Updates in the Treatment of Esophagogastric Cancer

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Update of Esophagogastric Cancers

- First line immunotherapy with chemotherapy – Updates
- HER2 + Cancer
- CLDN 18.2 – New target
- Perioperative therapy

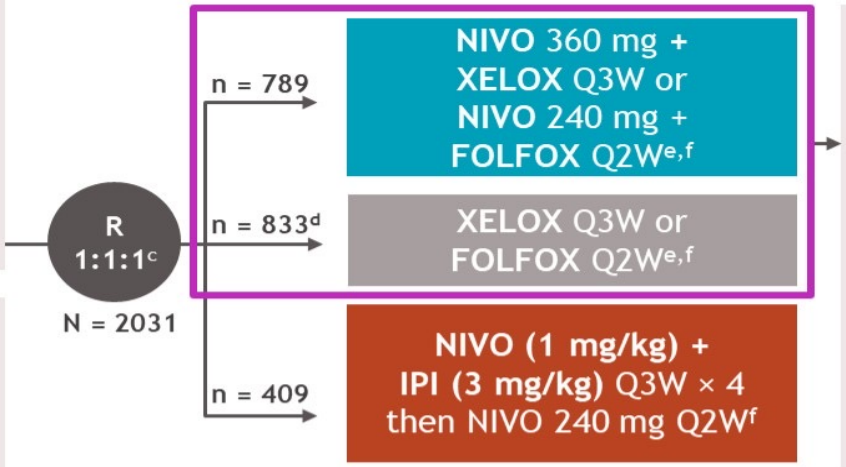
Advanced Esophagogastric Cancer

CheckMate 649 study design

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

Key eligibility criteria
- Previously untreated, unresectable, advanced or metastatic gastric/GEJ/esophageal adenocarcinoma
- No known HER2-positive status
- ECOG PS 0-1

Stratification factors
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[b])
- Region (Asia vs United States/Canada vs ROW)
- ECOG PS (0 vs 1)
- Chemo (XELOX vs FOLFOX)



Dual primary endpoints:
- **OS** and **PFS**[g] (PD-L1 CPS ≥ 5)

Secondary endpoints:
- **OS** (PD-L1 CPS ≥ 1, all randomized)
- **OS** (PD-L1 CPS ≥ 10)
- **PFS**[g] (PD-L1 CPS ≥ 10, ≥ 1, all randomized)
- **ORR**[g]

Exploratory endpoints:
- **Safety**
- **QoL**

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

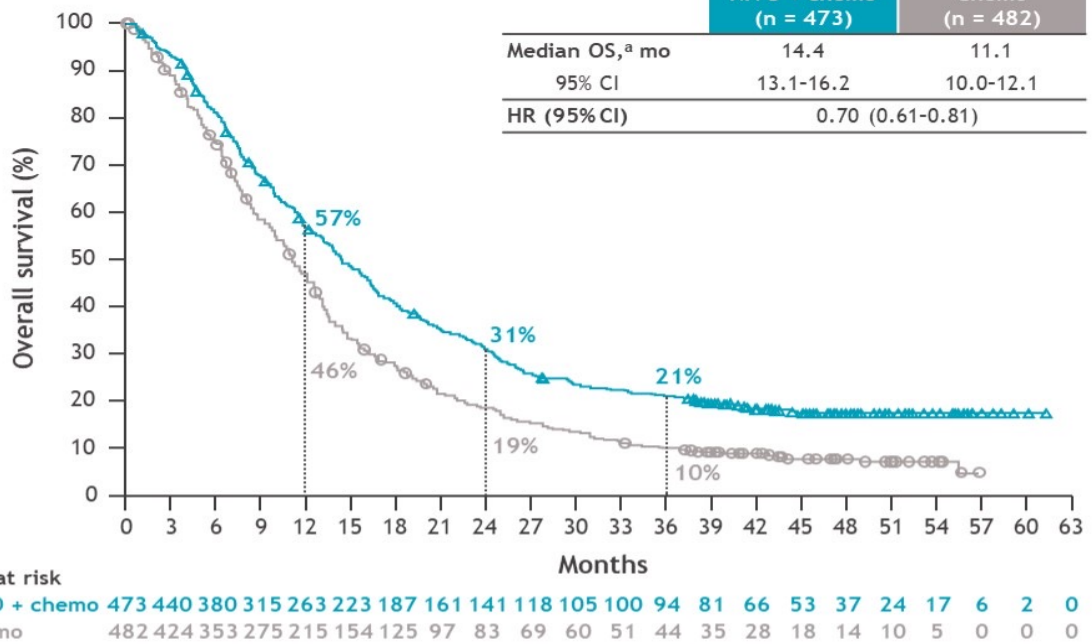
[a]ClinicalTrials.gov. NCT02872116; [b]Less than 1% includes indeterminate tumor cell PD-L1 expression; [c]During concurrent randomization period; [d]Includes patients concurrently randomized to chemo vs NIVO + IPI (October 2016-June 2018) and to NIVO + chemo (April 2017-April 2019); [e]XELOX: oxaliplatin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

Janjigian, Y et al, ASCO Gastrointestinal Symposium 2023, Abstract 291

Overall survival: 36-month follow-up

PD-L1 CPS ≥ 5

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

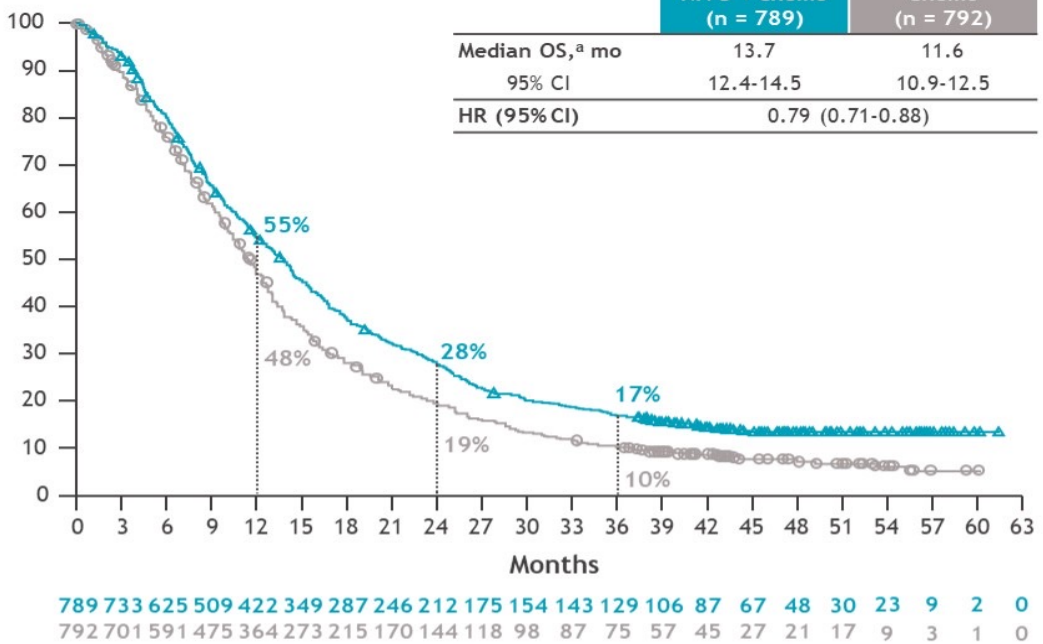


No. at risk

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

All randomized

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



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

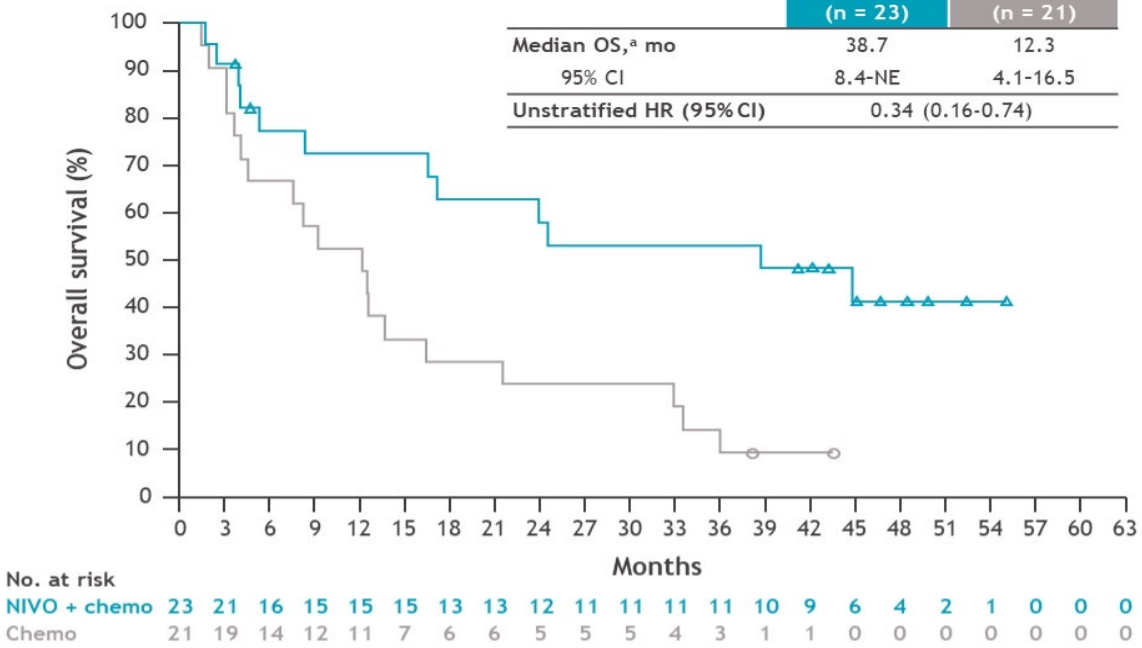
- Clinically meaningful improvement in OS with NIVO + chemo vs chemo was maintained with longer follow-up in PD-L1 CPS ≥ 5 and all randomized populations

[a]Minimum follow-up, 36.2 months.

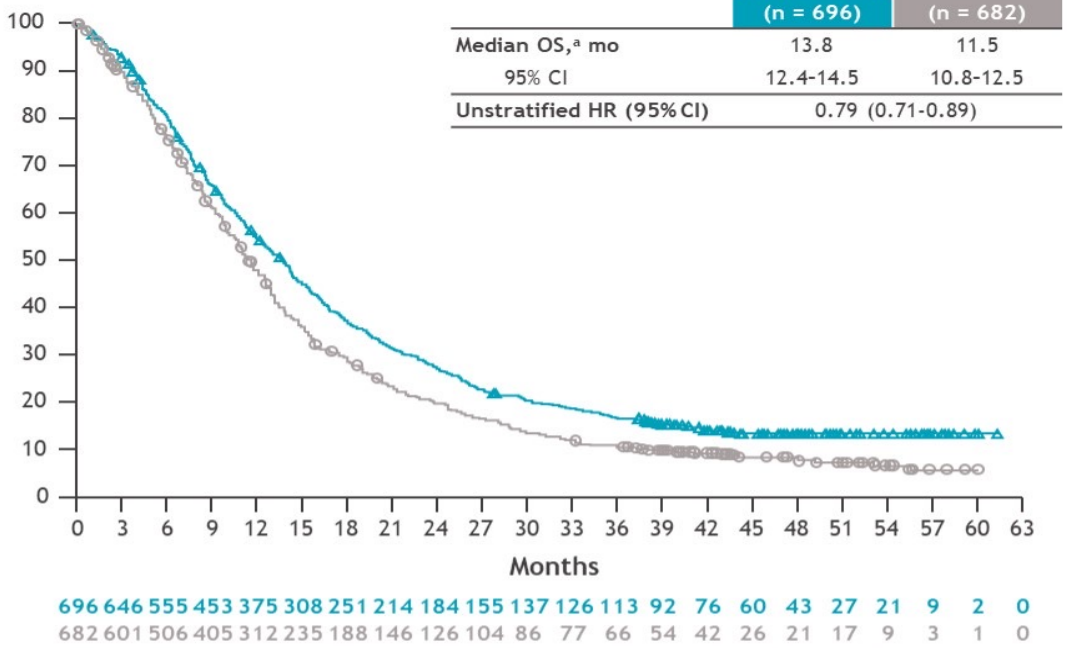
Janjigian, Y et al, ASCO 2023, Abstract 291

Overall survival by MSI status: 36-month follow-up

MSI-H



MSS



- Longer median OS was observed in all randomized patients with MSI-H and MSS tumors treated with NIVO + chemo vs chemo
  - The magnitude of benefit was greater in patients with MSI-H tumors
  - Patients with MSS tumors had results similar to the all randomized population

[a]Minimum follow-up, 36.2 months.

Janjigian, Y et al, ASCO 2023, Abstract 291

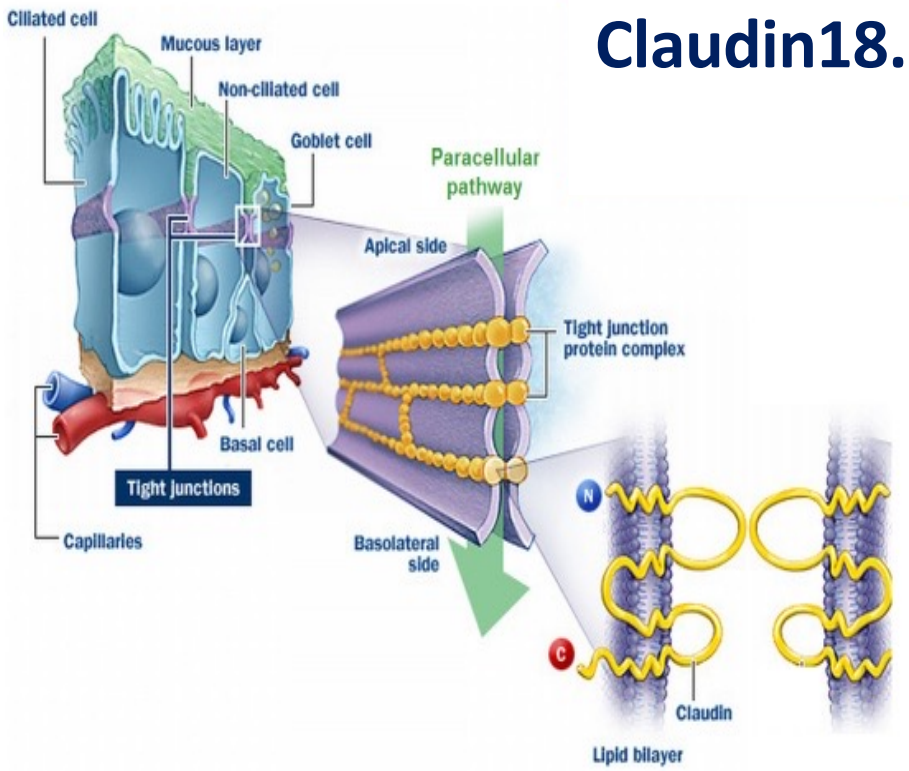
Summary

- First line immunotherapy in combination with chemotherapy superior to chemotherapy alone with longer follow up.
  - Pembrolizumab – KEYNOTE 590, KEYNOTE 859
    - Similar QofL
  - Nivolumab – CheckMate 659
  - *Cross trial comparison similar
- Benefit across subgroups, enriched in higher PDL1
- MSI High patients benefit
- Other exploratory markers, stroma-related and angiogenesis
- No new safety signals

New Targets - CLDN 18.2

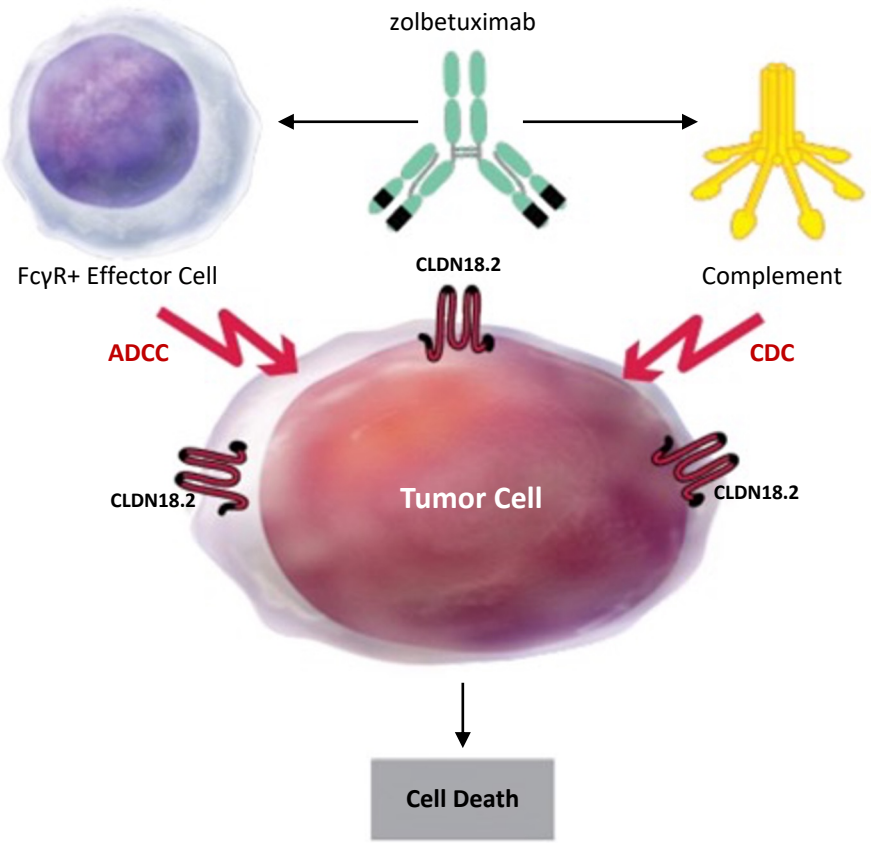
CLAUDIN18.2 – A NOVEL TARGET

Claudin18.2



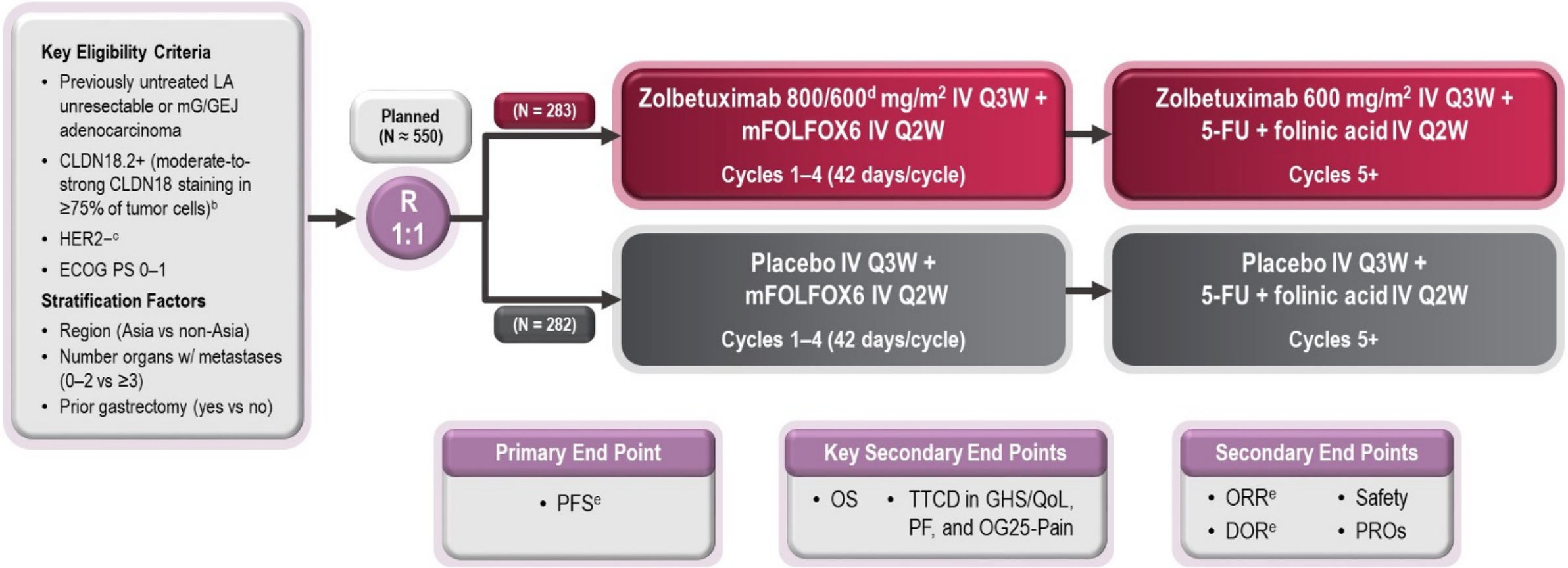
- Member of the claudin family
- Major structural component of tight junctions
- Seals intercellular space in epithelial sheets
- Not expressed in any healthy tissues, except: stomach mucosa

Mechanism of Action of Zolbetuximab



Sahin U et al. *Ann Oncol.* 2021 May;32(5):609-619

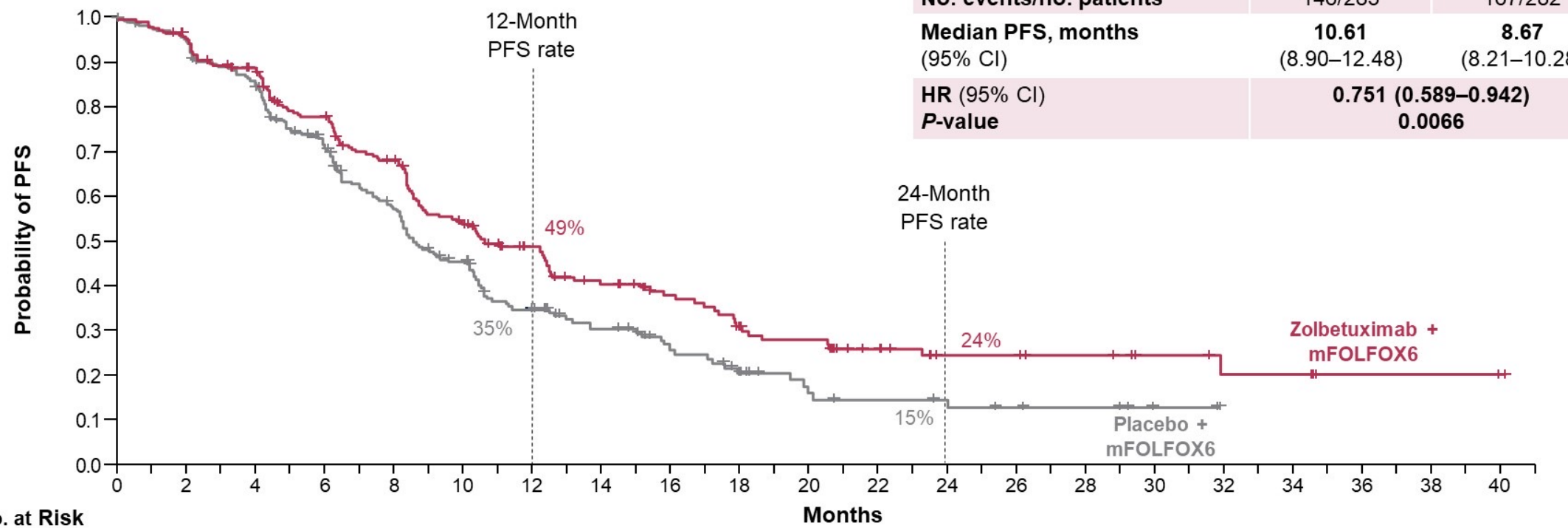
SPOTLIGHT: Phase III Study Design



Shitara K et al. Gastrointestinal Cancers Symposium 2023;Abstract LBA292.

Primary End Point: PFS by Independent Review Committee[a]

	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)	**0.751 (0.589–0.942)**	
***P*-value**	**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

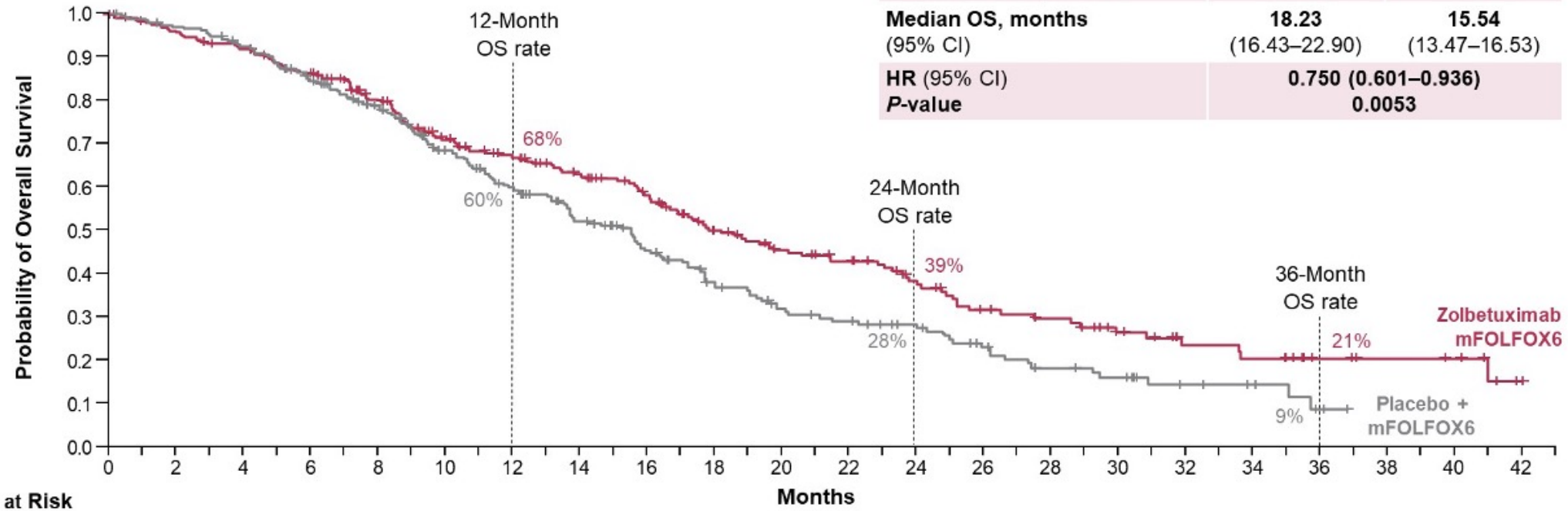
Data cutoff: September 9, 2022; Median follow-up = 12.94 months (zolbetuximab + mFOLFOX6) vs 12.65 months (placebo + mFOLFOX6).

[a]Per RECIST version 1.1.

Shitara K et al. Gastrointestinal Cancers Symposium 2023;Abstract LBA292.

SPOTLIGHT: Overall Survival (Key Secondary Endpoint)

	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).

Shitara K et al. Gastrointestinal Cancers Symposium 2023;Abstract LBA292.

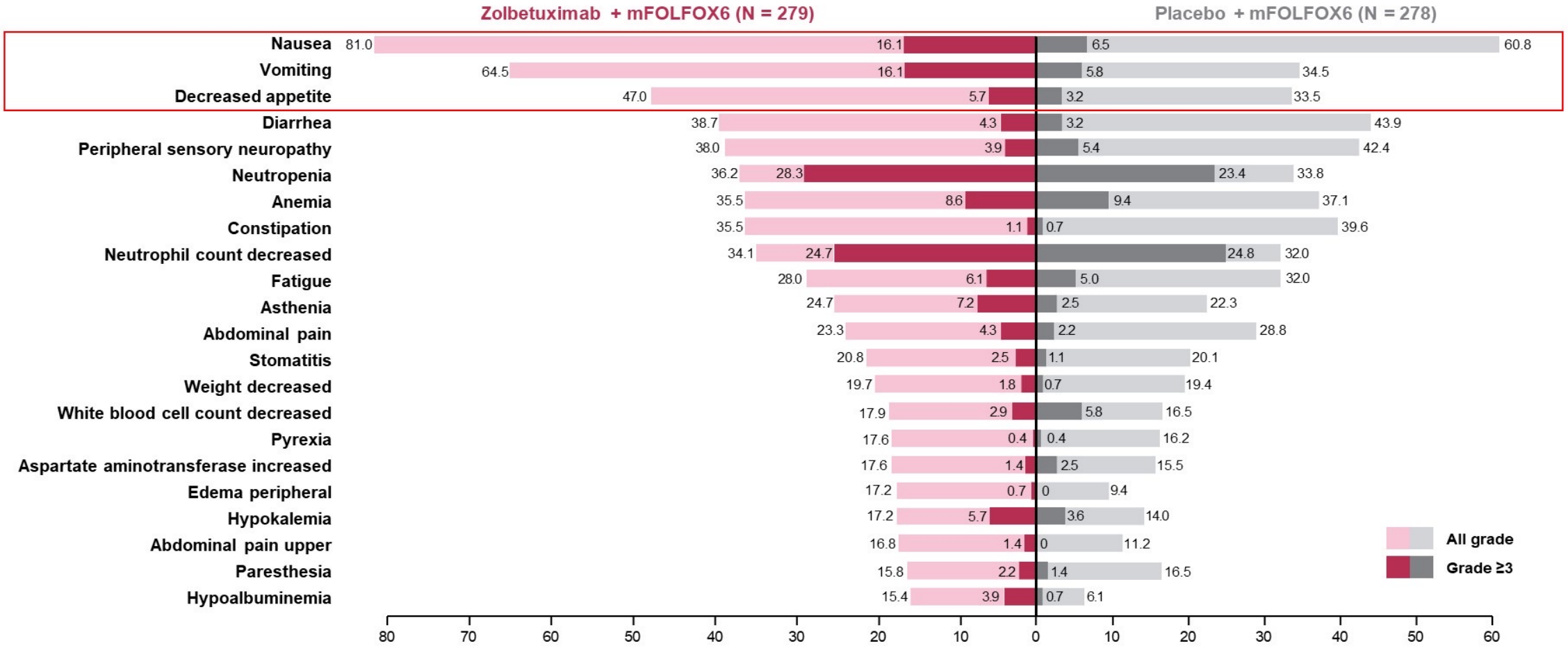
SPOTLIGHT: Response Rates (Key Secondary Endpoint)

	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

Shitara K et al. Gastrointestinal Cancers Symposium 2023;Abstract LBA292.

TEAEs[a] Occurring in ≥15% of All Treated Patients

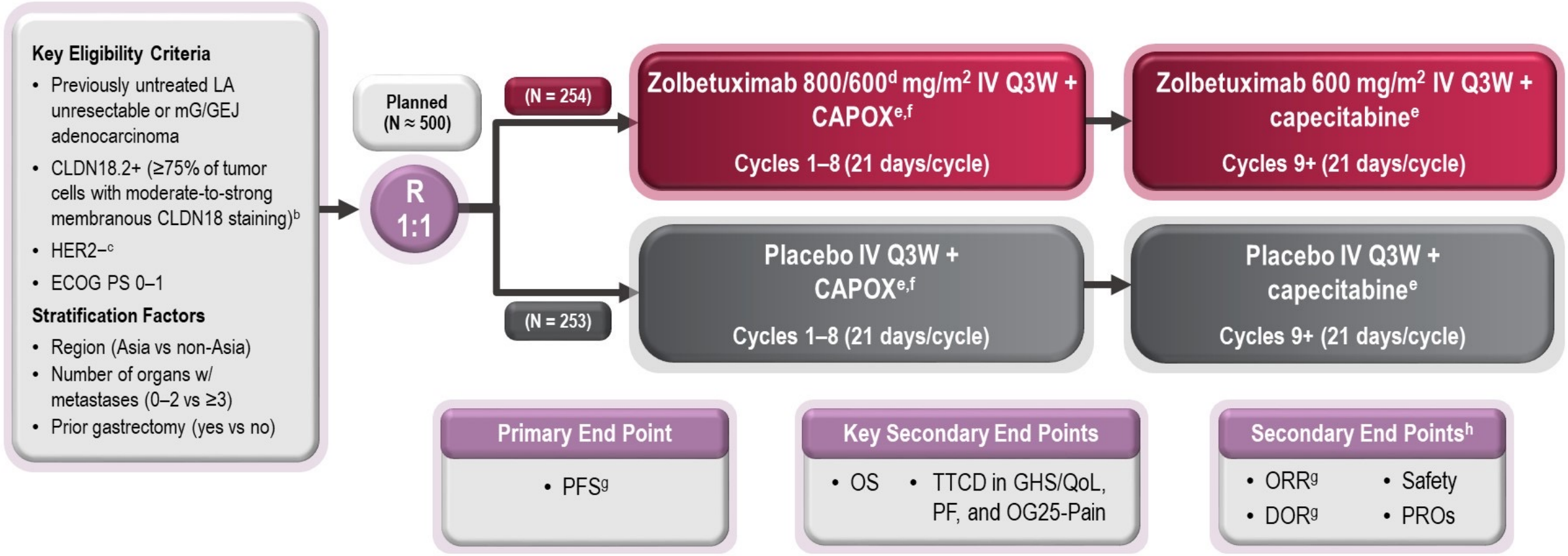


- The most common TEAEs with zolbetuximab + mFOLFOX6 were nausea and vomiting as on-target effects

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

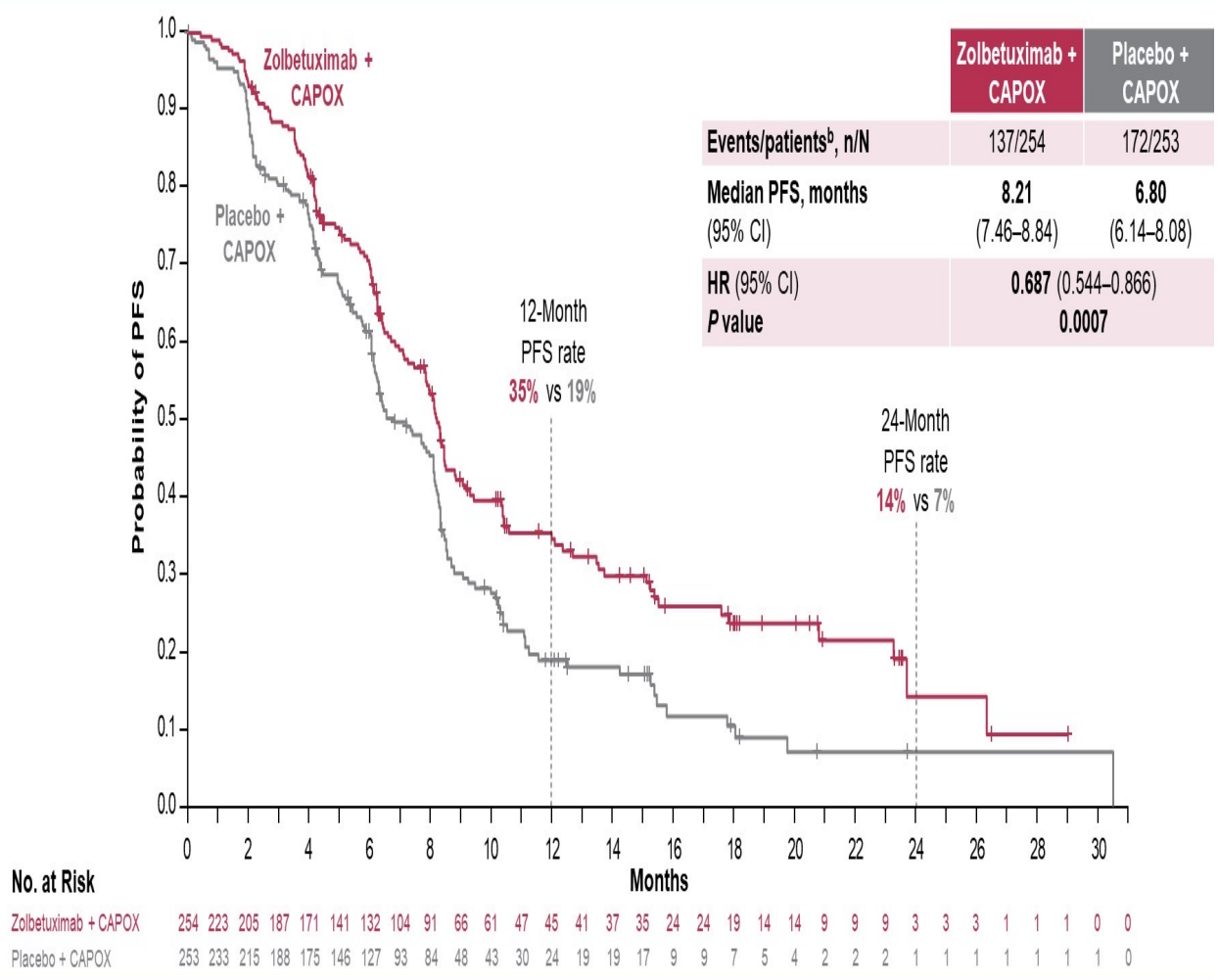
Shitara K et al. Gastrointestinal Cancers Symposium 2023;Abstract LBA292.

GLOW: A Phase III Study of First-Line Zolbetuximab and CAPOX for Claudin 18.2-Positive, HER2-Negative Advanced Gastric or Gastroesophageal Junction Adenocarcinoma



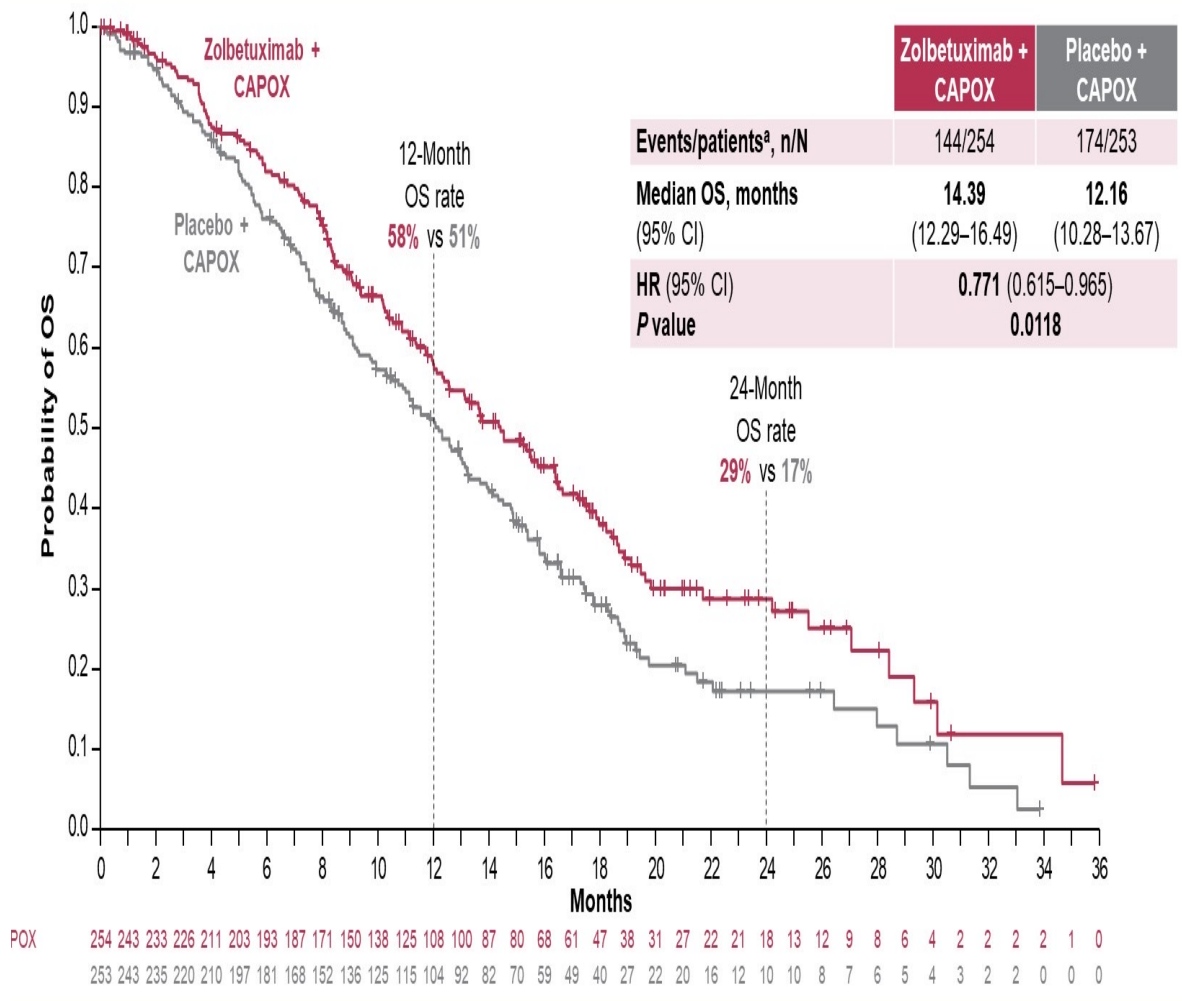
Shah M et al. ASCO Plenary Series, March 22, 2023;Abstract 405736.

PFS by Independent Review Committee (Primary Endpoint)



	Zolbetuximab + CAPOX	Placebo + CAPOX
Events/patients[b], n/N	137/254	172/253
Median PFS, months (95% CI)	8.21 (7.46–8.84)	6.80 (6.14–8.08)
HR (95% CI)	0.687 (0.544–0.866)	
P value	0.0007	

OS (Secondary Endpoint)



	Zolbetuximab + CAPOX	Placebo + CAPOX
Events/patients[a], n/N	144/254	174/253
Median OS, months (95% CI)	14.39 (12.29–16.49)	12.16 (10.28–13.67)
HR (95% CI)	0.771 (0.615–0.965)	
P value	0.0118	

Shah M et al. ASCO Plenary Series, March 22, 2023;Abstract 405736.

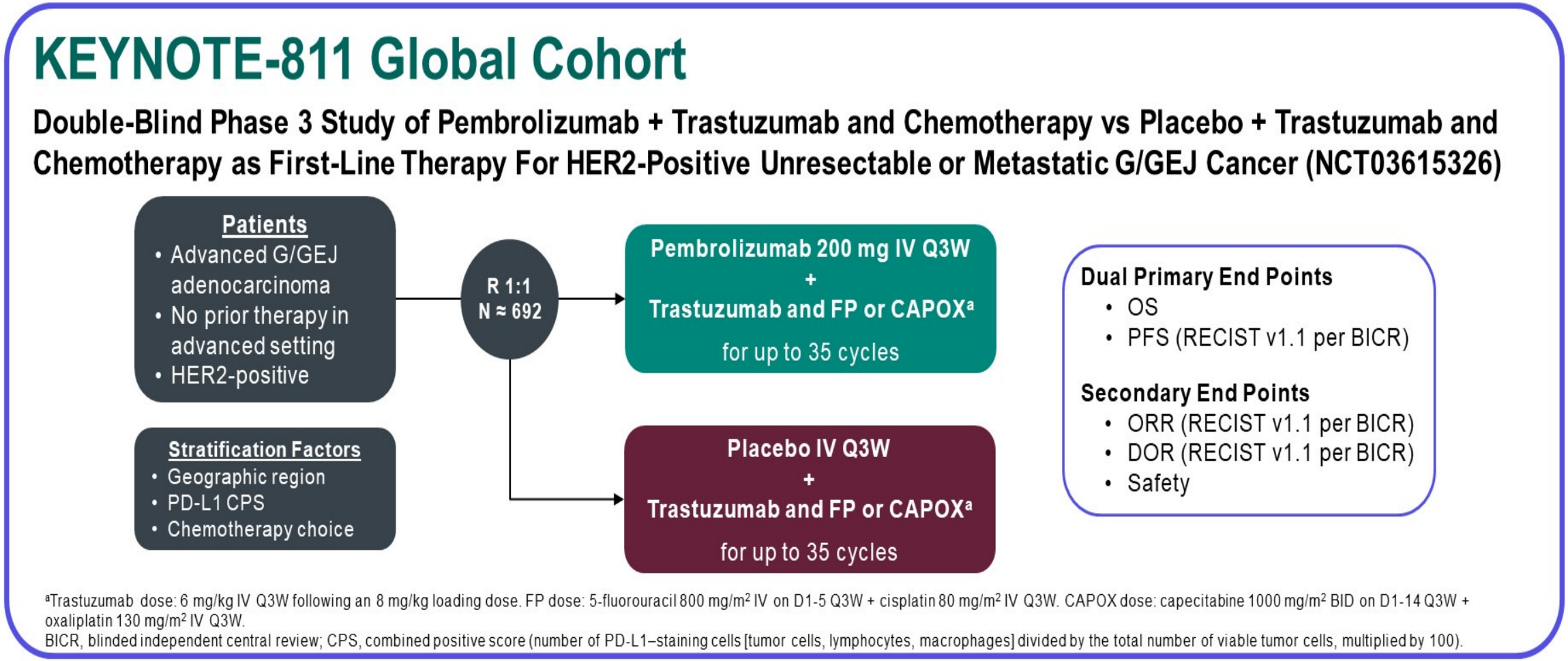
CLDN 18.2 - Summary

- CLDN 18.2 new target
- Zolbetuximab with mFOLFOX6 and CAPOX with improvement in PFS and OS
- Toxicity profile includes GI toxicity – nausea/vomiting
- Awaiting FDA approval

- Target for cell therapy and other trials, antibody-drug conjugate

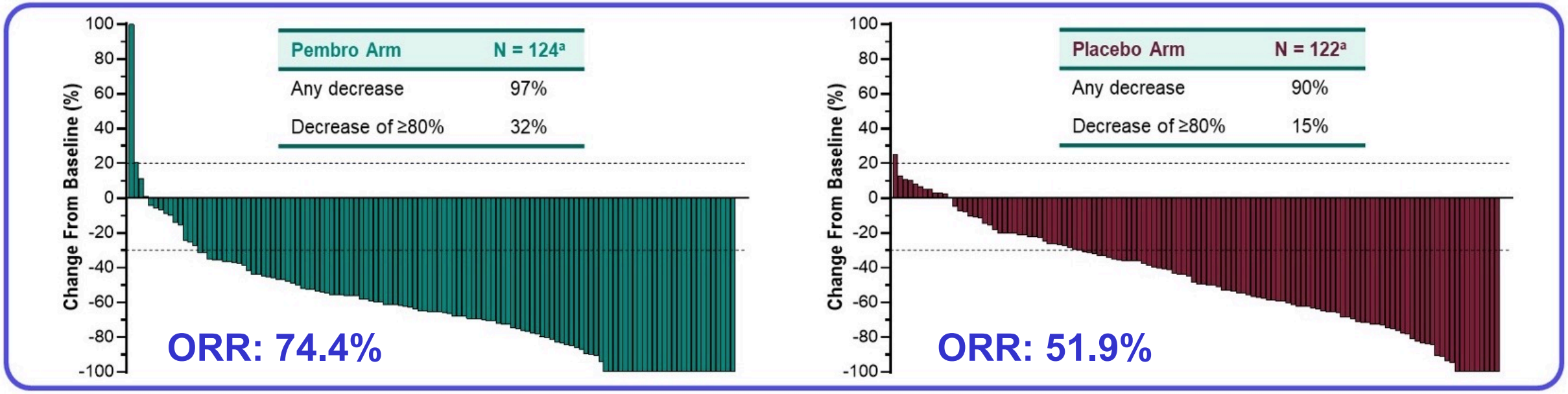
HER2-Positive

KEYNOTE-811: Pembrolizumab Plus Trastuzumab and Chemotherapy for HER2+ Metastatic Gastric or GEJ Cancer



Janjigian YY et al. ESMO World Congress on Gastrointestinal Cancer 2021;Abstract LBA4.

KEYNOTE-811: Confirmed Response at First Interim Analysis



ORR = objective response rate

Janjigian YY et al. ESMO World Congress on Gastrointestinal Cancer 2021;Abstract LBA4.

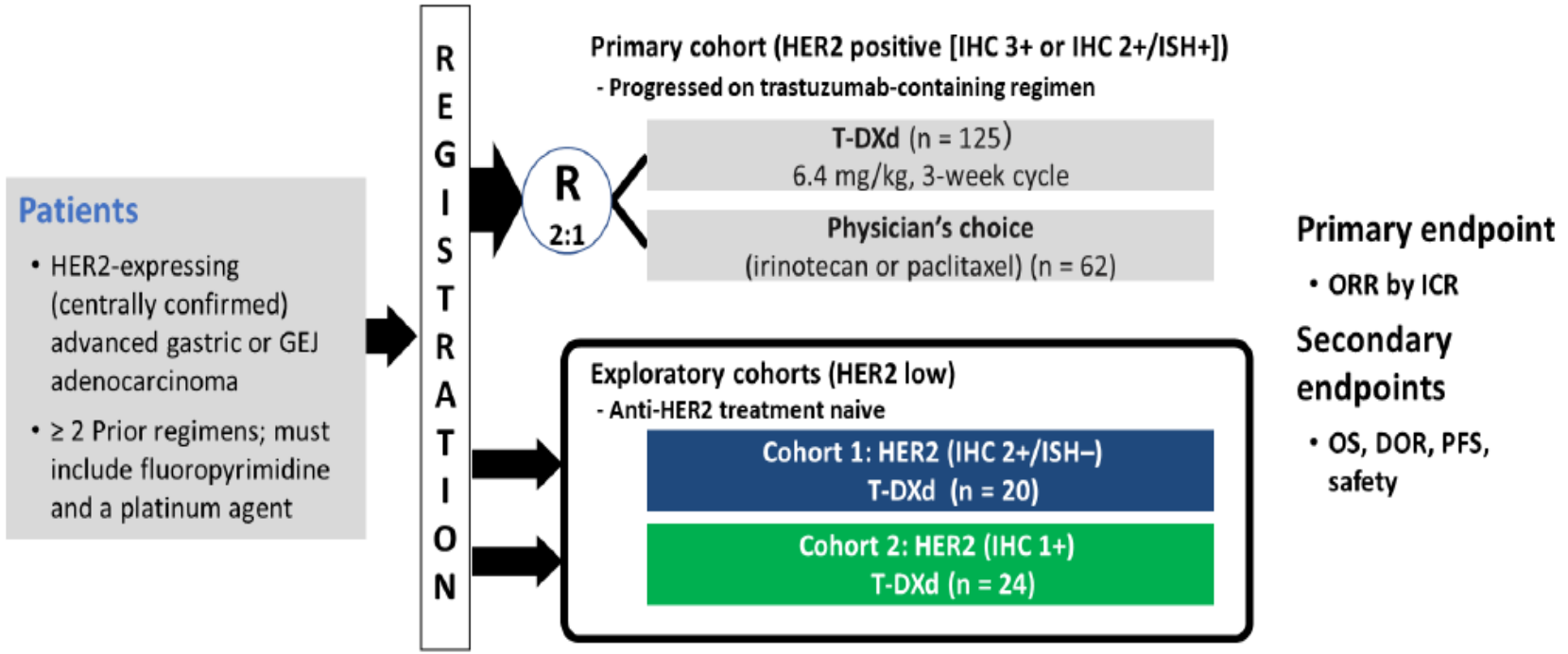
KEYNOTE 811 Press Release, June 2023

- PD-1 therapy, in combination with trastuzumab and chemotherapy **met one of its dual primary endpoints of progression-free survival (PFS)** … At a pre-specified interim analysis conducted by an independent Data Monitoring Committee, pembrolizumab in … the intention-to-treat (ITT) study population.

- Based on a pre-specified subgroup analysis by PD-L1 expression, the improvement in PFS observed in the ITT population was limited to patients whose tumors were **PD-L1 positive (Combined Positive Score [CPS] ≥1)**.

DESTINY-Gastric01

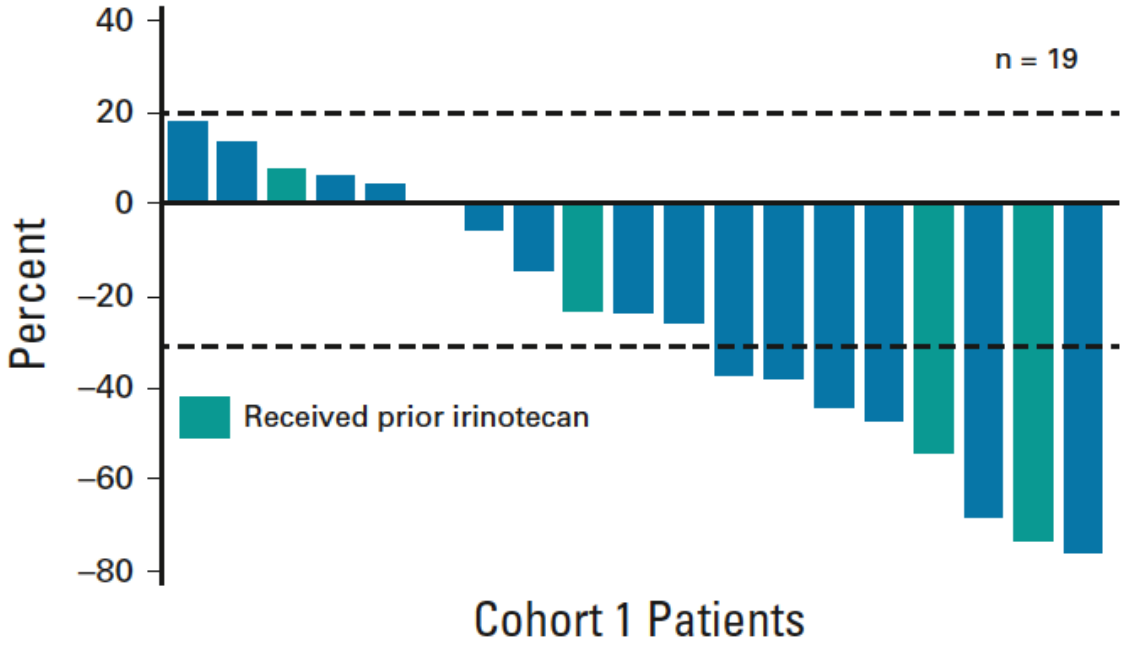
An open-label, multicenter, randomized, phase 2 study

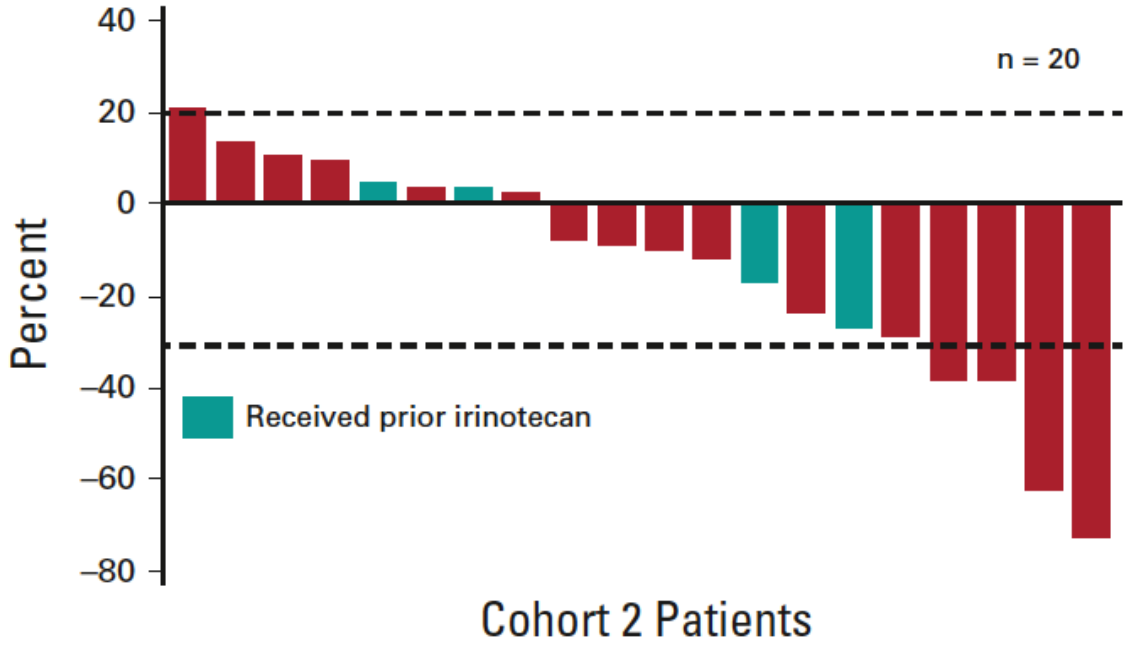


- All patients received T-DXd 6.4 mg/kg q3w
  - Cohort 1 IHC 2+/ISH− (n = 20); cohort 2 IHC 1+ (n = 24)
- Patients had not previously received anti-HER2 treatment
- Median of 2 prior lines of therapy for advanced/metastatic disease
  - 18% had irinotecan, 84% had ramucirumab, 32% had anti–PD-1/PD
- At data cutoff (8 November 2019), no patients in cohort 1 and 2 in cohort 2 (8.3%) remained on treatment

Shitara K, et al. *Lancet Oncol*. 2018;19:1437-48.
Yamaguchi K et al. *J Clin Oncol* 2023 February 1;41(4):816-25.

DESTINY-Gastric01: Best Percent Change from Baseline Tumor Size in Patients with Treatment-Naïve HER2-Low Advanced Gastric or GEJ Adenocarcinoma





Yamaguchi K et al. *J Clin Oncol* 2023 February 1;41(4):816-25.

Summary - HER2 Positive Cancer

- Chemotherapy with Trastuzumab and Pembrolizumab improved RR and PFS in PDL1>5 patient
- Refractory options – Trastuzumab-deruxtecan

- HER2 **low** being investigated with Ab-drug conjugates
- Multiple investigational Agents – TKI, Ab-drug, cell therapy

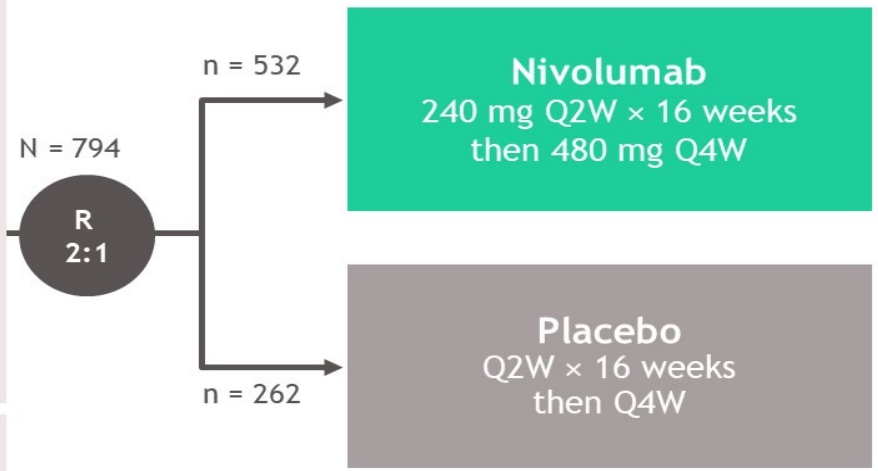
Perioperative Therapy Esophagogastric Cancers

CheckMate 577 study design

- CheckMate 577 is a global, phase 3, randomized, double-blind, placebo-controlled trial[a]

Key eligibility criteria
- Stage II/III EC/GEJC
- Adenocarcinoma or squamous cell carcinoma
- Neoadjuvant CRT + surgical resection (R0,[b] performed within 4-16 weeks prior to randomization)
- Residual pathologic disease
  - ≥ ypT1 or ≥ ypN1
- ECOG PS 0-1

Stratification factors
- Histology (squamous versus adenocarcinoma)
- Pathologic lymph node status (≥ ypN1 versus ypN0)
- Tumor-cell PD-L1 expression (≥ 1% versus < 1%[c])



Total treatment duration of up to 1 year[d]

Primary endpoint:
- DFS[e]

Secondary endpoints:
- OS[f]
- OS rate at 1, 2, and 3 years

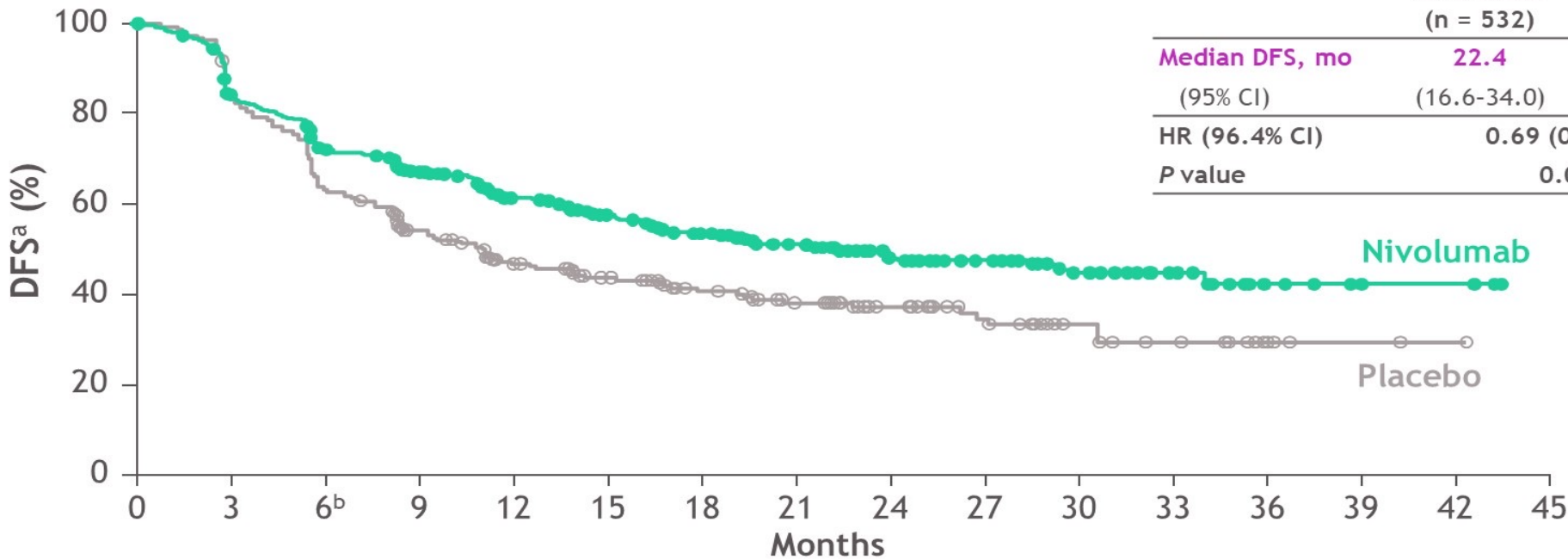
Exploratory endpoints included:
- Safety
- DMFS[g]
- PFS2[h]
- QoL

- Median follow-up was 24.4 months (range, 6.2–44.9)[i]
- Geographical regions: Europe (38%), United States and Canada (32%), Asia (13%), rest of the world (16%)

[a]ClinicalTrials.gov. NCT02743494; [b]Patients must have been surgically rendered free of disease with negative margins on resected specimens defined as no vital tumor present within 1 mm of the proximal, distal, or circumferential resection margins; [c]< 1% includes indeterminate/nonevaluable tumor cell PD-L1 expression; [d]Until disease recurrence, unacceptable toxicity, or withdrawal of consent; [e]Assessed by investigator, the study required at least 440 DFS events to achieve 91% power to detect an average HR of 0.72 at a 2-sided α of 0.05, accounting for a prespecified interim analysis; [f]The study will continue as planned to allow for future analysis of OS; [g]DMFS is defined as the time between randomization and the first distant recurrence or death, whichever occurs first; [h]PFS2 is defined as the time from randomization to progression after the first subsequent systemic therapy, initiation of second subsequent systemic therapy, or death, whichever is earlier; [i]Time from randomization date to clinical data cutoff (May 12, 2020).

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

Disease-free survival (DFS)



	Nivolumab (n = 532)	Placebo (n = 262)
Median DFS, mo	22.4	11.0
(95% CI)	(16.6-34.0)	(8.3-14.3)
HR (96.4% CI)	0.69 (0.56-0.86)	
P value	0.0003[c]	

No. at risk																
Nivolumab	532	430	364	306	249	212	181	147	92	68	41	22	8	4	3	0
Placebo	262	214	163	126	96	80	65	53	38	28	17	12	5	2	1	0

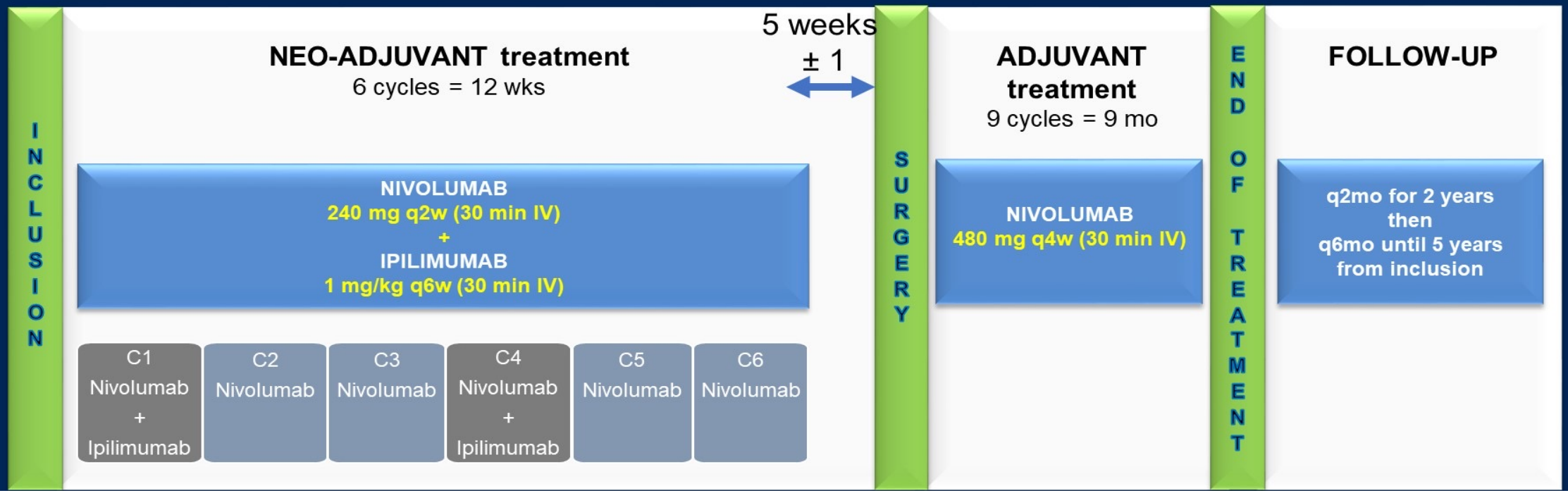
- Nivolumab provided superior DFS with a 31% reduction in the risk of recurrence or death and a doubling in median DFS versus placebo

[a]Per investigator assessment; [b]6-month DFS rates were 72% (95% CI, 68-76) in the nivolumab arm and 63% (95% CI, 57-69) in the placebo arm; [c]The boundary for statistical significance at the prespecified interim analysis required the *P* value to be less than 0.036.

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

Neoadjuvant nivolumab plus ipilimumab and adjuvant nivolumab in MSI/dMMR gastric or GEJ adenocarcinoma: NEONIPIGA phase II GERCOR Study

- Phase II study evaluating efficacy of neo-adjuvant nivolumab and ipilimumab followed by adjuvant nivolumab in pts with resectable OGA MSI/dMMR, T2-T4 NxM0
- The primary objective was pathological complete response rate (pCRR).



Andre, Thierry et al, ASCO GI 2022; Abstract 244

Surgery and TNM and Tumor Regression Grading (TRG)

Type of surgery (N=29)	N	%
R0	29	100
Total oesogastrectomy	1	3,5
Total gastrectomy	7	24
4/5 gastrectomy	9	31
Lewis-Santy procedure	11	38
Pancreaticoduodenectomy	1	3,5

ypT stage (N=32)	
ypT0*	19
ypT1a	1
ypT1b	2
ypT2	2
ypT3	5
unknown**	3
ypN stage (N=32)	
ypN0	23
ypN1	6
unknown*	3

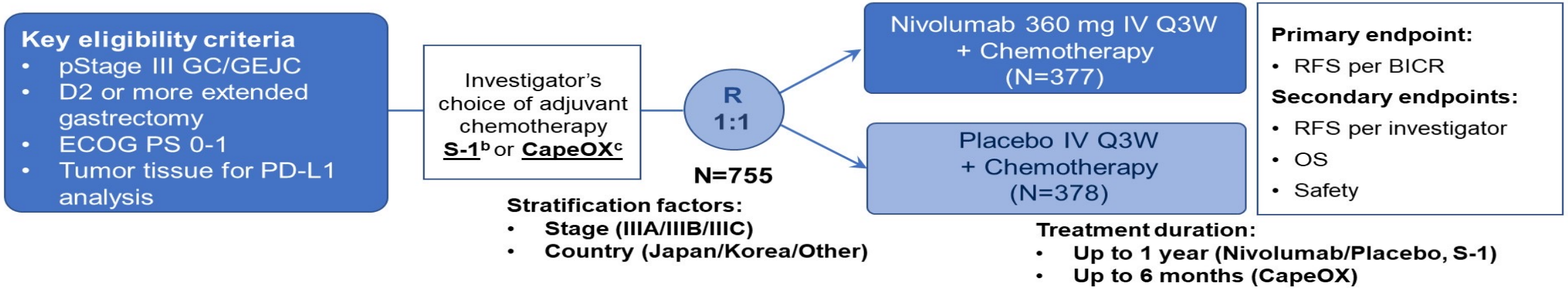
TRG Mandard (N=29)	N	%
TRG 1: complete regression/fibrosis with no tumor cells	17	58.6
TRG 2: fibrosis with scattered tumor cells	4	13.8
TRG 3: fibrosis and tumor cells with a dominance of fibrosis	2	6.9
TRG 4: fibrosis & tumor cells with dominance of tumor cells	4	13.8
TRG 5: tumor without evidence of regression	2	6.9
TRG Becker (N=29)		
TRG 1a: complete tumor regression without residual tumor	17	58.6
TRG 1b: < 10% residual tumor per tumor bed	4	13.8
TGR 2: 10% to 50% residual tumor	2	6.9
TRG 3: > 50% residual tumor cells	6	21.7

- * 2 patients ypT0 and ypN1 (residual tumoral cells < 10% in only one node)
- ** 3 patients without surgery, 1 in metastatic PD and 2 in complete response in endoscopy with no tumoral cell on biopsy

Andre, Thierry et al, ASCO GI 2022; Abstract 244

ATTRACTION-5: a Phase 3 study of nivolumab plus chemotherapy as postoperative adjuvant treatment for stage III gastric or gej cancer

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



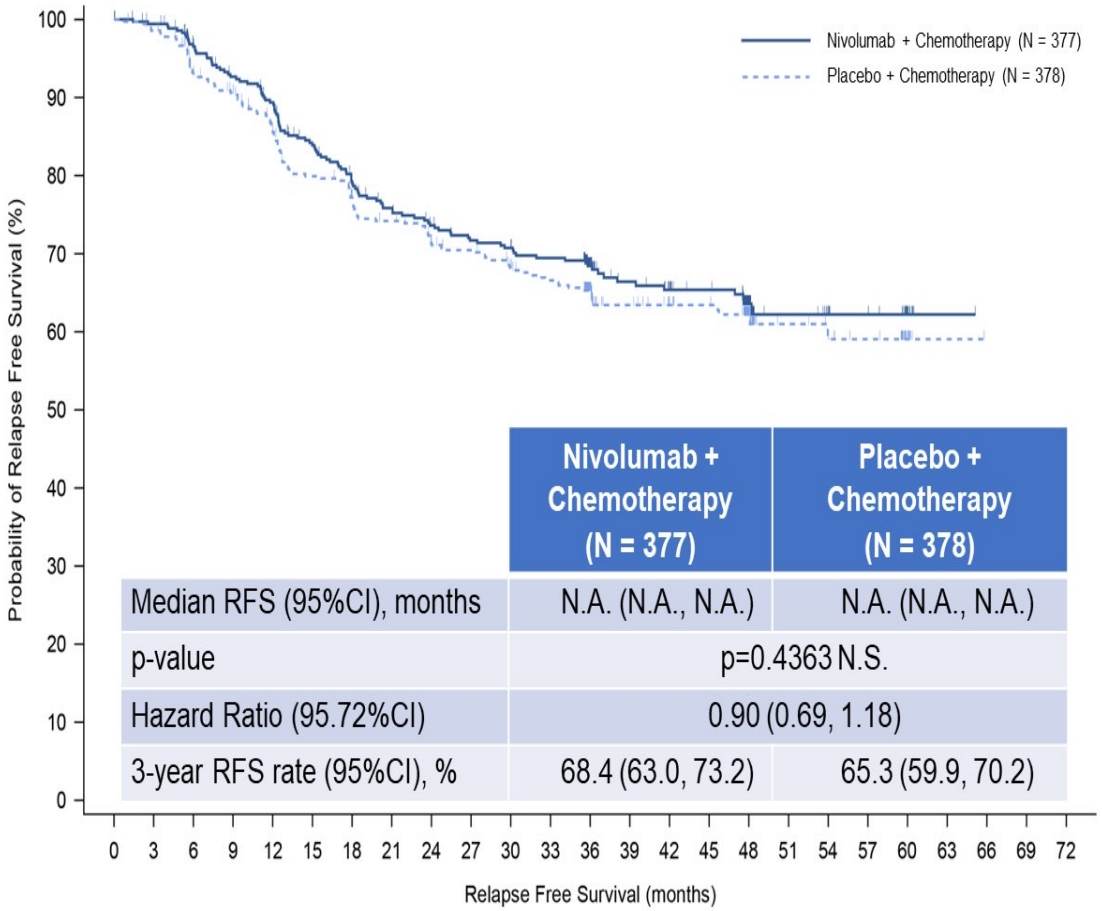
- Planned sample size: 700 patients (assuming HR=0.67; 3-year RFS, 71% vs 60%)
- Patients were randomized from February 2017 to August 2019
- All data are based on a clinical data cutoff of August 2022, at which point the minimum follow-up after the last patient randomized was 36 months

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

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

Terashima, Masanori, ASCO 2023

Primary endpoint: RFS per BICR



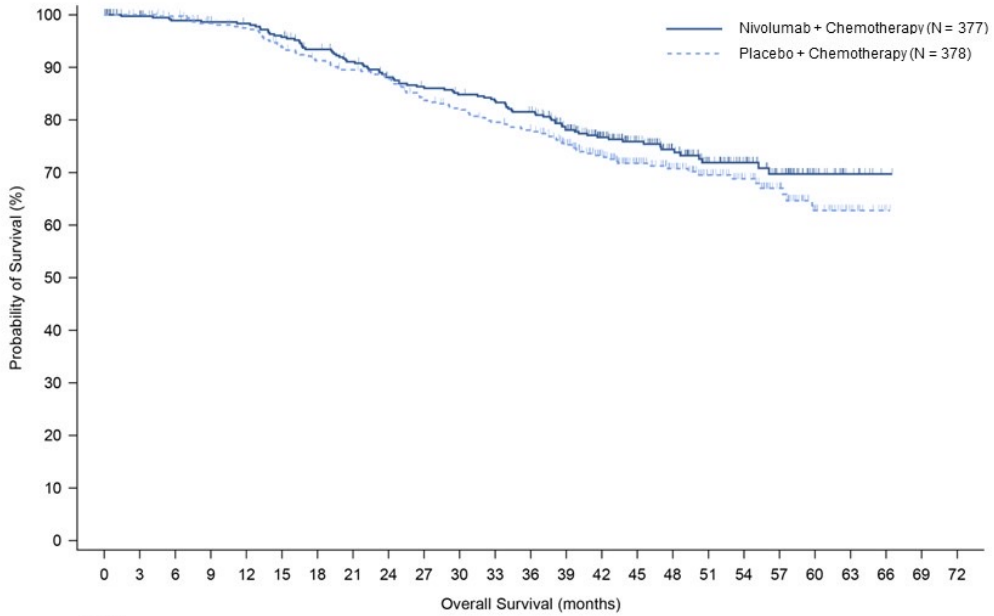
	Nivolumab + Chemotherapy (N = 377)	Placebo + Chemotherapy (N = 378)
Median RFS (95%CI), months	N.A. (N.A., N.A.)	N.A. (N.A., N.A.)
p-value	p=0.4363 N.S.	
Hazard Ratio (95.72%CI)	0.90 (0.69, 1.18)	
3-year RFS rate (95%CI), %	68.4 (63.0, 73.2)	65.3 (59.9, 70.2)

At Risk

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

Secondary endpoint: OS

OS



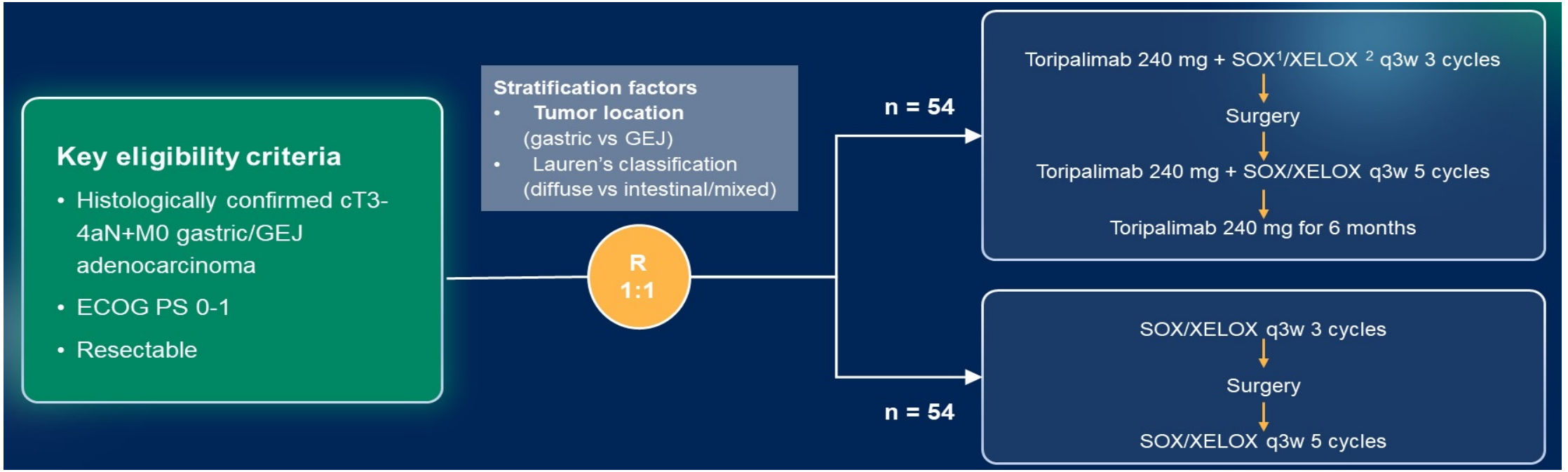
At Risk

Nivolumab + Chemotherapy	377	368	356	347	343	334	320	309	296	289	283	278	270	244	203	166	131	101	79	57	27	9	1	0	0
Placebo + Chemotherapy	378	367	364	352	345	329	318	311	304	285	277	267	259	236	199	160	132	104	85	60	30	12	2	0	0

	Nivolumab + Chemotherapy (N = 377)	Placebo + Chemotherapy (N = 378)
Median OS (95%CI), months	N.A. (N.A., N.A.)	N.A. (N.A., N.A.)
p-value	–	
Hazard ratio (95%CI)	0.88 (0.66, 1.17)	
3-year OS rate (95%CI), %	81.5 (77.0, 85.3)	78.0 (73.3, 82.1)

Terashima, Masanori, ASCO 2023

Perioperative PD-1 antibody toripalimab plux SOX or XELOX vs chemo alone; gastric, GEJ, prospective, randomized, open-lapel phase II



Primary endpoint

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

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

Yuan, Shuquiang et al., ASCO 2023

Pathological outcomes-tumor regression grade

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

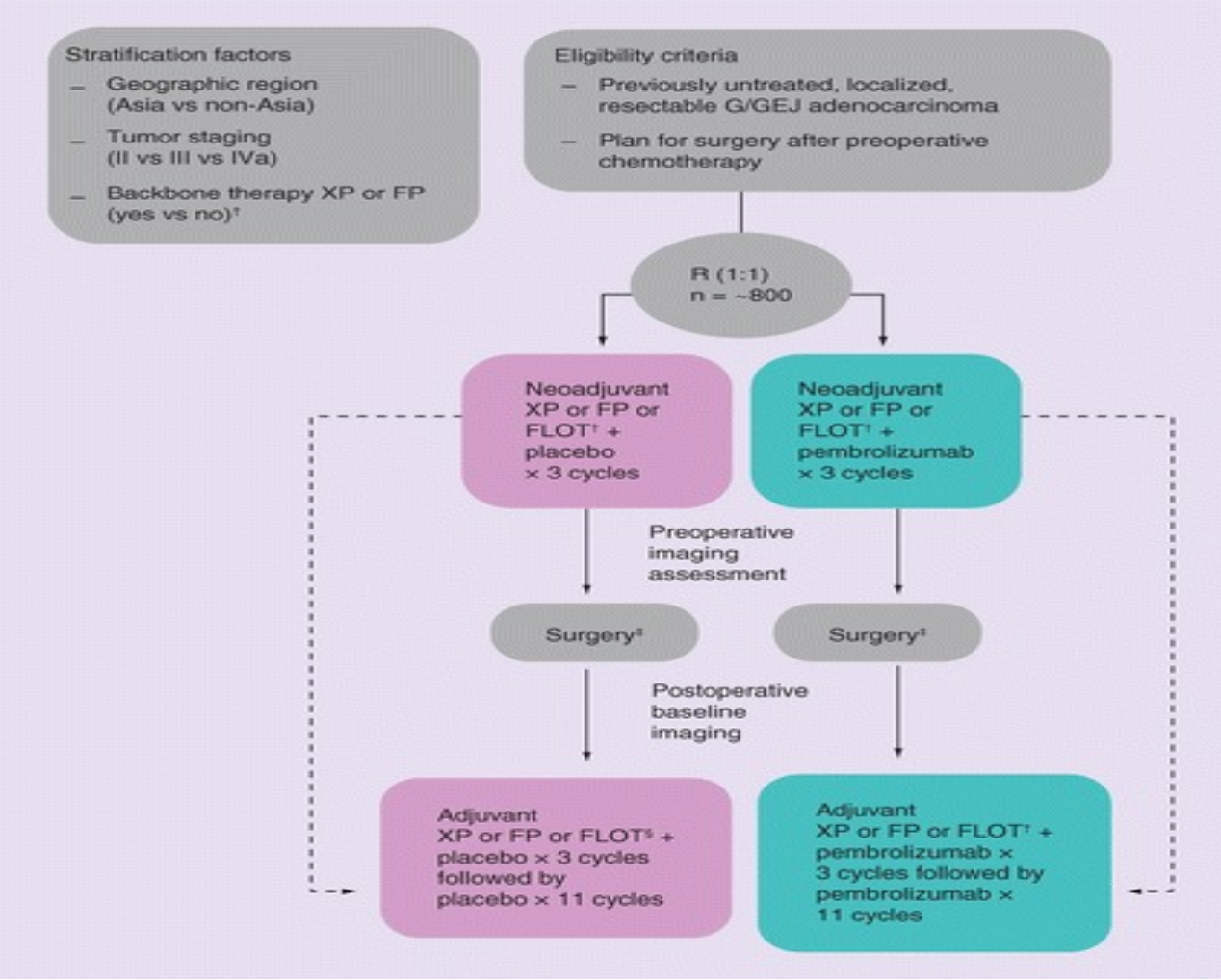
Primary endpoint

Yuan, Shuquiang et al., ASCO 2023

Pathological outcomes-TNM staging

	Toripalimab + chemotherapy (n = 54)	Chemotherapy (n = 54)
Pathological tumor stage (ypT)		
ypT0 (pCR of primary tumor)	**13 (24%)**	**5 (9%)**
ypT1	7 (13%)	5 (9%)
ypT2	5 (9%)	2 (4%)
ypT3	20 (37%)	28 (52%)
ypT4	6 (11%)	12 (22%)
Combined ypT0-2	**25 (46%)**	**12 (22%)**
Combined ypT3-4	26 (48%)	40 (74%)
Pathological node stage (ypN)		
ypN0	22 (41%)	21 (39%)
ypN1	9 (17%)	11 (20%)
ypN2	11 (20%)	9 (17%)
ypN3	9 (17%)	11 (20%)
Combined ypN0-1	31 (57%)	32 (59%)
Combined ypN2-3	20 (37%)	20 (37%)

KEYNOTE 585 Press Release, June 2023



"At a pre-specified interim analysis conducted by an independent Data Monitoring Committee, **the study met one of its primary endpoints of pathological complete response (pCR) rate and demonstrated a statistically significant improvement in pCR rates compared with chemotherapy alone**. For the primary endpoint of event-free survival (EFS), there was an improvement in the pembrolizumab arm; however, **results did not meet statistical significance per the pre-specified statistical analysis plan**. The endpoint of overall survival (OS) was not formally tested since superiority was not reached for EFS."

Perioperative Therapy - Summary

- Adjuvant immunotherapy in Esophageal Adenocarcinoma/SCC, CheckMate 577
  - Await OS
- Addition of IO did not improve OS/EFS
  - ATTRACTION 5
  - KEYNOTE 585 – press release
- Improvement in TRG/path CR
- MSI High perioperative therapy – IO only
- Awaiting final results of perioperative trials
  - KEYNOTE 585 - press release
  - Matterhorn FLOT/IO

Coexpression of Targets

Table 2. Immunohistochemical profiling of the considered series according to CLDN18 status (note that the sum of patients does not add to 350 patients for all the parameters due to missing clinical data or exhausting tumor tissue).

Patients' Characteristics		Total 350 *n*. (%)	CLDN18 < 75% Tot 233 *n*. (% of the Total)	CLDN18 ≥ 75% Tot 117 *n*. (%of the Total)	*p* Value
MMRd	Yes	54 (15.4)	39 (11.1)	15 (4.3)	0.2424
	No	296 (84.6)	194 (55.4)	102 (29.1)	
HER 2 status	Positive	52 (14.9)	35 (10.0)	17 (4.9)	1.000
	Negative	298 (85.1)	198 (56.6)	100 (28.6)	
PD-L1 CPS ≥ 1	Yes	98 (28)	68 (19.4)	30 (8.6)	0.5685
	No	252 (72)	165 (47.14)	87 (24.86)	
PD-L1 CPS ≥ 5	Yes	71 (20.29)	50 (14.29)	21 (6)	0.5290
	No	279 (79.71)	183 (52.29)	96 (27.43)	
EBER	Positive	8 (2.3)	1 (0.3)	7 (20.0)	**0.0024**
	Negative	342 (97.7)	232 (66.3)	110 (31.4)	
p53 status	Altered	168 (48.0)	111 (31.7)	57 (16.3)	0.9676
	wild type	181 (52.0)	121 (34.6)	60 (17.1)	
E-Cadheri *n* status	Positive	268 (77.0)	177 (50.9)	91 (26.1)	0.9148
	Negative	80 (23.0)	54 (15.5)	26 (7.5)	

Pellino, A J. Pers. Med. 2021,11, 1095.

Molecular Testing in Esophagogastric Cancer

- MMR testing in all Esophagogastric Cancers

- CPS testing in Esophagogastric CA
  - Nivolumab + chemo in CPS $\geq$ 5 HER2 negative GEA (CM649)
  - Pembrolizumab + chemo in CPS $\geq$ 10 HER2 negative esophageal CA (KN590)
  - Nivolumab/ipilumumab & Nivo +chemo in CPS$\geq$1 (CM 648)

- HER2 testing in all Esophagogastric CA
  - Trastuzumab + chemo + pembrolizumab in 1L HER2+ GEA (Keynote-811)
  - Trastuzumab deruxtecan (DS-8201) in 2L+ HER2+ GEA (Destiny-Gastric-01/02)

- CLDN18.2 – new treatment option
  - Zolbetuximab 1L (GLOW, SPOTLIGHT)