City of Hope®

Multidisciplinary Approaches to Cancer Symposium

Systemic Therapy for Gastroesophageal Cancer

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City of Hope

Disclosures

- I do not have any relevant financial relationships.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon must contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

XXX

XXXX

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

Locally advanced resectable :CRT vs. Perioperative chemotherapy

Current Treatment of resectable Esophageal Adenocarcinoma (EAC)

cT1<sm1, cN0: Endoscopic resection alone

cT1b/2, cN0: Surgery alone

cT2-4a, cN+/-: Neoadjuvant chemoradiation plus surgery

cT2-4a, cN+/-:

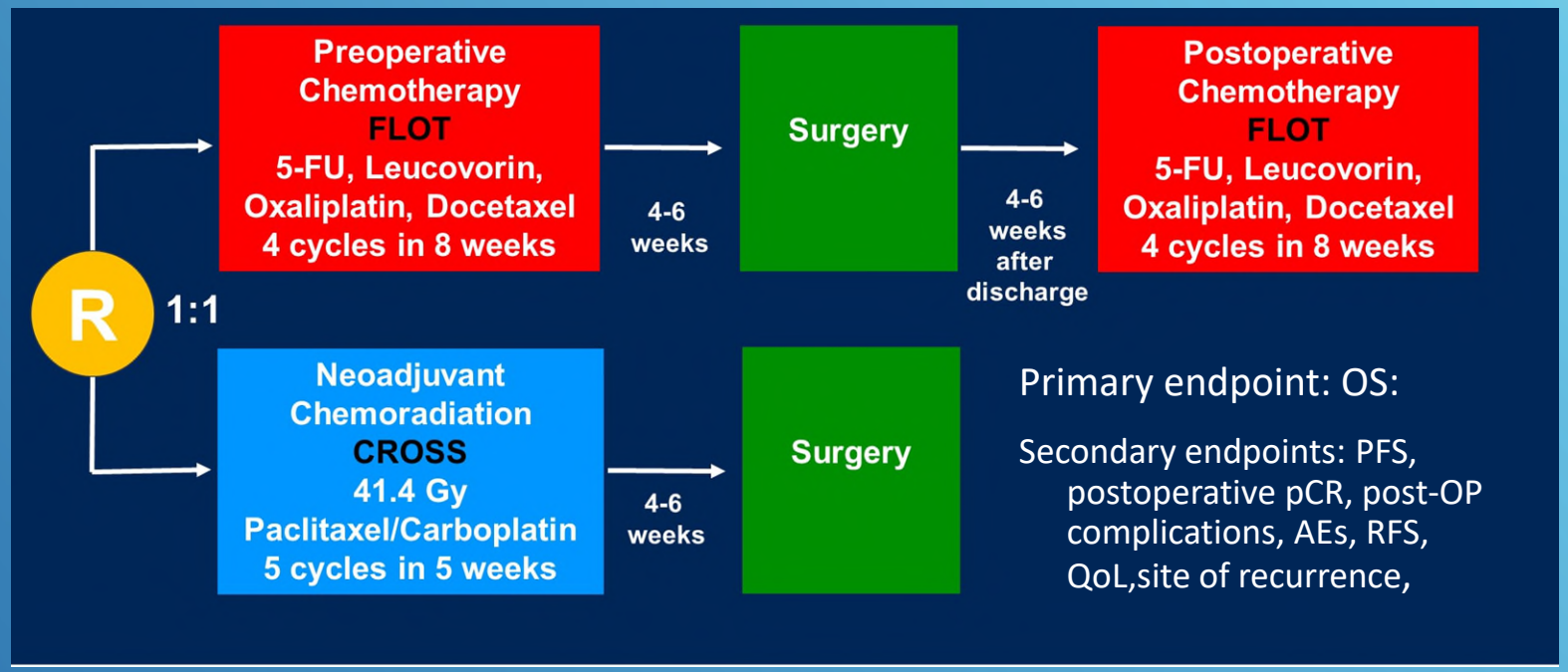
CROSS regimen: Local control

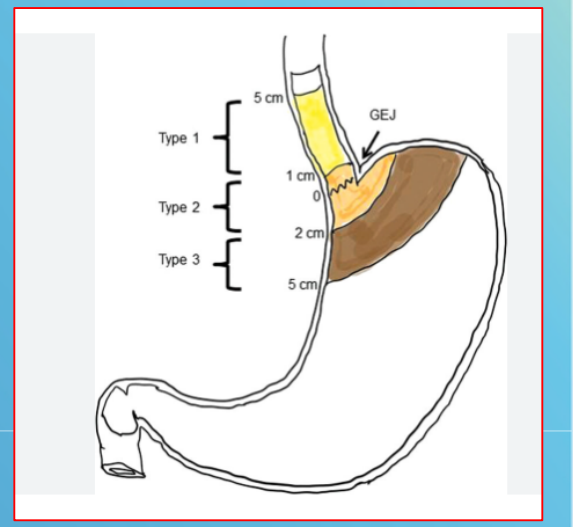
Perioperative Chemo: Systemic control given the high rate of systemic spread, early intervention for subclinical micrometastases

ESOPEC: Perioperative chemotherapy (FLOT) offers an OS and PFS advantage compared to the neoadjuvant chemoradiation approach (CROSS), along with an improved pathological complete response rate

TOPGEAR: Adding preoperative chemoradiotherapy to perioperative chemotherapy doubled pCR rates increased tumour downstaging in patients with resectable gastric and GEJ adenocarcinoma, but did not improve OS or PFS

ESOPEC Trial Scheme





41.4GY; CROSS trial had surgery at 6 to 8 weeks post chemoradiation.

Characteristics of ESOPEC Trial Patients

Parameter	FLOT Group	CROSS Group
Age mean (SD) in years	63.1 (8.6)	62.6 (9.8)
Sex male	89.1%	89.4%
ECOG > 0	26.7%	28.1%
cT1-2	19.5%	17.1%
cT3-4	79.1%	81.9%
cN0	22.2%	18.4%
cN+	77.8%	81.6%

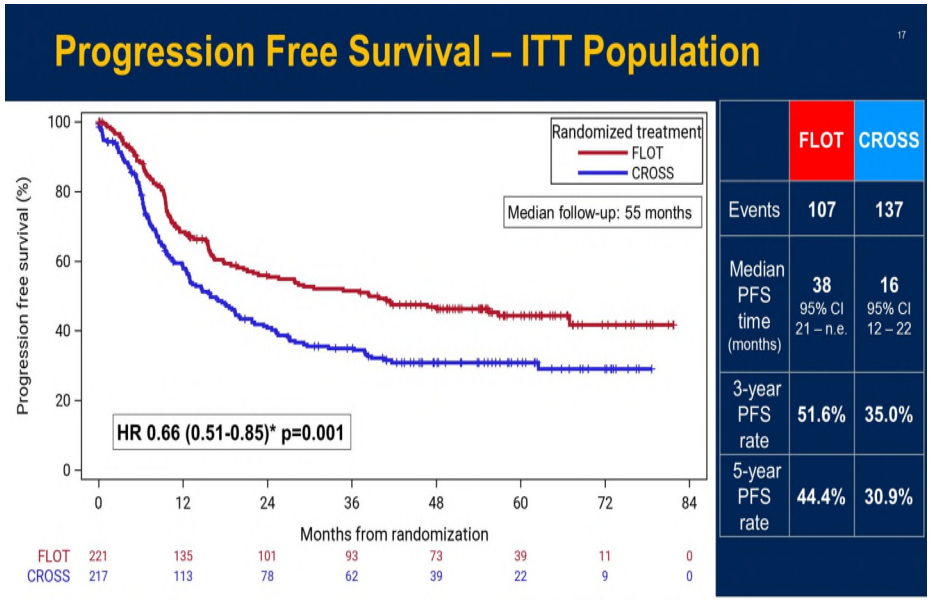
Metric	FLOT Group (%)	CROSS Group (%)
Started neoadjuvant treatment (PP population*)	93.7 %	90.3 %
Completed neoadjuvant treatment	87.3 %	67.7 %
Received neoadjuvant treatment plus surgery	86.0 %	82.9 %
Received adjuvant treatment	63.3 %	-
Completed adjuvant treatment	52.5 %	-

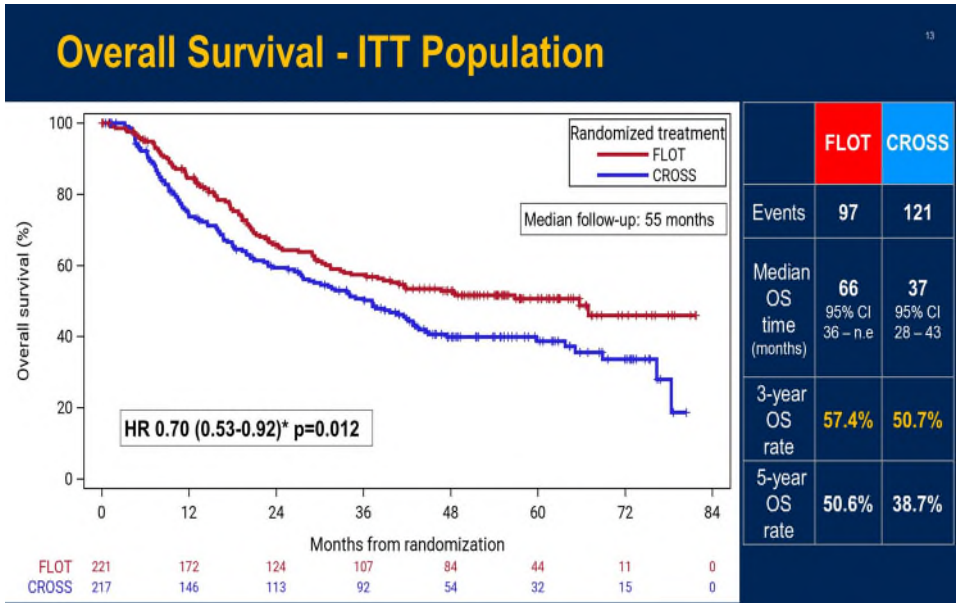
More than 80% had clinical T3 or T4 tumors at pre-treatment staging

Approximately 80% had clinical positive locoregional lymph nodes

Protocol: allows dose adjust or G-CSF on non radiation days?
The completion rate of neoadjuvant treatment was 87.3% in FLOT and 67% in CROSS. However, in this group, 98% completed the 41.4 gray radiotherapy

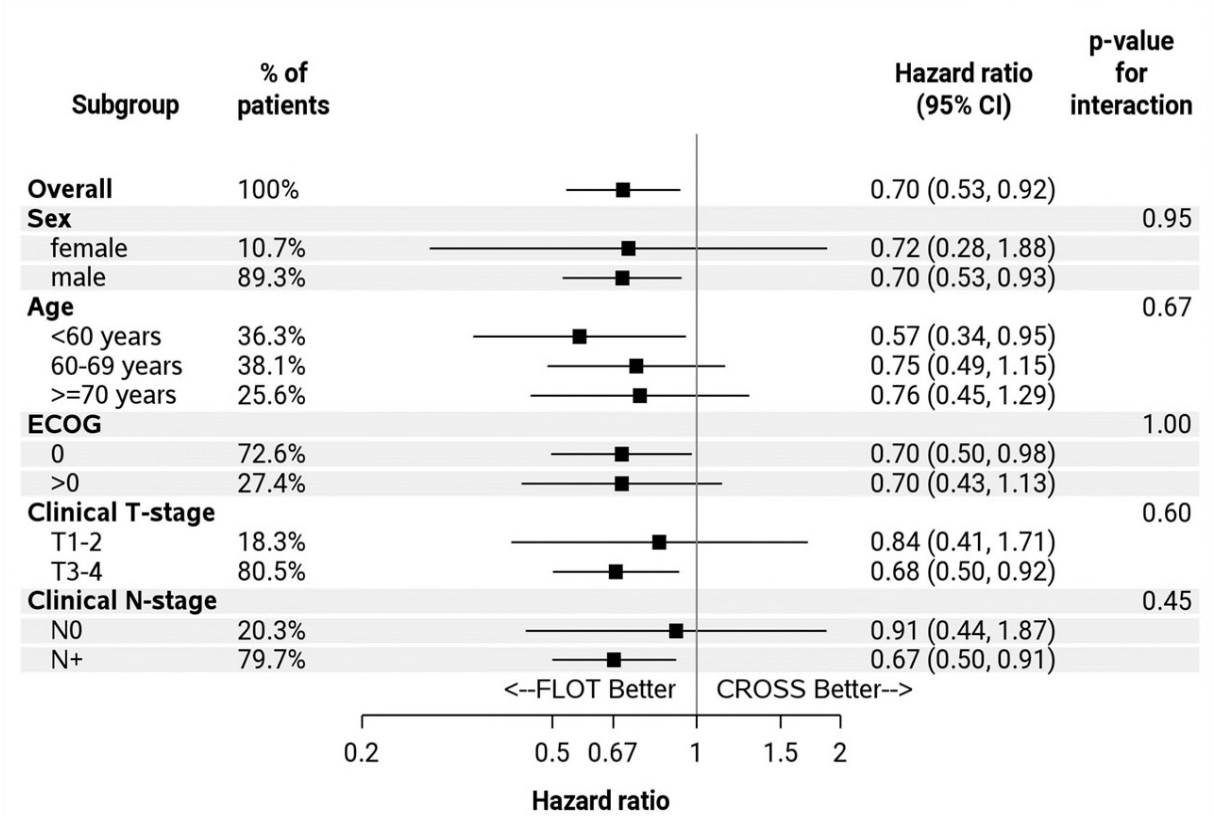
PFS and OS - ITT Population





ITT: Based on time of randomization regardless of crossover or drop out
PP: According to protocol plan and statistical analysis

Overall Survival in Exploratory Subgroups Surgical Complications



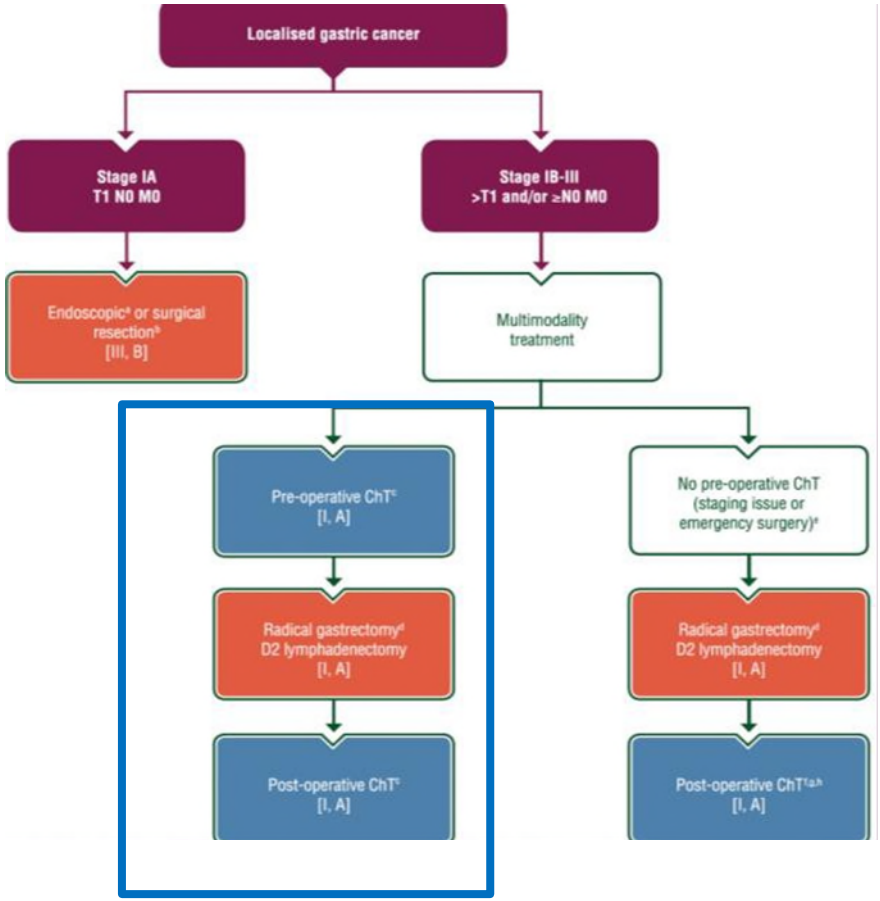
Postoperative Complications – Surgery Population [19]

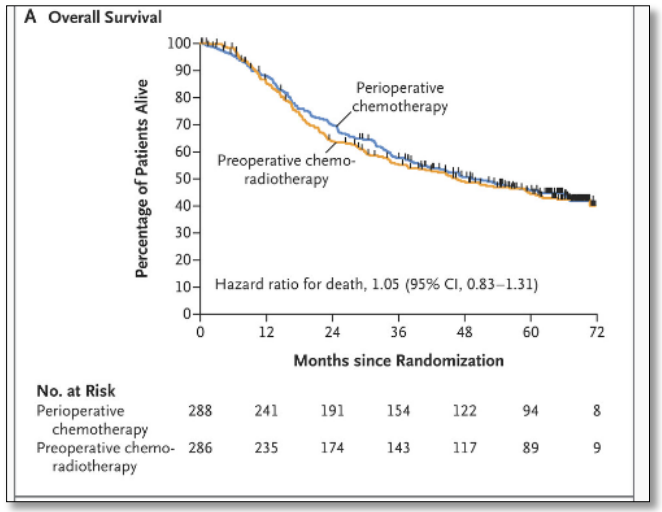
	FLOT Group	CROSS Group
N	191	180
Postoperative morbidity		
Clavien Dindo I	20.9%	20.0%
Clavien Dindo II	13.6%	15.0%
Clavien Dindo III	23.0%	23.3%
Clavien Dindo IV	6.8%	4.4%
Postoperative mortality		
30-days	1.0%	1.7%
90-days	3.2%	5.6%

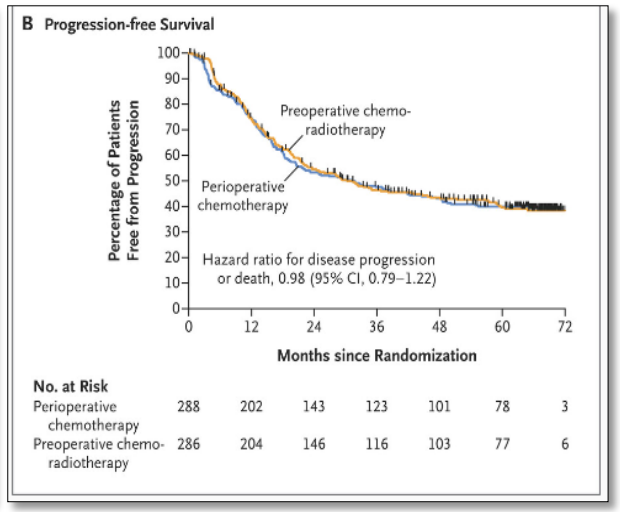
- Younger, or node positive pts benefit from FLOT; *For patients above 60 and 70 years, the hazard ratio crosses 1*
-
- Per NCDB, 52% EAC >65 y.o in US

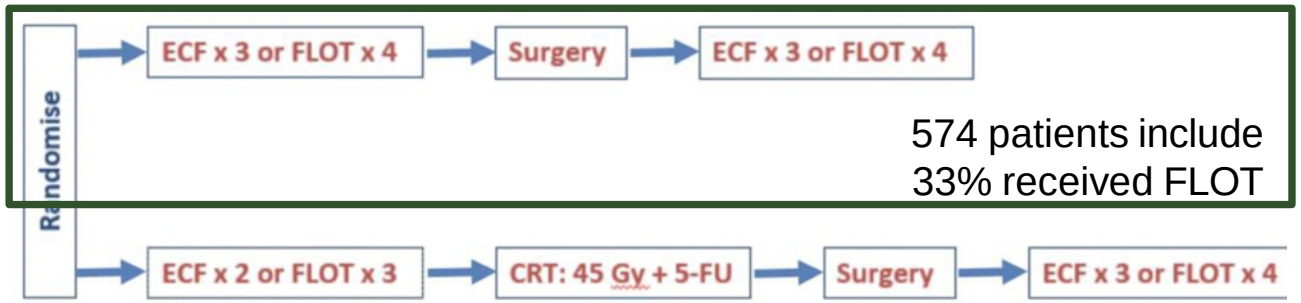
TOPGEAR: First phase III RCT testing complimentary CRT in perioperative treatment:

not a study to test FLOT vs chemoradiotherapy…





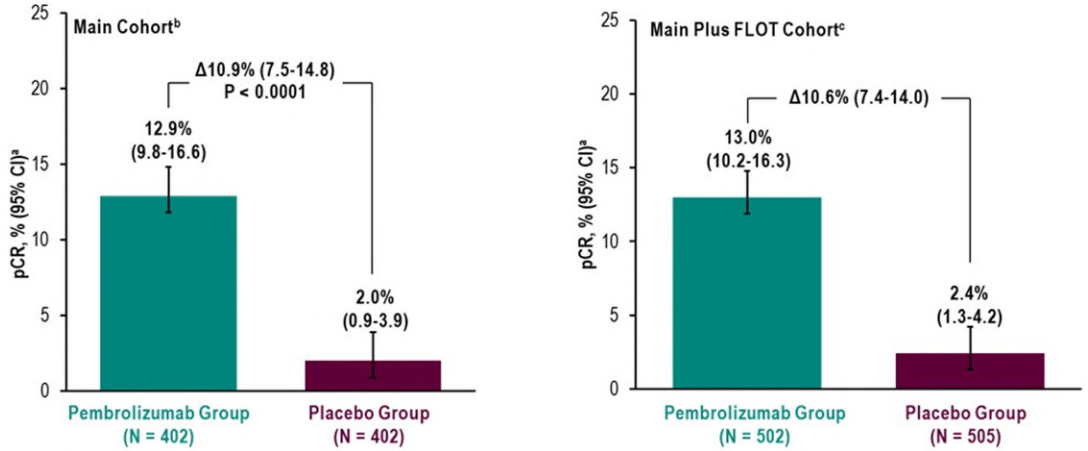




The addition of preoperative CRT to perioperative CT did not improve OS as compared with perioperative CT alone among patients with resectable GC and GEJ.

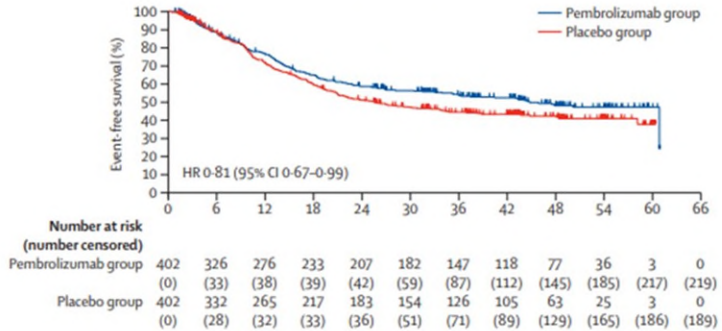
KEYNOTE 585: Phase 3 Study of Chemotherapy + Pembrolizumab vs. Chemotherapy + Placebo in G/GEJ adenocarcinoma

Improvement in pathologic complete response rates did not translate into improved EFS or OS.



Shitara et al, Lancet Oncol 2024 Feb;25(2):212-224

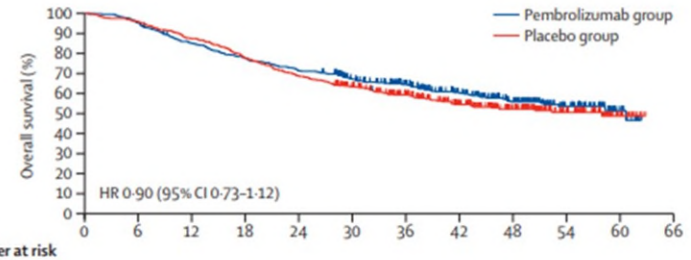
Event-Free Survival (Main Cohort)



Number at risk (number censored)												
Pembrolizumab group	402	326	276	233	207	182	147	118	77	36	3	0
	(0)	(33)	(38)	(39)	(42)	(59)	(87)	(112)	(145)	(185)	(217)	(219)
Placebo group	402	332	265	217	183	154	126	105	63	25	3	0
	(0)	(28)	(32)	(33)	(36)	(51)	(71)	(89)	(129)	(165)	(186)	(189)

44.4 vs 25.3 months; the *P* value did not meet the threshold for statistical significance (*P* = .0178)

Overall Survival (Main Cohort)



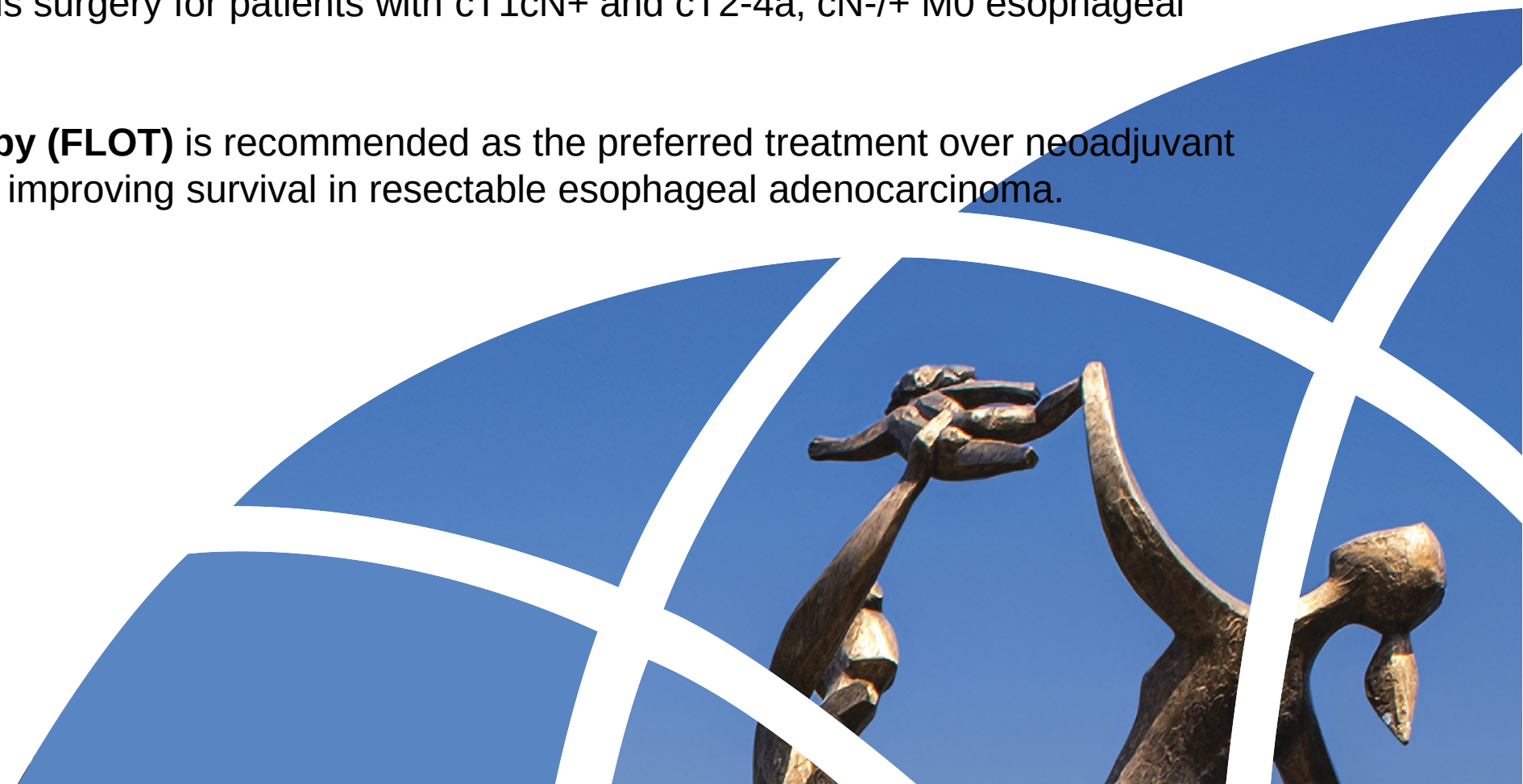
Number at risk (number censored)												
Pembrolizumab group	402	383	339	310	285	250	211	160	117	60	14	0
	(0)	(1)	(4)	(4)	(4)	(25)	(54)	(93)	(125)	(179)	(224)	(237)
Placebo group	402	386	352	313	278	242	197	147	96	49	13	0
	(0)	(0)	(0)	(0)	(0)	(15)	(45)	(81)	(127)	(172)	(207)	(220)

- Addition of pembrolizumab to perioperative chemotherapy in patients with resectable GA and GEJ. In this study, improvement in pCR did not translate into improved OS and EFS.
- Look at different markers of response when evaluating pathological specimens. We have seen from prior analyses of MAGIC trial OE05 and ST03 trial that tumor LN downstaging was the only independent predictor of survival, rather than tumor regression grade/ pathologic response.

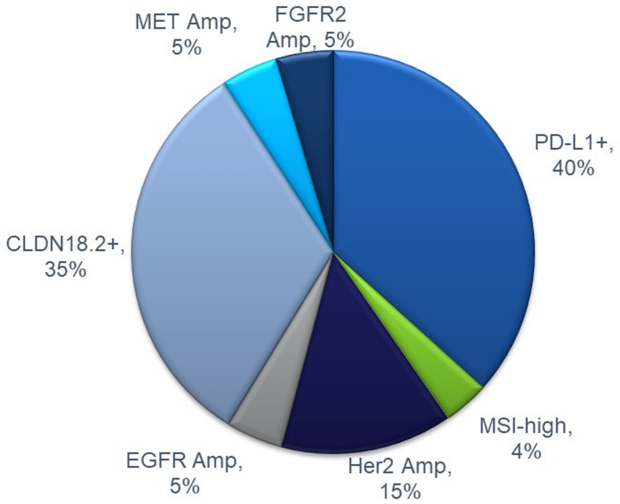
Take Home Messages

•**Perioperative chemotherapy (FLOT) plus surgery** improves overall survival compared to neoadjuvant chemoradiation (CROSS) plus surgery for patients with cT1cN+ and cT2-4a, cN-/+ M0 esophageal adenocarcinoma.

•**Perioperative chemotherapy (FLOT)** is recommended as the preferred treatment over neoadjuvant chemoradiation (CROSS) for improving survival in resectable esophageal adenocarcinoma.



Systemic Therapies Drive Improvement in Gastroesophageal Cancers



KEY MARKERS IN ADVANCED DISEASE

- **HER2** positive – 15%-20% of patients, improved survival with non-chemo antibody trastuzumab
- **MSI** high – 3%-5% of patients, high response rates to immunotherapies
- **PD-L1** positive – 30%-50% of patients, identifies those more likely to benefit from immune therapies, likely gradation within PD-L1+
- **CLDN18.2** high – 30%-35% of patients, response predictor for zolbetuximab

INVESTIGATIONAL BIOMARKERS

- **FGFR2** amp – 5%-10% of patients, multiple trials of inhibitors
- **FGFR2** high- May be up to 30% of HER2 negative
- **EGFR** amp – 5%-7%, may predict response to EGFR drugs like cetuximab

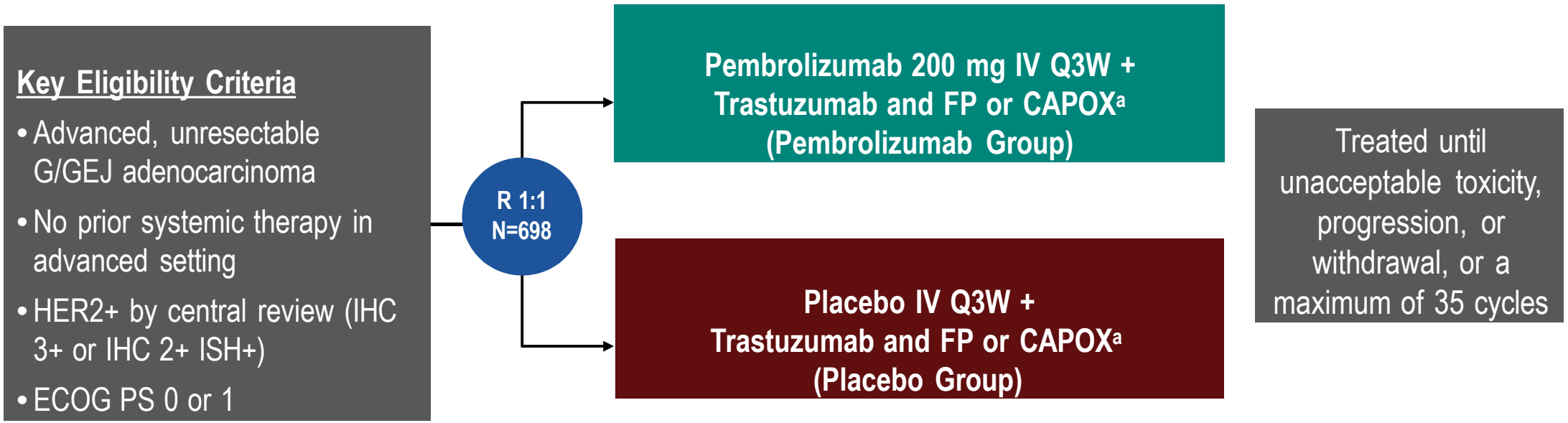
First-Line Systemic Treatment	Biomarker	mOS
Nivolumab + Chemotherapy Checkmate 649	PDL1 CPS ≥ 5	**14.4 mo**
Pembrolizumab + Chemotherapy KEYNOTE 859	PDL1 CPS ≥ 1	**13 mo**
Pembrolizumab + Chemotherapy + Trastuzumab KEYNOTE 811	PDL1 CPS ≥ 1 HER2 +	**20 mo**
Zolbetuximab + Chemotherapy SPOTLIGHT	CLDN 18.2	**19.2 mo**
Bemarituzumab + Chemotherapy FIGHT	FGFR2b	**18.2 mo**

- **The ARMANI Trial:** Ramucirumab & paclitaxel switch maintenance prolonged survival, but increased toxicities. Applicability of this approach in the era of biomarker-based therapies is uncertain.

- **UPDATE on KN811 :** At final analysis, OS was significantly improved with pembro + SOC (median 20.0 vs 16.8 mo). In pts with PD-L1 CPS ≥1, median OS was 20.1 vs 15.7 mo (HR 0.79; 95% CI, 0.66-0.95). ORR was 72.6% vs 60.1%

- **SPOTLIGHT/GLOW studies:** Biomarker driven therapy in front line

Phase 3 Randomized, Placebo-Controlled Study of First-Line Pembrolizumab Plus Chemotherapy and Trastuzumab Versus Placebo in HER2+ G/GEJ Cancer (NCT03615326)

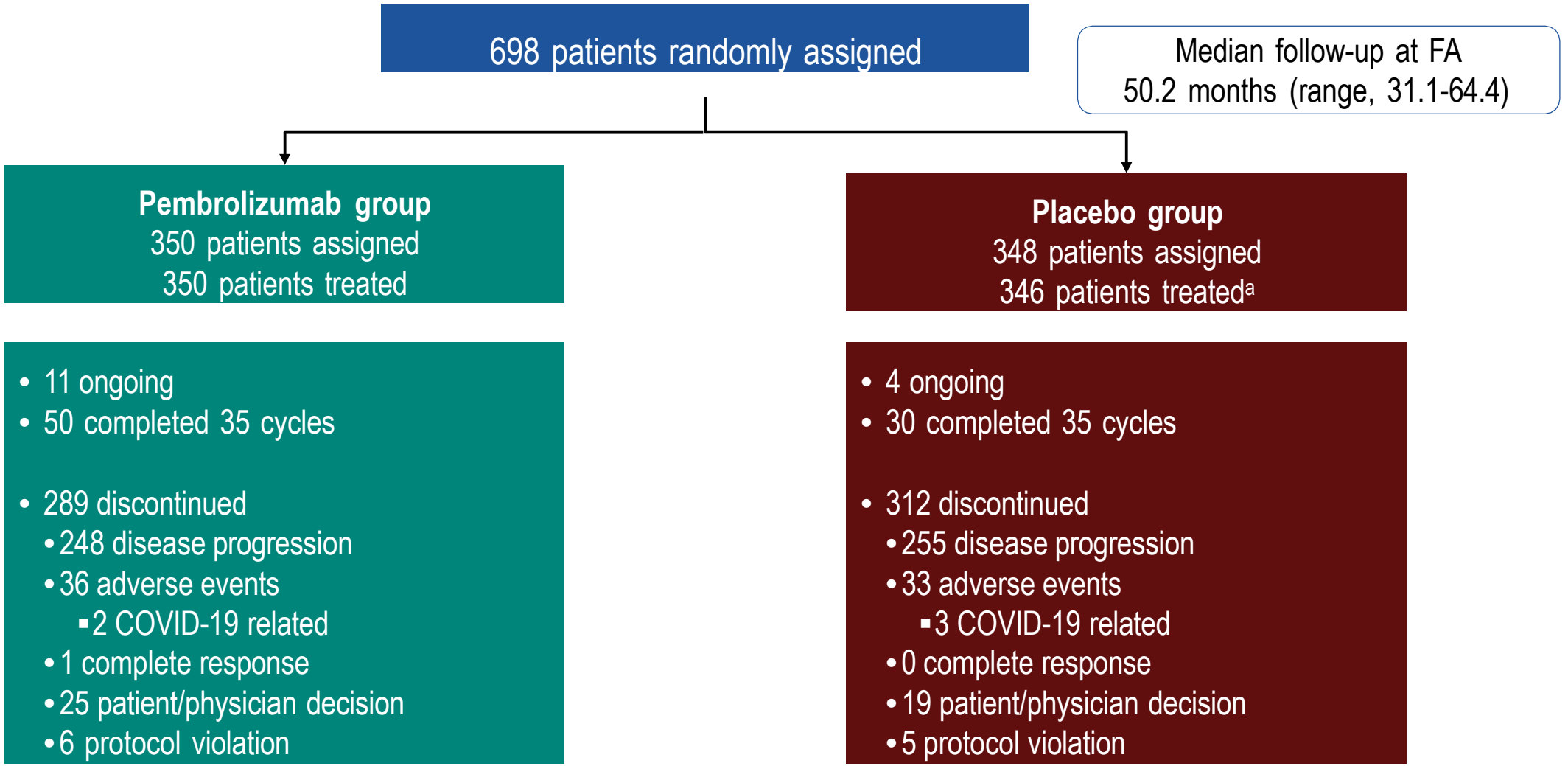


Stratification factors
- Geographic region
- PD-L1 status (CPS <1 vs CPS ≥1)
- Chemotherapy choice

Endpoints:
- Dual primary: OS, PFS
- Key secondary: ORR, DOR, safety

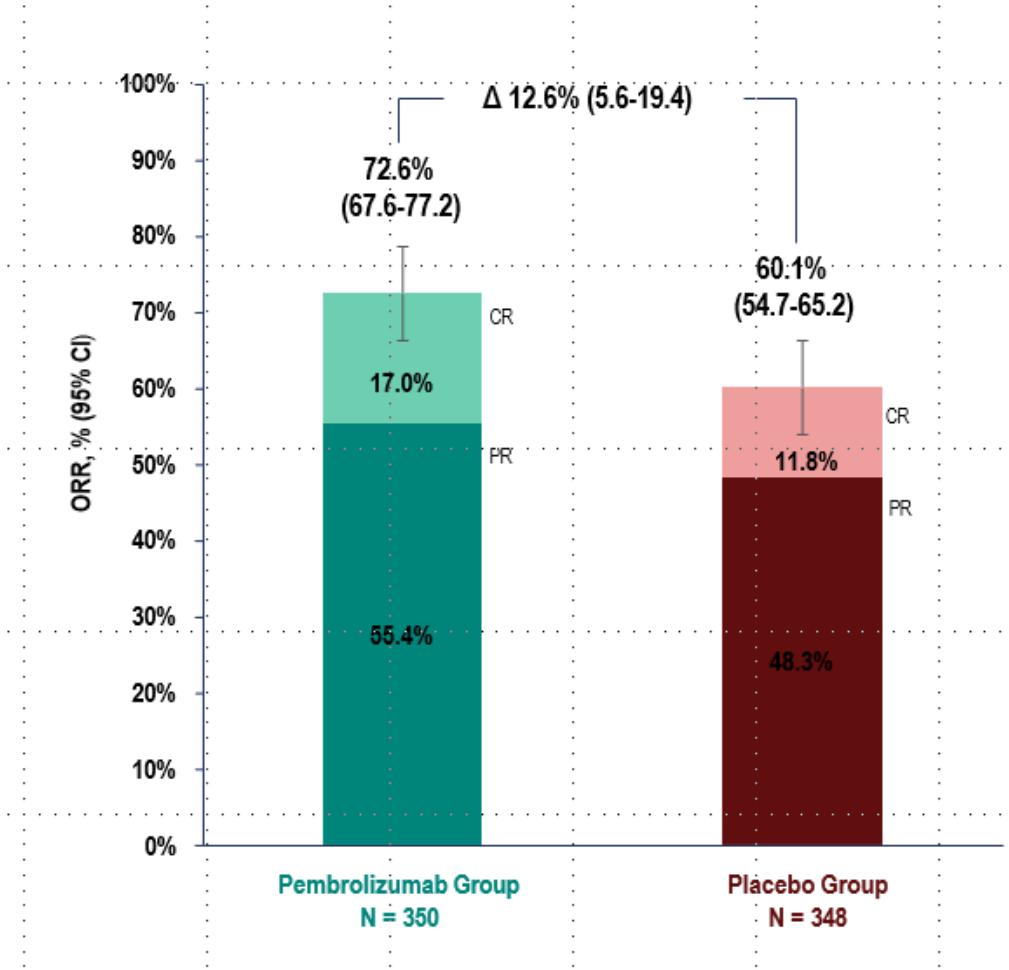
[a]Trastuzumab: 6 mg/kg IV Q3W following an 8 mg/kg loading dose. FP: 5-fluorouracil 800 mg/m^2 IV on D1-5 Q3W + cisplatin 80 mg/m^2 IV Q3W. CAPOX: capecitabine 1000 mg/m^2 BID on D1-14 Q3W + oxaliplatin 130 mg/m^2 IV Q3W. PFS, ORR, DOR per RECIST by BICR.

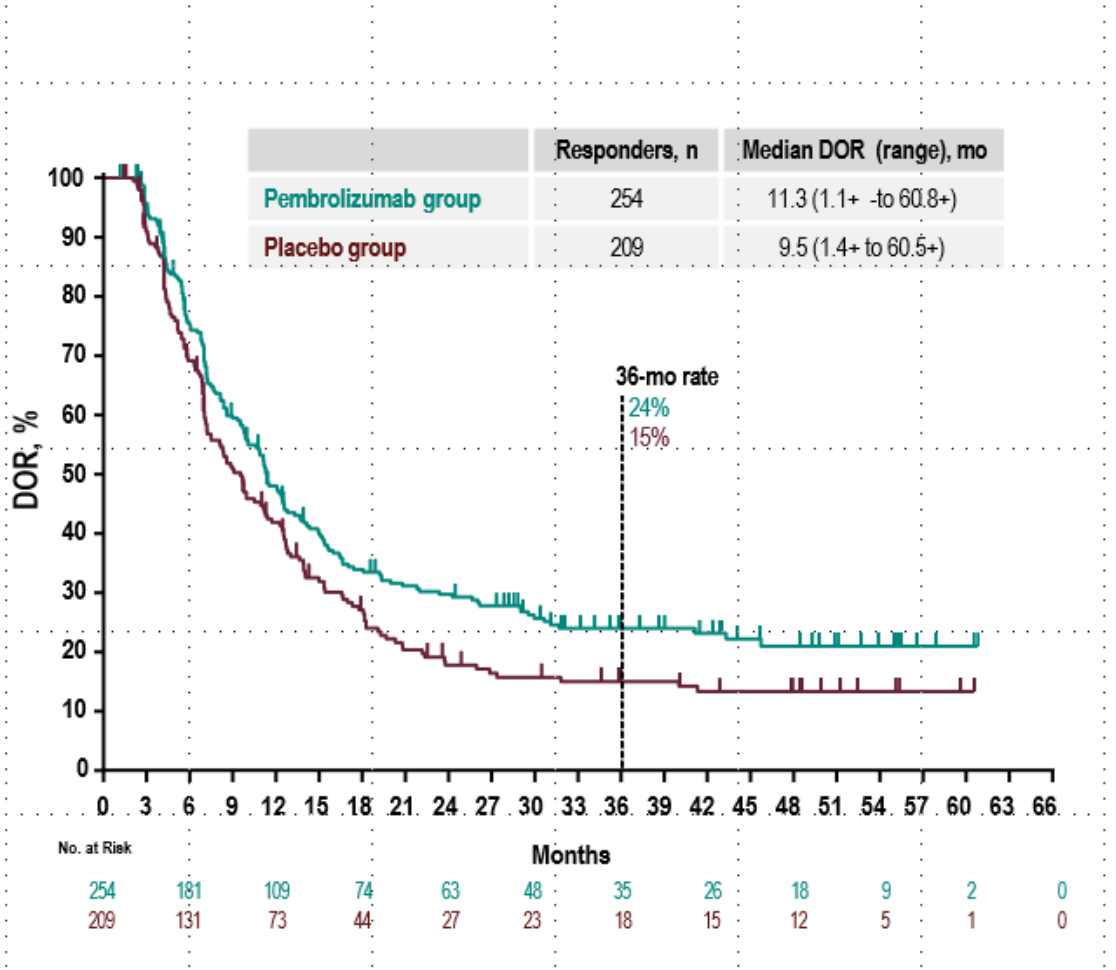
Treatment Disposition



Data cutoff date: 20 Mar 2024. Follow-up defined as time from randomization to data cut-off. [a]Two patients in the placebo arm were randomized but did not receive treatment due to rapid decline and death (n = 1) and withdrawal of consent (n = 1).

Summary of Antitumor Response at Final Analysis (ITT)



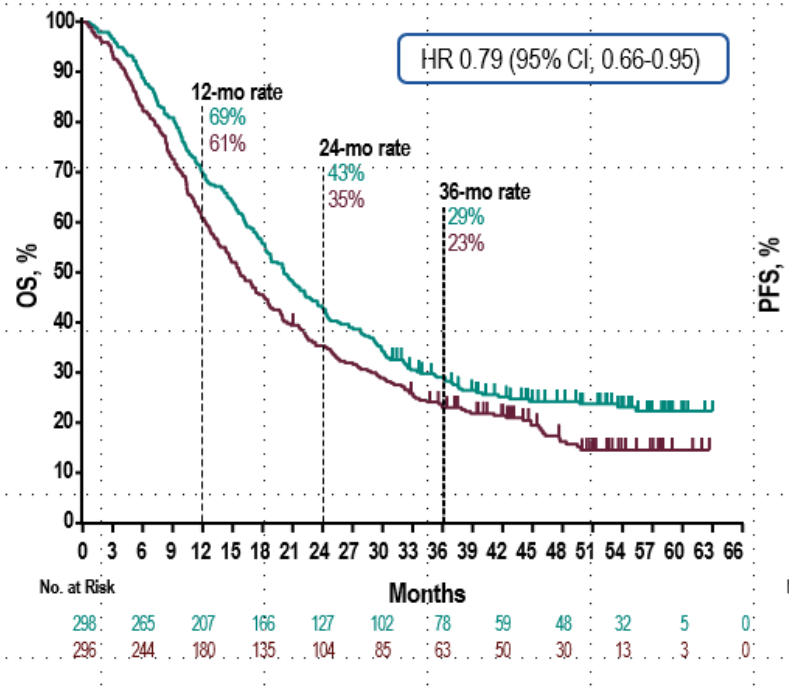


After a median follow-up of 50.2 months (Range, 31.1-64.4), the median OS was 20.0 months (95% CI, 17.8-22.1) in the pembrolizumab arm compared with 16.8 months (95% CI, 14.9-18.7) in the control arm (HR, 0.80; 95% CI, 0.67-0.94; P = .004). The 36-month OS rate was also higher with pembrolizumab (28%) than with the control arm (23%).

Antitumor Activity in CPS ≥1 Subgroup at Final Analysis

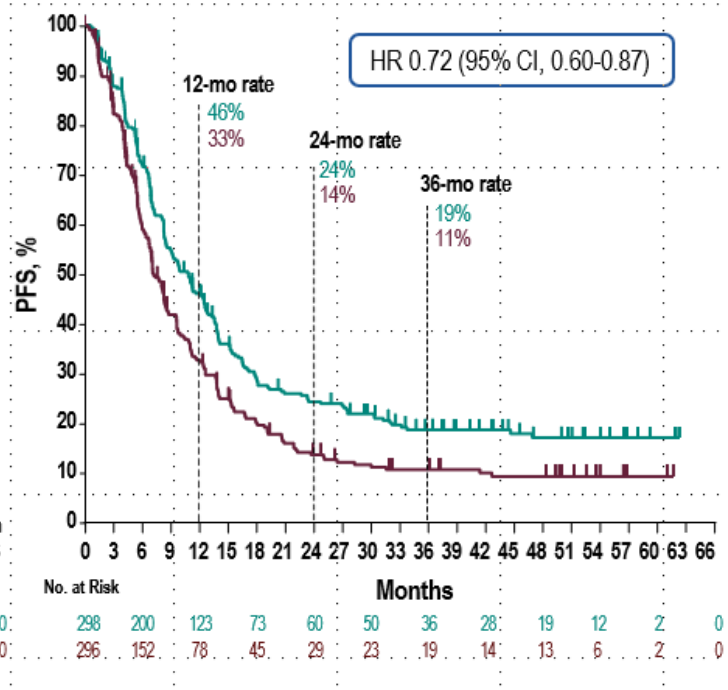
OS

	Events, n (%)	Median (95% CI), mo
Pembrolizumab group	226 (76%)	20.1 (17.9-22.9)
Placebo group	244 (82%)	15.7 (13.5-18.5)



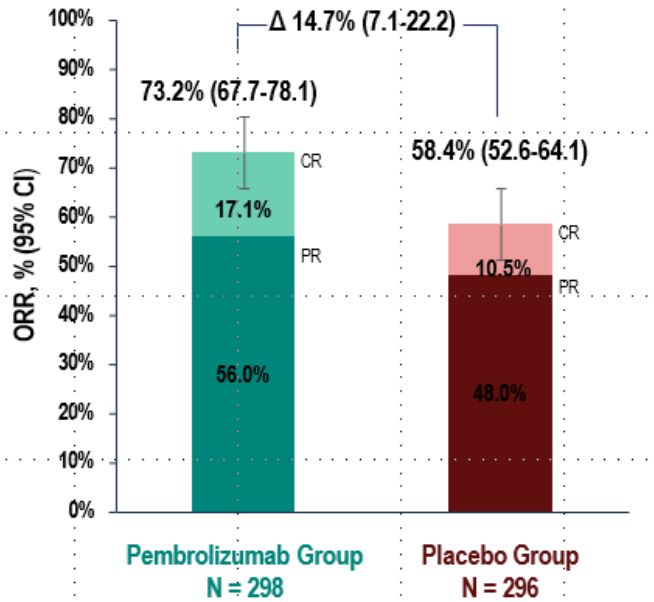
PFS

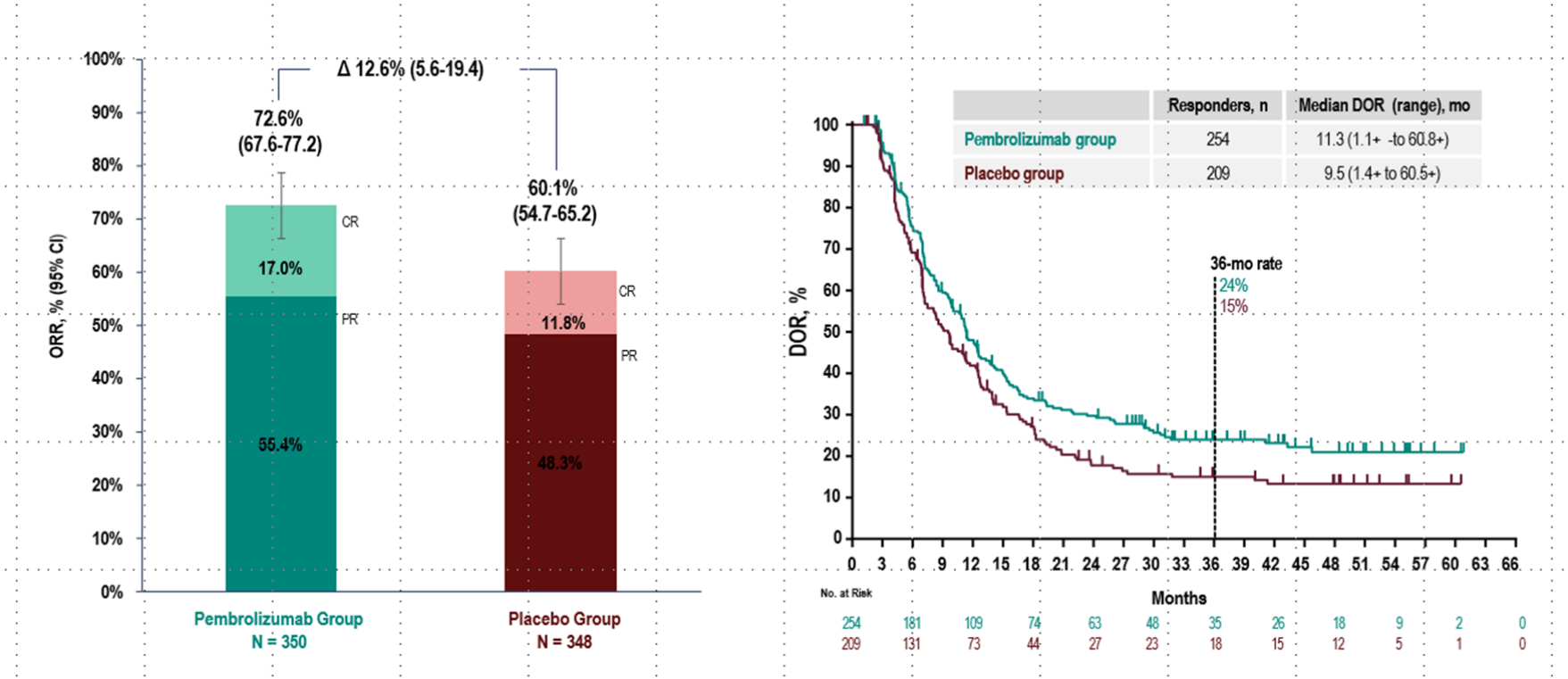
	Events, n (%)	Median (95% CI), mo
Pembrolizumab group	221 (74%)	10.9 (8.5-12.5)
Placebo group	226 (76%)	7.3 (6.8-8.4)



ORR and DOR

	Responders, n	Median DOR (range), mo
Pembrolizumab group	218	11.3 (1.1+ -to 60.8+)
Placebo group	173	9.5 (1.4+ to 60.5+)

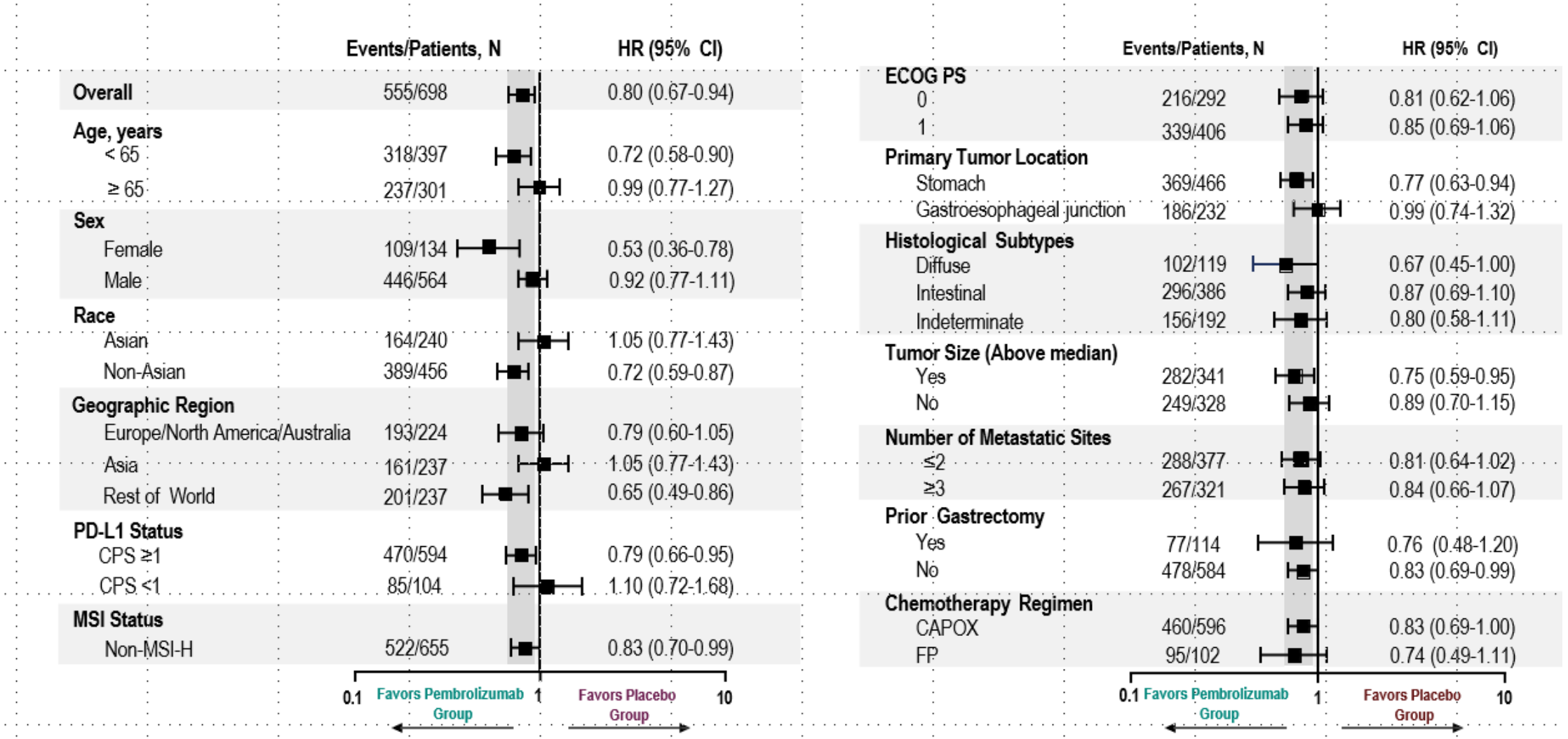




Survival Outcomes by Pre-specified Subgroup PD-L1 CPS 1 Status

	PD-L1 CPS ≥1		PD-L1 CPS <1	
	Pembrolizumab Group N = 298	Placebo Group N = 296	Pembrolizumab Group N = 52	Placebo Group N = 52
PFS, median (95% CI), mo	10.9 (8.5-12.5)	7.3 (6.8-8.4)	9.5 (8.3-12.6)	9.5 (7.9-13.0)
HR (95% CI)	0.72 (0.60-0.87)		0.99 (0.62-1.56)	
OS, median (95% CI), mo	20.1 (17.9-22.9)	15.7 (13.5-18.5)	18.2 (13.9-22.9)	20.4 (16.4-24.7)
HR (95% CI)	0.79 (0.66-0.95)		1.10 (0.72-1.68)	

Overall Survival in Key Subgroups at Final Analysis (ITT)



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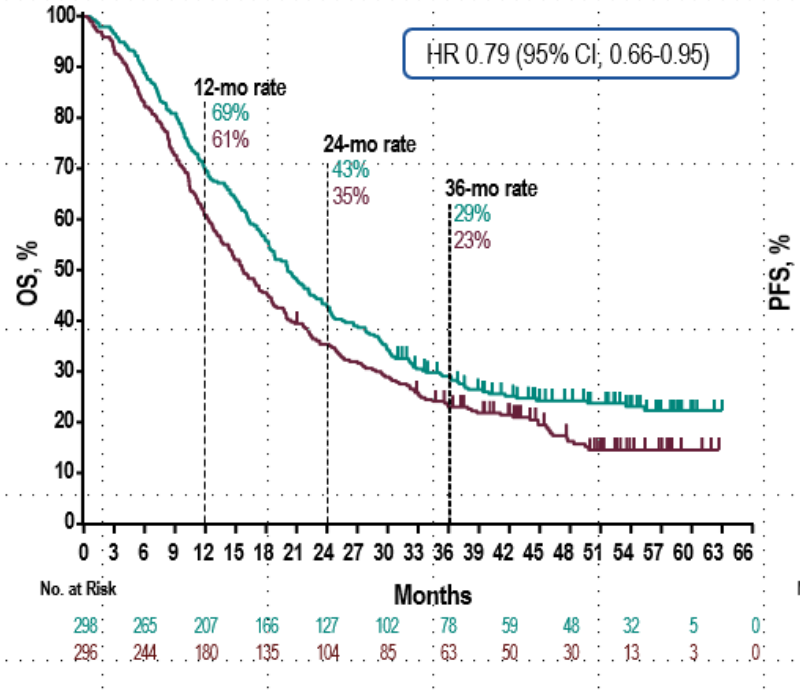

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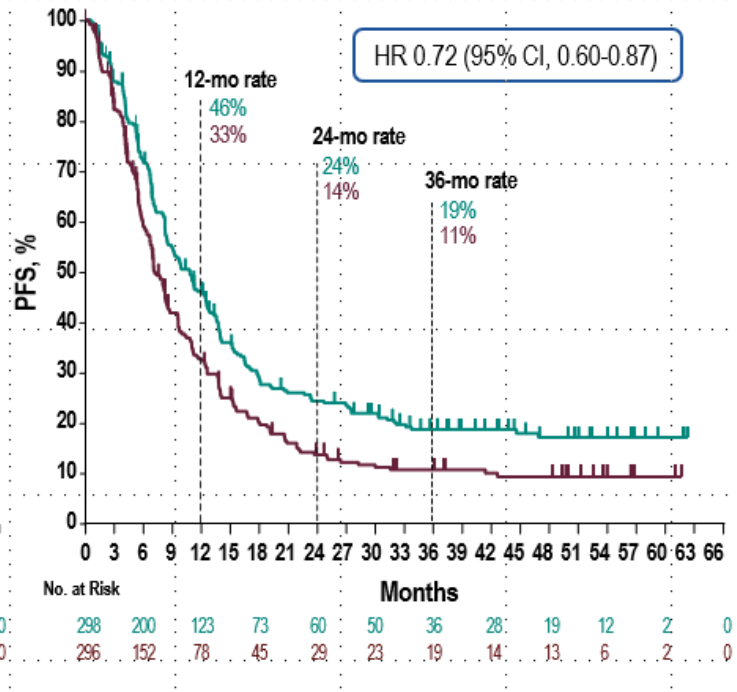

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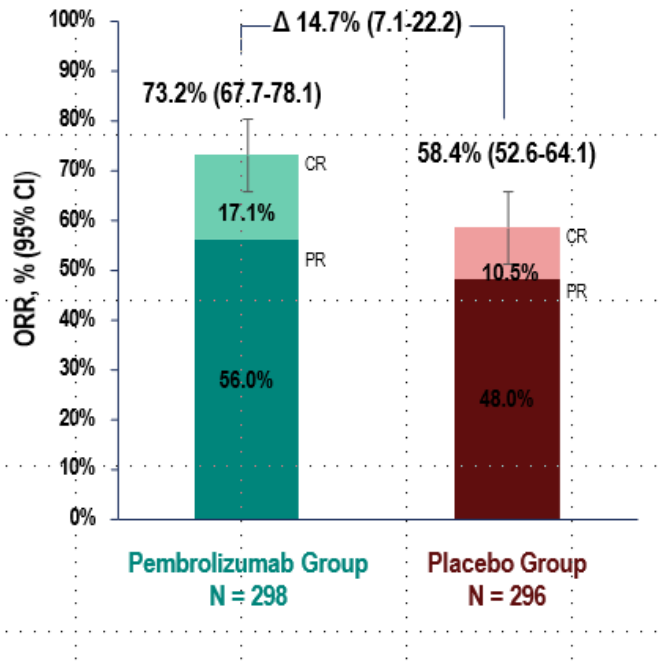
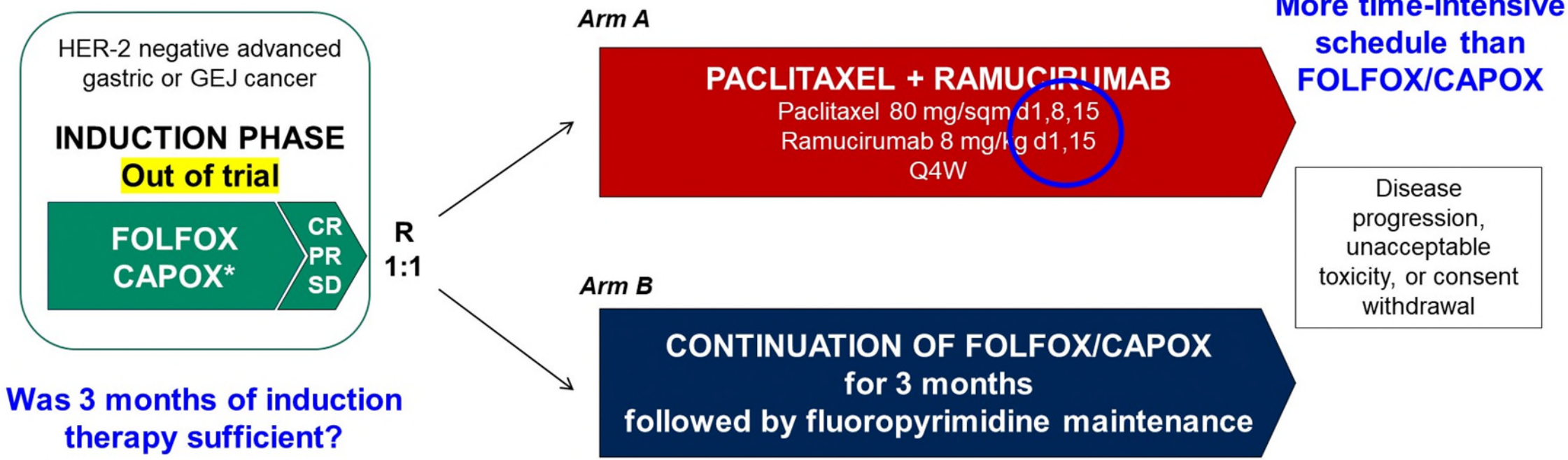


The ARMANI Study Design



Stratification factors:
Prior gastrectomy: Y vs N
Peritoneal disease: Y vs N
Site of origin: Gastric vs GEJ

Primary Endpoint: Progression Free Survival
- ✓ Expected mPFS in arm B = 4 months
- ✓ Expected mPFS in arm A = 6 months
- ✓ Target HR 0.67

- The study picked non-refractory tumors on 1L treatment

Why Use Paclitaxel and Ramucirumab Earlier in the Treatment?

Study details	Year	Treatment	n	ORR %	mPFS months	mOS months	Safety (3 most frequent grade ≥3 TEAEs)
RAINBOW Global, phase III, double-blind, randomized, placebo-controlled trial	2014	Ram + PTX	330	28	4.4	9.6	Neutropenia: 41% Leukopenia: 17% Hypertension: 14%
		PBO + PTX	335	16	2.9	7.4	Neutropenia: 19% Leukopenia: 7% Hypertension: 2%

Many patients do not receive systemic treatment post first-line

Study	Total N	Subsequent Therapies (% of patients)	
		Experimental Arm	Control Arm
CheckMate 649	955	**37%**	**40%**
KEYNOTE 859	1579	**45%**	**47%**
SPOTLIGHT	565	**48%**	**53%**
GLOW	507	**46.5%**	**55.3%**
KENOYTE 062	748	**50%**	**54.1%**
FIGHT	98	**60.9%**	**51.9%**

GC/GEJ often diagnosed at an advanced stage

- leads to a poor prognosis.
- patients health deteriorates rapidly following the initial disease progression.

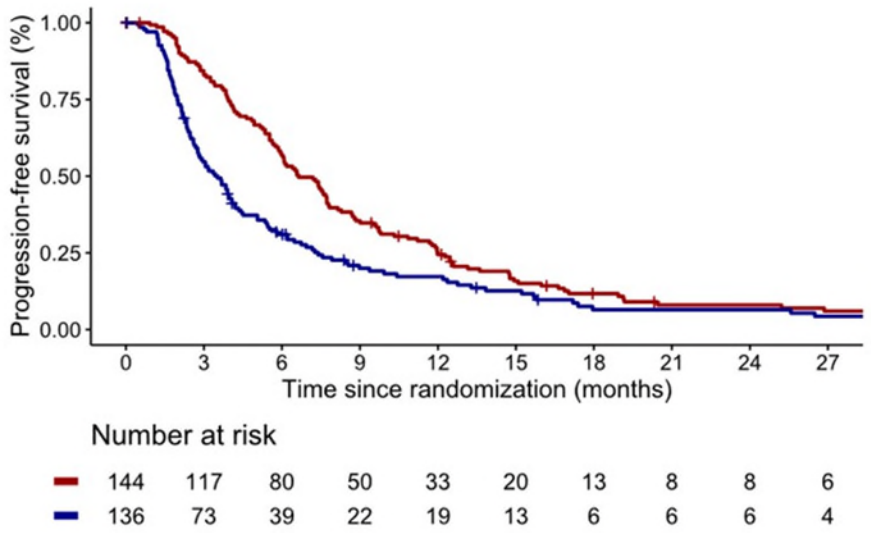
Janjigian, Y.Y., et al. (2021). Lancet, 398(10294), 27-40.; Rha, S.Y., et al. (2023). Lancet Oncology, 24(10), 1181-1195; Shitara, K., et al. (2023). Lancet, 401(10380), 1655-1668.; Shah, M.A., et al. (2023). Nature Medicine, 29(12), 2133-2141. Wainberg, Z.A., et al. (2024). Gastric Cancer, 27(3), 558-570.

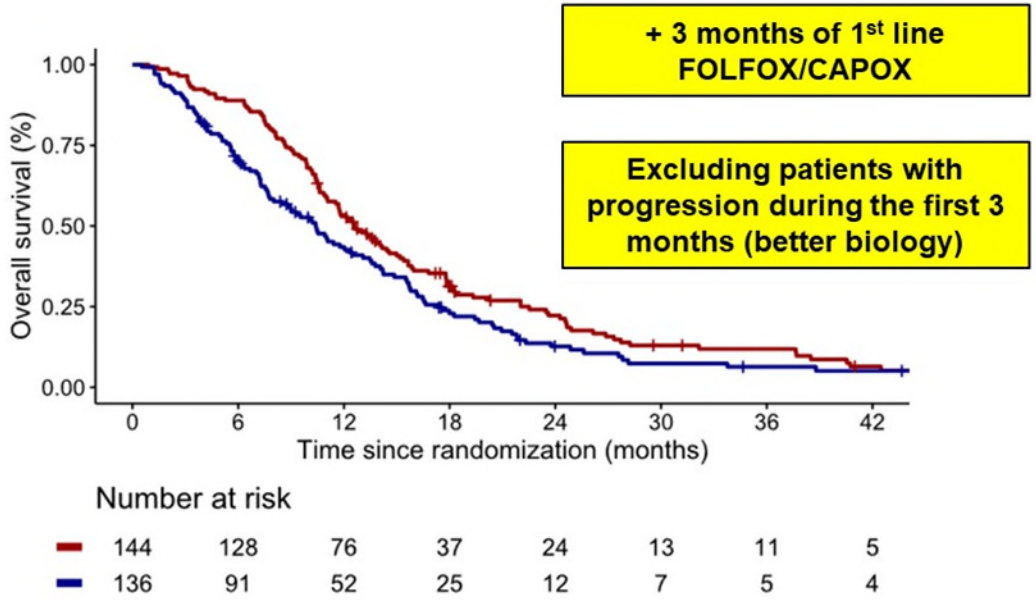
The ARMANI Study Patient Characteristics

Baseline Characteristics	Arm A (PTX-RAM) *N*=144 (%)	Arm B (FOLFOX/CAPOX) *N*=136 (%)
Gender (M/F)	67/33	61/39
Median age (years, IQR)	64 (57-71)	66 (57-72)
ECOG performance status (0/1)	74/26	64/36
Site of origin (gastric/GEJ)	74/26	74/26
Prior gastrectomy (Y/N)	28/72	23/77
Peritoneal metastases (Y/N) **Numerically higher in Arm A**	53/47	43/57
Liver metastases (Y/N)	24/76	30/70
Number of metastatic sites (0-1/>1)	48/62	42/68
Synchronous metastases (Y/N)	76/23	81/19
Histotype (intestinal/diffuse/NOS)	41/40/19	34/43/23
First line induction regimen (FOLFOX/CAPOX)	81.2/18.8	86.8/13.2

PFS and OS Improved with Switching to Ramucirumab and Paclitaxel

Median follow-up of 43.7 months





	Arm A (PTX-RAM) n=144	Arm B (FOLFOX/CAPOX) n=136
Events, (%)	91%	90%
Median, mos (95%CI)	**6.6** (6.0-7.8)	**3.5** (2.8-4.2)
HR (95%CI)	**0.64 (0.49-0.81)**	
2-sided p value	**P<0.001**	

	Arm A (PTX-RAM) n=144	Arm B (FOLFOX/CAPOX) n=136
Events, (%)	86%	85%
Median, mos (95%CI)	**12.6** (11.5-15.0)	**10.4** (8.0-13.1)
HR (95%CI)	**0.75 (0.58-0.97)**	
2-sided p value	**P=0.028**	

- PFS was significantly improved by switching to paclitaxel plus ramucirumab
- With more than 90% of PFS events in both arms, mPFS was 3.5 months in the control arm and 6.6 months in the experimental arm, with an absolute gain of mor e than 3 months

Safety Concerns:
Grade ≥3 Toxicities 40.4% in Arm A vs. 20.7% in Arm B

Adverse Events	Arm A (PTX-RAM) *N*= 141		Arm B (FOLFOX/CAPOX) *N* = 135	
	Any Grade (%)	Grade ≥ 3 (%)	Any Grade (%)	Grade ≥ 3 (%)
Stomatitis/Oral mucositis	14.2	1.4	14.0	1.5
Nausea	12.8	0	18.5	0
Vomiting	6.4	0	6.7	0
Diarrhea	16.3	0	8.9	0
Hand-foot syndrome	1.4	0	11.8	0
Peripheral Neuropathy	**61.7**	**5.7**	**45.2**	**6.7**
Neutropenia	**55.3**	**26.2**	**23.0**	**9.6**
Febrile neutropenia	1.4	1.4	0	0
Anemia	27.7	2.1	13.3	3.0
Thrombocytopenia	14.2	0	28.1	0
Hypertension	**23.4**	**6.4**	**0.7**	**0**
Venous thromboembolism	**5.7**	**2.8**	**2.2**	**0**

Expected Ramucirumab related toxicities

ICI

Key Eligibility Criteria

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

R 1:1

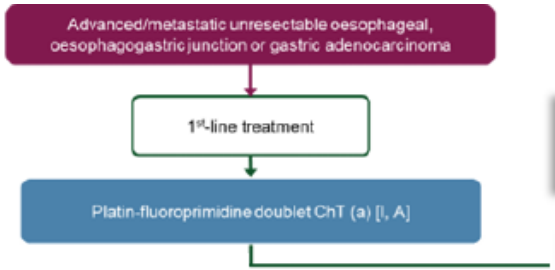
Pembrolizumab 200 mg IV Q3W for ≤35 cycles (~2 yr) + Chemotherapy[a] (FP or CAPOX)

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

Stratification Factors

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

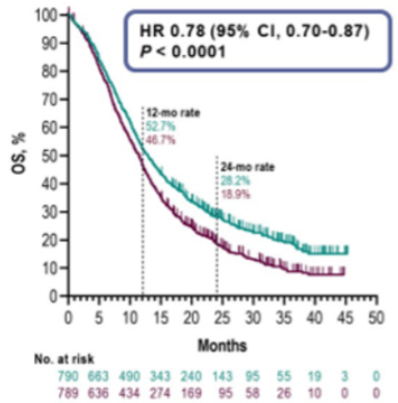
- **Primary Endpoint:** OS
- **Secondary Endpoints:** PFS,[b] ORR,[b] DOR,[b] and safety



Primary Endpoint: OS

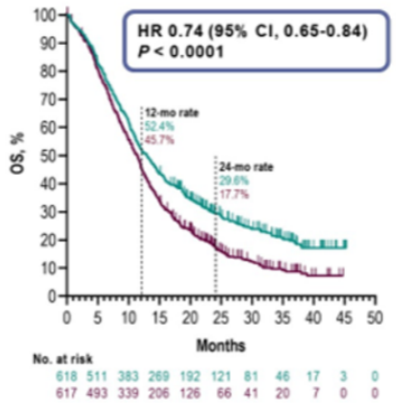
Overall[1]

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



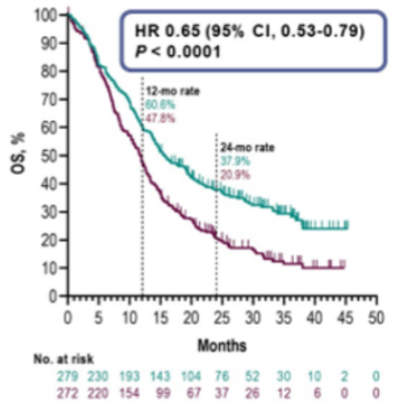
PD-L1 CPS ≥1

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



PD-L1 CPS ≥10

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

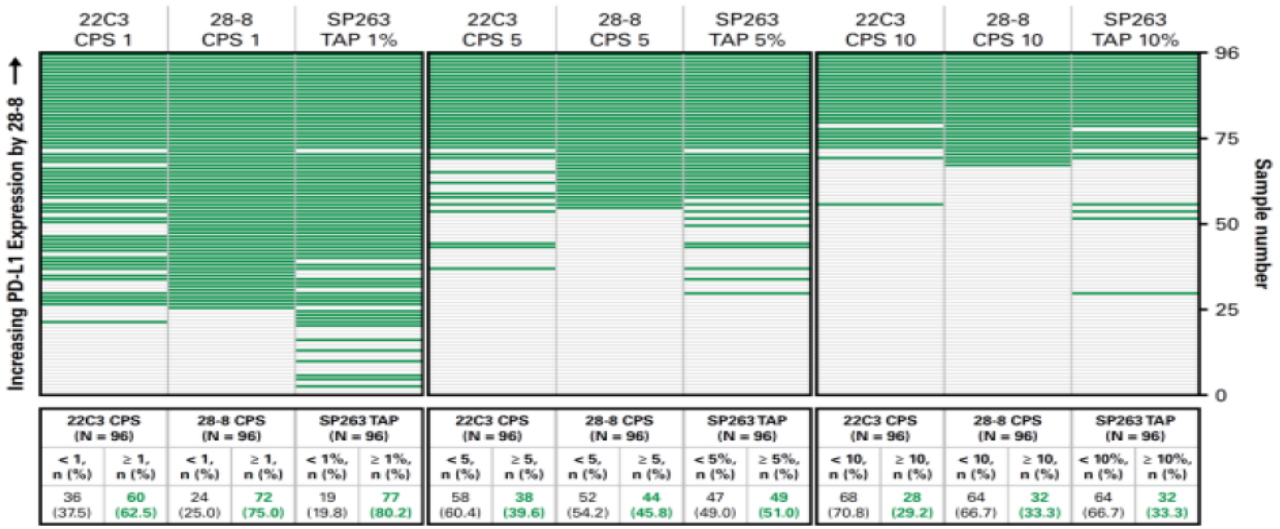


PD-L1 & ICI benefit

- PD-L1 ≥ 5: benefit ++
  - ➢ **ADD anti-PD-1**
- PD-L1 1-4: benefit +/-
  - ➢ ***Consider*** **anti-PD-1**

	CHECKMATE-649	RATIONALE-305	KEYNOTE 859
Anti-PD-1	Nivolumab	Tislelizumab	Pembrolizumab
OS	All HR 0.80 CPS ≥ 1 HR 0.77 **CPS ≥ 5 HR 0.71** **CPS ≥ 10 HR 0.66**	**TAP ≥ 5 HR 0.74**	All HR 0.78 CPS ≥ 1 HR 0.73 **CPS ≥ 10 HR 0.64**

PD-L1 in gastric cancer is an unreliable biomarker



MSI high unresectable GC/GEJ

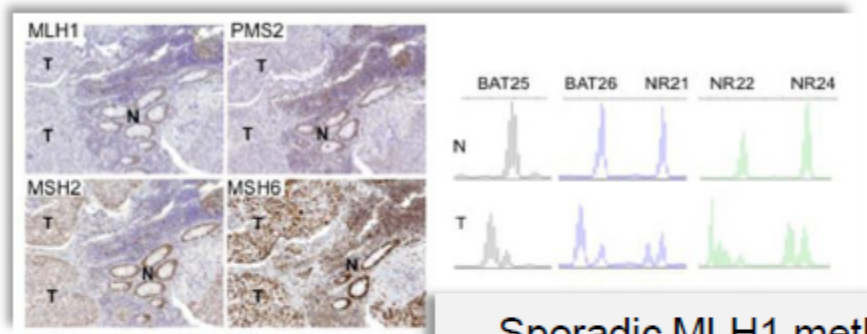
KEY MARKERS IN ADVANCED DISEASE

- **HER2** positive – 15%-20% of patients, improved survival with non-chemo antibody trastuzumab
- **MSI** high – 3%-5% of patients, high response rates to immunotherapies
- **PD-L1** positive – 30%-50% of patients, identifies those more likely to benefit from immune therapies, likely gradation within PD-L1+
- **CLDN18.2** high – 30%-35% of patients, response predictor for zolbetuximab

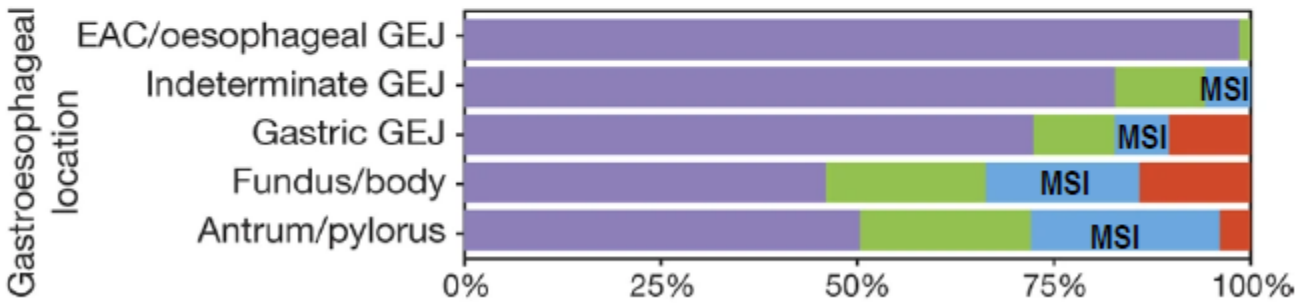
INVESTIGATIONAL BIOMARKERS

- **FGFR2** amp – 5%-10% of patients, multiple trials of inhibitors
- **FGFR2** high- May be up to 30% of HER2 negative
- **EGFR** amp – 5%-7%, may predict response to EGFR drugs like cetuximab

MMRD/MSI as the prime biomarker



Sporadic MLH1 methylation ~ 90%



↑ Older, female, distal cancers but *not exclusively*

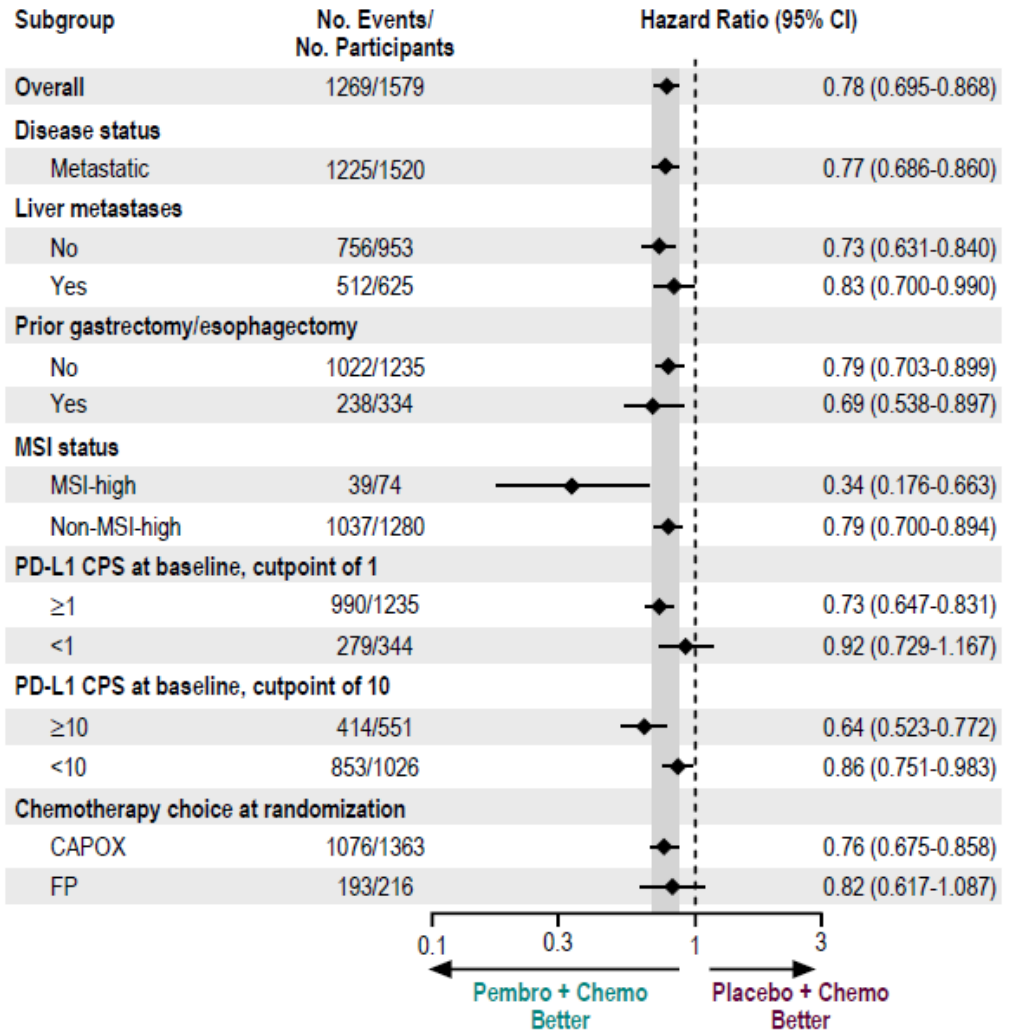
dMMR/MSI-H status is a strong predictive biomarker for ICI therapy

Baseline Characteristics, ITT Population

	Pembro + Chemo (n=790)	Placebo + Chemo (n=789)
Age, median (range)	61 y (28-86)	62 y (21-85)
≥65 years	304 (38.5%)	310 (39.3%)
Male	527 (66.7%)	544 (68.9%)
Geographic region		
Asia	263 (33.3%)	262 (33.2%)
W Europe/Israel/N America/Australia	201 (25.4%)	202 (25.6%)
Rest of World	326 (41.3%)	325 (41/2%)
ECOG PS 1	509 (64.4%)	488 (61.9%)
Primary tumor location[a]		
Adenocarcinoma of the GEJ	149 (18.9%)	185 (23.4%)
Adenocarcinoma of the stomach	640 (81.0%)	603 (76.4%)
Disease status[b]		
Locally advanced	28 (3.5%)	30 (3.8%)
Metastatic	761 (96.3%)	759 (96.2%)

	Pembro + Chemo (n=790)	Placebo + Chemo (n=789)
Histologic subtype[c]		
Diffuse	318 (40.3%)	301 (38.1%)
Indeterminate	186 (23.5%)	215 (27.2%)
Intestinal	284 (35.9%)	273 (34.6%)
Liver metastases present[d]	314 (39.7%)	311 (39.4%)
Prior gastrectomy/esophagectomy[e]	172 (21.8%)	162 (20.5%)
HER2-negative status	790 (100%)	789 (100%)
MSI-high status[f]	39 (5.0%)	35 (4.4%)
PD-L1 CPS ≥1 at baseline	618(78.2%)	617 (78.2%)
PD-L1 CPS ≥10 at baseline[g]	279 (35.3%)	272 (34.5%)
Combination chemotherapy at randomization		
CAPOX	682 (86.3%)	681 (86.3%)
FP	108 (13.7%)	108 (13.7%)

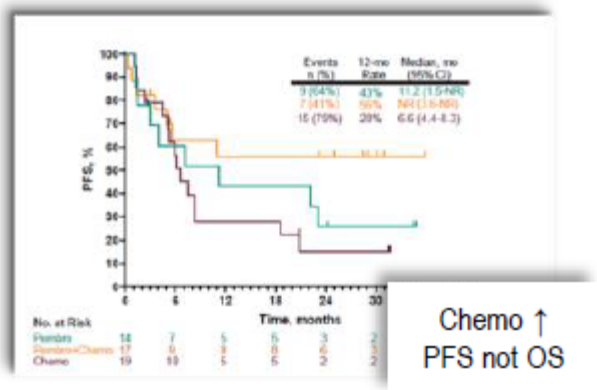
[a]Other in 1 (0.1%) patient in the placebo + chemo group and missing in 1 (0.1%) in the pembro + chemo group. [b]Missing in 1 (0.1%) patient in the pembro + chemo group. [c]Unknown in 1 (0.1%) patient in the pembro + chemo group and missing in 1 (0.1%) patient in the pembro + chemo group. [d]Missing in the 1 (0.1%) patient in the pembro + chemo group. [e]Missing in 5 (0.6%) patients in each group. [f]Missing in 106 (13.5%) patients in the pembro + chemo group and 112 (14.2%) in the placebo + chemo group. [g]Missing in 2 (0.3%) patients in the pembro + chemo group. Data cutoff date: October 3, 2022.



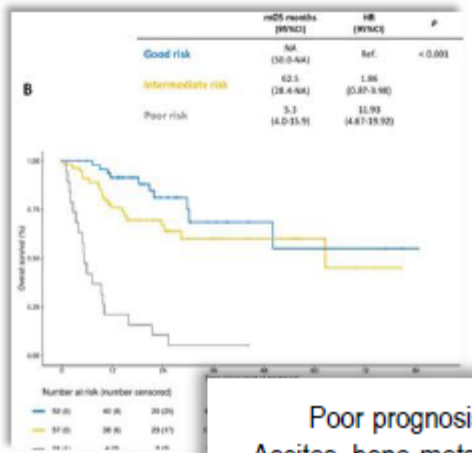
Most MSI-H/dMMR GCs arise sporadically, primarily due to MLH1 epigenetic silencing.
Unlike MSS/pMMR GCs, MSI-H/dMMR GCs are rare but distinct, marked by genomic instability, high mutational burden, and favorable immunogenicity.
MSI-H GCs respond differently to treatment and have a distinct prognosis., owing to high neoantigen load, abundant tumor-infiltrating lymphocytes.

Chemo needed with PD-1?

For some patients



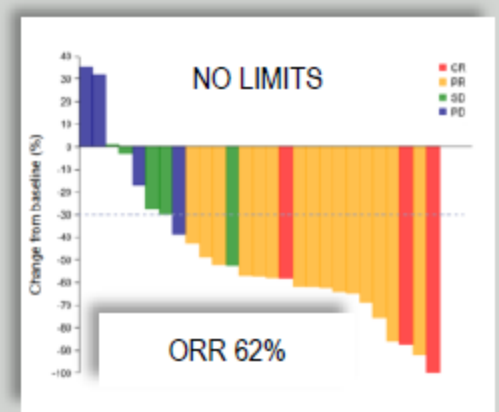
Chemo ↑
PFS not OS



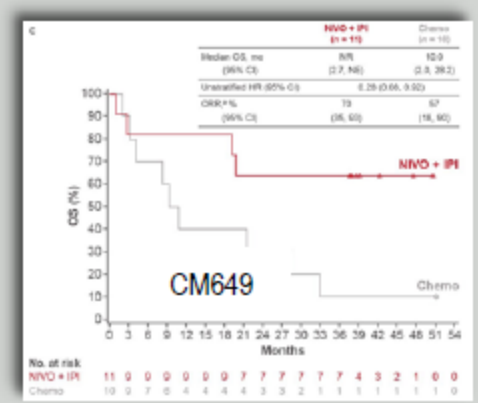
Poor prognosis
Ascites, bone mets, PS2

Adding a second ICI?

Higher ORR and OS



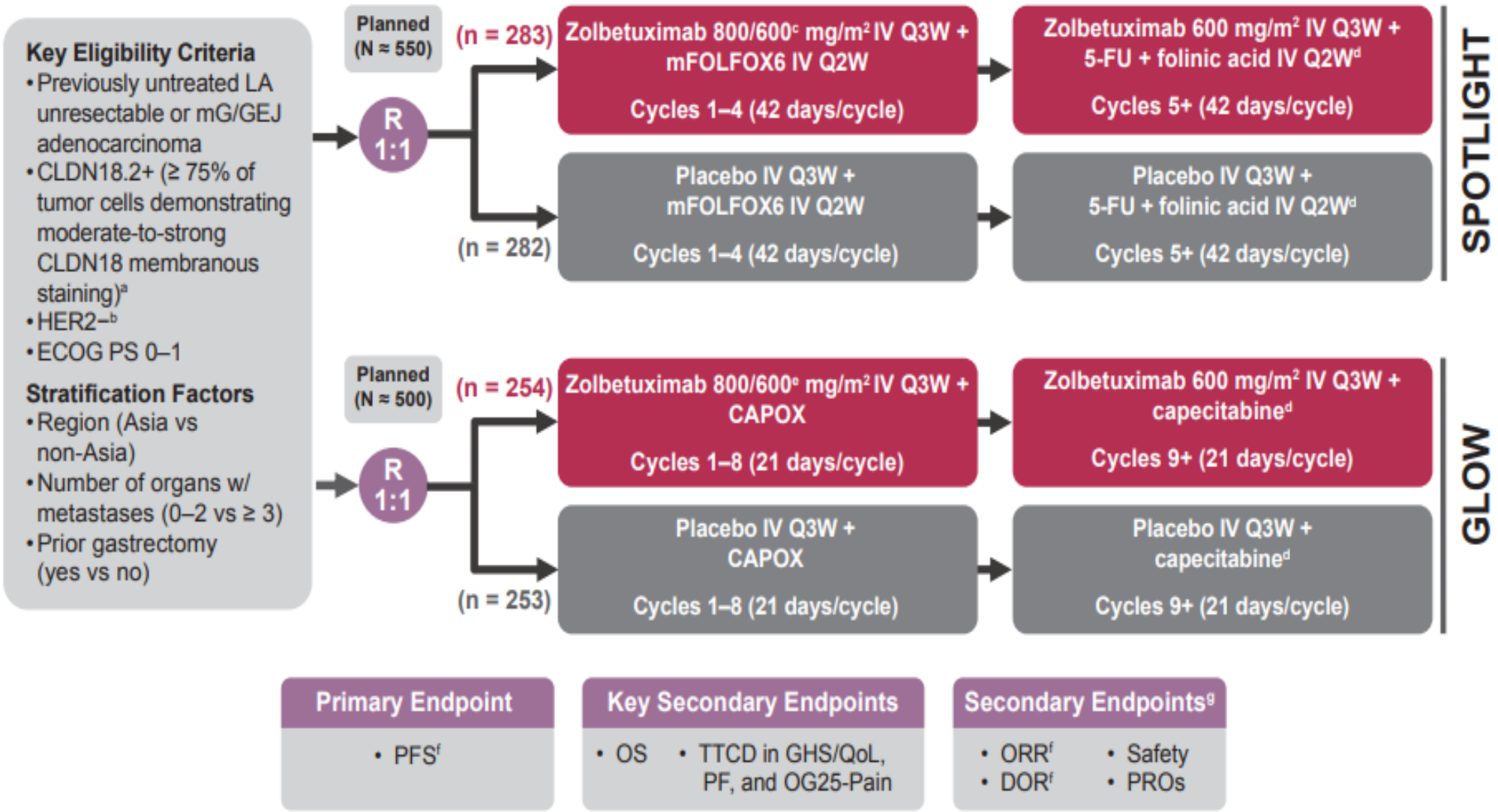
ORR 62%



Next step questions in MSI

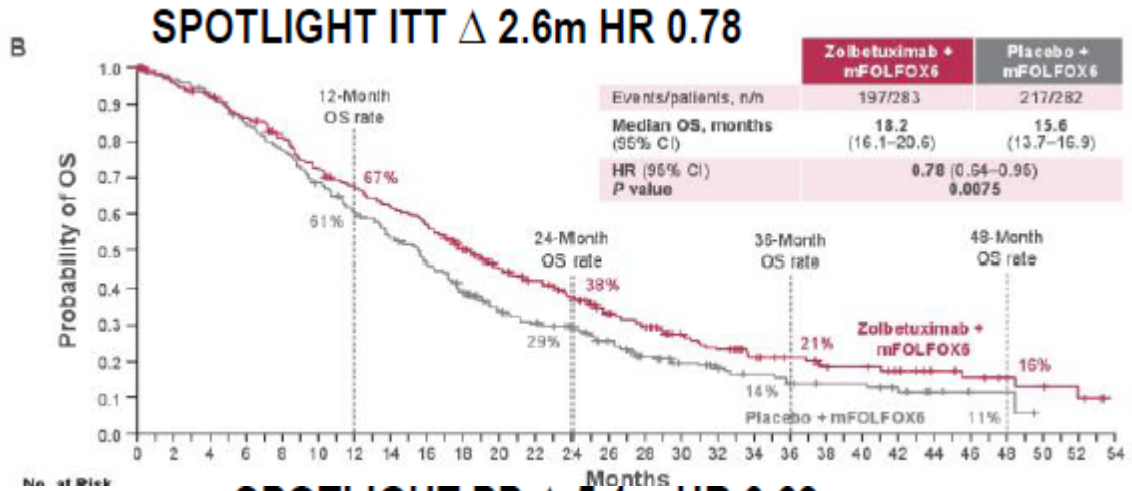
- **When to stop treatment**
  - ctDNA, imaging
- **Next generation ICI**
  - LAG3 effective in ICI refractory MSI CRC
- **Secondary targets**
  - Werners helicase, fusions

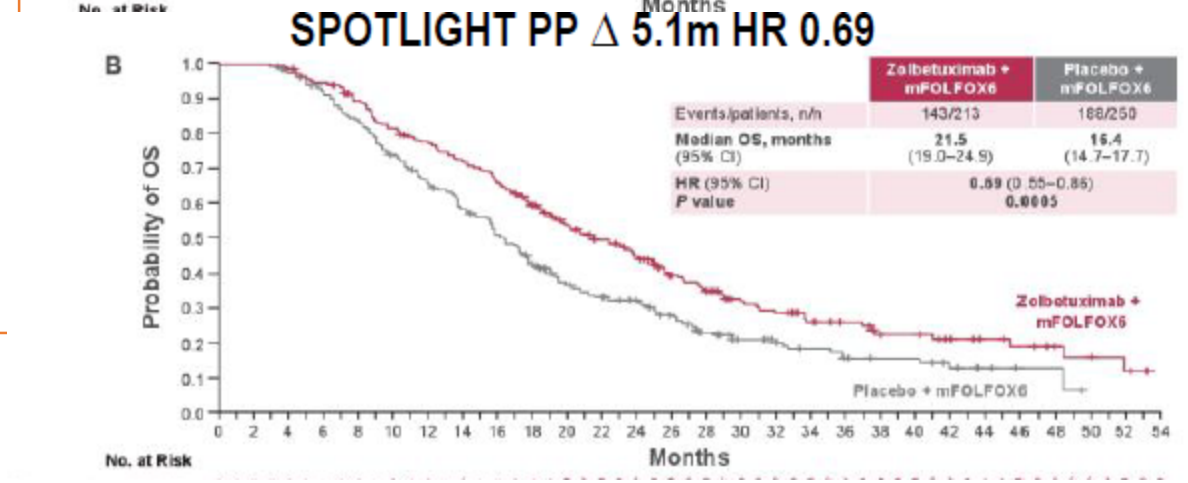
Zolbetuximab approved as a first-line (1L) treatment in gastric cancer



Biomarker driven in 1L treatment improves outcomes compared to SOC alone

	Full analysis set[a]		Patients with measurable disease	
	Zolbetuximab + chemotherapy (n = 537)	Placebo + chemotherapy (n = 535)	Zolbetuximab + chemotherapy (n = 406)	Placebo + chemotherapy (n = 414)
ORR[b], n (%)	244 (45.4)	233 (43.6)	233 (57.4)	229 (55.3)
95% CI	41.2–49.8	39.3–47.9	52.4–62.3	50.4–60.2
BOR[c,d], n (%)				
CR	32 (6.0)	17 (3.2)	21 (5.2)	13 (3.1)
PR	212 (39.5)	216 (40.4)	212 (52.2)	216 (52.2)
SD	91 (16.9)	108 (20.2)	91 (22.4)	108 (26.1)
PD	27 (5.0)	45 (8.4)	24 (5.9)	39 (9.4)
Median DOR[b,e] months (95% CI)	8.1 (6.4–9.0)	6.5 (6.2–7.7)	7.7 (6.3–8.9)	6.5 (6.2–7.9)





Sequencing of PD-L1 blockade and zolbetuximab.

Debate: Considering the role of claudin is not the oncogenic driver, we can explain the RR is similar to CTx. > High disease burden is high that needs to reduce tumor size, I think starting with IO combo might be good. > 2nd line clinical trial with caludin ADC might be reasonable

Take Home Message

Know tumor better:	Focus on tumor characterization. Key markers include MMR (Mismatch Repair), HER2, PD-L1, and CLD 18.2.
Use chemotherapy judiciously:	Reduce doses in elderly or frail patients. Consider triplet chemotherapy in selected patients.
Right target, right treatment:	Utilize biomarker-selected antibody therapy.
Surgery as research:	Patient selection for surgery is crucial.
Continue to recruit to clinical trials:	Include early phase trials in treatment plans.

SUPPLEMENTAL SLIDE

Biomarker Overlap

What Do We Know?

Feature/Biomarker	Kubota Y et al.		Pellino A et al.		Jia K et al.	
	CLDN18.2+ (n= 98)	CLDN18.2- (n = 310)	CLDN18.2+ (n = 117)	CLDN18.2- (n = 233)	CLDN18.2+ (n = 42)	CLDN18.2- (n = 38)
HER2-	83 (85%)	267 (85%)	100 (85%)	198 (85%)	33 (79%)	25 (66%)
HER2+	15 (15%)	43 (14%)	17 (15%)	35 (15%)	9 (21%)	13 (34%)
FGFR2b+	N/A	N/A	N/A	N/A	N/A	N/A
FGFR2b-	N/A	N/A	N/A	N/A	N/A	N/A
pMMR/MSS	93 (96%)	291 (94%)	102 (87%)	194 (83%)	36 (86%)	33 (87%)
dMMR/MSI	5 (5%)	19 (6%)	15 (13%)	39 (17%)	6 (14%)	5 (13%)
EBV+	4 (4%)	11 (4%)	7 (6%)	1 (0.4%)	8 (19%)	2 (5%)
EBV-	94 (96%)	299 (96%)	110 (94%)	232 (99.5%)	34 (81%)	36 (95%)
PD-L1- (CPS <1)	24 (26%)	68 (23%)	87 (74%)	165 (71%)	9 (21%)	8 (21%)
PD-L1+ (CPS ≥1)	69 (74%)	225 (77%)	30 (26%)	68 (29%)	33 (79%)	30 (79%)
PD-L1+ (CPS ≥5)	39 (42%)	293 (52%)	21 (18%)	50 (21%)	N/A	N/A
PD-L1+ (CPS ≥10)	N/A	N/A	N/A	N/A	19 (45%)	17 (45%)
Diffuse Type	47 (48%)	137 (44%)	47 (40%)	70 (30%)	12 (29%)	22 (58%)
Intestinal Type	51 (52%)	173 (56%)	54 (46%)	132 (57%)	16 (38%)	6 (16%)