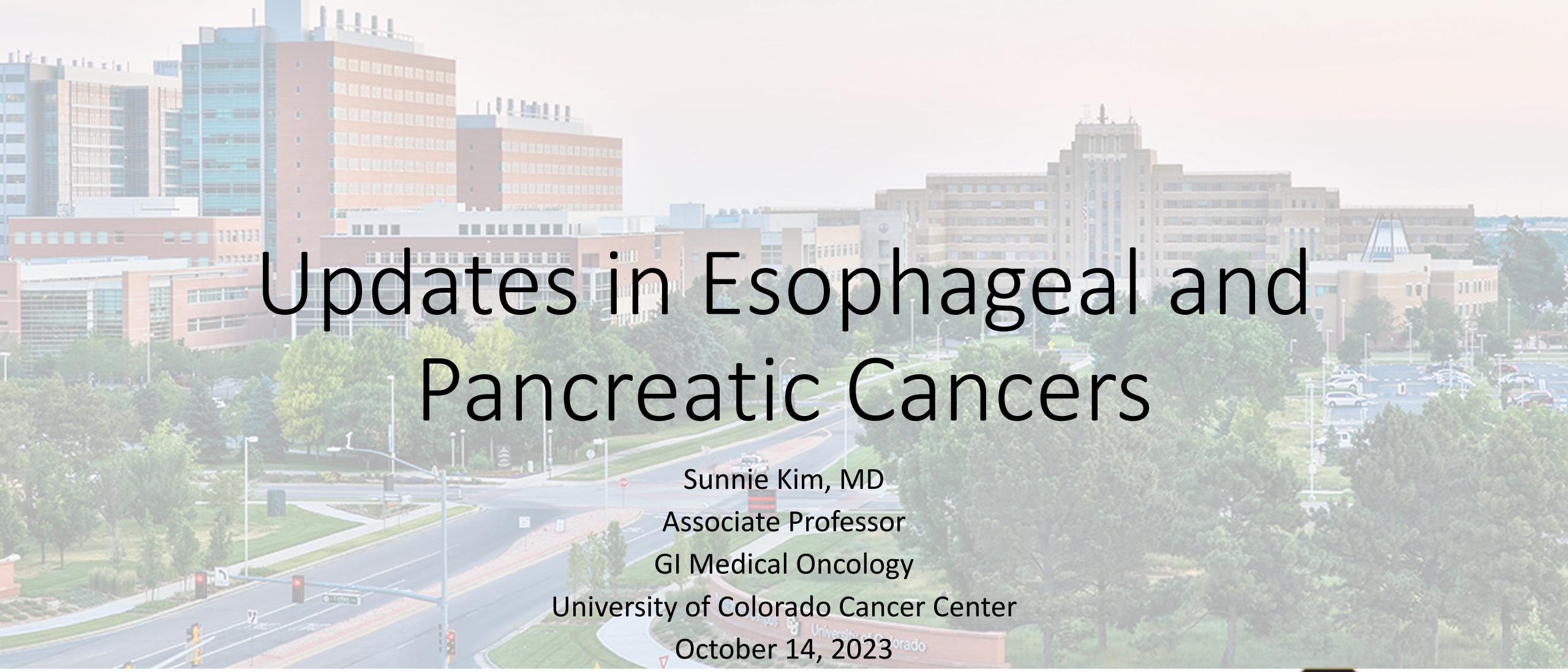

Updates in Esophageal and Pancreatic Cancers

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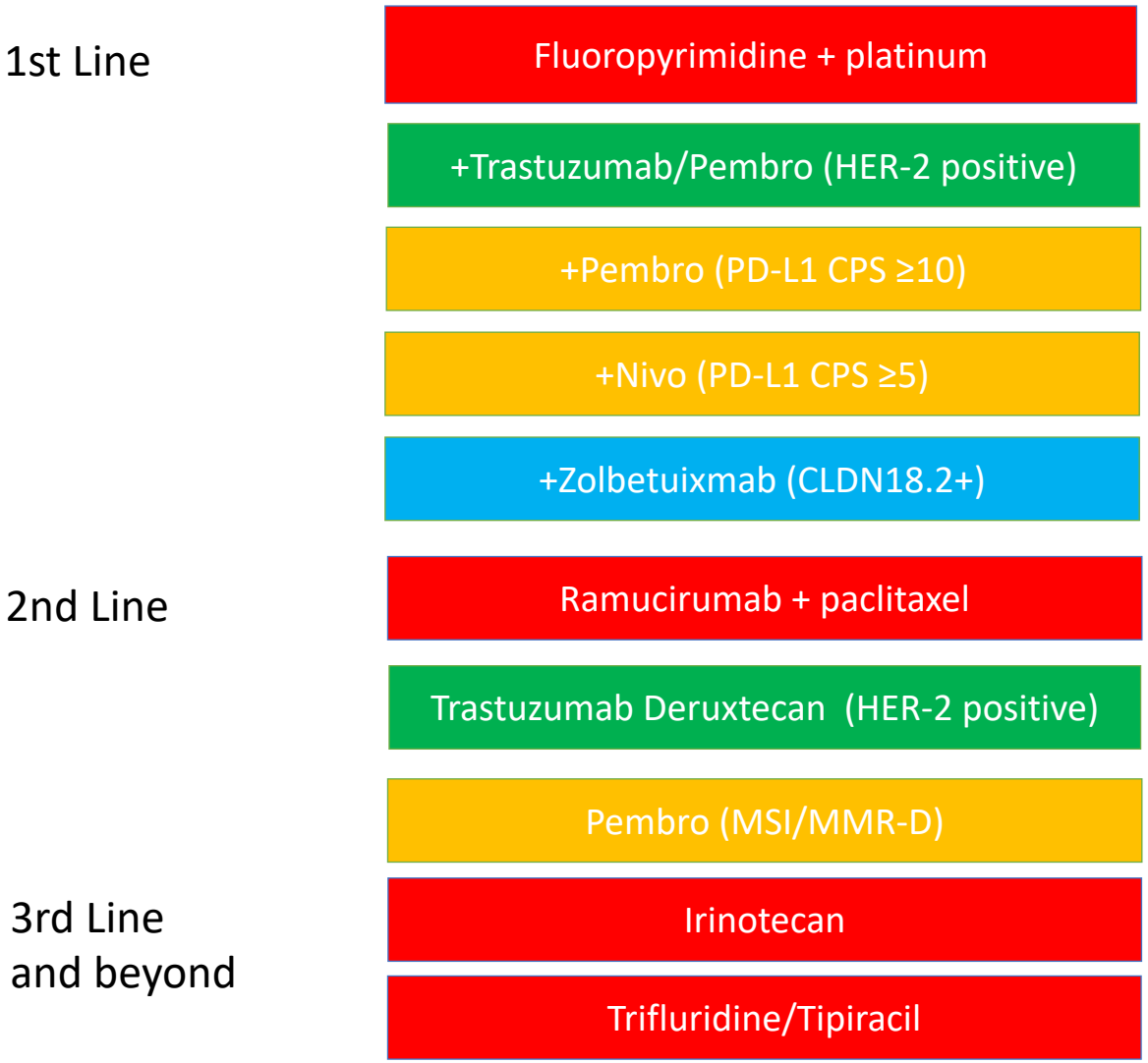
University of Colorado
Cancer Center

Today's Agenda

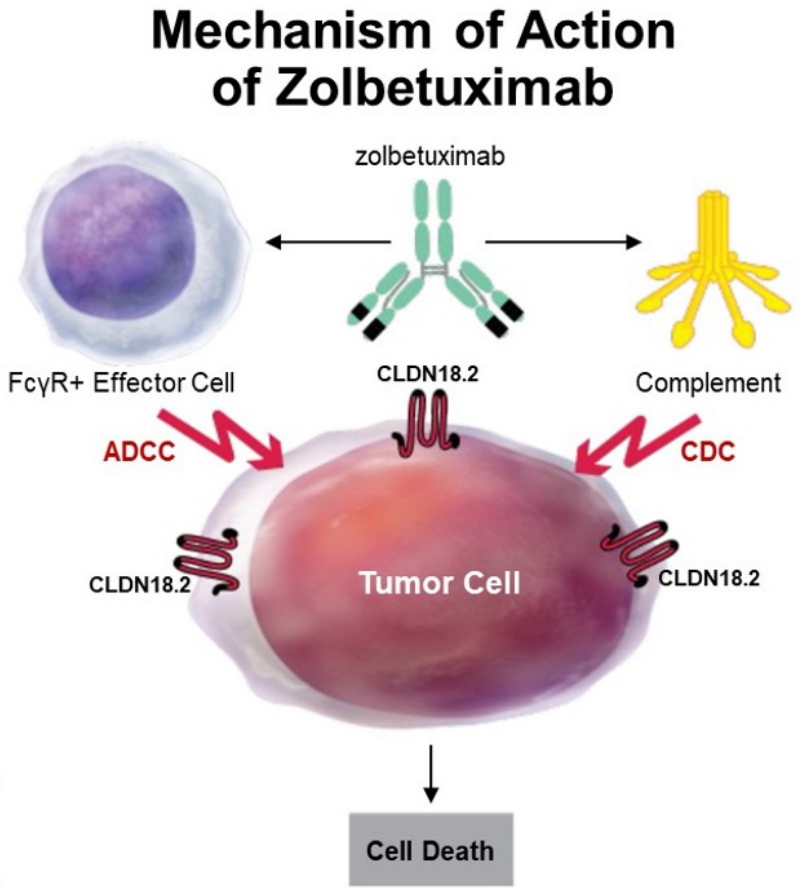
- Esophageal Cancer
  - New biomarker alert! – Claudin 18.2
    - SPOTLIGHT
  - Esophageal SCC
    - CheckMate-648 (chemo+nivolumab and ipilimumab/nivolumab)
  - Updates on targeting HER2
    - KEYNOTE-811 (chemo+pembrolizumab+trastuzumab)
  - Updates on perioperative strategies
    - KEYNOTE-585 (chemo+pembrolizumab)
- Pancreatic Cancer
  - NAPOLI-3 (NALIRIFOX versus gemcitabine/abraxane)
  - Targeted therapies

Therapy options in advanced gastric/esophageal cancers



Introduction: Zolbetuximab Targets CLDN18.2

- 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



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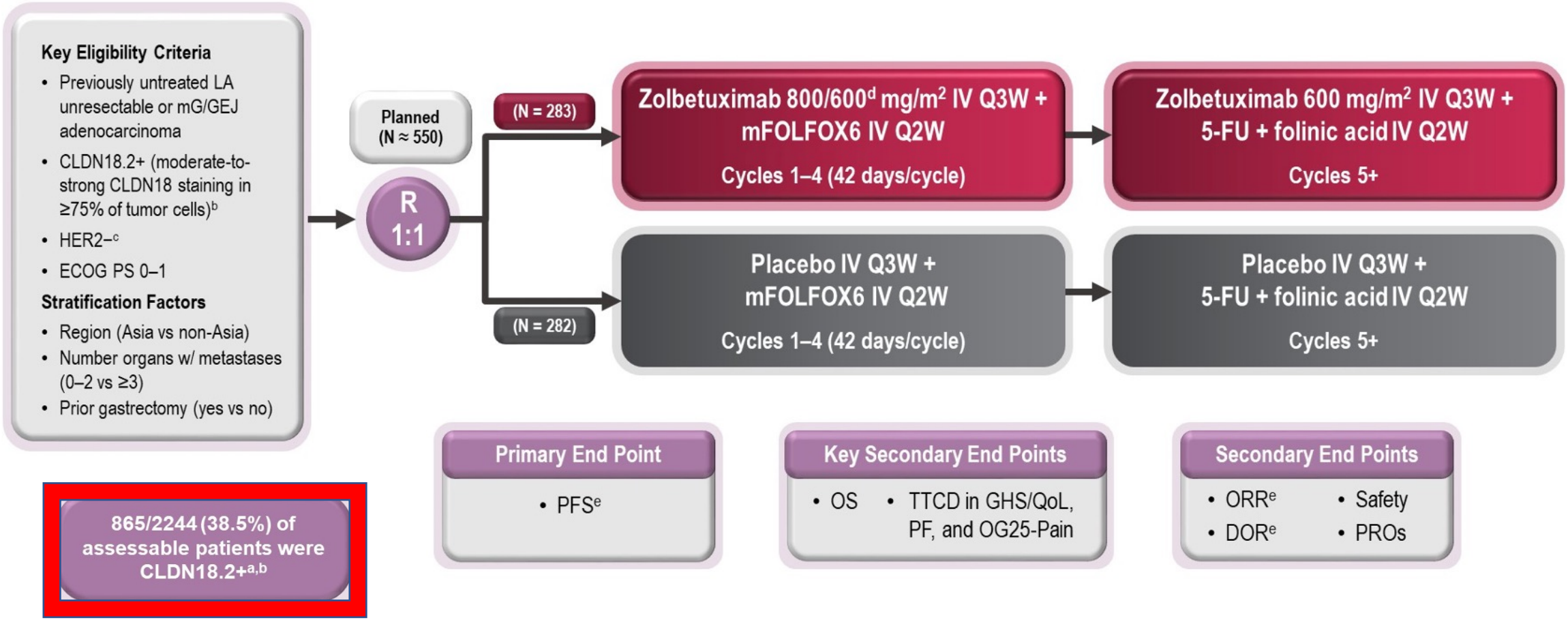
Study Design: SPOTLIGHT

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.

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Baseline Characteristics

		Zolbetuximab + mFOLFOX6 (N = 283)	Placebo + mFOLFOX6 (N = 282)
Age, years (range)	Median	62.0 (27–83)	60.0 (20–86)
Sex, n (%)	Male	176 (62.2)	175 (62.1)
Region, n (%)	Asia	88 (31.1)	89 (31.6)
	Non-Asia	195 (68.9)	193 (68.4)
Organs with metastases, n (%)	0–2	219 (77.4)	219 (77.7)
	≥3	64 (22.6)	63 (22.3)
Prior gastrectomy, n (%)	Yes	84 (29.7)	82 (29.1)
	No	199 (70.3)	200 (70.9)
Primary site, n (%)	Stomach	219 (77.4)	210 (74.5)
	GEJ	64 (22.6)	72 (25.5)
Lauren classification, n (%)	Diffuse	82 (29.1)	117 (42.1)
	Intestinal	70 (24.8)	66 (23.7)
	Mixed/others[a]	130 (45.9)	95 (33.7)
ECOG PS[b,c], n (%)	0	125 (44.8)	115 (41.4)
	1	153 (54.8)	163 (58.6)

- As an ad hoc analysis, 41/311 (13.2%) of assessable patients had tumors with PD-L1 CPS ≥5[d]
- Subsequent anticancer therapies were administered to 48% of patients in the zolbetuximab arm and 53% in the placebo arm

[a]Patients with Lauren classification "Mixed/others" include those classified as "mixed," "other," or "unknown" (unknown represents patients with adenocarcinoma without Lauren classification); [b]A patient in the zolbetuximab arm with ECOG PS 2 at baseline who was enrolled with ECOG PS 1 at screening is not shown here; [c]Four patients in each arm with ECOG PS missing at baseline who were enrolled with ECOG PS 0 or 1 at screening are not shown here (did not receive treatment and therefore did not have baseline measurements at C1D1); [d]Using the Dako PD-L1 IHC 28-8 pharmDx assay for samples within test stability and with subject consent.

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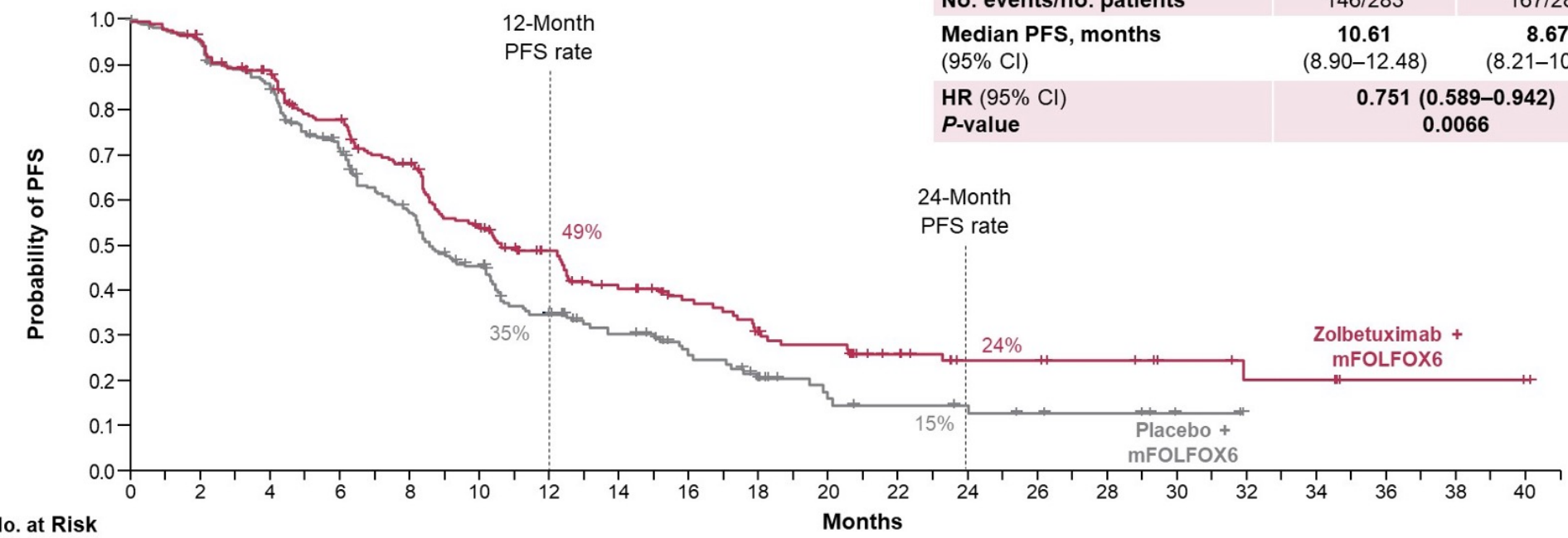
Progression Free Survival improvement

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



No. at Risk

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

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

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

[a]Per RECIST version 1.1.

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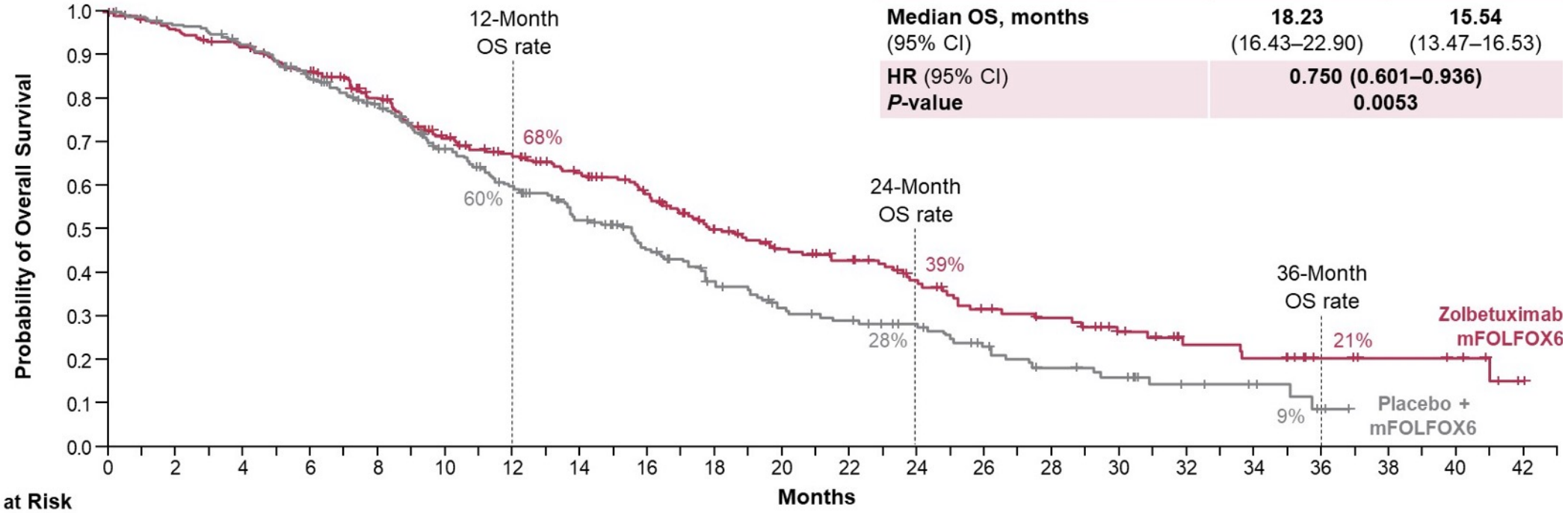
Overall Survival Benefit

	Zolbetuximab + mFOLFOX6	Placebo + mFOLFOX6
No. events/no. patients	149/283	177/282
Median OS, months (95% CI)	**18.23** (16.43–22.90)	**15.54** (13.47–16.53)
HR (95% CI)	**0.750 (0.601–0.936)**	
***P*-value**	**0.0053**	



No. at Risk

Zolbetuximab + mFOLFOX6	283	270	264	255	251	241	233	217	196	178	164	152	146	135	125	117	107	93	83	75	70	67	62	58	49	42	34	32	30	27	23	20	15	15	13	13	9	8	7	7	6	4	1	0
Placebo + mFOLFOX6	282	277	271	266	253	242	224	210	197	183	164	152	139	129	108	101	85	77	64	60	49	42	40	36	34	30	25	21	18	17	15	9	8	7	6	5	2	0	0	0	0	0	0	0

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

Data cutoff: September 9, 2022; Median follow-up = 22.14 months (zolbetuximab + mFOLFOX6) vs 20.93 months (placebo + mFOLFOX6).

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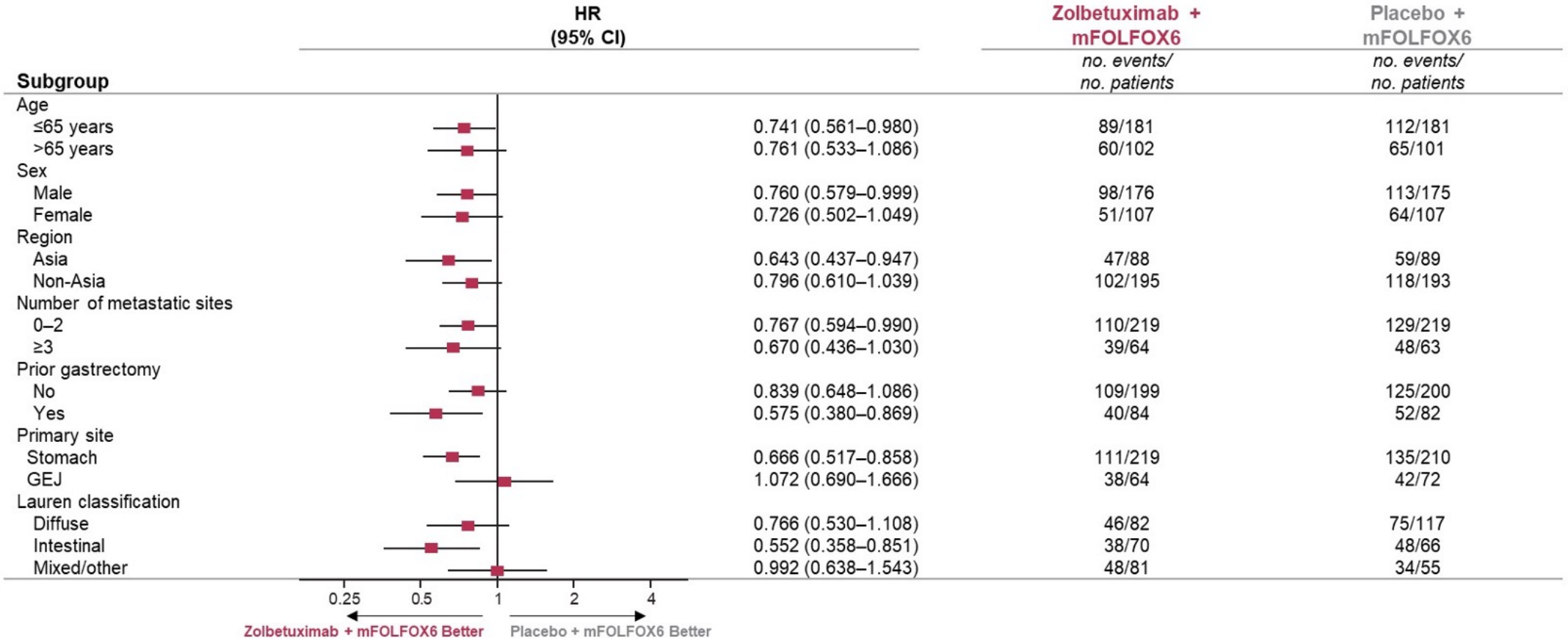
OS Subgroup Analysis



Subgroup	HR (95% CI)	Zolbetuximab + mFOLFOX6 no. events/ no. patients	Placebo + mFOLFOX6 no. events/ no. patients
Age			
≤65 years	0.741 (0.561–0.980)	89/181	112/181
>65 years	0.761 (0.533–1.086)	60/102	65/101
Sex			
Male	0.760 (0.579–0.999)	98/176	113/175
Female	0.726 (0.502–1.049)	51/107	64/107
Region			
Asia	0.643 (0.437–0.947)	47/88	59/89
Non-Asia	0.796 (0.610–1.039)	102/195	118/193
Number of metastatic sites			
0–2	0.767 (0.594–0.990)	110/219	129/219
≥3	0.670 (0.436–1.030)	39/64	48/63
Prior gastrectomy			
No	0.839 (0.648–1.086)	109/199	125/200
Yes	0.575 (0.380–0.869)	40/84	52/82
Primary site			
Stomach	0.666 (0.517–0.858)	111/219	135/210
GEJ	1.072 (0.690–1.666)	38/64	42/72
Lauren classification			
Diffuse	0.766 (0.530–1.108)	46/82	75/117
Intestinal	0.552 (0.358–0.851)	38/70	48/66
Mixed/other	0.992 (0.638–1.543)	48/81	34/55

- OS was significantly longer in patients treated with zolbetuximab + mFOLFOX6 across most subgroups

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Secondary Endpoints (ORR, BOR, mDOR)

	Zolbetuximab + mFOLFOX6 (N = 211)	Placebo + mFOLFOX6 (N = 211)
Patients[a], n	128	131
ORR[b], % (95% CI)	60.7 (53.72–67.30)	62.1 (55.17–68.66)
BOR[c,d], n (%)		
CR	12 (5.7)	7 (3.3)
PR	116 (55.0)	124 (58.8)
SD	45 (21.3)	52 (24.6)
PD	14 (6.6)	14 (6.6)
Median DOR[b], months, (95% CI)	8.51 (6.80–10.25)	8.11 (6.47–11.37)
3rd quartile, months (95% CI)	29.9 (10.41–NE)	15.5 (13.27–NE)

- Response rates were similar between treatment arms
- Formal analysis of PROs is pending
  - Initial descriptive analysis did not indicate differences between treatment arms

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Summary of Adverse Events

Event, n (%)	Zolbetuximab + mFOLFOX6 (N = 279)		Placebo + mFOLFOX6 (N = 278)	
	All Grade	Grade ≥3	All Grade	Grade ≥3
All TEAEs	278 (99.6)	242 (86.7)	277 (99.6)	216 (77.7)
Serious TEAEs	125 (44.8)	-	121 (43.5)	-
TRAEs leading to discontinuation of any study drug	106 (38.0)	-	82 (29.5)	-
TRAEs leading to discontinuation of zolbetuximab or placebo	38 (13.6)	-	6 (2.2)	-
TRAEs leading to death	5 (1.8)		4 (1.4)	

- The incidence of overall TEAEs was similar between treatment arms

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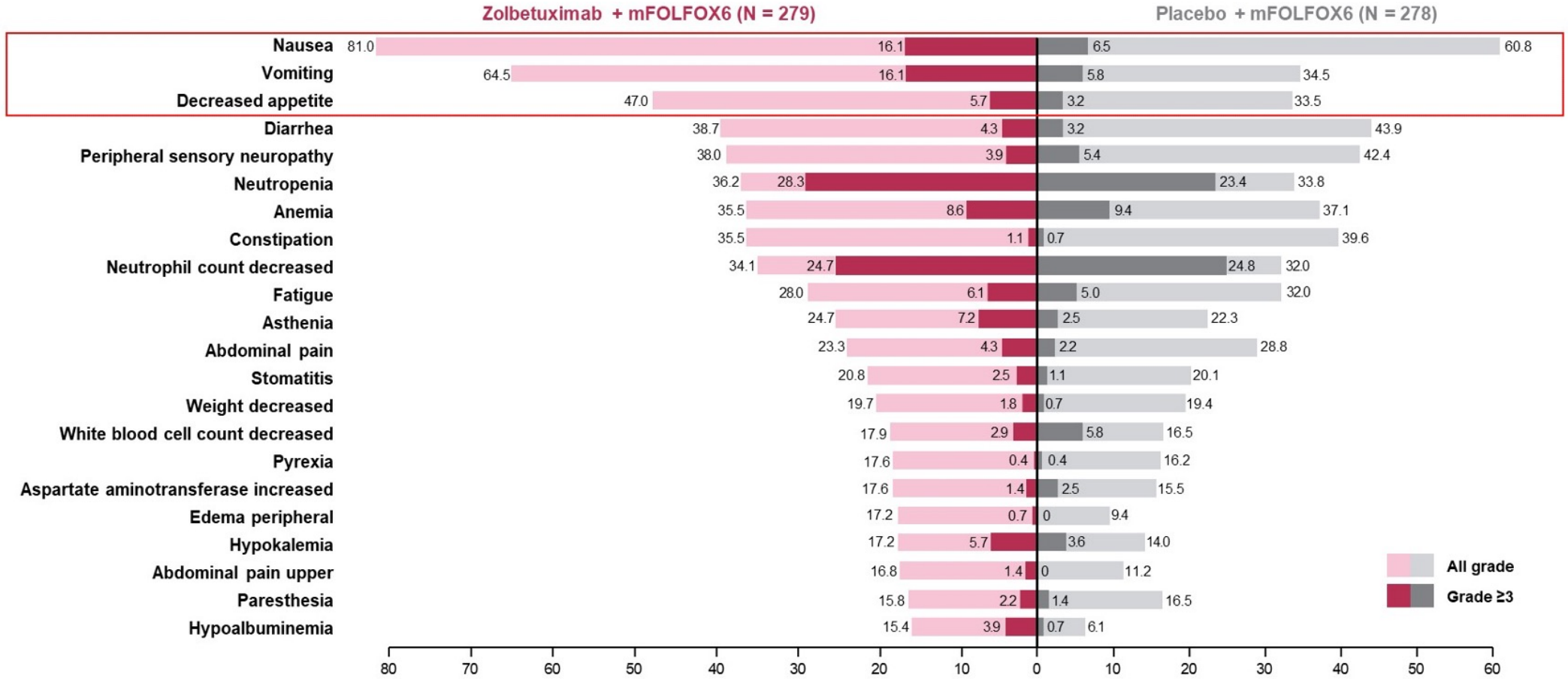
Nausea, Vomiting and Anorexia are Key AEs



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

[a]Preferred terms were defined according to the Medical Dictionary for Regulatory Activities terminology version 25.0.

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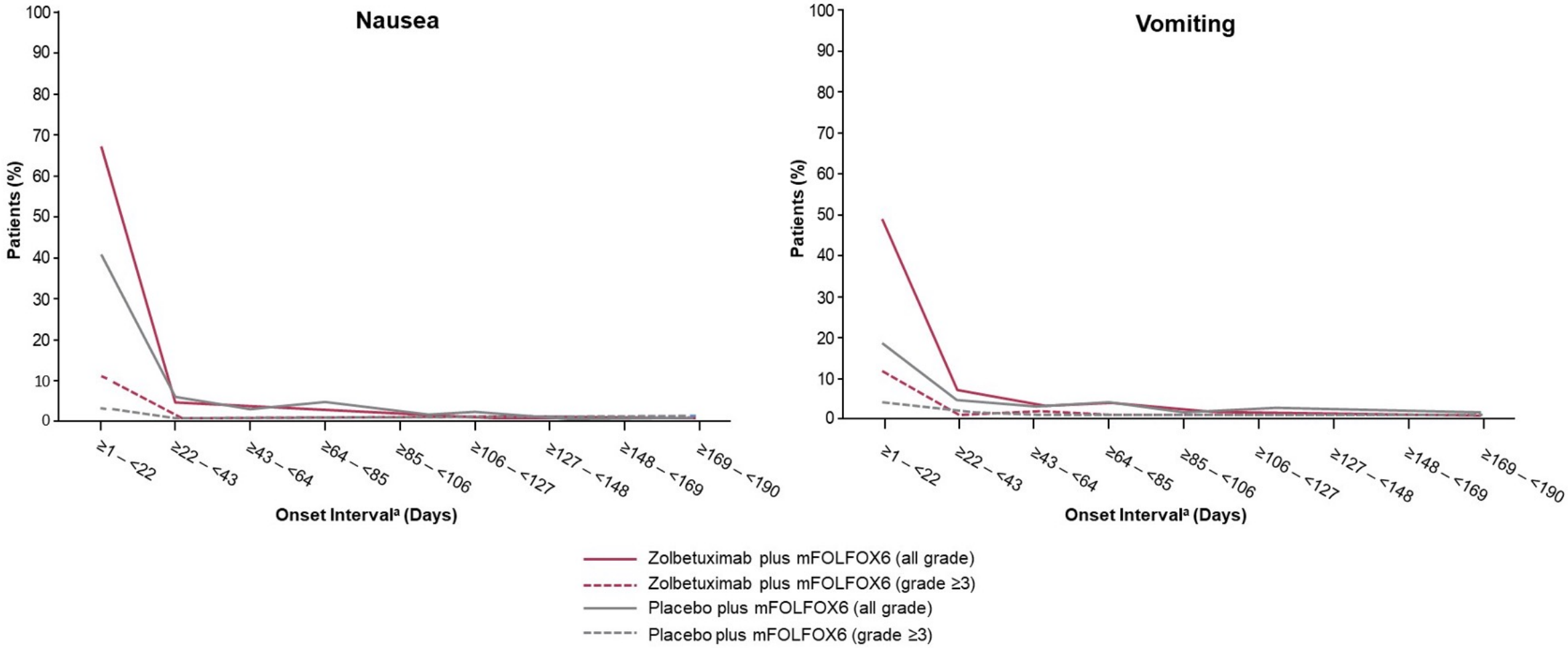
Nausea/Vomiting Peak with 1st Dose



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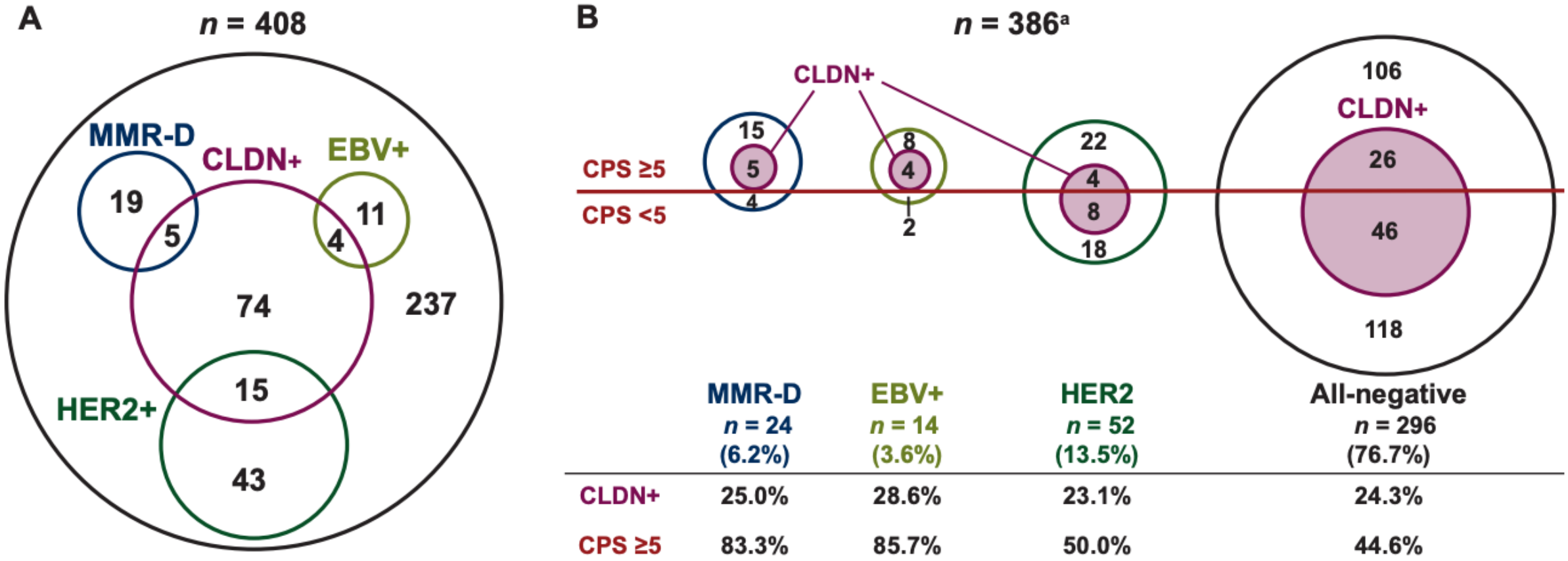
Ongoing Questions

- For PD-L1+ and CLDN18.2+ tumor, how to choose between adding PD-1 inhibitor or zolbetuximab?
  - Only 13% had PD-L1 CPS$\geq$5 and CLDN18.2 +
  - Increased disease burden favors chemo+nivo (no improvement in ORR + zolbe)
  - Toxicity profiles are different (n/v with zolbe, immune related AEs with nivo)
  - PD-1 inhibitors are more readily available as later line options
- Why did control arm do well?
  - Patient selection, patients with tumor biology able to wait for CLDN18.2 testing

Clinical and Molecular Characterization of CLDN 18.2+ tumors



	MMR-D *n* = 24 (6.2%)	EBV+ *n* = 14 (3.6%)	HER2 *n* = 52 (13.5%)	All-negative *n* = 296 (76.7%)
CLDN+	25.0%	28.6%	23.1%	24.3%
CPS ≥5	83.3%	85.7%	50.0%	44.6%

Kubota, ESMO Open 2023

Conclusions and Future Directions for CLDN18.2 directed therapy

- Adding Zolbetuximab to doublet chemo represents a new 1L standard of care for CLDN18.2+ gastric/GEJ cancers
- In a minority of cases, will need to choose between a CLDN18.2 approach versus PD-1 inhibitor
- ILLUSTRO (ongoing cohort study) will investigate safety and efficacy signal of combination zolbetuximab and IO
- Consider moving to periop setting

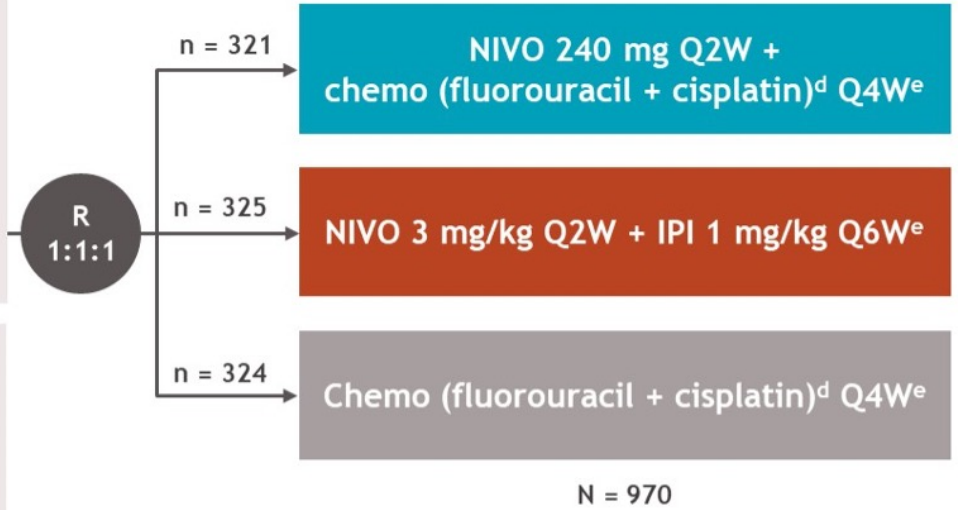
Advanced Esophageal Squamous Cell Cancers

CheckMate-648: New 1L option for ESCC

- CheckMate 648 is a global, randomized, open-label phase 3 study[a]

Key eligibility criteria
- Unresectable advanced, recurrent or metastatic ESCC
- ECOG PS 0-1
- No prior systemic treatment for advanced disease
- Measurable disease

Stratification factors
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[b])
- Region (East Asia[c] vs rest of Asia vs ROW)
- ECOG PS (0 vs 1)
- Number of organs with metastases (≤ 1 vs ≥ 2)



Primary endpoints:
- OS and PFS[f] (tumor cell PD-L1 ≥ 1%)

Secondary endpoints:
- OS and PFS[f] (all randomized)
- ORR[f] (tumor cell PD-L1 ≥ 1% and all randomized)

- At data cutoff (May 17, 2022), the minimum follow-up[g] was 28.8 months

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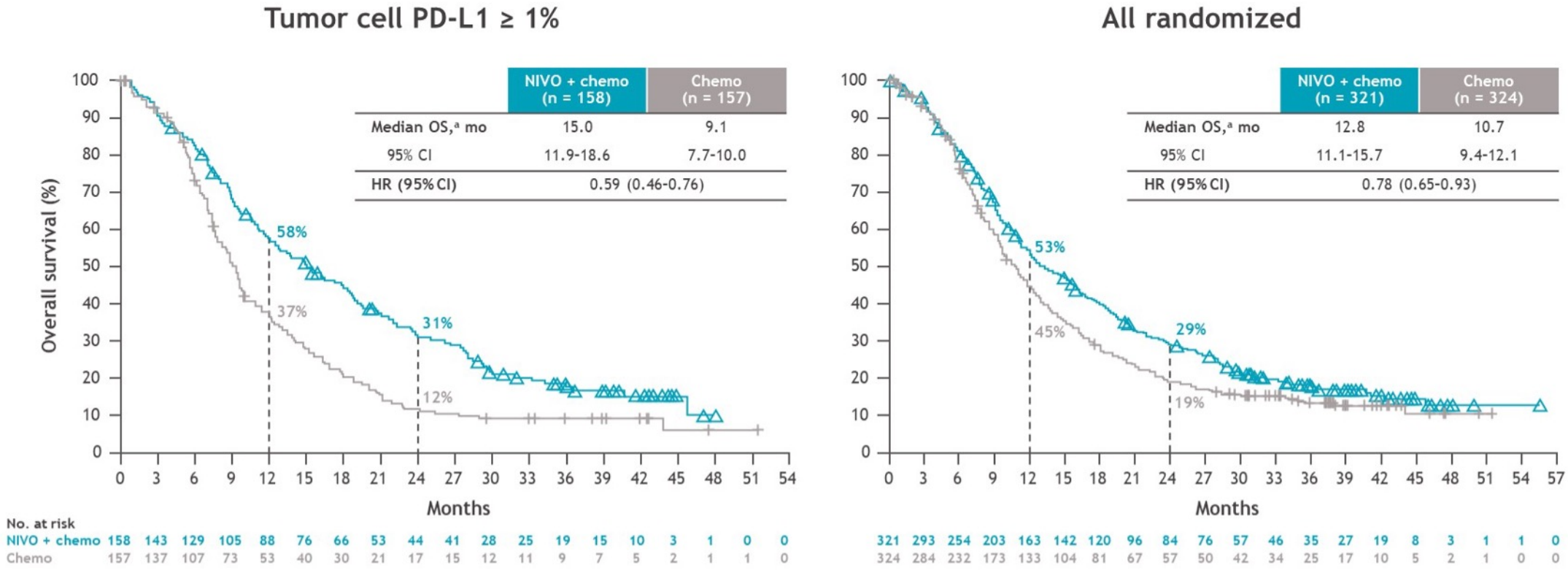
CM-648: Baseline Characteristics

All randomized	NIVO + chemo (n = 321)	NIVO + IPI (n = 325)	Chemo (n = 324)[a]
Median age, years (range)	64 (40-90)	63 (28-81)	64 (26-81)
Male, %	79	83	85
Asian,[b] %	70	70	70
ECOG PS 1, %	53	54	52
ESCC,[c] %	97	> 99	98
Tumor cell PD-L1 expression,[d] %			
≥ 1%	49	49	48
≥ 5%	37	37	36
≥ 10%	32	32	30
Disease status at study entry, %			
De novo metastatic	57	60	58
Recurrent - locoregional	7	8	8
Recurrent - distant	22	22	19
Unresectable advanced	14	10	16
Number of organs with metastases[e]			
≤ 1	49	49	49
≥ 2	51	51	51
Current or former smoker, %	79	82	79

- Of the 906 patients with quantifiable PD-L1 expression at baseline across all three treatment arms, a total of 288 (32%) had both tumor cell PD-L1 ≥ 1% and PD-L1 CPS ≥ 10, and 339 (37%) had both tumor cell PD-L1 < 1% and PD-L1 CPS < 10

Chau, ESMO GI 2022

OS with nivo + chemo versus chemo



- 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.

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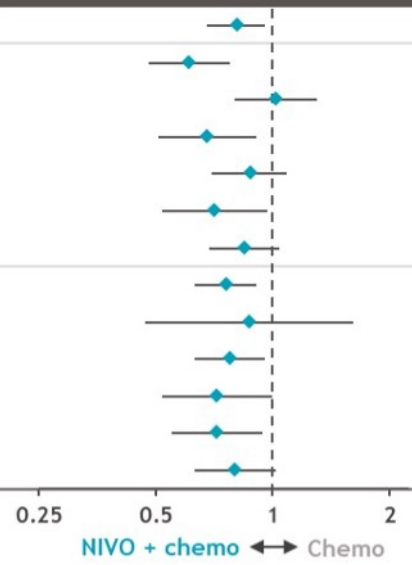
OS by PD-L1 status

Category (all randomized)	Subgroup	Median OS, months		Unstratified HR for death	Unstratified HR (95% CI)
		NIVO + chemo	Chemo		
Overall (N = 645)		12.8	10.7	0.81	
Tumor cell PD-L1 expression[a]	≥ 1% (n = 314)	15.0	9.2	0.61	
	< 1% (n = 329)	12.0	12.2	1.02	
	≥ 5% (n = 235)	13.7	9.5	0.68	
	< 5% (n = 408)	12.5	11.1	0.88	
	≥ 10% (n = 199)	14.7	9.6	0.71	
	< 10% (n = 444)	12.1	10.8	0.85	
PD-L1 CPS[b,c]	≥ 1 (n = 558)	13.7	9.9	0.76	
	< 1 (n = 51)	9.9	12.1	0.87	
	≥ 5 (n = 421)	14.9	11.1	0.78	
	< 5 (n = 188)	11.7	9.4	0.72	
	≥ 10 (n = 280)	15.5	11.6	0.72	
	< 10 (n = 329)	12.0	9.7	0.80	



- Results across baseline PD-L1 status subgroups were generally consistent with those previously reported[1]
  - HRs were below 1 across most PD-L1 expression subgroups, favoring NIVO + chemo vs chemo
  - The largest magnitude of OS benefit was observed in patients with tumor cell PD-L1 ≥ 1%, with no further enrichment in higher tumor cell PD-L1 expression subgroups

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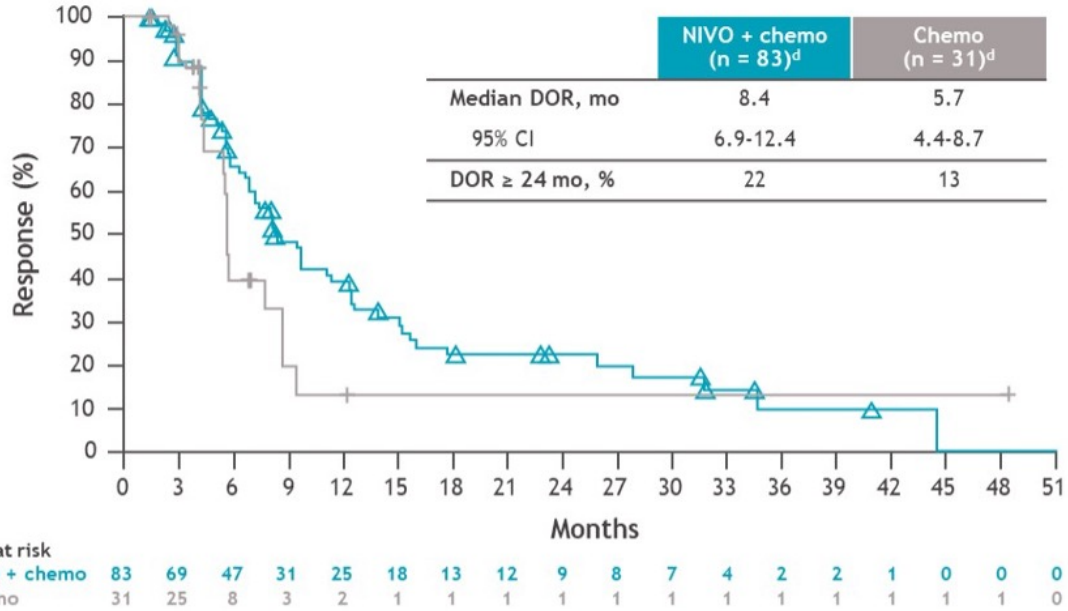
ORR improved with chemo + nivo

Tumor cell PD-L1 ≥ 1%

Response per BICR	NIVO + chemo (n = 158)	Chemo (n = 157)
ORR,[a] % (95% CI)	53 (44-61)	20 (14-27)
CR[b]	17	4
PR[b]	35	15
SD	25	46
PD	15	16



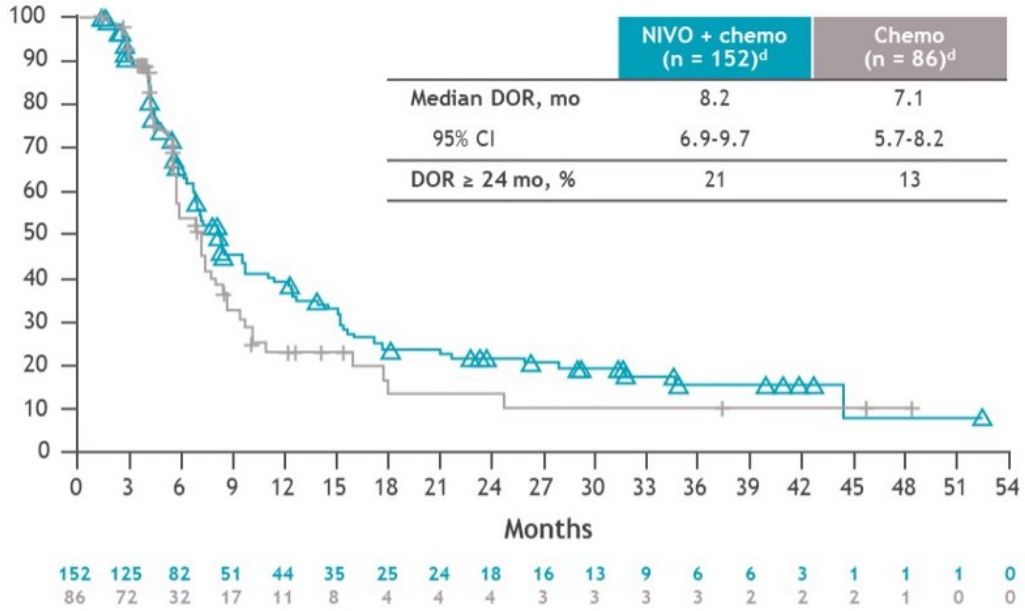
	NIVO + chemo (n = 83)[d]	Chemo (n = 31)[d]
Median DOR, mo	8.4	5.7
95% CI	6.9-12.4	4.4-8.7
DOR ≥ 24 mo, %	22	13

No. at risk

NIVO + chemo	83	69	47	31	25	18	13	12	9	8	7	4	2	2	1	0	0	0
Chemo	31	25	8	3	2	1	1	1	1	1	1	1	1	1	1	1	0	0

All randomized

Response per BICR	NIVO + chemo (n = 321)	Chemo (n = 324)
ORR,[c] % (95% CI)	47 (42-53)	27 (22-32)
CR[b]	15	6
PR[b]	33	21
SD	32	46
PD	13	12



	NIVO + chemo (n = 152)[d]	Chemo (n = 86)[d]
Median DOR, mo	8.2	7.1
95% CI	6.9-9.7	5.7-8.2
DOR ≥ 24 mo, %	21	13

NIVO + chemo	152	125	82	51	44	35	25	24	18	16	13	9	6	6	3	1	1	1	0
Chemo	86	72	32	17	11	8	4	4	4	3	3	3	3	2	2	2	1	0	0

- ORR remained higher and responses remained more durable with NIVO + chemo vs chemo with longer follow-up

[a]Unable to determine best overall response in patients with tumor cell PD-L1 ≥ 1%: NIVO + chemo, n = 12; chemo, n = 29; [b]Percentages may not add up to ORR due to rounding; [c]Unable to determine best overall response in all randomized patients: NIVO + chemo, n = 24; chemo, n = 50; [d]Number of responders.

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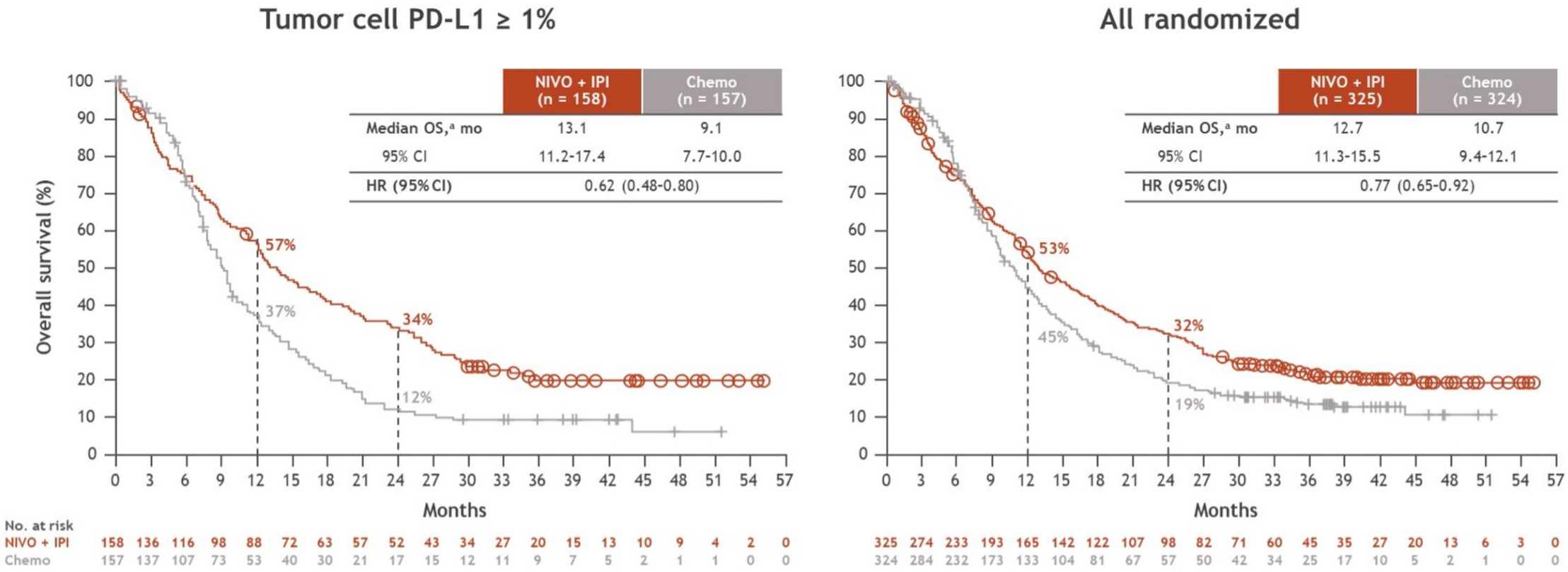
OS (nivo/ipi versus chemo)



- Clinically meaningful improvement in OS with NIVO + IPI vs chemo in the tumor cell PD-L1 ≥ 1% and all randomized populations was maintained with longer follow-up
  - Tumor cell PD-L1 ≥ 1%: 38% reduction in the risk of death and a 4.0-month improvement in median OS
  - All randomized: 23% reduction in the risk of death and a 2.0-month improvement in median OS

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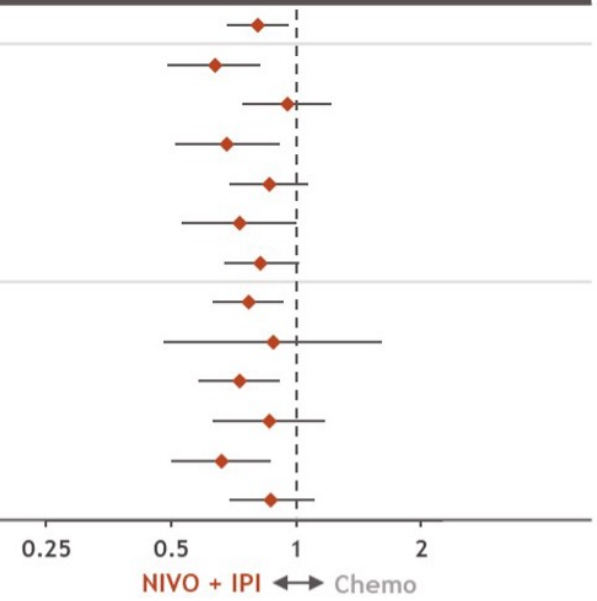
OS by baseline PD-L1 status

Category (all randomized)	Subgroup	Median OS, months		Unstratified HR for death	Unstratified HR (95% CI)
		NIVO + IPI	Chemo		
Overall (N = 649)		12.7	10.7	0.79	
Tumor cell PD-L1 expression[a]	≥ 1% (n = 314)	13.1	9.2	0.64	
	< 1% (n = 330)	11.9	12.2	0.95	
	≥ 5% (n = 235)	13.0	9.5	0.68	
	< 5% (n = 409)	12.4	11.1	0.86	
	≥ 10% (n = 200)	13.0	9.6	0.73	
	< 10% (n = 444)	12.5	10.8	0.82	
PD-L1 CPS[b,c]	≥ 1 (n = 546)	12.5	9.9	0.77	
	< 1 (n = 55)	11.5	12.1	0.88	
	≥ 5 (n = 404)	14.5	11.1	0.73	
	< 5 (n = 197)	11.4	9.4	0.86	
	≥ 10 (n = 271)	17.0	11.6	0.66	
	< 10 (n = 330)	11.2	9.7	0.87	



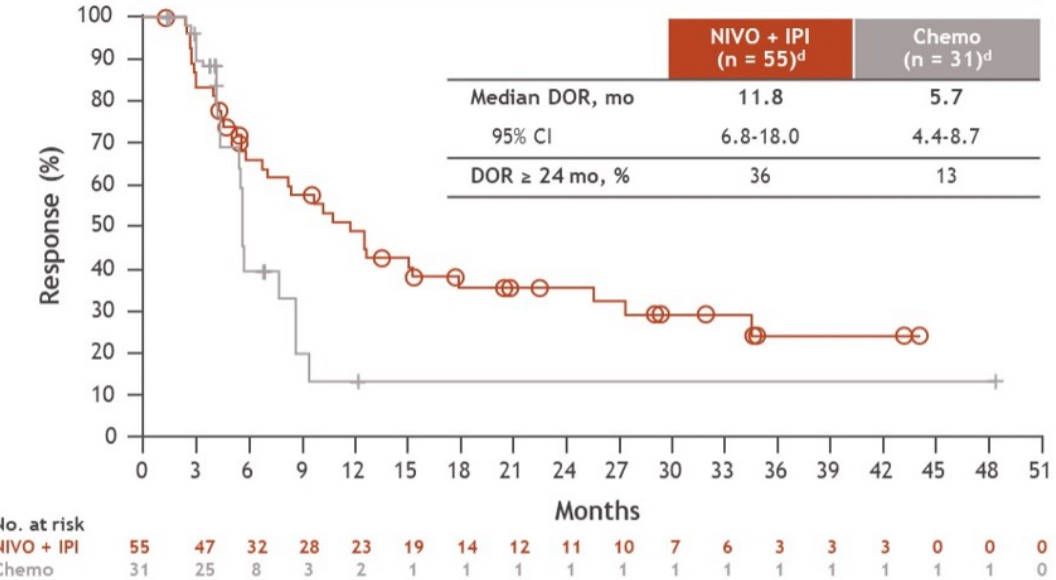
- Results across baseline PD-L1 status subgroups were generally consistent with those previously reported[1]
  - HRs were below 1 across all PD-L1 expression subgroups, favoring NIVO + IPI vs chemo
  - The largest magnitude of OS benefit was observed in patients with tumor cell PD-L1 ≥ 1%, with no further enrichment in higher tumor cell PD-L1 expression subgroups

Kato, GI ASCO 2023

ORR improved with ipi/nivo versus chemo

Tumor cell PD-L1 ≥ 1%

Response per BICR	NIVO + IPI (n = 158)	Chemo (n = 157)
ORR,[a] % (95% CI)	35 (27-43)	20 (14-27)
CR[b]	16	4
PR[b]	18	15
SD	27	46
PD	31	16

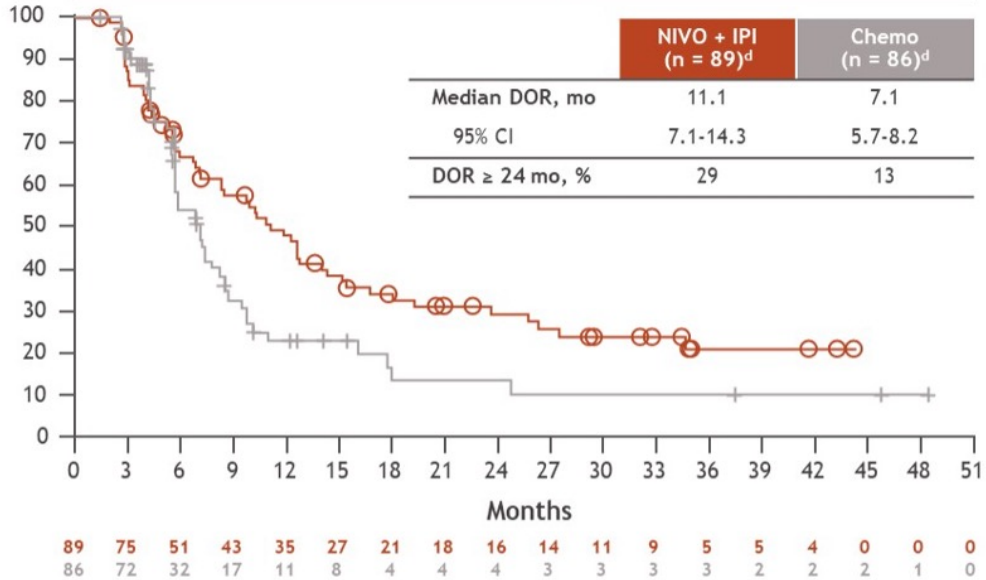


	NIVO + IPI (n = 55)[d]	Chemo (n = 31)[d]
Median DOR, mo	11.8	5.7
95% CI	6.8-18.0	4.4-8.7
DOR ≥ 24 mo, %	36	13

No. at risk																		
NIVO + IPI	55	47	32	28	23	19	14	12	11	10	7	6	3	3	3	0	0	0
Chemo	31	25	8	3	2	1	1	1	1	1	1	1	1	1	1	1	1	0

All randomized

Response per BICR	NIVO + IPI (n = 325)	Chemo (n = 324)
ORR,[c] % (95% CI)	27 (23-33)	27 (22-32)
CR	11	6
PR	16	21
SD	32	46
PD	32	12



	NIVO + IPI (n = 89)[d]	Chemo (n = 86)[d]
Median DOR, mo	11.1	7.1
95% CI	7.1-14.3	5.7-8.2
DOR ≥ 24 mo, %	29	13

NIVO + IPI	89	75	51	43	35	27	21	18	16	14	11	9	5	5	4	0	0	0
Chemo	86	72	32	17	11	8	4	4	4	3	3	3	3	2	2	2	1	0

- ORR remained higher in patients with tumor cell PD-L1 ≥ 1%, and responses remained more durable in patients with tumor cell PD-L1 ≥ 1% and all randomized patients with NIVO + IPI vs chemo with longer follow-up

[a]Unable to determine best overall response in patients with tumor cell PD-L1 ≥ 1%: NIVO + IPI, n = 11; chemo, n = 29; [b]Percentages may not add up to ORR due to rounding; [c]Unable to determine best overall response in all randomized patients: NIVO + IPI, n = 29; chemo, n = 50; [d]Number of responders.

Kato, GI ASCO 2023

TRAEs of immunologic etiology

All treated,[a-c] n (%)	NIVO + chemo (n = 310)		NIVO + IPI (n = 322)		Chemo (n = 304)	
	Any grade	Grade 3/4[d]	Any grade	Grade 3/4[d]	Any grade	Grade 3/4
Endocrine	38 (12)	5 (2)	88 (27)	19 (6)	1 (< 1)	0
Gastrointestinal	63 (20)	7 (2)	38 (12)	5 (2)	47 (15)	7 (2)
Hepatic	32 (10)	7 (2)	42 (13)	14 (4)	12 (4)	2 (< 1)
Pulmonary	19 (6)	2 (< 1)	28 (9)	10 (3)	1 (< 1)	0
Renal	73 (24)	8 (3)	8 (2)	2 (< 1)	57 (19)	5 (2)
Skin	55 (18)	1 (< 1)	111 (34)	13 (4)	12 (4)	0

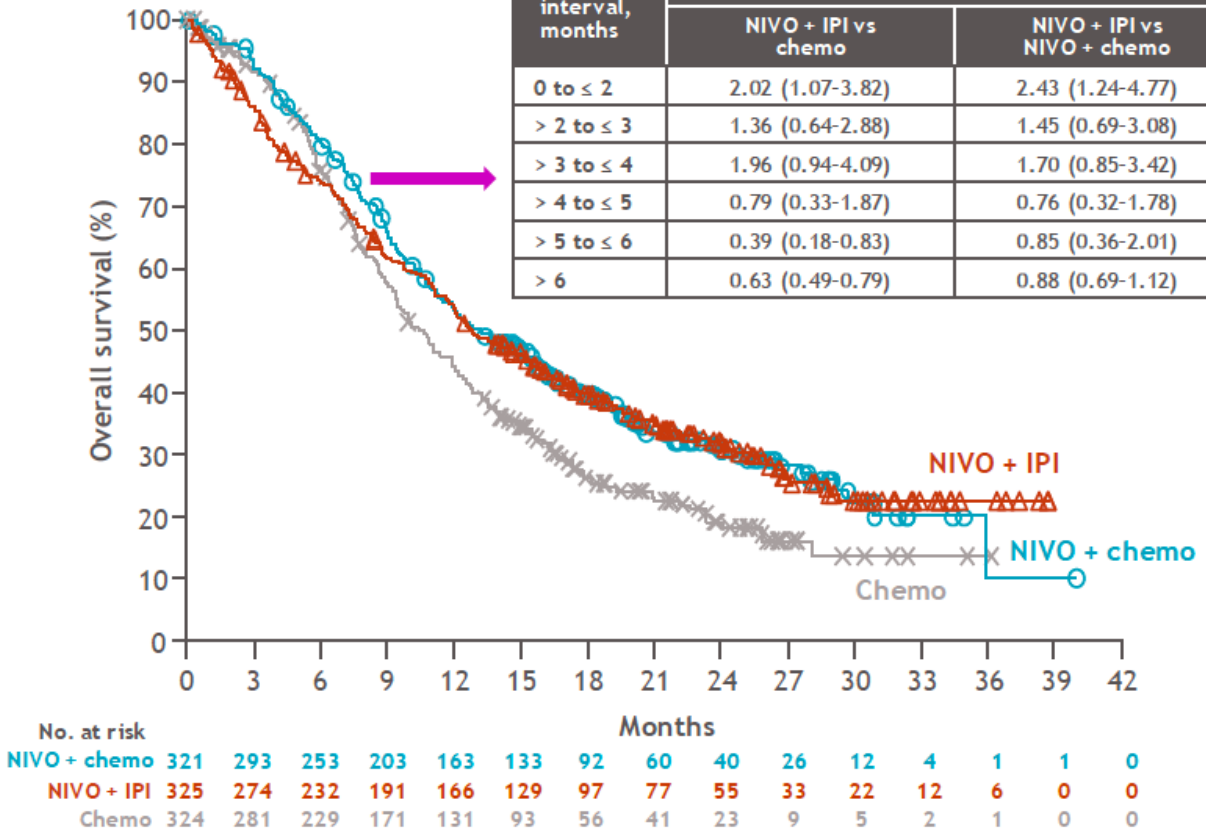
- The incidence of TRAEs with potential immunologic etiology was consistent with previously reported results[1]
  - The majority of events with potential immunologic etiology were grade 1 or 2
  - Grade 3/4 events occurred in ≤ 6% of patients across organ categories

Summary and questions for CM 648

- How to choose between 2 regimens?
  - Toxicity
  - Timing of response
  - Patient preference

Factors leading to delayed benefit of ipi/nivo

OS interval, months	Piecewise HRs of OS (95% CI)[a]	
	NIVO + IPI vs chemo	NIVO + IPI vs NIVO + chemo
0 to ≤ 2	2.02 (1.07-3.82)	2.43 (1.24-4.77)
> 2 to ≤ 3	1.36 (0.64-2.88)	1.45 (0.69-3.08)
> 3 to ≤ 4	1.96 (0.94-4.09)	1.70 (0.85-3.42)
> 4 to ≤ 5	0.79 (0.33-1.87)	0.76 (0.32-1.78)
> 5 to ≤ 6	0.39 (0.18-0.83)	0.85 (0.36-2.01)
> 6	0.63 (0.49-0.79)	0.88 (0.69-1.12)



Factors associated with delayed onset of effect of NIVO + IPI vs NIVO + chemo or chemo[b]
Age (< 65 yr)[c]
Weight (< 60 kg)[d]
Disease status at current diagnosis (de novo metastatic)[c]
Baseline neutrophil/lymphocyte ratio (< 4)[c]
Baseline tumor burden (≥ Q3)[c,e]
Liver metastasis (yes)[d]
Alcohol use (never/unknown)[c,d]

Chau, ESMO GI 2022

Article

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

https://doi.org/10.1038/s41586-021-04161-3

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Yelena Y. Janjigian[1]✉, Akihito Kawazoe[2], Patricio Yañez[3], Ning Li[4], Sara Lonardi[5], Oleksii Kolesnik[6], Olga Barajas[7], Yuxian Bai[8], Lin Shen[9], Yong Tang[10], Lucjan S. Wyrwicz[11], Jianming Xu[12], Kohei Shitara[2], Shukui Qin[13], Eric Van Cutsem[14], Josep Tabernero[15], Lie Li[16], Sukrut Shah[16], Pooja Bhagia[16] & Hyun Cheol Chung[17]

KEYNOTE-811: New 1L Therapy for HER2+ Gastric/GEJ Cancers

- Phase 3 Study of chemo+trastuzumab +/- pembrolizumab for HER2+ metastatic G/GEJ cancer.
  - CAPOX was chosen for 87.1%
- Primary Endpoints are PFS and OS.
- Secondary endpoints are ORR and DOR and safety.

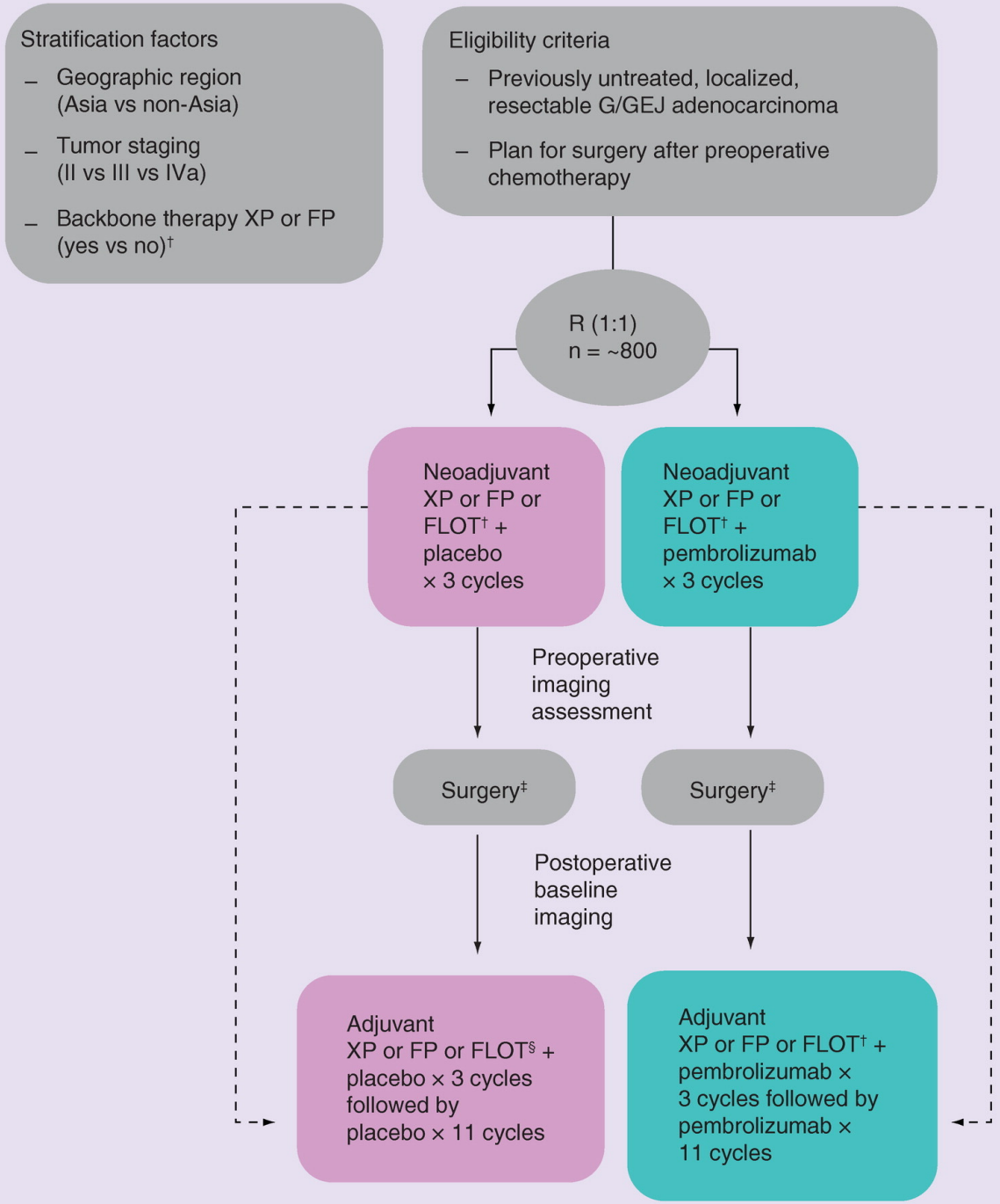
KEYNOTE-811 Interim Results

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

Janjigian, Nature 2021

KEYNOTE-811 Final Results

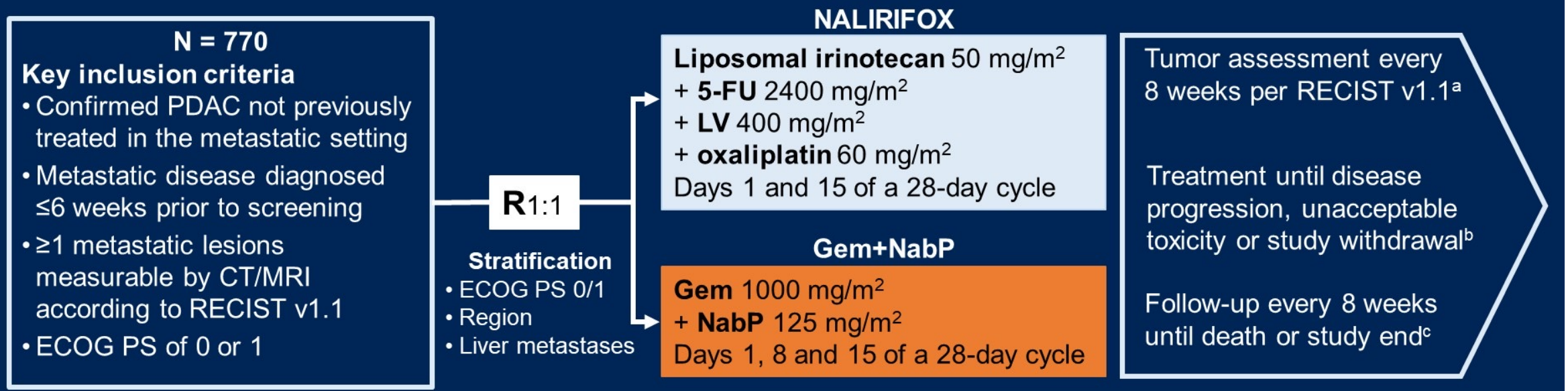
- Improvement in PFS, NOT OS was noted
  - Limited to PD-L1 CPS≥1 (more than 80% had tumors that were PD-L1+)
  - Await final presentation and see if FDA will amend current indication.



Update on KEYNOTE-585

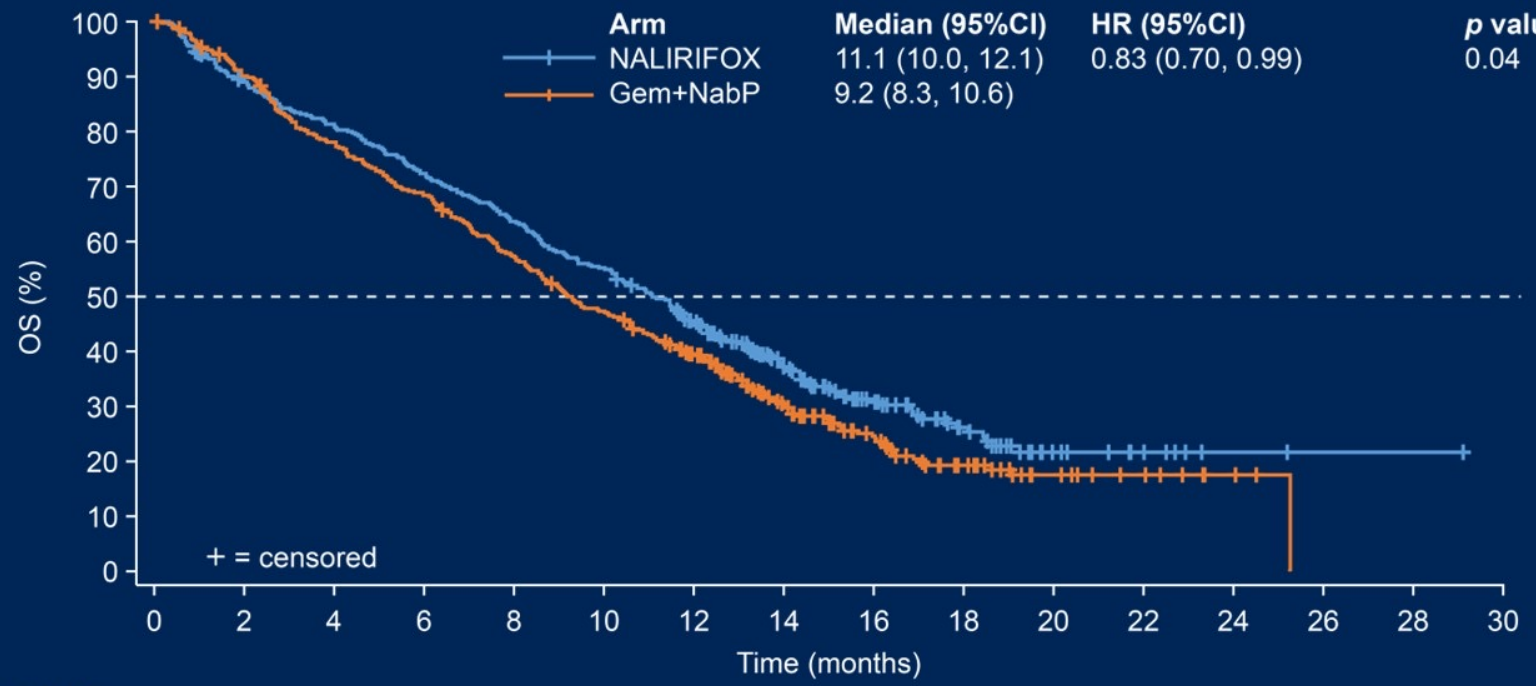
- Statistical improvement pathologic complete response (pCR)
- No improvement in Event Free Suvival

NAPOLI 3: Study design



[a]Tumor assessments (RECIST v1.1) were performed at baseline and every 8 weeks until radiologically progressive disease or until the start of another anti-cancer treatment, whichever came first. [b]Dose delays were permitted; if oxaliplatin was not well tolerated, patients in arm 1 could continue to receive liposomal irinotecan + 5-FU/LV. [c]The study will be completed once all patients have discontinued the study treatment and at least 543 OS events have occurred in randomized patients.
5-FU, 5-fluorouracil; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; Gem, gemcitabine; LV, leucovorin; MRI, magnetic resonance imaging; NabP, nab-paclitaxel; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors.

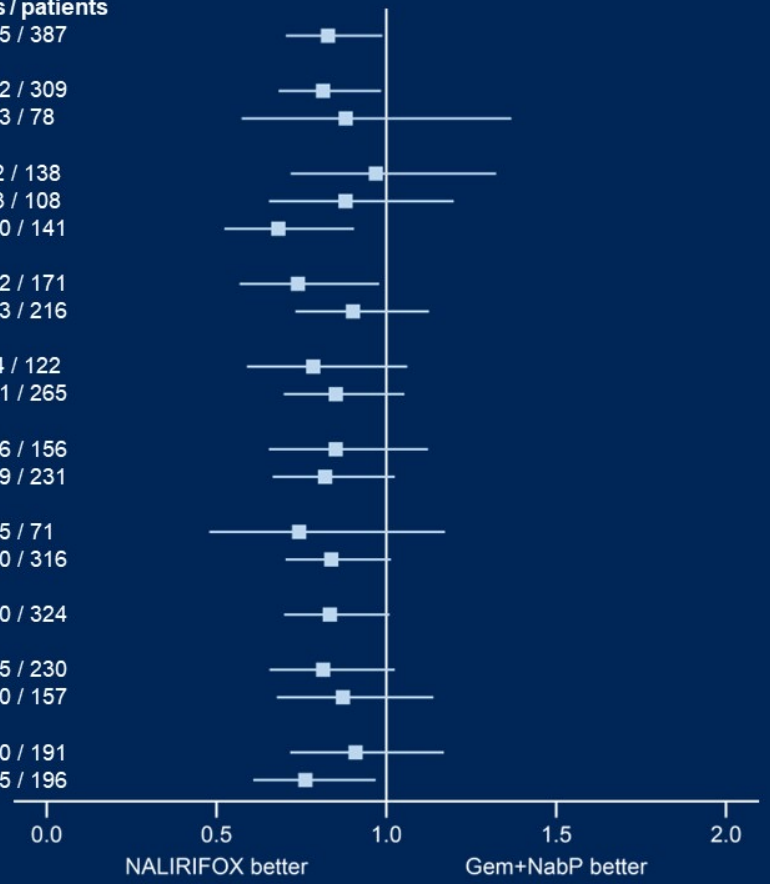
NAPOLI 3: mOS (ITT population)



Stratified by ECOG PS (0 vs 1), region (North America vs ROW), live metastases (yes vs no) per IRT. P boundary for efficacy claim *p* value < 0.048.
CI, confidence interval; Gem, gemcitabine; HR, hazard ratio; IRT, interactive response technology; ITT, intention-to-treat; mOS, median overall survival; NabP, nab-paclitaxel.

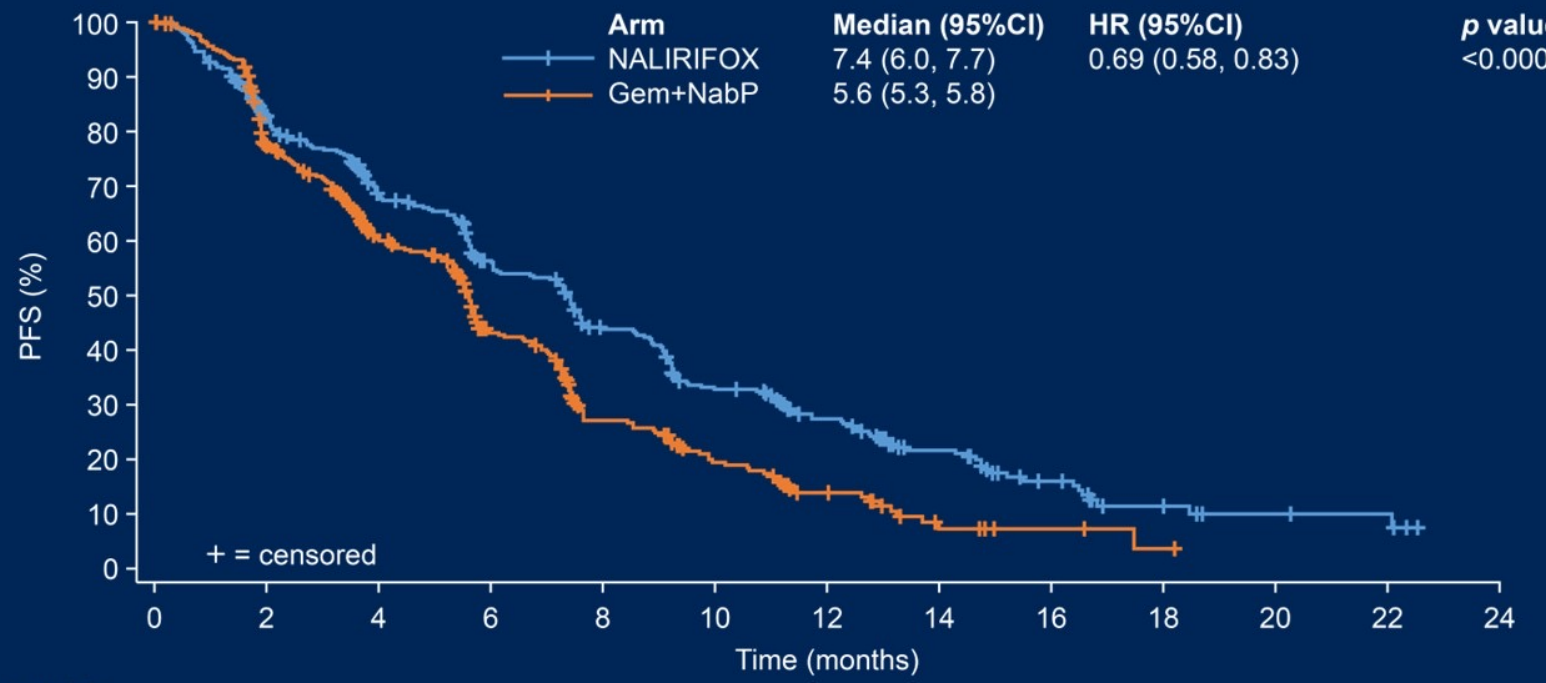
NAPOLI 3: OS subgroup analyses (ITT population)

Subgroup	NALIRIFOX, events / patients	Gem+NabP, events / patients	HR (95% CI)
Overall	259 / 383	285 / 387	0.83 (0.70, 0.99)
Presence of liver metastases at baseline			
Yes	220 / 309	242 / 309	0.82 (0.68, 0.98)
No	39 / 74	43 / 78	0.89 (0.57, 1.37)
Number of metastatic sites			
1	75 / 114	92 / 138	0.98 (0.72, 1.32)
2	87 / 120	83 / 108	0.89 (0.65, 1.20)
≥3	97 / 149	110 / 141	0.69 (0.52, 0.90)
Baseline ECOG performance status			
0	97 / 168	112 / 171	0.75 (0.57, 0.98)
1	162 / 215	173 / 216	0.91 (0.73, 1.13)
Region			
North America	85 / 120	94 / 122	0.79 (0.59, 1.06)
Rest of the world	174 / 263	191 / 265	0.86 (0.70, 1.05)
Main pancreatic tumor location			
Head	97 / 147	116 / 156	0.86 (0.65, 1.12)
Other	162 / 236	169 / 231	0.83 (0.67, 1.02)
Baseline CA 19-9			
<37 U/mL	34 / 60	45 / 71	0.75 (0.48, 1.17)
≥37 U/mL	223 / 321	240 / 316	0.84 (0.70, 1.01)
Race			
White	218 / 315	240 / 324	0.84 (0.70, 1.01)
Sex			
Male	139 / 204	175 / 230	0.82 (0.66, 1.02)
Female	120 / 179	110 / 157	0.88 (0.68, 1.14)
Age			
<65 years	127 / 193	130 / 191	0.92 (0.72, 1.17)
≥65 years	132 / 190	155 / 196	0.77 (0.61, 0.97)



CA 19-9, cancer antigen 19-9; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; Gem, gemcitabine; HR, hazard ratio; ITT, intention-to-treat; NabP, nab-paclitaxel; OS, overall survival.

NAPOLI 3: mPFS per investigator (ITT population)



Stratified by ECOG PS (0 vs 1), region (North America vs ROW), live metastases (yes vs no) per IRT. P boundary for efficacy claim *p* value < 0.048.
CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; Gem, gemcitabine; HR, hazard ratio; IRT, interactive response technology; ITT, intention-to-treat; mPFS, median progression-free survival; NabP, nab-paclitaxel; PFS, progression-free survival; ROW, rest of world.

NAPOLI 3: Tumor response[a]

	NALIRIFOX (N = 383)	Gem+NabP (N = 387)
Objective response rate (95% CI), %	41.8 (36.8–46.9)	36.2 (31.4–41.2)
Best overall response, %		
Complete response	0.3	0.3
Partial response	41.5	35.9
Stable disease	25.8	26.1
Progressive disease	9.9	14.5
Not evaluable[b]	22.5	23.3

[a]Stratified by ECOG PS (0 vs 1), region (North America vs ROW), liver metastases (yes vs no) per IRT. P boundary for efficacy claim *p* value < 0.048. [b]Included are 68 patients (17.8%) in the NALIRIFOX group and 64 (16.5%) in the Gem+NabP group who did not have an assessment after the baseline visit.
CI, confidence interval; Gem, gemcitabine; NabP, nab-paclitaxel.

NAPOLI 3: Selected any-cause TEAEs in ≥10% of patients

	NALIRIFOX (N = 370)		Gem+NabP (N = 379)	
Any-cause TEAEs in ≥10% of patients, %[a]	Any grade	Grade 3–4	Any Grade	Grade 3–4
Hematologic				
Neutropenia / neutrophil count decreased / febrile neutropenia	29.5 / 20.5 / 2.4	14.1 / 9.7 / 2.4	31.9 / 18.7 / 2.6	24.5 / 13.5 / 2.4
Anemia	26.2	10.5	40.4	17.4
Thrombocytopenia / platelet count decreased	13.5 / 10.5	0.8 / 0.8	22.7 / 17.9	3.7 / 2.4
Non-hematologic				
Diarrhea	70.5	20.3	36.7	4.5
Nausea	59.5	11.9	42.7	2.6
Vomiting	39.7	7.0	26.4	2.1
Hypokalemia	31.6	15.1	12.9	4.0
Peripheral neuropathy	17.8	3.2	17.4	5.8
Peripheral sensory neuropathy	15.1	3.5	13.5	2.9
Paresthesia	11.9	0.3	8.7	0.5
Pyrexia	10.5	0.8	23.0	1.6

[a]Grouped by system organ class (safety population).
Gem, gemcitabine; NabP, nab-paclitaxel; TEAE, treatment-emergent adverse event.

Slightly more diarrhea and slightly less neuropathy than FOLFIRINOX

School of Medicine
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Palliative targeted therapies

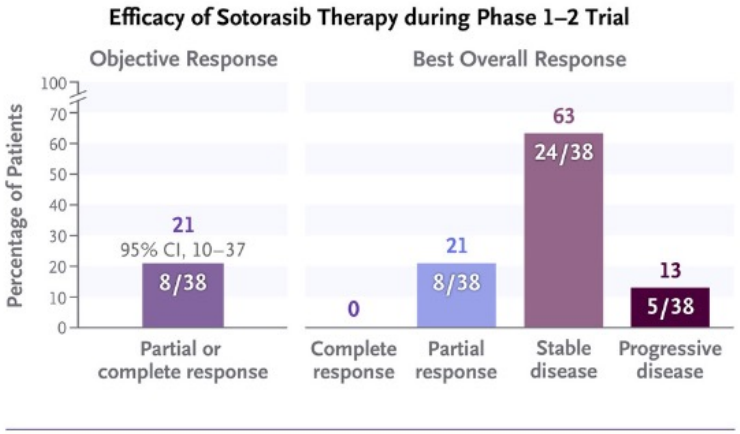
- Germline or somatic BRCA1/2 mutation: 4-7%
  - PARPi (if did not receive as maintenance therapy) – off label
  - Limited data: TAPUR study (N=30 with PDAC, treated with olaparib), ORR 4%, DCR 31%, mPFS 8 weeks[1]
  - Benefit further unknown with other HRD mutations
- MSI-H/dMMR: 1-2%
  - Pembrolizumab (tissue-agnostic approval). KN-158 (N=22 with MSI-H PDAC): ORR 18% (N=1 complete), mDOR 13.4 mo[2]
  - (MSS + TMB-H very rare in PDAC; no good evidence of pembro benefit)
- TRK-fusion: <1%
  - Larotrectinib or entrectinib (tissue-agnostic approval)
- BRAF V600E: <1%
  - Dabrafenib/trametinib (tissue-agnostic approval)
- KRAS G12C: 1-2% of KRAS MT (next slide)
  - Sotorasib (off-label)
  - Adagrasib (off-label)
- Clinical trials
- NGS for all metastatic PDAC

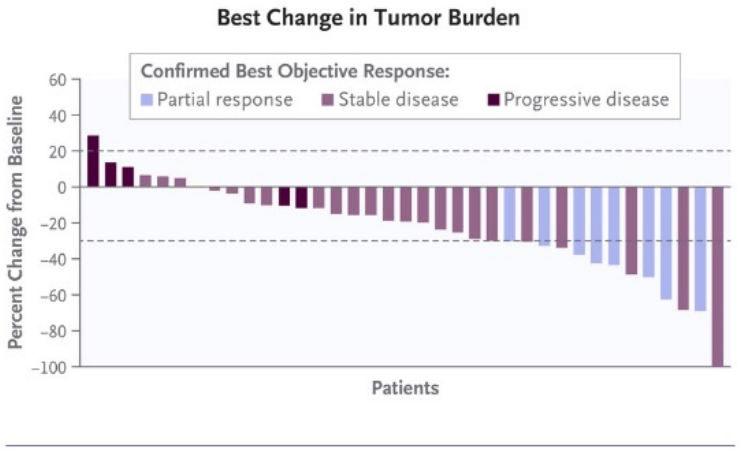
Courtesy of R. Lentz

1. Ahn et al. JCO. 2020.
2. Marabelle et al. JCO. 2020.
3. Strickler et al. ASCO Plenary abstract. 2022.

KRAS G12C

- Sotorasib (CodeBreak 100): N=38 with previously treated PDAC with KRAS G12C
  - mPFS: 4 mo; mOS: 6.9 mo

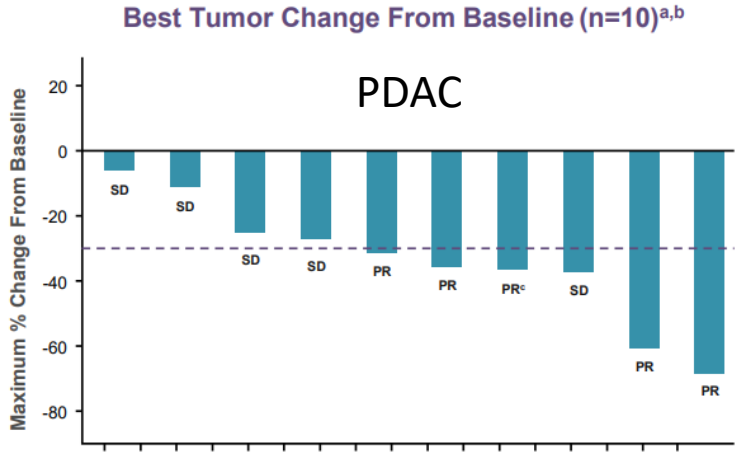




KRYSTAL-1: Updated activity and safety of adagrasib (MRTX849) in patients (Pts) with unresectable or metastatic pancreatic cancer (PDAC) and other gastrointestinal (GI) tumors harboring a $KRAS^{G12C}$ mutation.

- N=30 with non-CRC GI cancers (N=12 PDAC)

Efficacy outcome[b], n (%)	PDAC (n=10)[c]	Other GI cancers (n=17)[d]	Overall GI cancers[a] (n=27)[c,d]
Objective response rate	5 **(50)**[e]	6 **(35)**[f]	11 **(41)**[g]
Best overall response			
Complete response (CR)	0 (0)	0 (0)	0 (0)
Partial response (PR)	5 (50)[e]	6 (35)[f]	11 (41)[g]
Stable disease (SD)	5 (50)	11 (65)	16 (59)
Disease control rate	10 **(100)**	17 **(100)**	27 **(100)**



Courtesy of R. Lentz

1. Strickler et al. NEJM. 2023
2. Bekaii-Saab et al. GI ASCO Abstract. 2022.

Conclusions

- Esophageal Cancer
  - CLDN18.2 is a new biomarker and is awaiting FDA approval for 1L therapy with doublet chemotherapy
  - Doublet chemotherapy+nivolumab and ipilimumab/nivolumab are new 1L options in ESCC
  - For HER2 space, adding pembrolizumab to 1L therapy should be considered but without an OS benefit, need to weigh benefits versus risk
  - Peri-op chemo+IO for GEJ cancers does not result in improved event free survival
- Pancreatic Cancer
  - NAPOLI-3 (NALIRIFOX > gemcitabine/abraxane)
    - Unclear if NALIRIFOX > mFOLFIRINOX
  - Targeting KRAS is now a reality with promising results