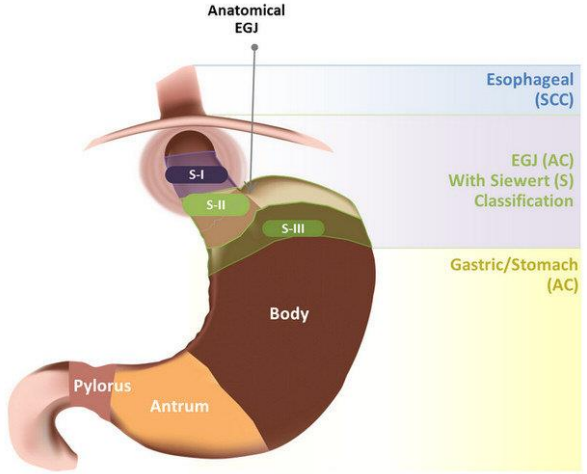
20th Annual California Cancer Consortium Conference
August 24, 2024



New Developments in Esophageal and Gastric Cancer

Sandy Algaze, MD

USC Norris Comprehensive Cancer Center
Keck Medicine of USC

Update of Esophagogastric Cancer

Early Stage:

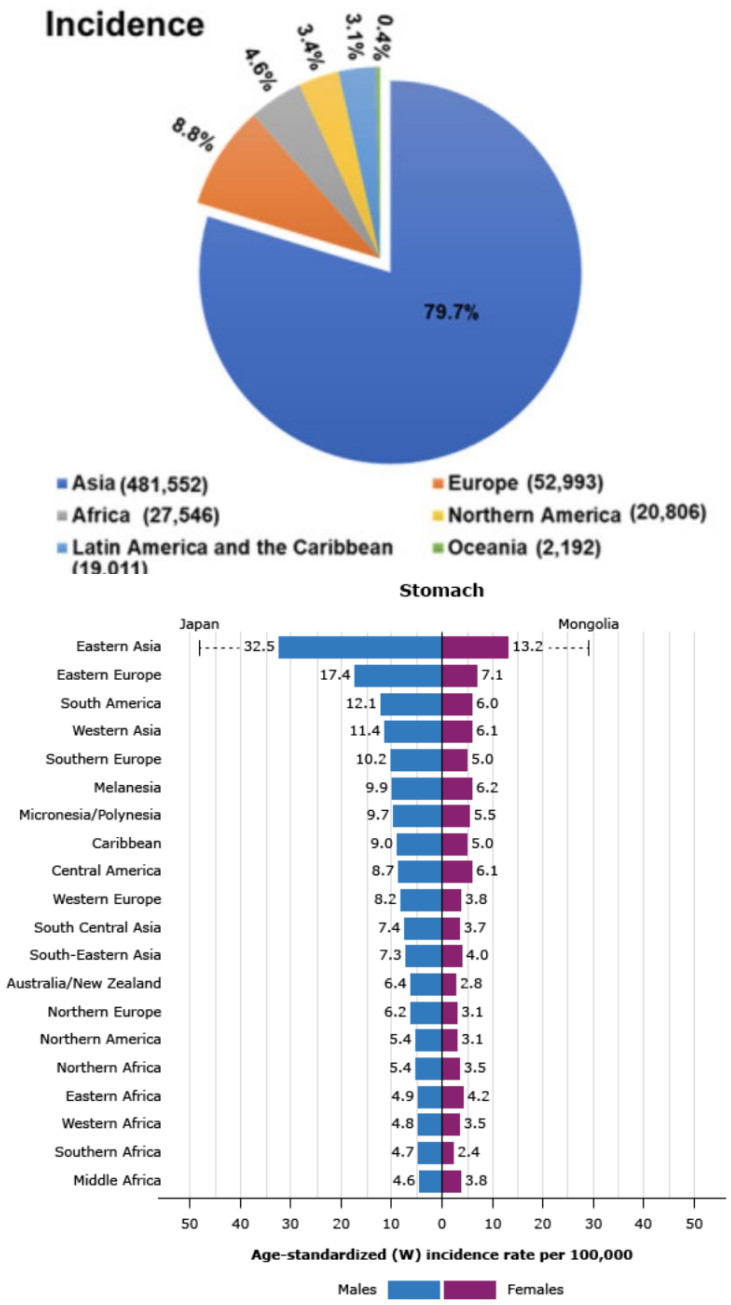
- Perioperative FLOT vs Chemoradiation
- Perioperative Chemotherapy and Immunotherapy

Advanced:

- First line Chemotherapy and Immunotherapy
- Claudin 18.2 – New Target
- HER2 + Gastric Cancer
- Novel Targets

Esophagogastric Cancers

- > 22,000 annual cases of esophageal cancer (EC) with > 16,000 deaths from the disease in the US
- Gastric cancer is the fifth leading cause of cancer and fourth leading cause of cancer deaths worldwide
- incidence varies worldwide by geographic region



GLOBOCAN 2020

Work up and Staging

WORKUP

- H&P
- Upper gastrointestinal (GI) endoscopy and biopsy[a]
- Chest/abdomen CT with oral and IV contrast
- Pelvis CT with contrast as clinically indicated
- FDG-PET/CT evaluation (skull base to mid-thigh) if no evidence of M1 disease
- Complete blood count (CBC) and comprehensive chemistry profile
- Endoscopic ultrasound (EUS), if no evidence of M1 unresectable disease
- Endoscopic resection (ER) is recommended for the accurate staging of early-stage cancers (T1a or T1b).[a,b] Early-stage cancers can best be diagnosed by ER
- Biopsy of metastatic disease as clinically indicated
- Universal testing for microsatellite instability (MSI) by PCR/next-generation sequencing (NGS) or MMR by IHC is recommended in all newly diagnosed patients[c]
- Programmed death ligand 1 (PD-L1) testing if advanced/metastatic disease is documented/suspected[c]
- HER2 testing if metastatic adenocarcinoma is documented/suspected[c]
- NGS should be considered[c]
- Bronchoscopy, if tumor is at or above the carina with no evidence of M1 disease
- Assign Siewert category[d]
- Nutritional assessment and counseling
- Smoking cessation advice, counseling, and pharmacotherapy as indicated[e]
- Screen for family history[f]

CLINICAL STAGE[g]	HISTOLOGIC CLASSIFICATION[c]	
Stage I–IVA[g,h] (locoregional disease, except T4b or unresectable N3[h])	Squamous cell carcinoma	ESOPH-2
	Adenocarcinoma	ESOPH-11
Stage IVA[g] (includes T4b or unresectable N3 only) and IVB (metastatic disease)	Squamous cell carcinoma	ESOPH-10
	Adenocarcinoma	ESOPH-19

NCCN Guidelines Esophageal and Esophagogastric Junction Cancers Version 4.2024

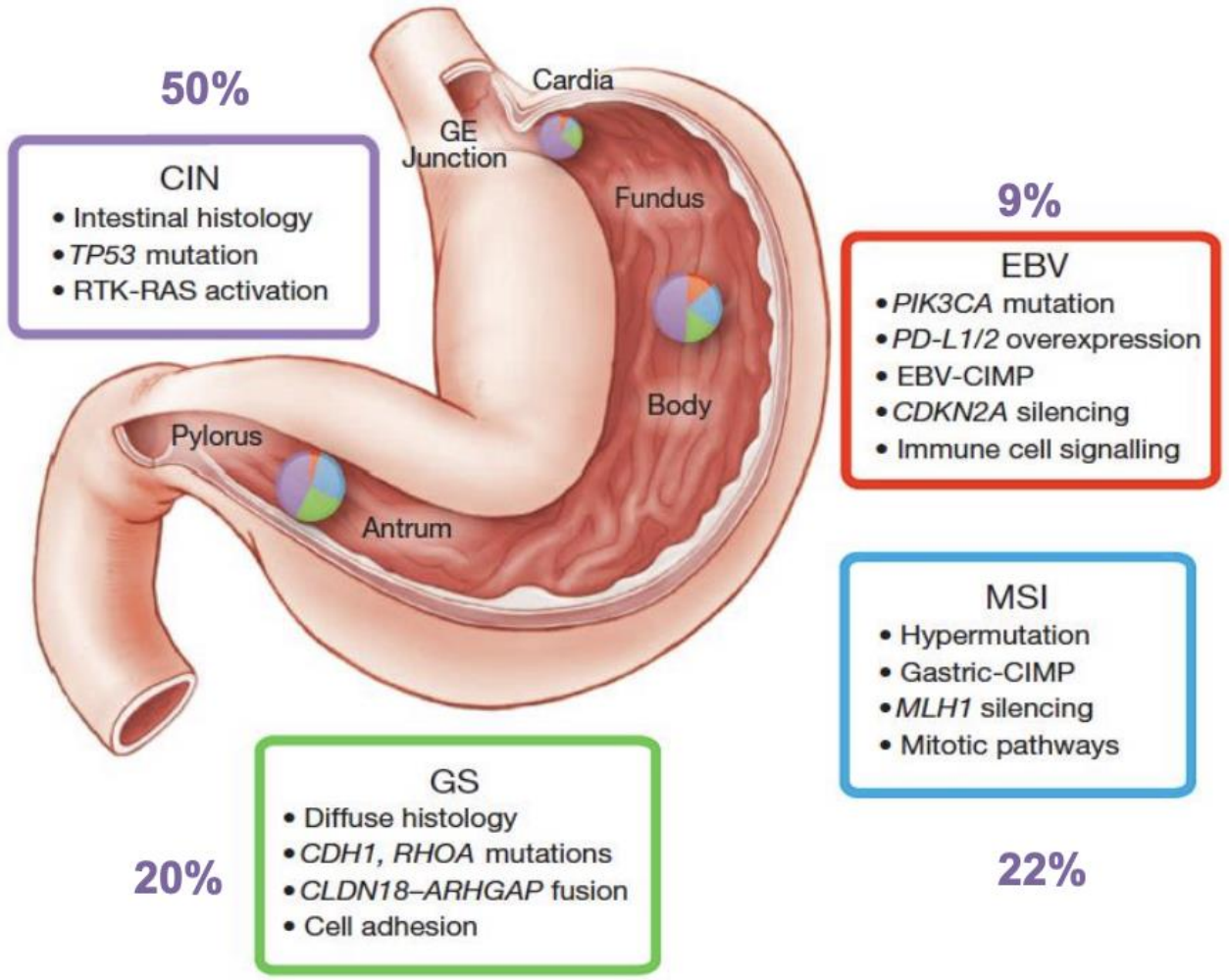
Molecular Testing in Esophagogastric Cancer

- **MMR** testing in all Esophagogastric Cancers
- **PDL-1** CPS testing in Esophagogastric CA
  - Nivolumab + chemo in CPS ≥ 5 HER2 negative GEA (CM649)
  - Pembrolizumab + chemo in CPS ≥ 10 esophageal CA (KN590)
  - Pembrolizumab +chemo in CPS ≥1 gastric, GEJ (KN859)
- **HER2** testing in all Esophagogastric CA
  - Trastuzumab + chemo + pembrolizumab in 1L HER2+ GEA (KN-811) in CPS ≥1
  - Trastuzumab deruxtecan (DS-8201) in 2L+ HER2+ GEA (Destiny-Gastric-01/02)
- **CLDN18.2** – emerging treatment option
  - Zolbetuximab 1L (GLOW, SPOTLIGHT)

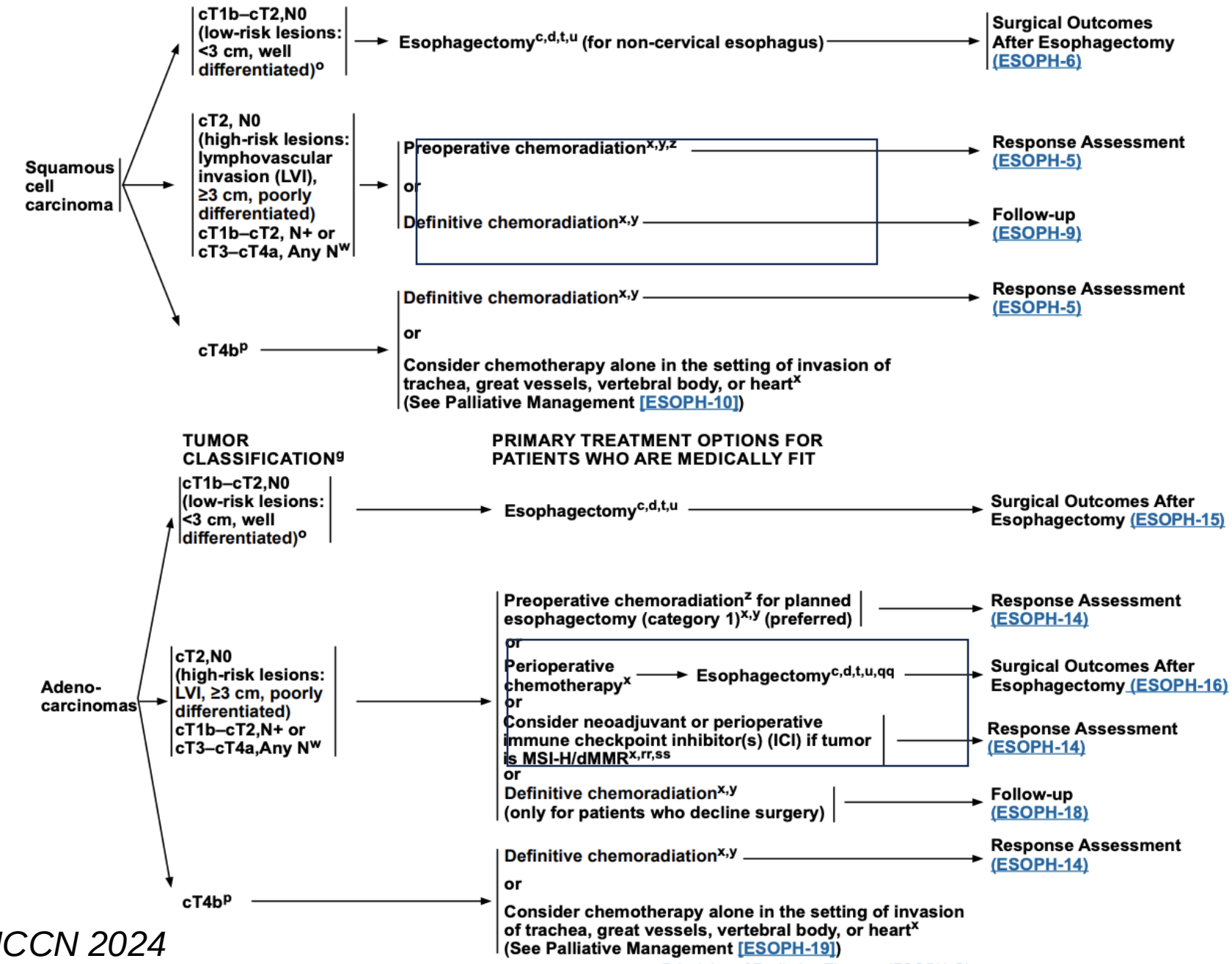
Patients' Characteristics		Total 350 *n.* (%)	CLDN18 < 75% Tot 233 *n.* (% of the Total)	CLDN18 ≥ 75% Tot 117 *n.* (%of the Total)	*p* Value
MMRd	Yes	54 (15.4)	39 (11.1)	15 (4.3)	0.2424
	No	296 (84.6)	194 (55.4)	102 (29.1)	
HER 2 status	Positive	52 (14.9)	35 (10.0)	17 (4.9)	1.000
	Negative	298 (85.1)	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 Classification

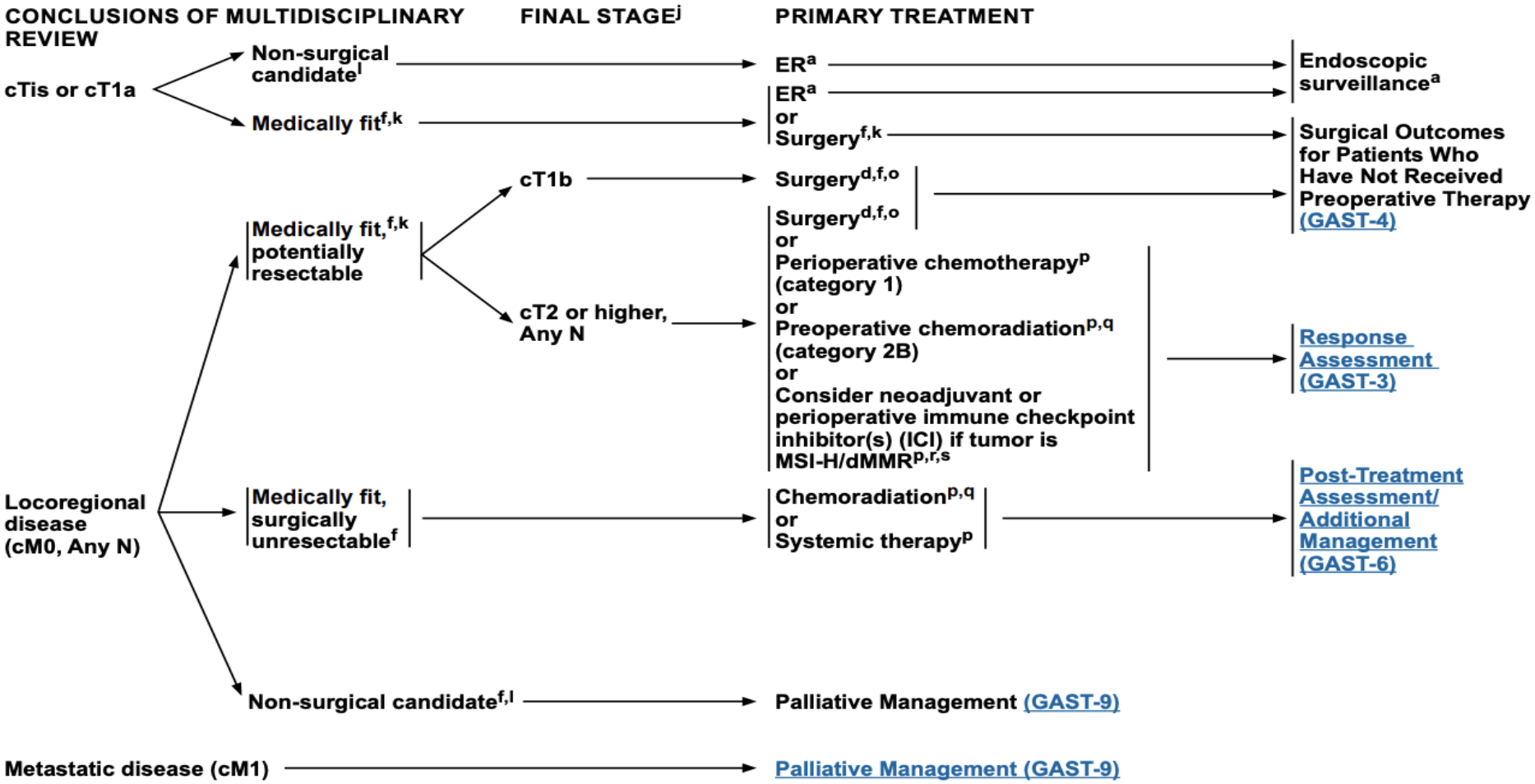


Early Esophageal Cancer



NCCN 2024

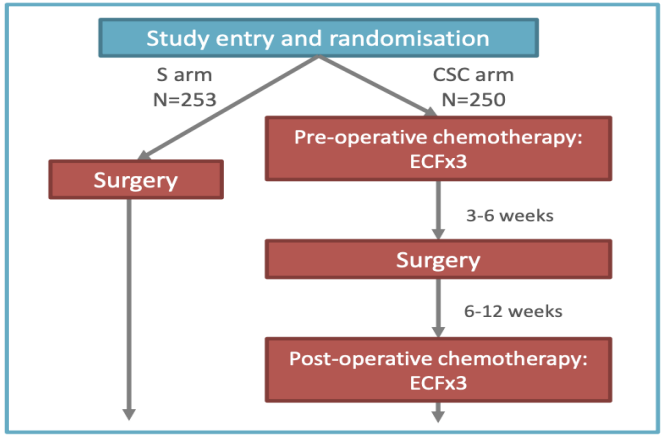
Early Gastric Cancer

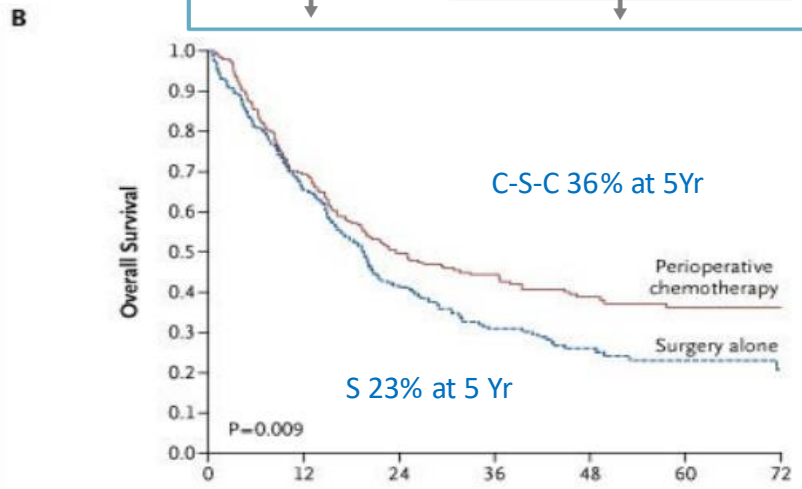


NCCN 2024

Perioperative Chemotherapy

MAGIC Trial





C-S-C 36% at 5Yr

S 23% at 5 Yr

	2 year survival	5 year survival	Median survival
CSC	50%	36%	24 mo
S	41%	23%	20 mo
Benefit to CSC arm	9%	13%	4 mo

Cunningham et al. NEJM 2012

FLOT4

Randomised, multicentre, Phase II/III Study

- Gastric or EGJ cancer typ I-III
- Medically and anatomically operable
- cT2-4/cN-any/cM0 or cT-any/cN+/cM0

Stratification → R → n=716

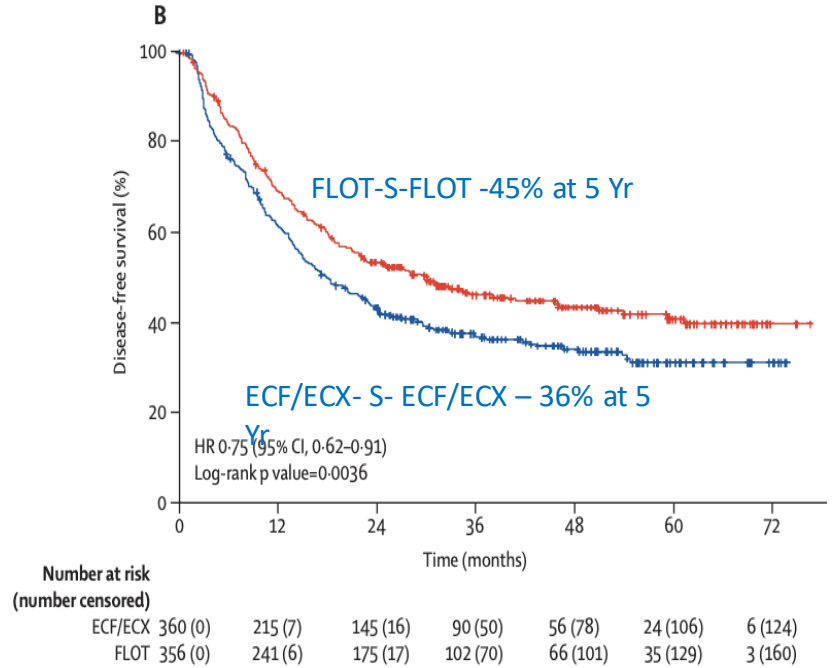
FLOT x4 - RESECTION - FLOT x4

FLOT: Docetaxel 50mg/m2, d1; 5-FU 2600 mg/m², d1; Leucovorin 200 mg/m², d1; Oxaliplatin 85 mg/m², d1, q2w

ECF/ECX x3 - RESECTION - ECF/ECX x3

ECF/ECX: Epirubicin 50 mg/m2, d1; Cisplatin 60 mg/m², d1; 5-FU 200 mg/m² (or Capecitabin 1250 mg/m² p.o. geteilt in 2 doses d1-d21), q2w

Stratification: **ECOG** (0 or 1 *vs.* 2), **localisation** (GEJ Type I *vs.* Type II/III *vs.* Gastric), **age** (< 60 *vs.* 60-69 *vs.* ≥70 years) and **nodal status** (cN+ *vs.* cN-)



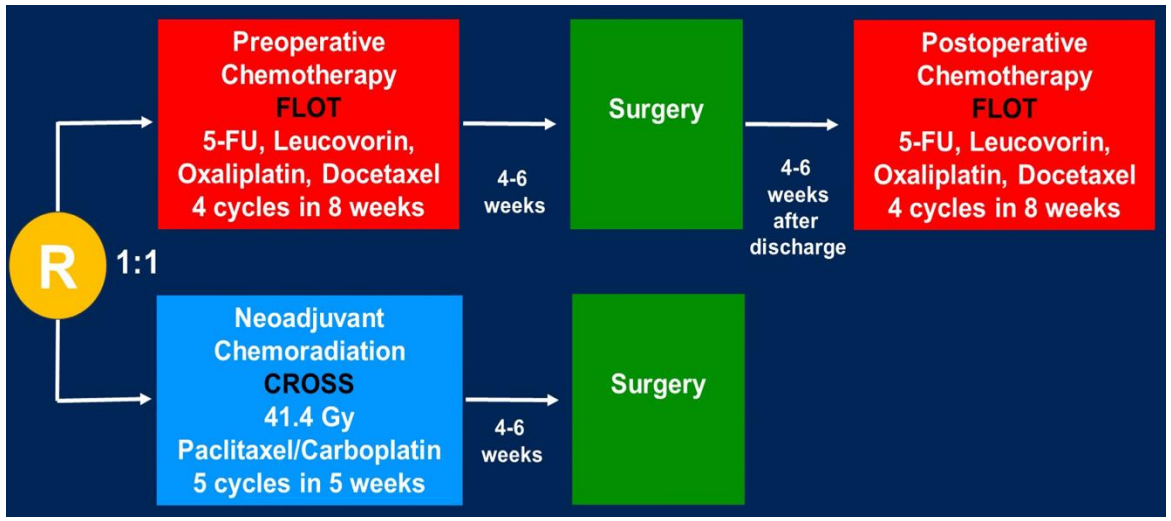
FLOT-S-FLOT -45% at 5 Yr

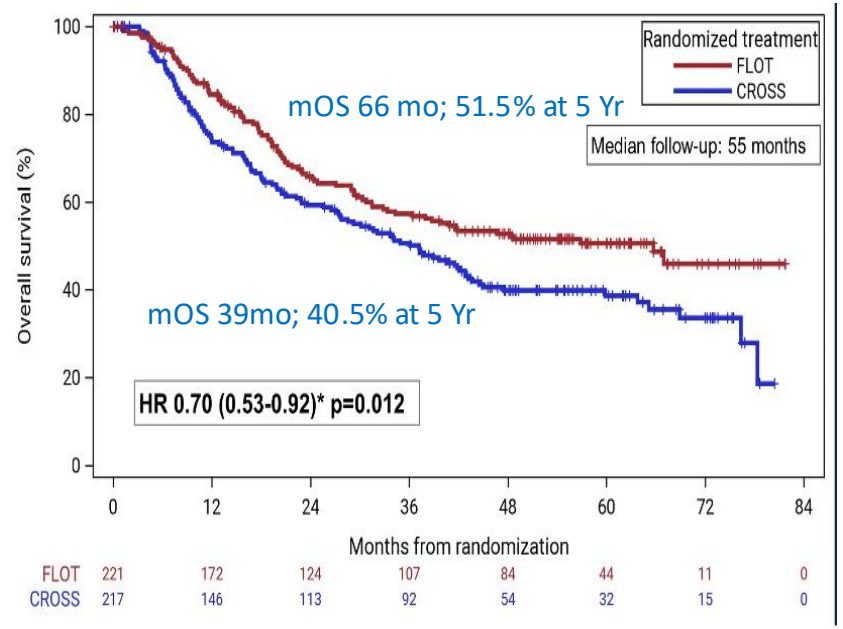
ECF/ECX- S- ECF/ECX – 36% at 5 Yr

Al-Batran et al. Lancet 2019

Perioperative Chemotherapy

ESOPEC





Hoeppner et al. ASCO 2024

Neo-AEGIS

Esophageal and GEJ adenocarcinoma:
AEG I-III
cT2-3N0-3M0

Arm B 15% superior to A (n= 366)
Arm B 10% superior to A (n= 628)

R

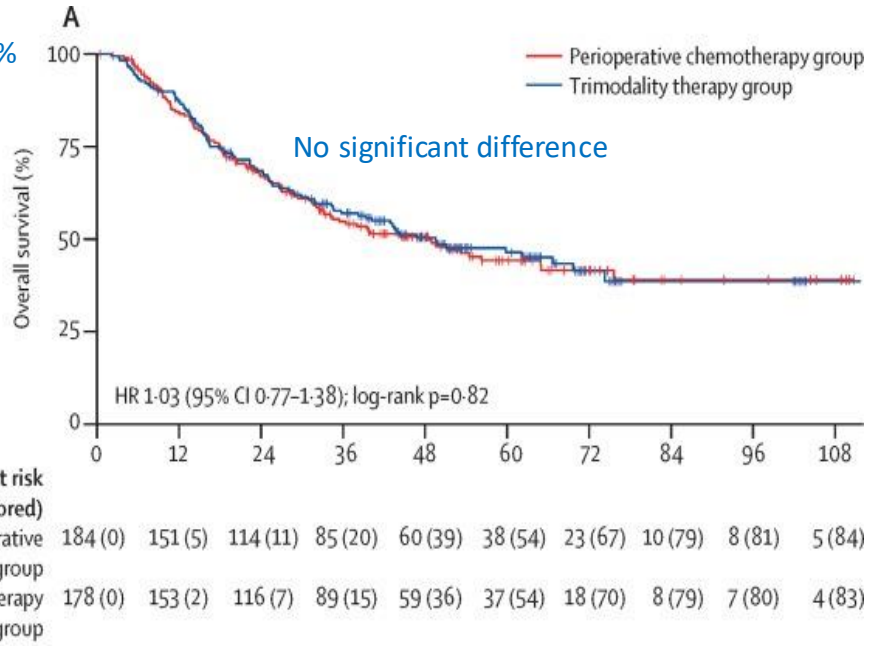
EC(O)F(X) x 3 → Surgery → EC(O)F(X) x 3 — **Arm A**

Neo CRT (CROSS)
wCP-RT(41.4Gy)+Surgery — **Arm B**

Primary endpoint: Overall survival

Secondary end points: Disease free survival;
Time to treatment failure: TRG: R0: Toxicity: Postoperative complications; HR-QL

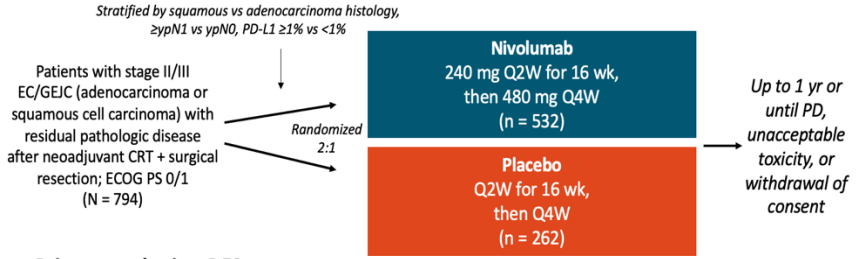
ARDS 0.6% vs 4.3%



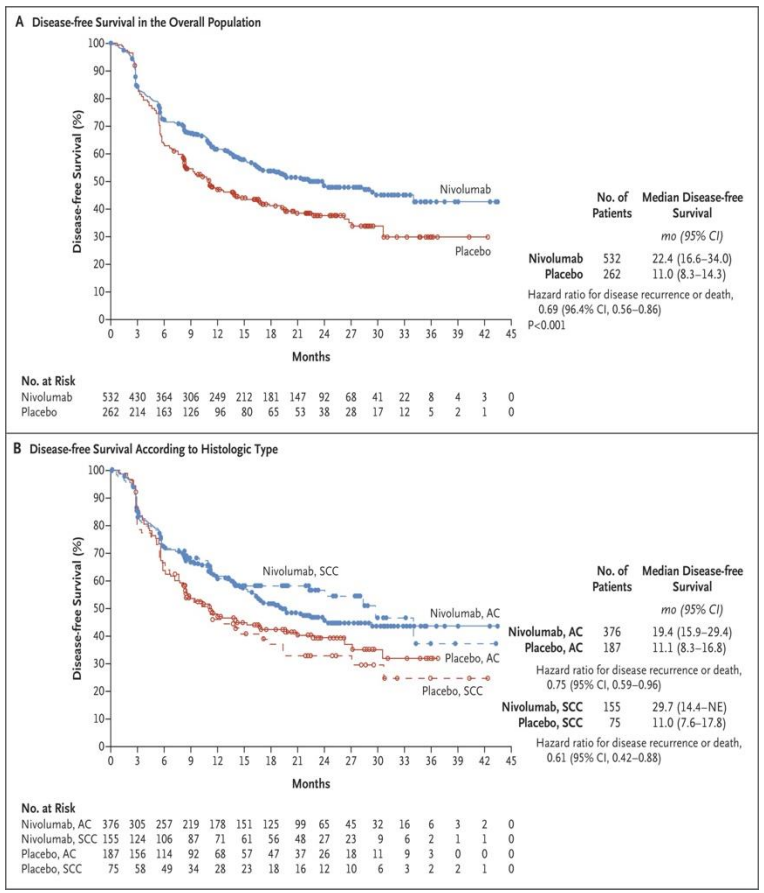
Reynolds et al. Lancet Gastro& Hep 2023

Adjuvant Immunotherapy

Checkmate 577



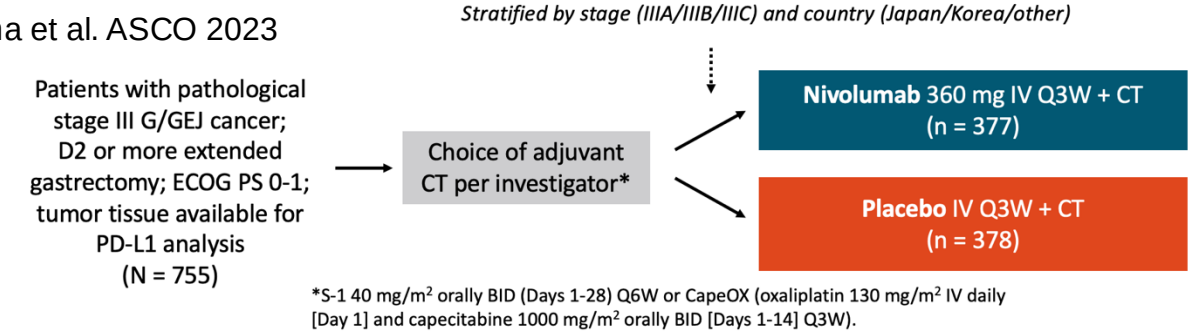
- **Primary endpoint:** DFS
- **Secondary endpoints:** OS, OS rate at Yr 1, 2, and 3
- **Exploratory endpoints:** safety, DMFS, PFS2, QoL



Kelly RJ et al. N Engl J Med2021;384:1191-1203

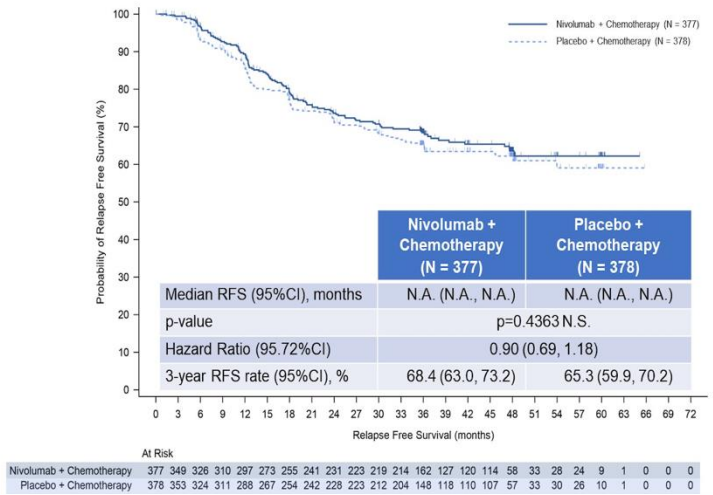
ATTRACTION-5

Terashima et al. ASCO 2023

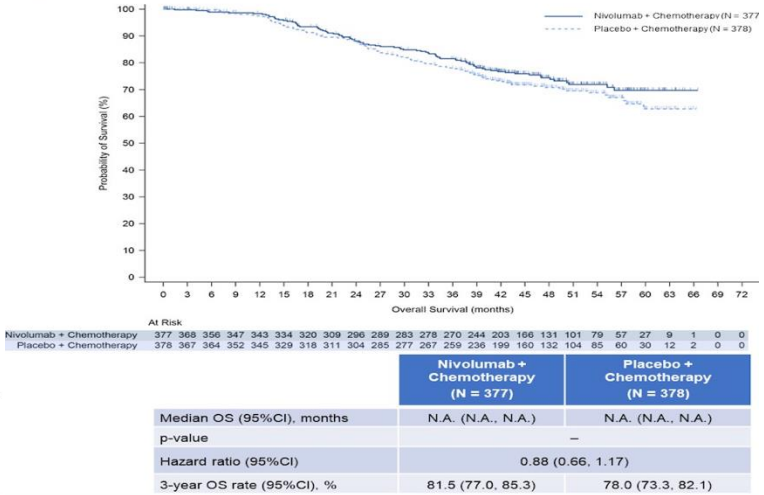


*S-1 40 mg/m² orally BID (Days 1-28) Q6W or CapeOX (oxaliplatin 130 mg/m² IV daily [Day 1] and capecitabine 1000 mg/m² orally BID [Days 1-14] Q3W).

OS

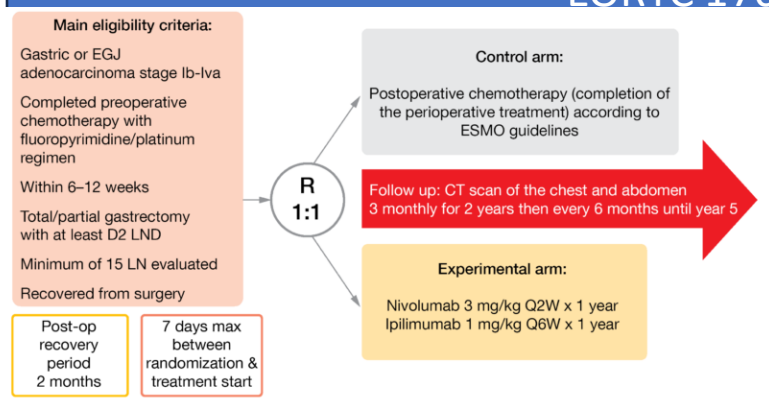


	Nivolumab + Chemotherapy (N = 377)	Placebo + Chemotherapy (N = 378)
Median RFS (95%CI), months	N.A. (N.A., N.A.)	N.A. (N.A., N.A.)
p-value	p=0.4363 N.S.	
Hazard Ratio (95.72%CI)	0.90 (0.69, 1.18)	
3-year RFS rate (95%CI), %	68.4 (63.0, 73.2)	65.3 (59.9, 70.2)



	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)

EORTC 1707 VESTIGE



mDFS: 11.9 vs 23.3 mo (p=0.02)
mOS: 25.1 vs NR mo (p=0.1)

Enrollment Closed Early

Smyth et al. Annals of Oncol ESMO 2023

Keynote 585

Key Eligibility Criteria

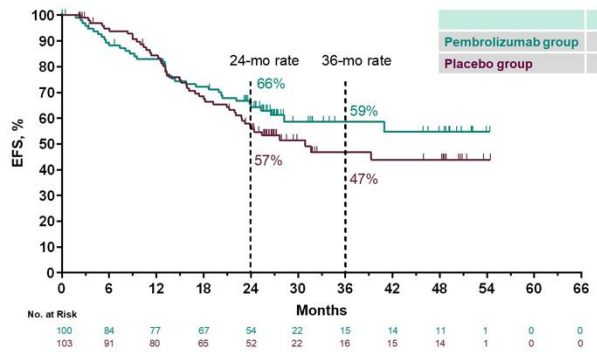
- Localized G/GEJ adenocarcinoma defined by T3 or greater primary lesion or presence of N+ nodes
- No prior therapy
- Able to undergo surgery
- Provision of tumor sample for PD-L1 testing[a]
- ECOG PS 0-1

R 1:1
N = 804[b,c]

Pembrolizumab arm: Pembrolizumab 200 mg IV Q3W + Cisplatin and Capecitabine/XP or Cisplatin and 5-FU/FP for up to 3 cycles → Surgery → Pembrolizumab IV Q3W + Chemotherapy for up to 3 cycles → Pembrolizumab IV Q3W for up to 11 cycles

Placebo arm: Placebo IV Q3W + Cisplatin and Capecitabine/XP or Cisplatin and 5-FU/FP for up to 3 cycles → Surgery → Placebo IV Q3W + Chemotherapy for up to 3 cycles → Placebo IV Q3W for up to 11 cycles

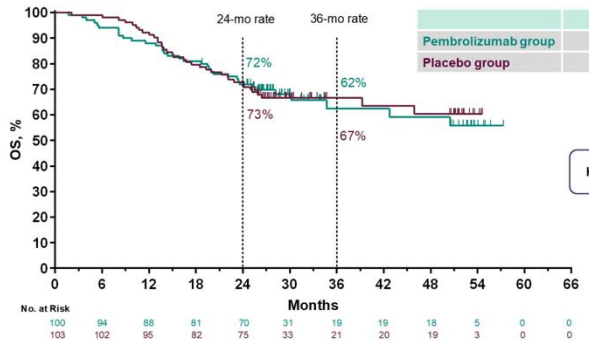
Event-Free Survival: FLOT Cohort



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

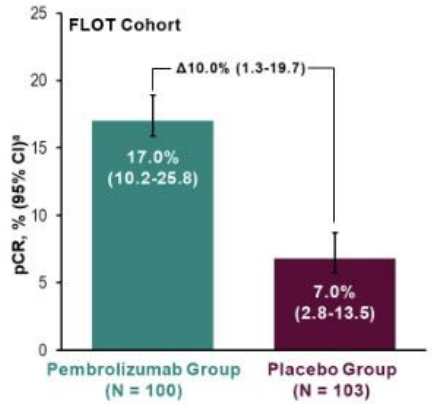
HR 0.79 (95% CI, 0.52-1.22)

Overall Survival: FLOT Cohort



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

HR 1.04 (95% CI, 0.66-1.66)



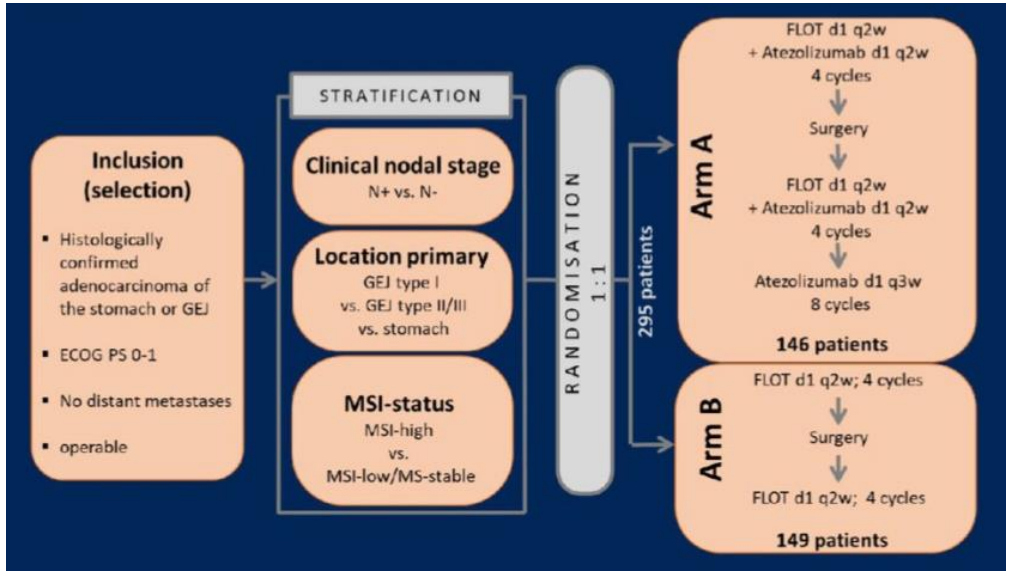
Summary of AEs by Treatment Phase

	Neoadjuvant Phase[a]		Adjuvant Phase	
AEs, n (%)	**Pembrolizumab Group N = 99**	**Placebo Group N = 103**	**Pembrolizumab Group N = 77**	**Placebo Group N = 76**
Any grade AEs	97 (98)	102 (99)	76 (99)	75 (99)
Treatment-Related AEs	96 (97)	96 (93)	73 (95)	68 (89)
Grade 3-4	54 (55)	56 (54)	43 (56)	33 (43)
Grade 5	2 (2)	1 (1)	1 (1)	0
Led to discontinuation of any drug	15 (15)	11 (11)	21 (27)	7 (9)
Surgery-Related AEs	19 (19)	13 (13)	1 (1)	2 (3)

Al-Batran et al. ASCO 2024

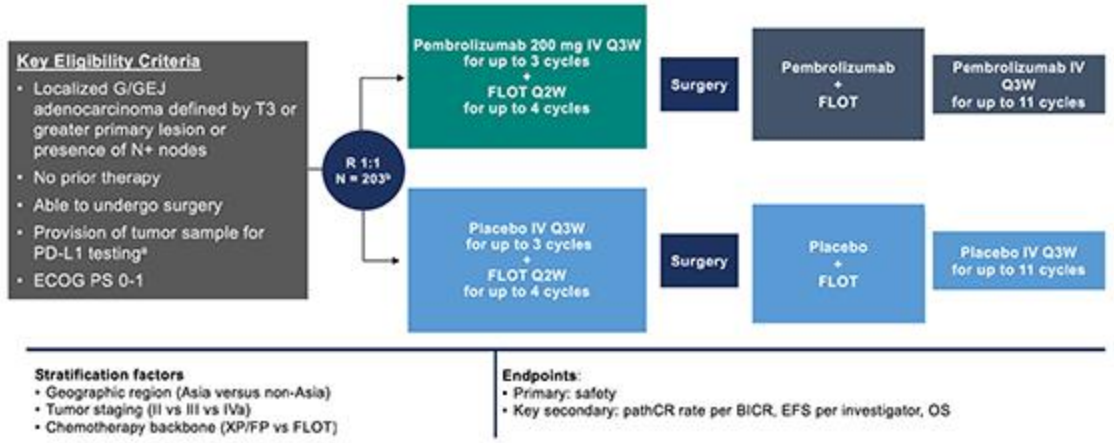
Neo-adjuvant/Adjuvant Immunotherapy

Dante Trial



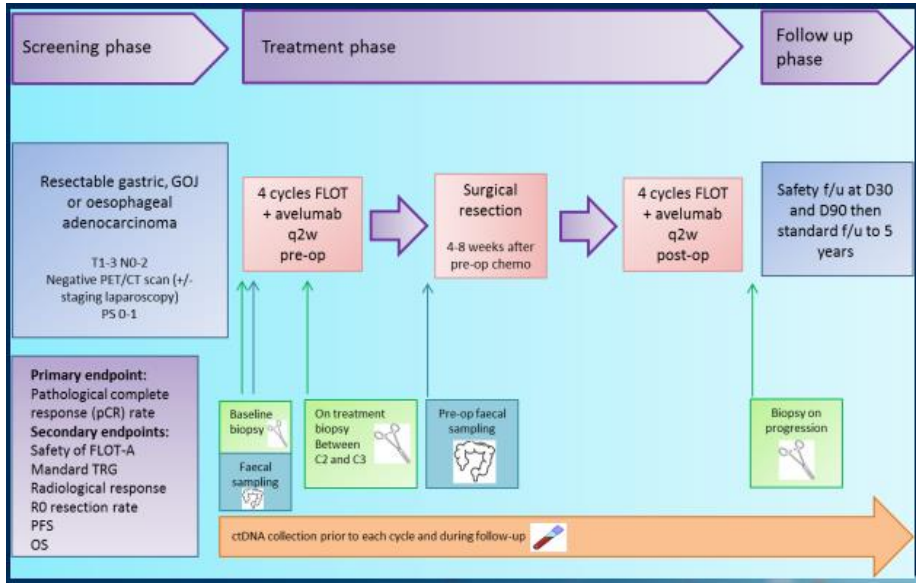
pCR/TRG1a:
All: 24% vs 15%
PD-L1 CPS ≥10: pCR 33 vs 12%
MSI-H: 63% vs 27%

MATTERHORN



pCR 19% vs 7% CR/nCR: 27% vs 14%
pCR in Asia consistent with global outcomes.

ICONIC Trial

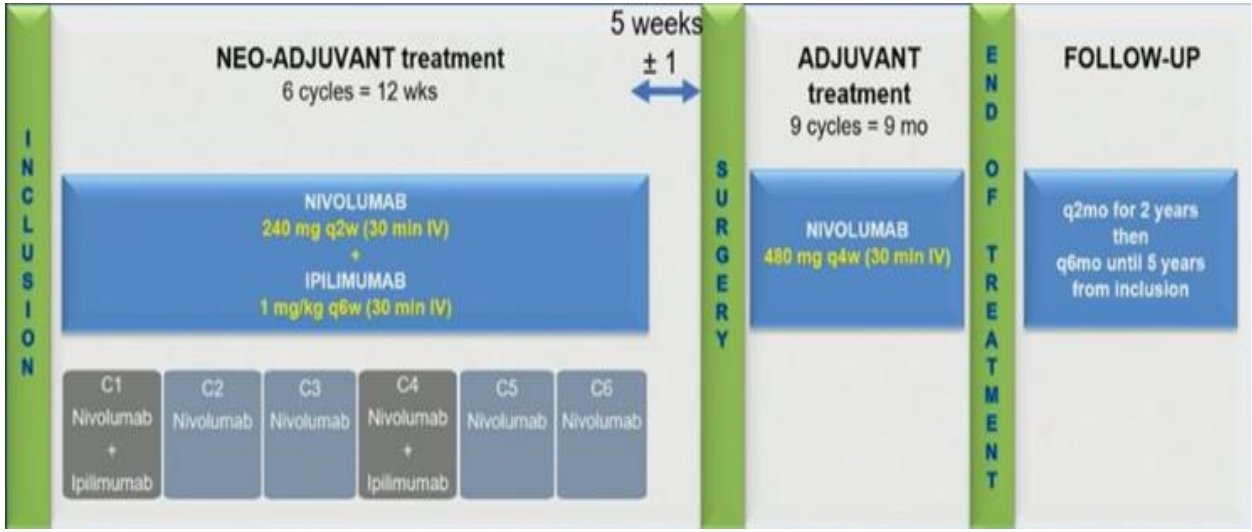


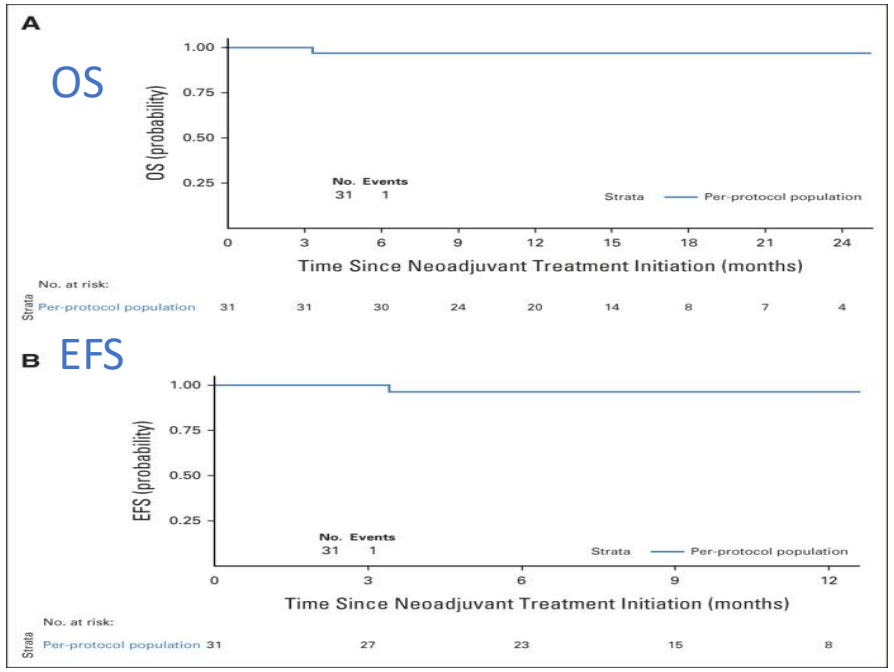
pCR: 15% for 34 pts

The trial closed early (pre-specified aim 25% in 40 pts)

Neo-adjuvant Immunotherapy

GERCOR NEONIPIGA





Andre et al. JCO 2022

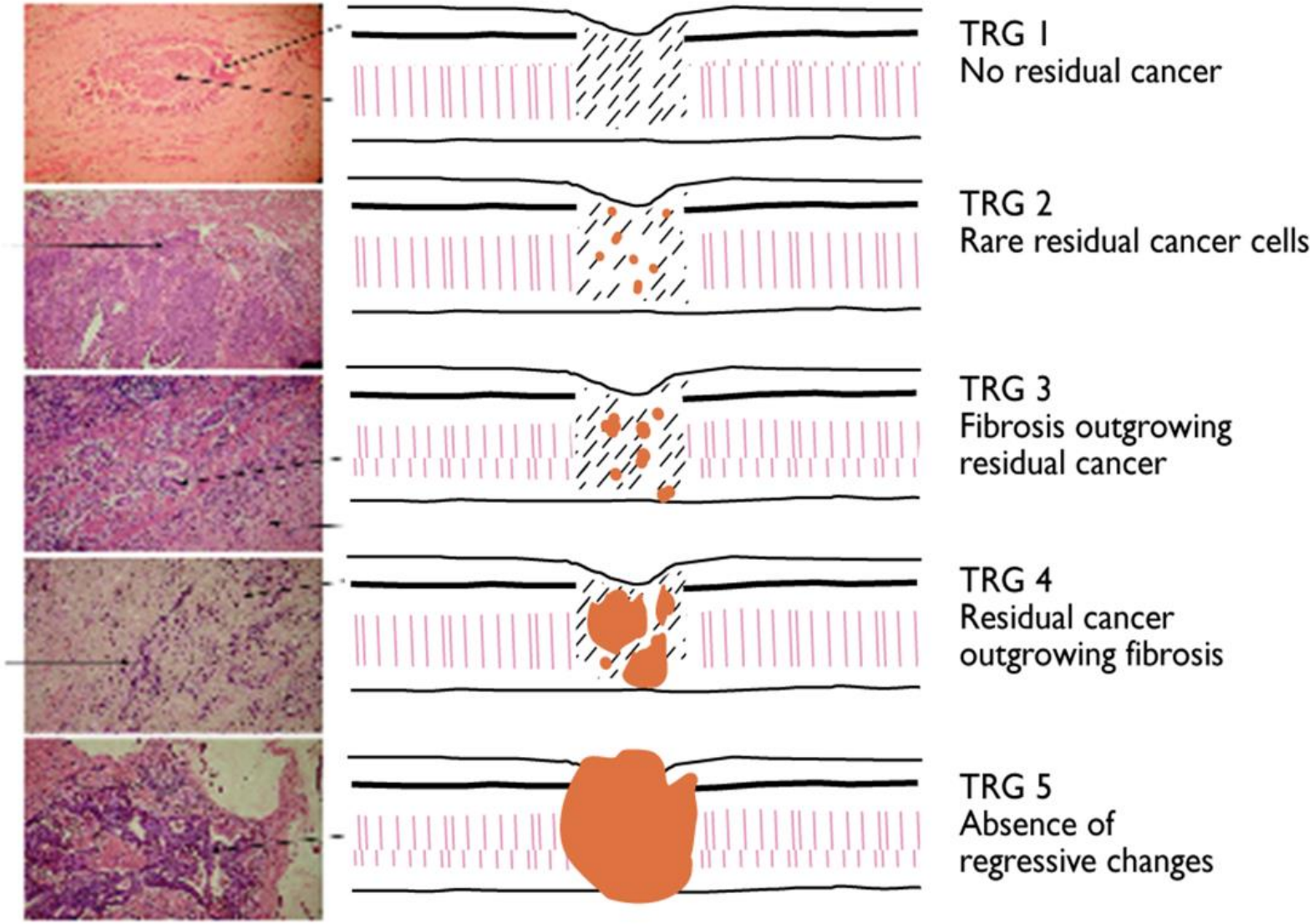
Infinity Trial

MSI/dMMR
resectable cT2-4 Nx
GAC/GEJAC

→ Durva/Trem(3)

15 evaluable patients, 14 underwent resection
pCR 60%

Tumor Regression (TRG)



TRG 1
No residual cancer

TRG 2
Rare residual cancer cells

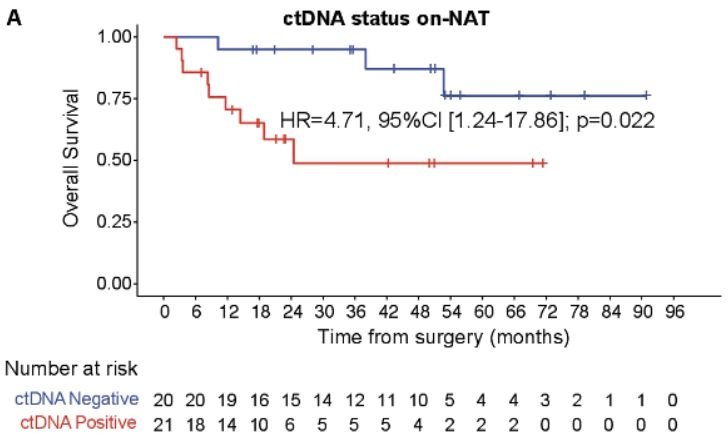
TRG 3
Fibrosis outgrowing residual cancer

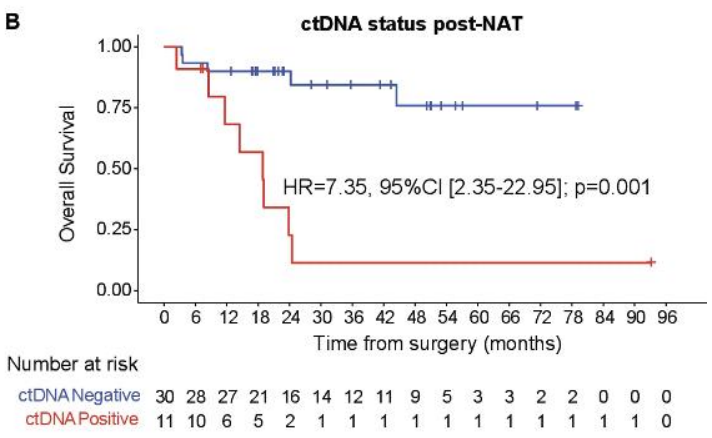
TRG 4
Residual cancer outgrowing fibrosis

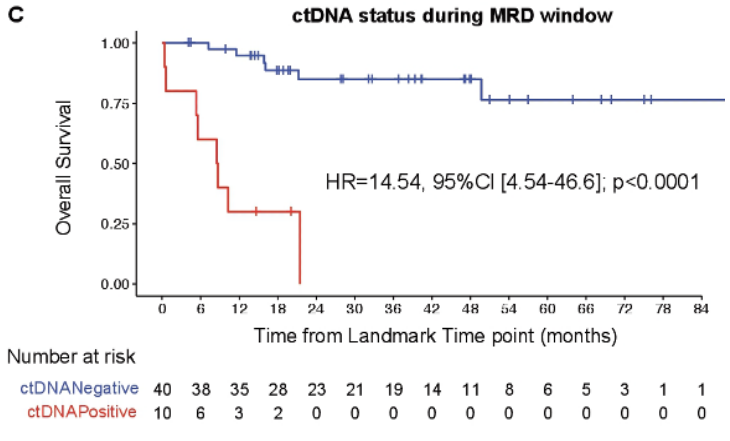
TRG 5
Absence of regressive changes

ctDNA

Longitudinal analysis of ctDNA during treatment of locally advanced gastric/GEJ adenocarcinoma - Prospective biomarker study







Zaanan et al. ASCO 2024

Perioperative Therapy - Summary

- Perioperative FLOT is the new standard for resectable cT2+/N+ esophageal adenocarcinoma
- Benefit of adjuvant immunotherapy in Esophageal Adenocarcinoma is unclear (CheckMate 577/ATTRACTION-5/ICONIC/VESTIGE)
  - Awaiting OS for Checkmate 577
- Addition of IO improves pCR, but unclear if this leads to improved OS/EFS (KEYNOTE 585, MATTERHORN)
- MSI High perioperative therapy – IO only; neonipiga and infinity
- ctDNA is being evaluated as a prognostic biomarker

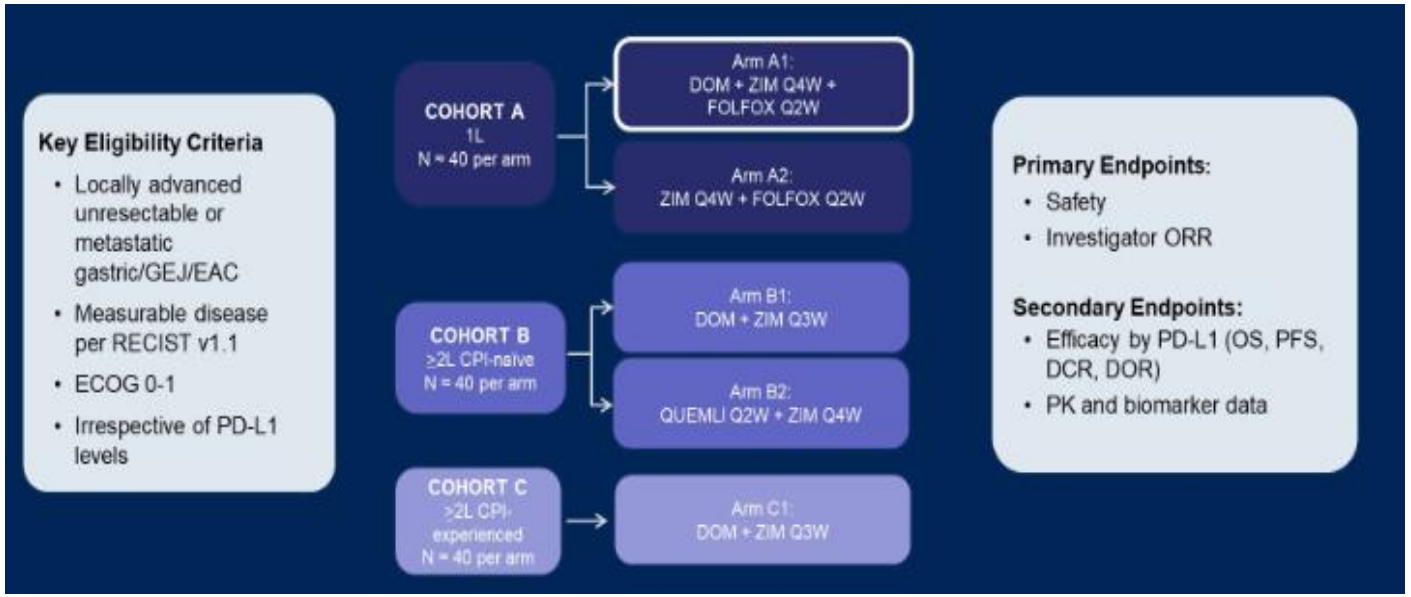
Update of Esophagogastric Cancer

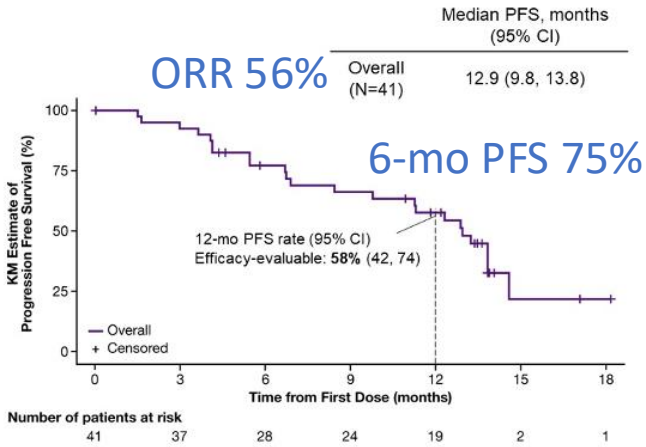
Advanced:

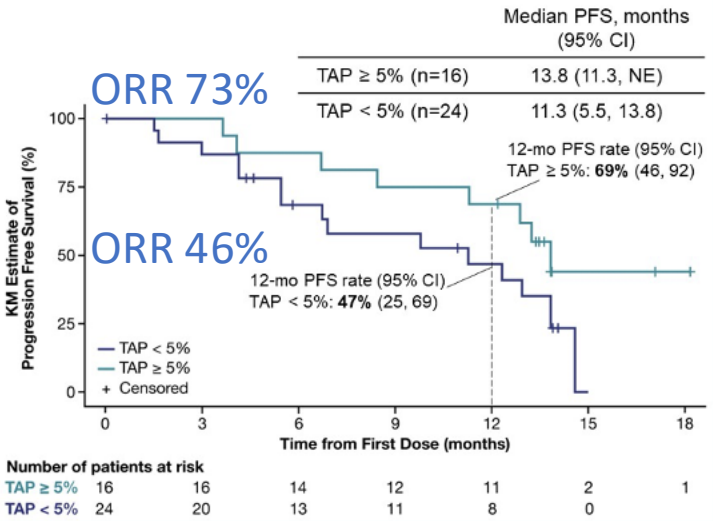
- First line Chemotherapy and Immunotherapy

Immunotherapy in Advanced Disease

EDGE Gastric

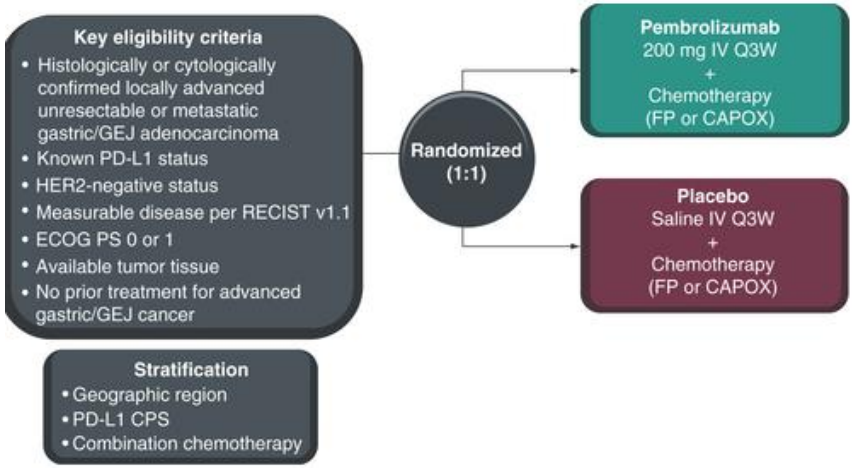






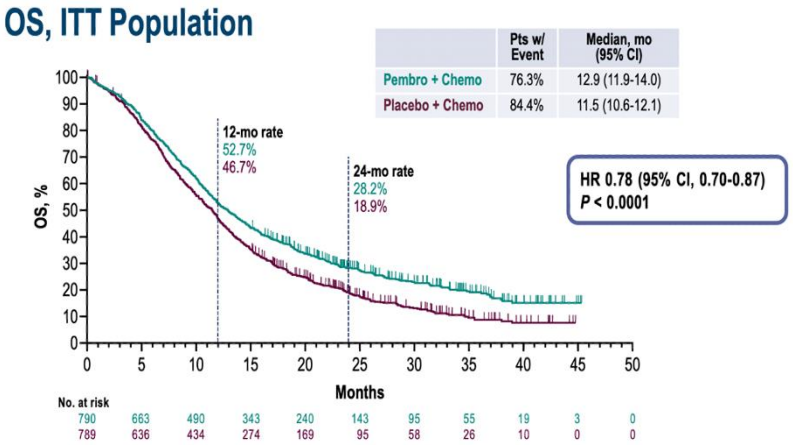
Janjigian et al. JCO 2023

Keynote-859



ORR 52.1% vs 42.6%
mDOR was 8.3 mo vs 5.6 mo

PD-L1 CPS ≥10
mOS 15.7 vs 11.8 mo
mPFS 8.1 vs 5.6 mo
ORR 60.6% vs 43%
mDOR 10.9 vs 5.8 mo



Rha et al. Lancet Oncology 2024

Checkmate 649

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

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

R 1:1:1[c]
N = 2031

- n = 789: NIVO 360 mg + XELOX Q3W or NIVO 240 mg + FOLFOX Q2W[e,f]
- n = 833[d]: XELOX Q3W or FOLFOX Q2W[e,f]
- n = 409: NIVO (1 mg/kg) + IPI (3 mg/kg) Q3W × 4 then NIVO 240 mg Q2W[f]

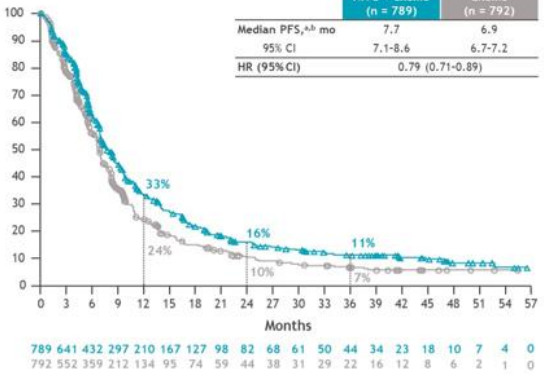
Dual primary endpoints:
- OS and PFS[g] (PD-L1 CPS ≥ 5)

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]

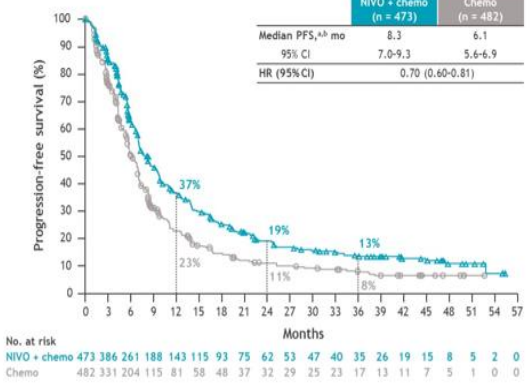
Exploratory endpoints:
- Safety
- QoL

Greater benefit in pts with MSI-H
MSI-H– mOS 38.7 vs 12.3mo
MSS mOS 13.8 vs 11.5 mo

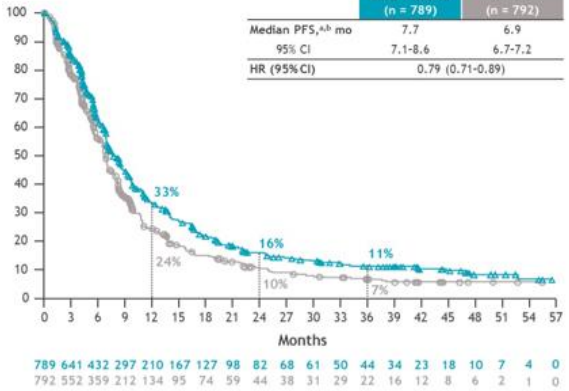
PFS — All randomized



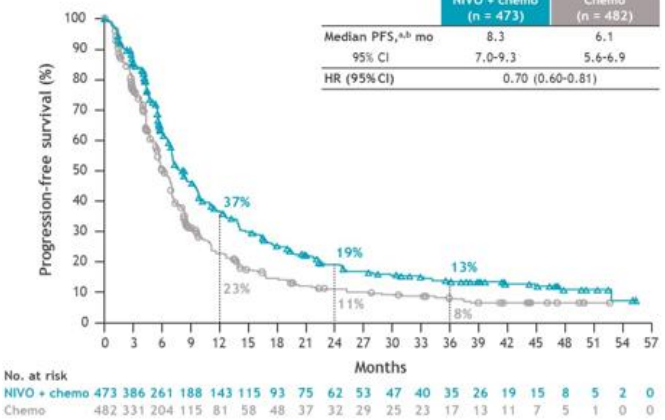
PFS — PD-L1 CPS ≥ 5



OS — All randomized



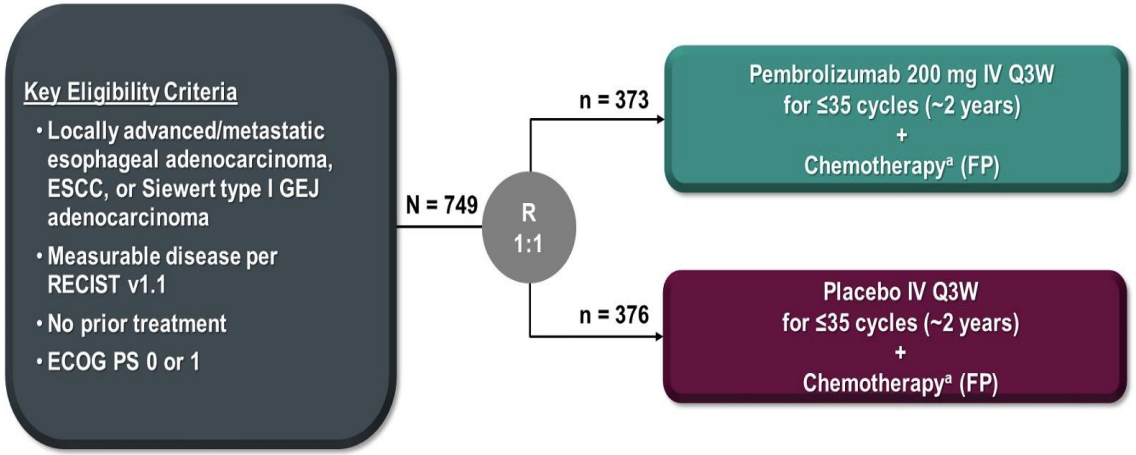
OS — PD-L1 CPS ≥ 5



Efficacy	PD-L1 CPS ≥ 5		All randomized	
	NIVO + chemo (n = 473)	Chemo (n = 482)	NIVO + chemo (n = 789)	Chemo (n = 792)
mOS (95% CI) mo	14.4 (13.1–16.2)	11.1 (10.1–12.1)	13.7 (12.4–14.5)	11.6 (10.9–12.5)
HR (95% CI)	0.70 (0.61–0.81)		0.79 (0.71–0.88)	
48-mo OS rate (95% CI) %	17 (14–21)	8 (6–11)	13 (11–16)	8 (6–10)
mPFS[a] (95% CI) mo	8.3 (7.0–9.3)	6.1 (5.6–6.9)	7.7 (7.1–8.6)	6.9 (6.7–7.2)
HR (95% CI)	0.71 (0.61–0.82)		0.80 (0.71–0.89)	
ORR[a,b] (95% CI) %	60 (55–65)	45 (40–50)	58 (54–62)	46 (42–50)
mDuration of response[a,c] (95% CI) mo	9.6 (8.3–12.4)	7.0 (5.7–8.0)	8.5 (7.7–9.9)	6.9 (5.9–7.6)

Janjigian, Y et al. JCO 2024

KEYNOTE 590



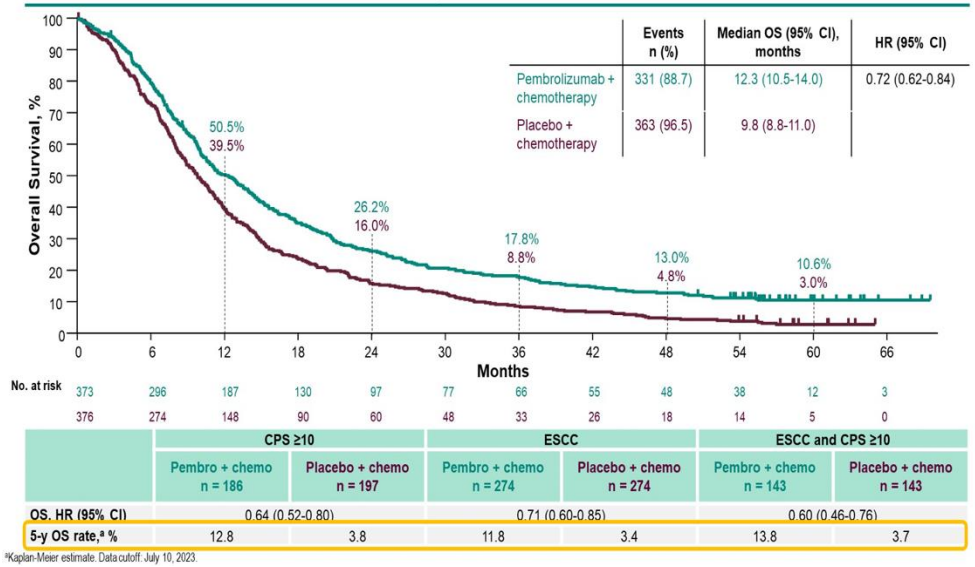
Stratification Factors

- Geographic region (Asia vs rest of world)
- Histology (adenocarcinoma vs squamous cell carcinoma)
- ECOG PS (0 vs 1)

End Points

- Primary: OS,[b] PFS[c,d]
- Secondary: ORR[d], DOR[d], safety, PROs[e]

Overall Survival: ITT Population



OS and PFS	ITT n = 749	ESCC n = 548	CPS ≥10 n = 383	ESCC and CPS ≥10 n = 286
OS, median, HR (95% CI)[a,b]	0.72 (0.62-0.84)	0.71 (0.60-0.85)	0.64 (0.52-0.80)	0.60 (0.46-0.76)
5-yr OS rate,[a,b] %	10.6 vs 3.0	11.8 vs 3.4	12.8 vs 3.8	13.8 vs 3.7
PFS, median, HR (95% CI)[a,b,c]	0.64 (0.54-0.75)	0.65 (0.54-0.78)	0.51 (0.40-0.64)	0.53 (0.41-0.69)
ORR,[b,c] %	45.0 vs 29.3	43.8 vs 31.0	51.1 vs 26.9	51.0 vs 28.0
DOR,[a,b,c] median, mo (range)	8.3 (1.2+ to 65.9+) vs 6.0 (1.5+ to 31.1)	9.1 (1.2+ to 65.9+) vs 6.1 (1.5+ to 31.1)	10.4 (1.9 to 65.9+) vs 5.6 (1.5+ to 31.1)	10.4 (2.2+ to 65.9+) vs 4.4 (1.5+ to 31.1)

NR, not reached.

[a]Kaplan-Meier estimate.

Shah et al. 2024

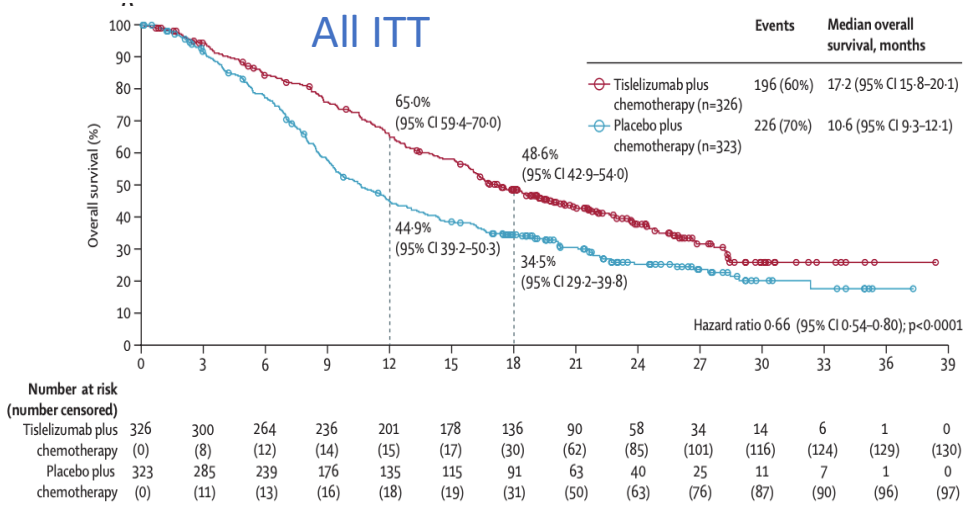
Esophageal Squamous Cell Carcinoma

RATIONALE-306

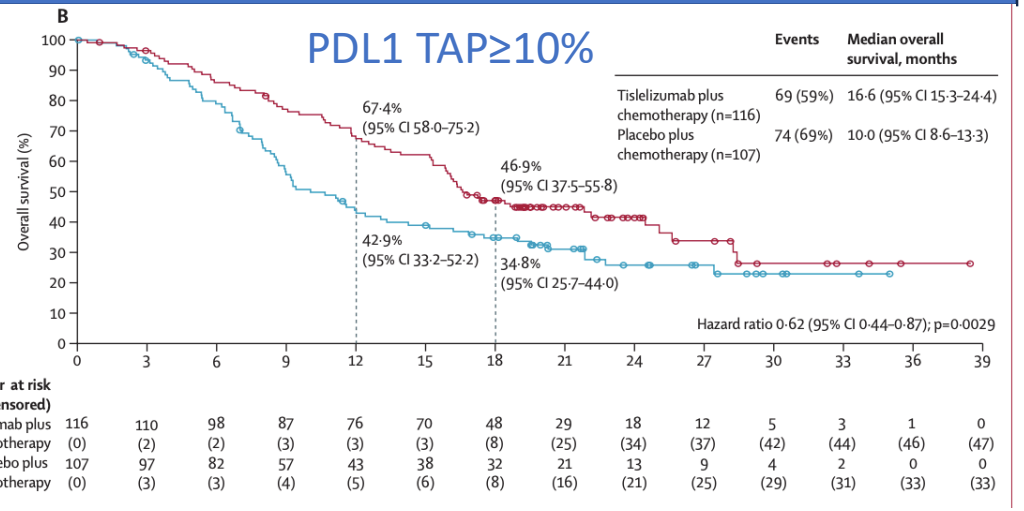
Advanced ESCC

- platinum plus fluoropyrimidine or platinum plus paclitaxel) + tislelizumab
- platinum plus fluoropyrimidine or platinum plus paclitaxel)

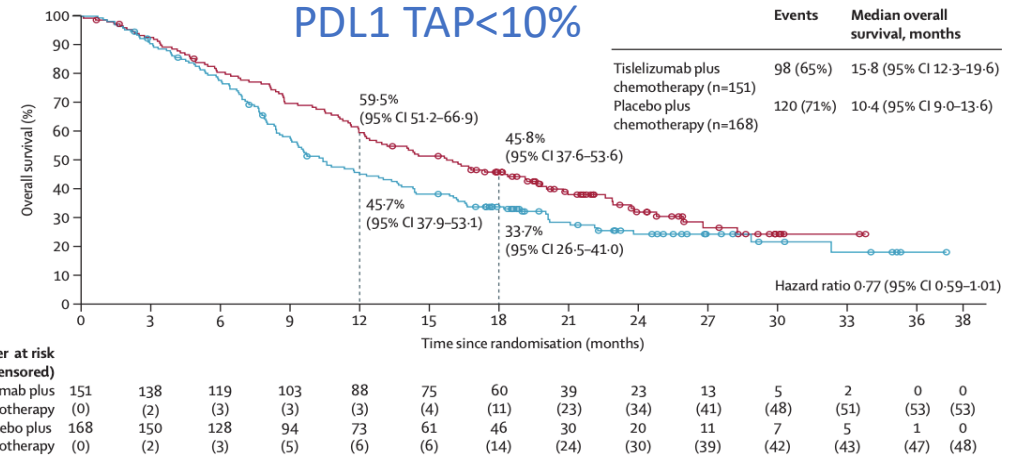
All ITT



PDL1 TAP≥10%



PDL1 TAP<10%



	Arm A: TIS + chemo (n=326)	Arm B: PBO + chemo (n=323)
Median OS, mo (95% CI)	17.2 (15.8, 20.1)	10.6 (9.3, 12.0)
24-mo OS, % (95% CI)	37.9 (32.5, 43.2)	24.8 (20.1, 29.8)
36-mo OS, % (95% CI)	22.1 (17.6, 27.0)	14.1 (10.4, 18.4)
24-mo PFS, % (95% CI)	18.1 (13.6, 23.1)	7.2 (4.4, 11.0)
36-mo PFS, % (95% CI)	15.0 (10.8, 19.9)	2.9 (1.1, 6.2)
24-mo DoR, % (95% CI)[a]	19.9 (14.3, 26.3)	10.1 (5.0, 17.1)
36-mo DoR, % (95% CI)[a]	17.7 (12.3, 24.0)	5.0 (1.5, 11.8)

Yoon et al JCO 2024

CHECKMATE 648

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)

R 1:1:1

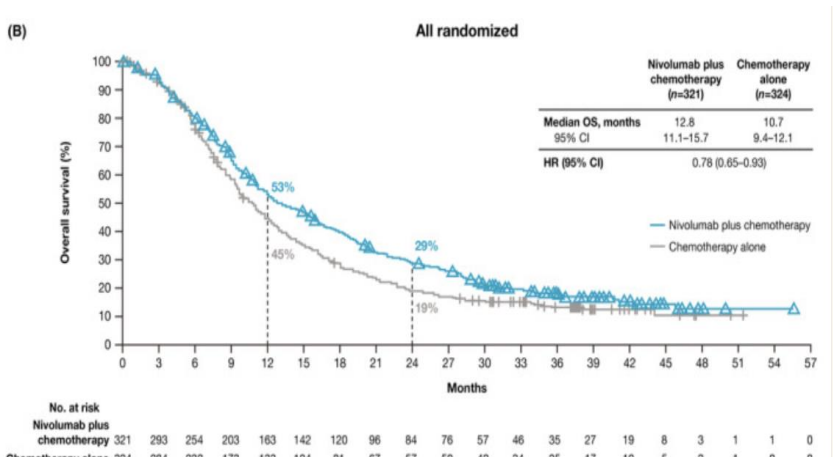
- n = 321 → NIVO 240 mg Q2W + chemo (fluorouracil + cisplatin)[d] Q4W[e]
- n = 325 → NIVO 3 mg/kg Q2W + IPI 1 mg/kg Q6W[e]
- n = 324 → Chemo (fluorouracil + cisplatin)[d] Q4W[e]

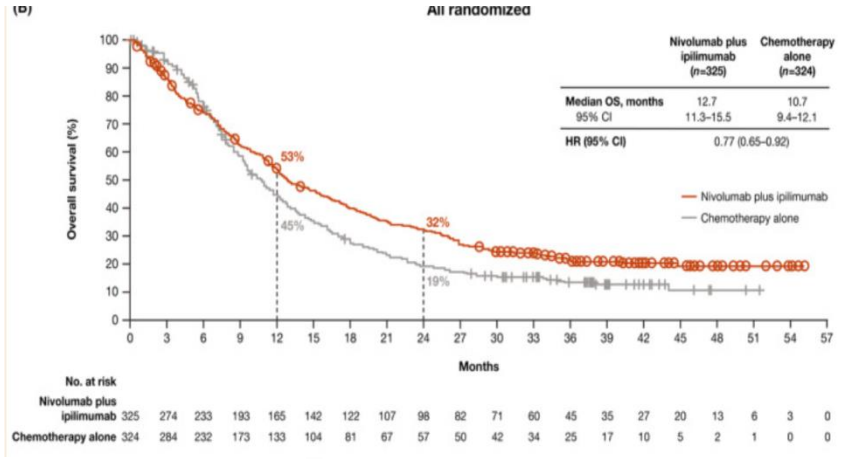
N = 970

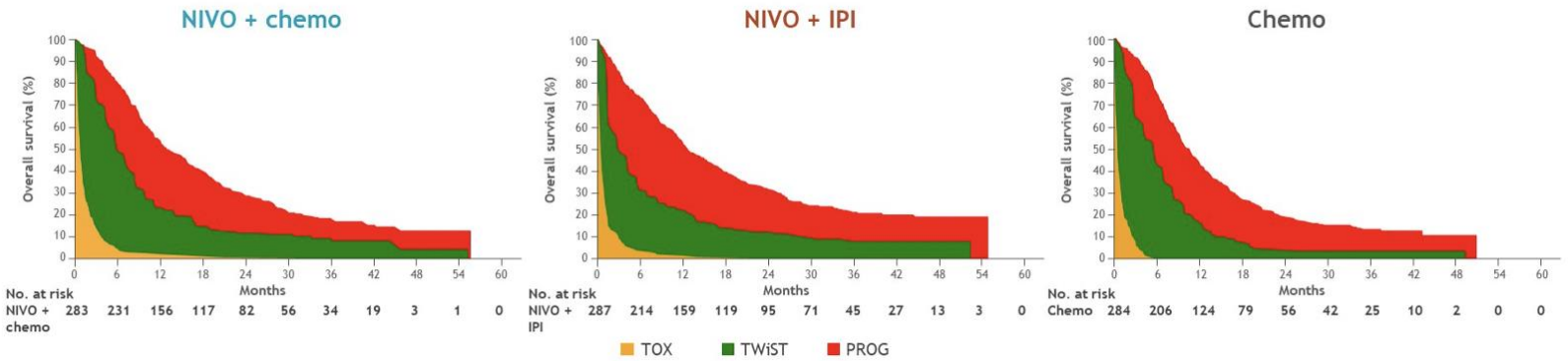
Primary endpoints:
- OS and PFS[f] (tumor cell PD-L1 ≥ 1%)

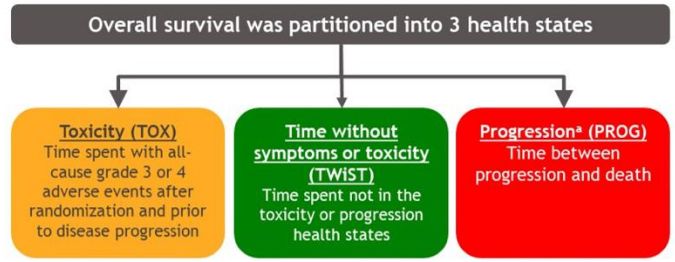
Secondary endpoints:
- OS and PFS[f] (all randomized)
- ORR[f] (tumor cell PD-L1 ≥ 1% and all randomized)

Exploratory endpoint:
- Patient reported outcomes using EQ-5D-3L and FACT-E









Doki et al. NEJM 2022;Chau et al. JCO 2024

Advanced Esophagogastric – Role of Immunotherapy

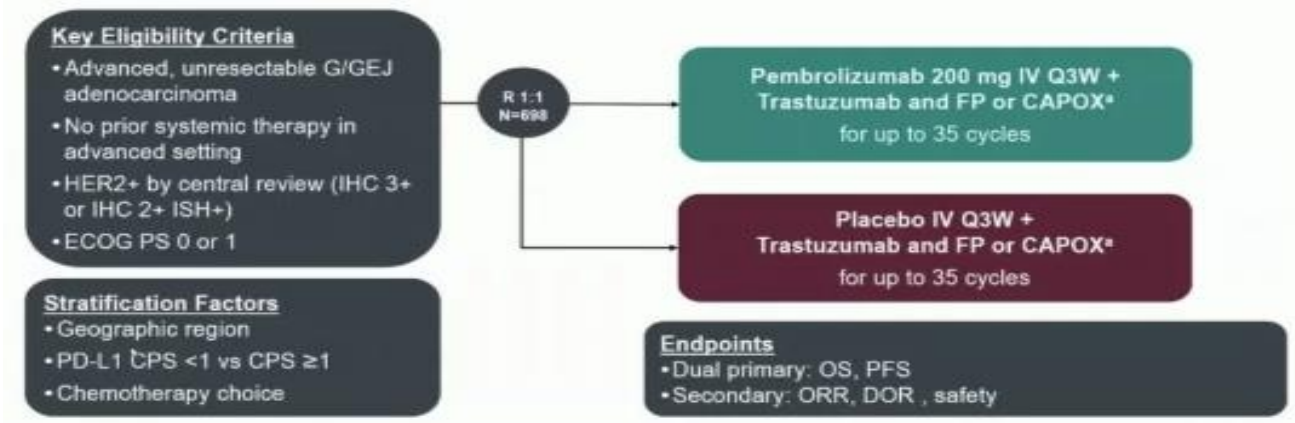
- First line immunotherapy in combination with chemotherapy superior to chemotherapy alone with longer follow up.
- Benefit across subgroups, enriched in higher PDL1
- MSI-H patients benefit more
- Chemo + PD-1 Inhibitor + TIGIT Inhibitor promising results in first line

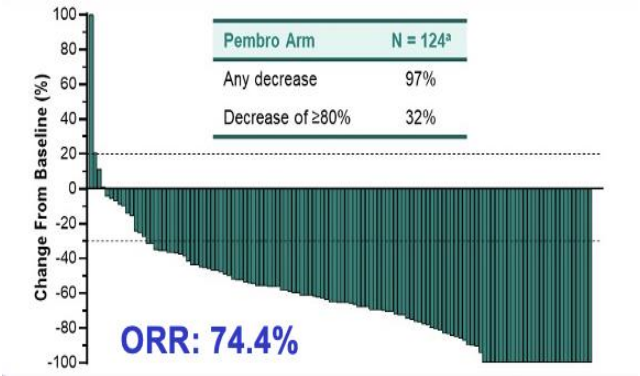
Update of Esophagogastric Cancer

Advanced:

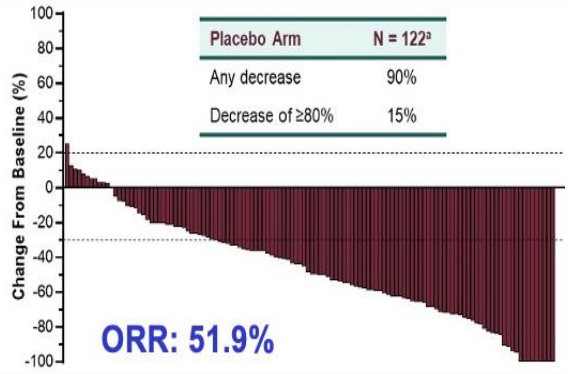
- HER2 + Gastric cancer

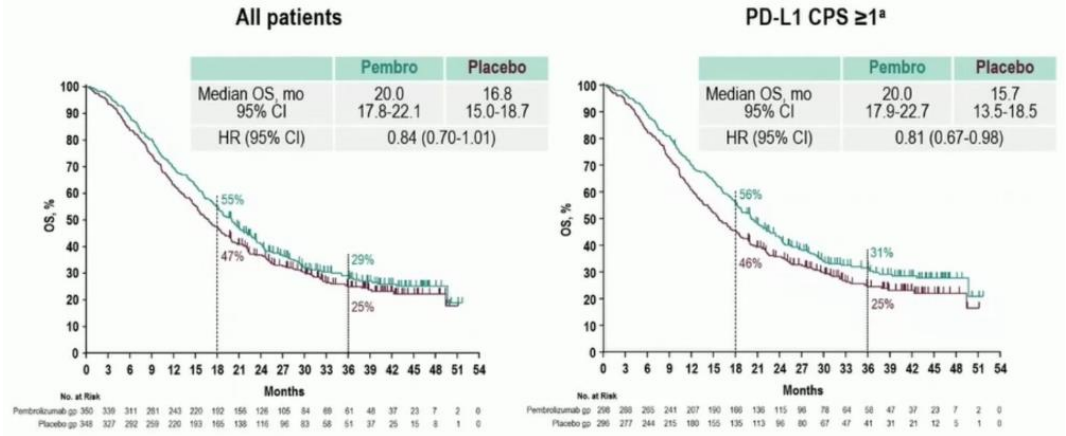
KEYNOTE- 411





FDA granted accelerated approval to pembro plus trastuzumab and chemo





Janjigian et al. Lancet Oncol 2023

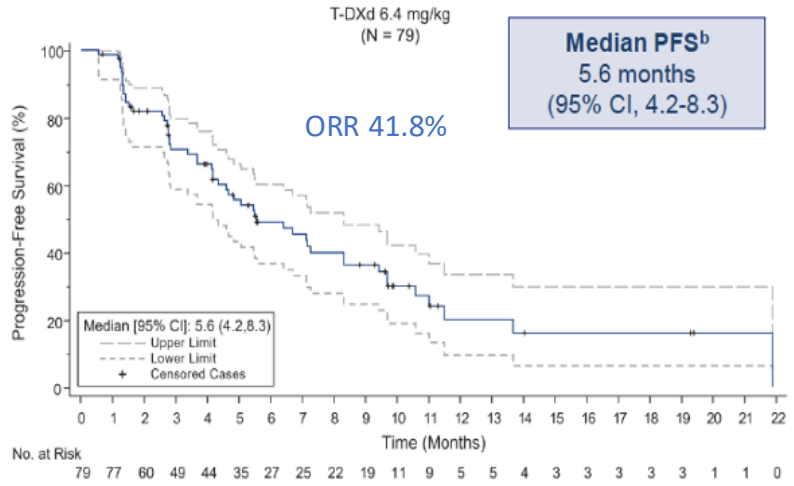
HER 2+

DESTINY GASTRIC-02

Advanced G/GEJ AC

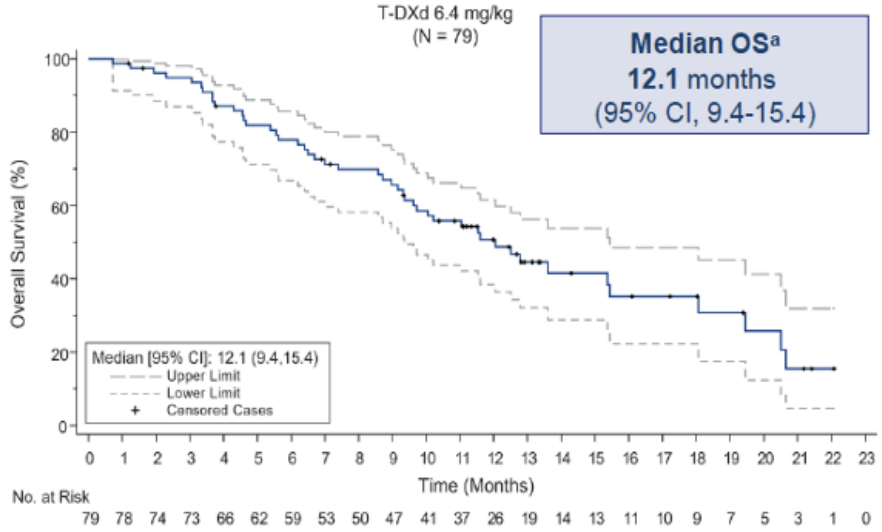
HER2+

→ T-DXd 6.4mg/kg q3w



Median PFS[b]
5.6 months
(95% CI, 4.2-8.3)

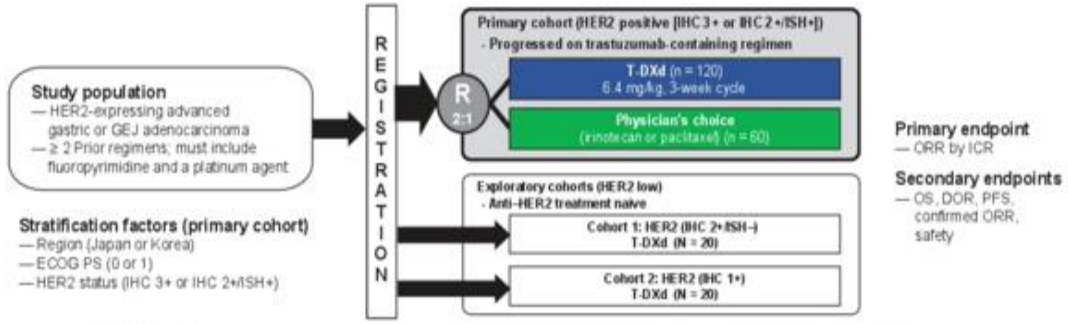
ORR 41.8%



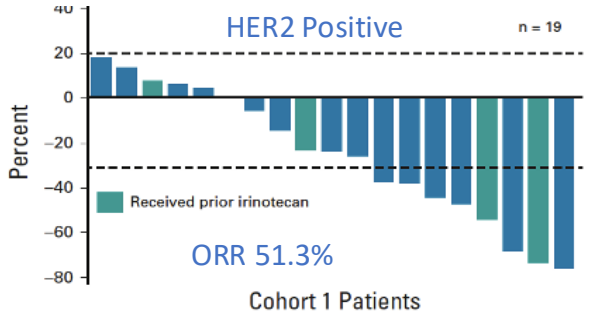
Median OS[a]
12.1 months
(95% CI, 9.4-15.4)

Ku G et al. ESMO 2022;Abstract 1205MO.

DESTINY GASTRIC-01

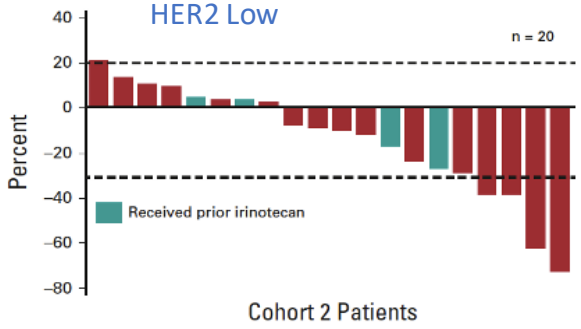


DOR, duration of response; EGOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; ISH, in situ hybridization; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan.



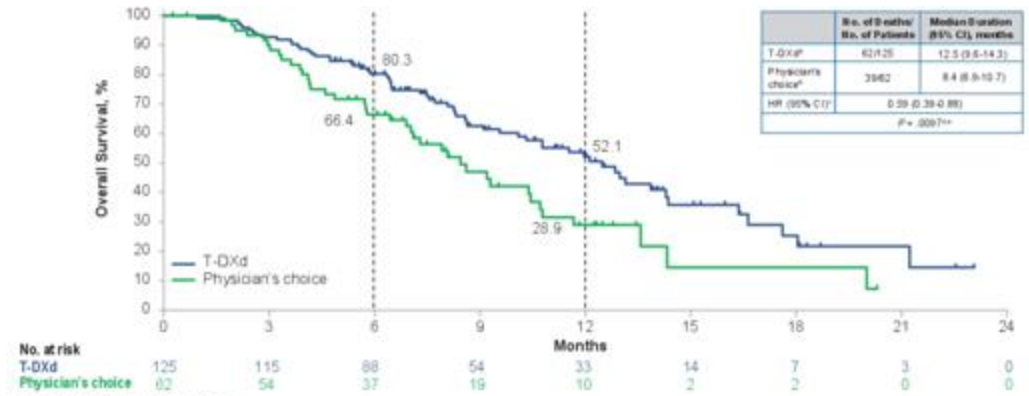
ORR 51.3%

Cohort 1 Patients



Cohort 2 Patients

Overall Survival



Shitara K, et al. *Lancet Oncol*. 2018; Yamaguchi K et al. J Clin Oncol 2023

Summary - HER2 Positive Cancer

- Chemotherapy with Trastuzumab and Pembrolizumab improved ORR and PFS with PDL-1 $\geq$ patient
- Refractory options – Trastuzumab-deruxtecan
- HER2 **low** being investigated with Ab-drug conjugates
- Multiple investigational Agents – TKI, Antibody drugs, cell therapy

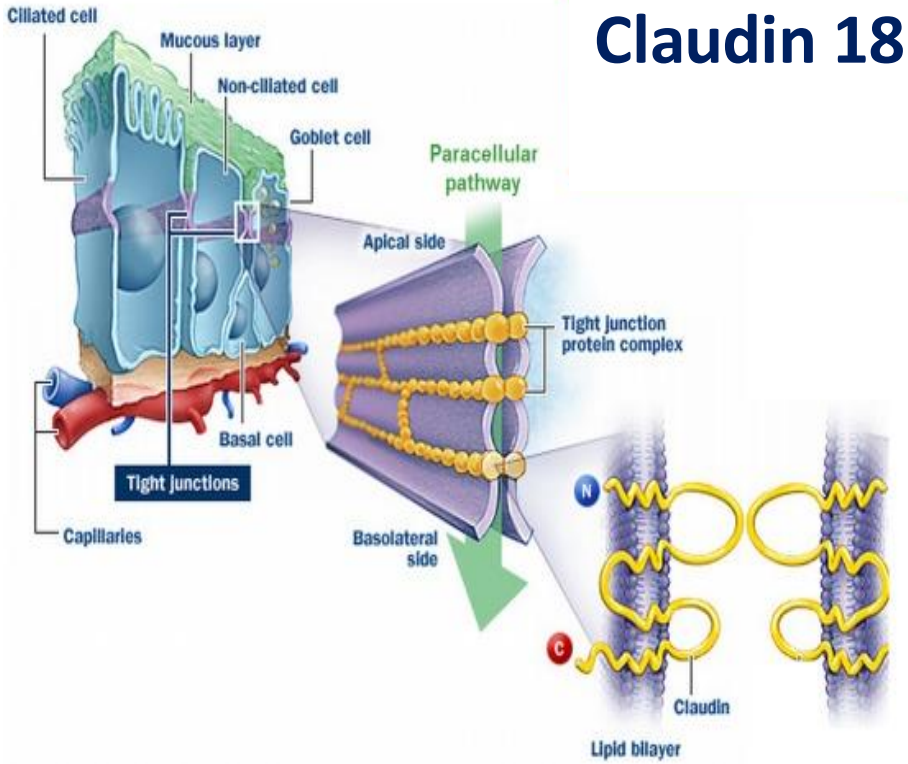
Update of Esophagogastric Cancer

Advanced:

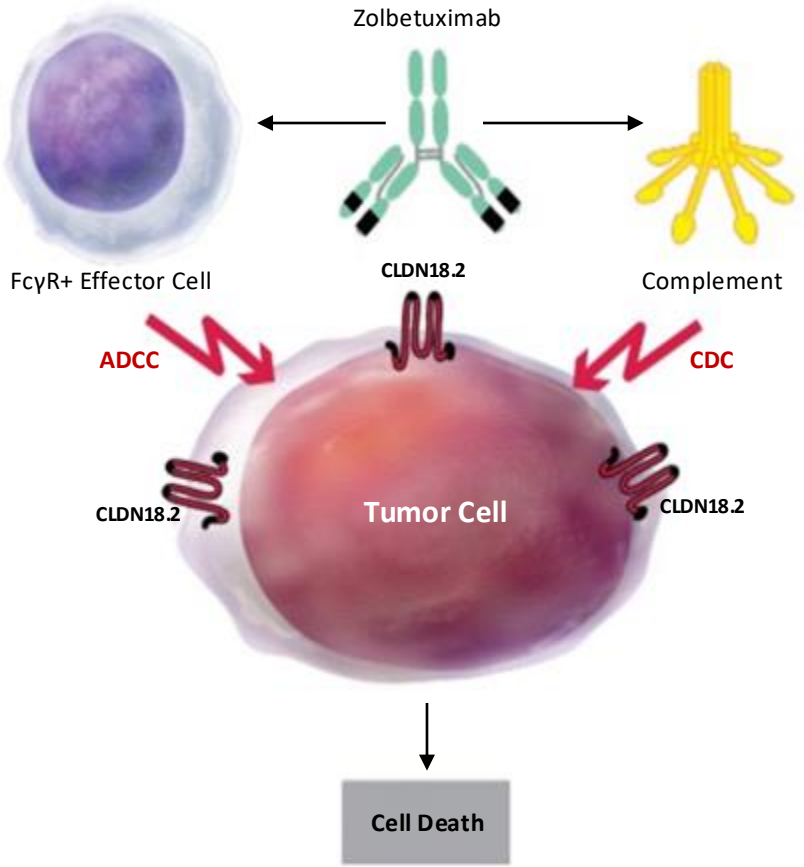
- Claudin 18.2 – New Target

CLAUDIN18.2 – A NOVEL TARGET

Claudin 18.2



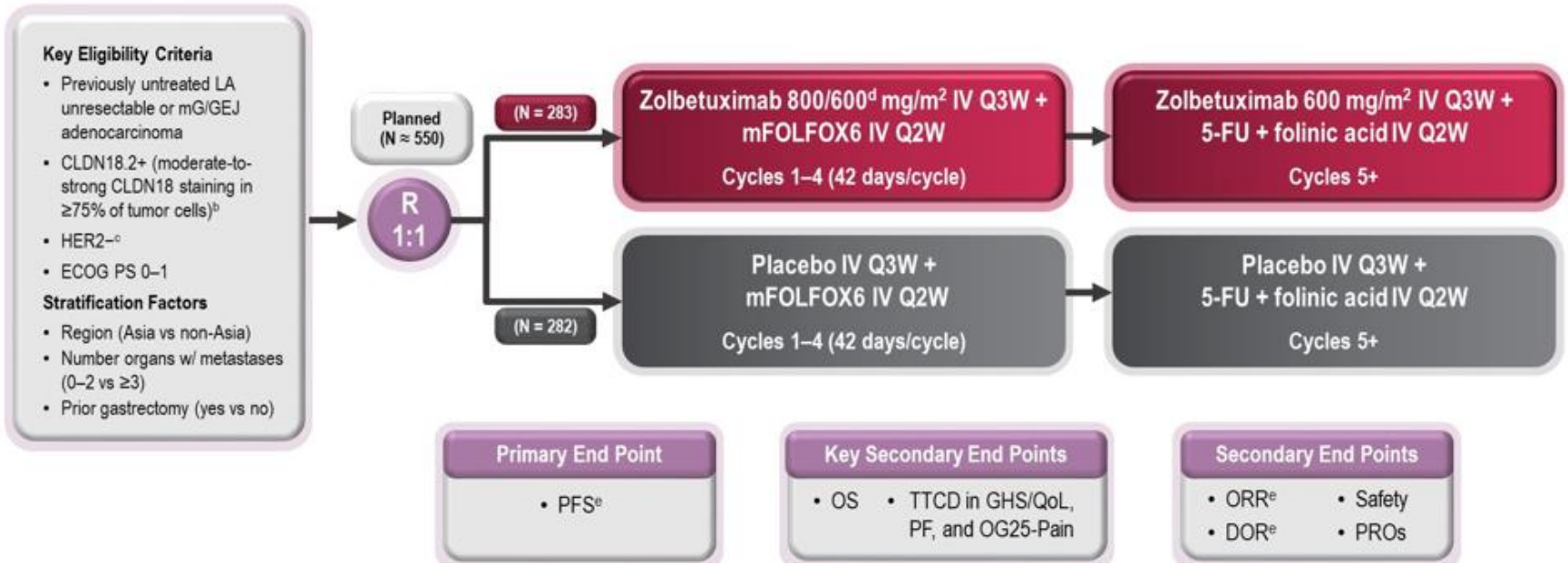
Mechanism of Action of Zolbetuximab



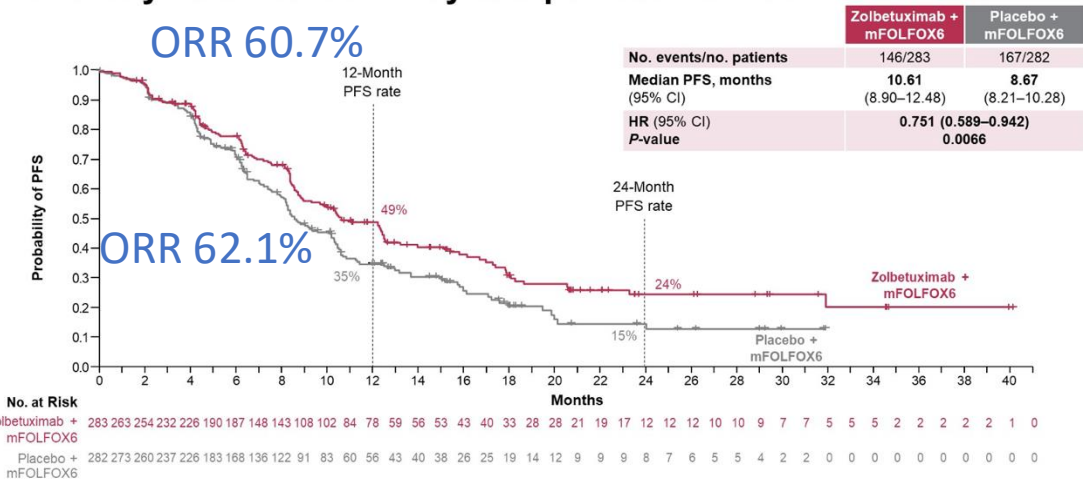
- Claudin 18.2 is a tight junction protein expressed in normal and malignant gastric mucosa cells
- During malignant transformation, CLDN18.2 is exposed on the surface of G/GEJ AC
- Zolbetuximab is a chimeric antibody targeting CLD18.2 and its ADCC/CDC

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

Claudin 18.2

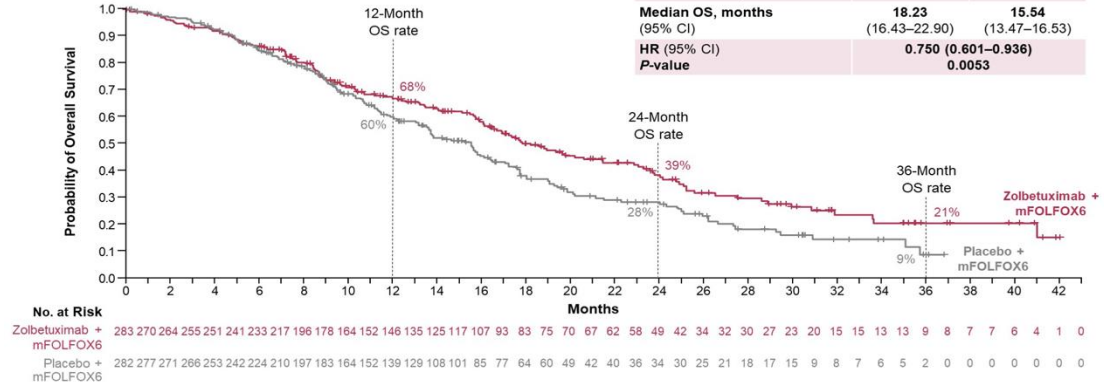


Primary End Point: PFS by Independent Review Committee[a]



	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) *P*-value	0.751 (0.589–0.942) 0.0066	

Key Secondary End Point: OS



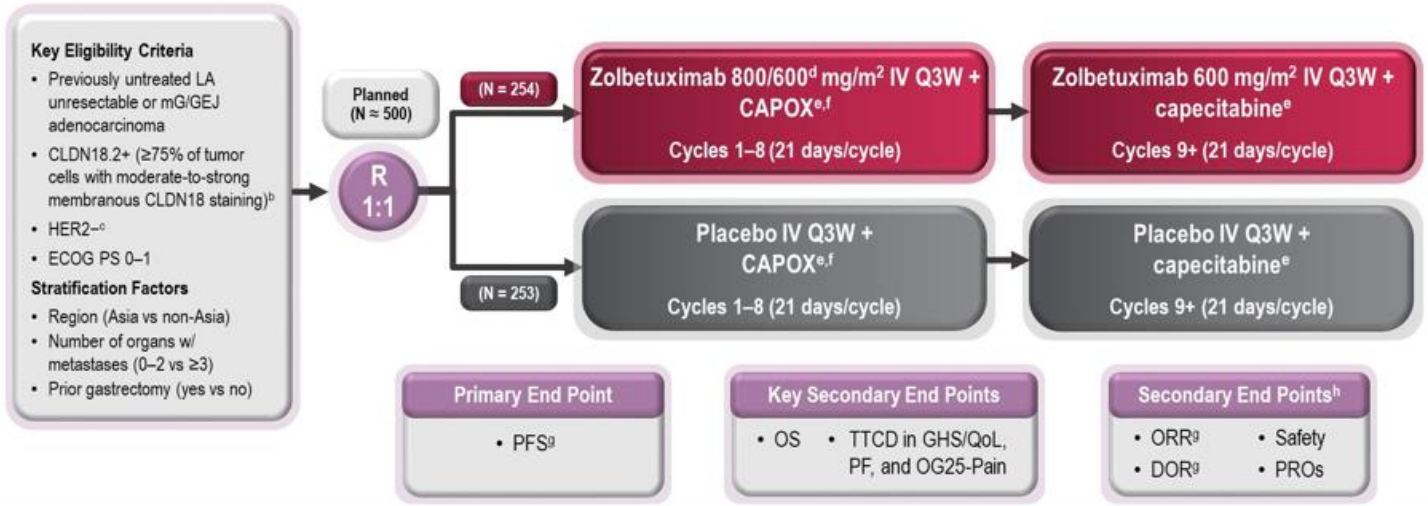
	Zolbetuximab + mFOLFOX6	Placebo + mFOLFOX6
No. events/no. patients	149/283	177/282
Median OS, months (95% CI)	18.23 (16.43–22.90)	15.54 (13.47–16.53)
HR (95% CI) *P*-value	0.750 (0.601–0.936) 0.0053	

Grade ≥3 AEs 86.7% vs 60.7% - Nausea/Vomiting Most common

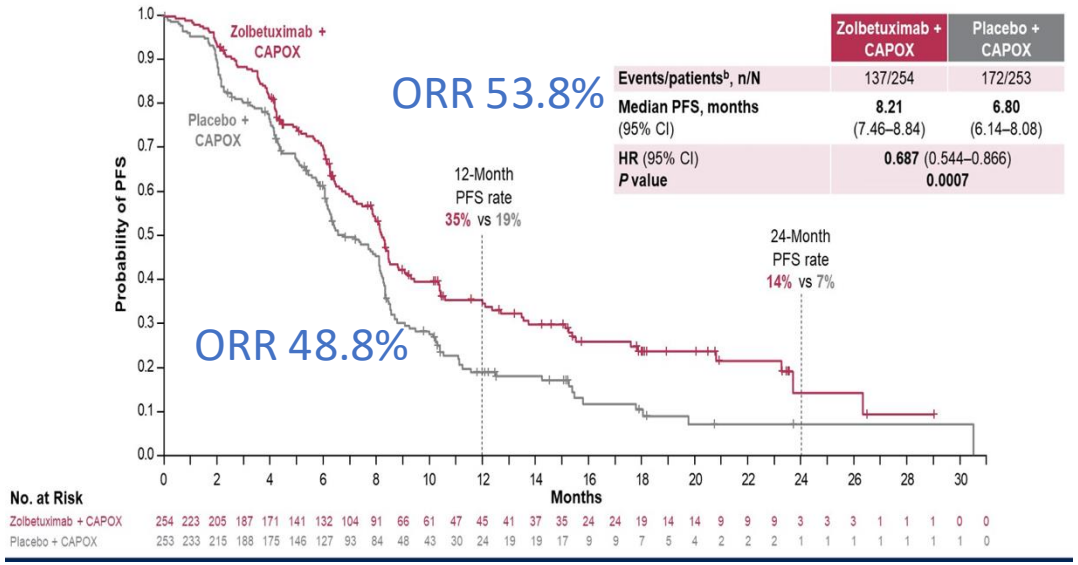
Shitara K et al. Gastrointestinal Cancers Symposium 2023;Abstract LBA292.

GLOW

Claudin 18.2

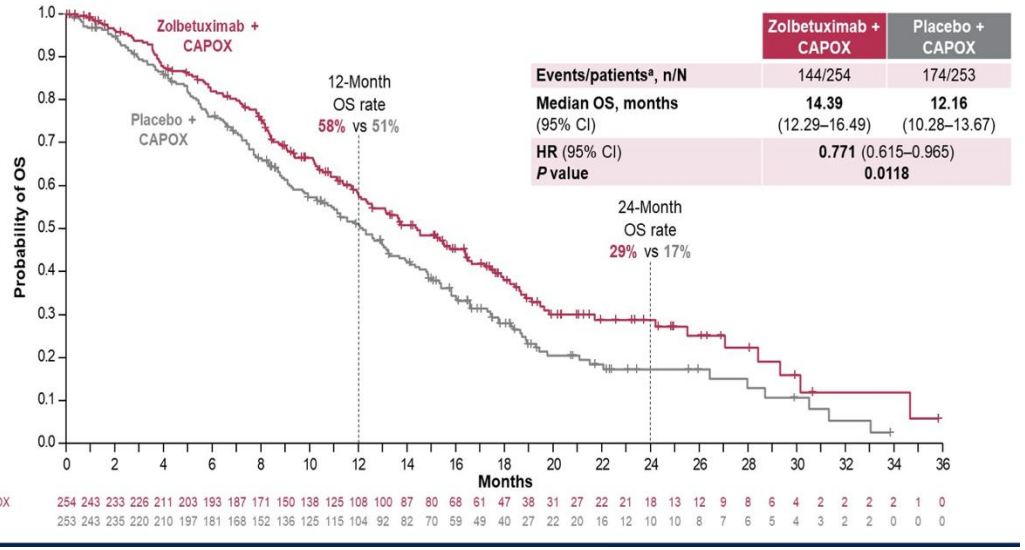


Progression free Survival



	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	

Overall Survival



	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	

Stomach more benefit than GEJ

Grade ≥3 AEs 72.8 vs 69.9%

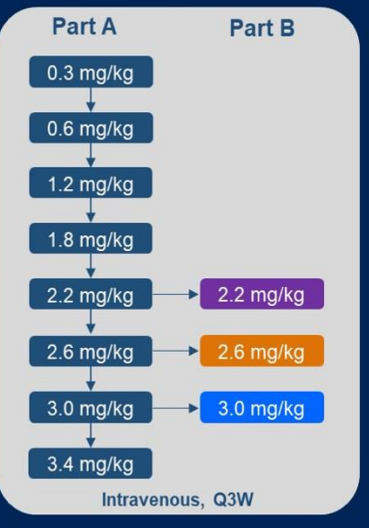
Xu et al. JCO 2023;Abstract 405736.

Claudin 18.2

KYM-01 Claudin 18.2 ADC Trial

Key Eligibility Criteria:

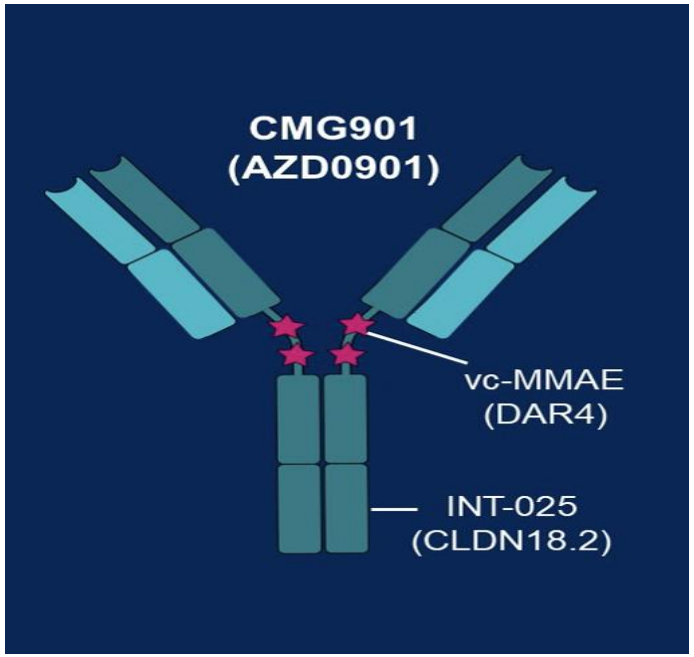
- Pathologically confirmed advanced solid tumor, evaluable by RECIST v1.1
- Refractory/intolerant to standard therapies
- ECOG PS ≤1
- Part A dose escalation:
  - CLDN18.2 expression not required
- Part B dose expansion:
  - CLDN18.2 expression of ≥2+ membrane staining intensity in ≥5% tumor cells required



Primary Endpoints
Part A: Adverse events and DLT
Part B: ORR[a] and RP2D

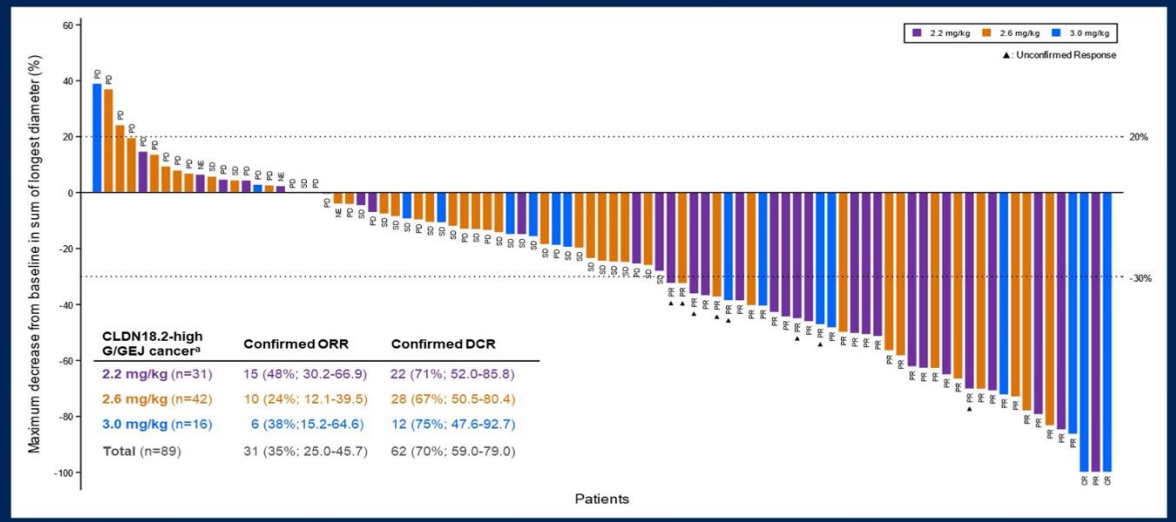
Focus on the 113 patients with G/GEJ cancer dosed at 2.2-3.0 mg/kg (107 patients from part B plus 6 patients from part A).

Data cut-off: February 24, 2024



Best Overall Response in CLDN18.2-High[a] G/GEJ Cancer

24-48% of patients achieved a confirmed objective response, and 67-75% of patients achieved a confirmed disease control



CLDN18.2-high G/GEJ cancer[a]	Confirmed ORR	Confirmed DCR
2.2 mg/kg (n=31)	15 (48%; 30.2-66.9)	22 (71%; 52.0-85.8)
2.6 mg/kg (n=42)	10 (24%; 12.1-39.5)	28 (67%; 50.5-80.4)
3.0 mg/kg (n=16)	6 (38%;15.2-64.6)	12 (75%; 47.6-92.7)
Total (n=89)	31 (35%; 25.0-45.7)	62 (70%; 59.0-79.0)

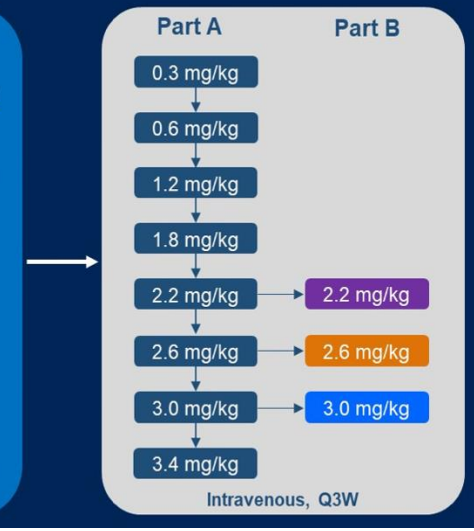
Data cut-off date: February 24, 2024.
Data are presented as n (%, 95%CI). [a] In patients with CLDN18.2 expression of ≥2+ membrane staining in ≥20% tumor cells, who received ≥1 dose of CMG901, with at least one post-treatment evaluation.
Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; DCR, disease control rate; CI, confidence interval; IHC, immunohistochemistry.

Claudin 18.2

KYM-01 Claudin 18.2 ADC Trial

Key Eligibility Criteria:

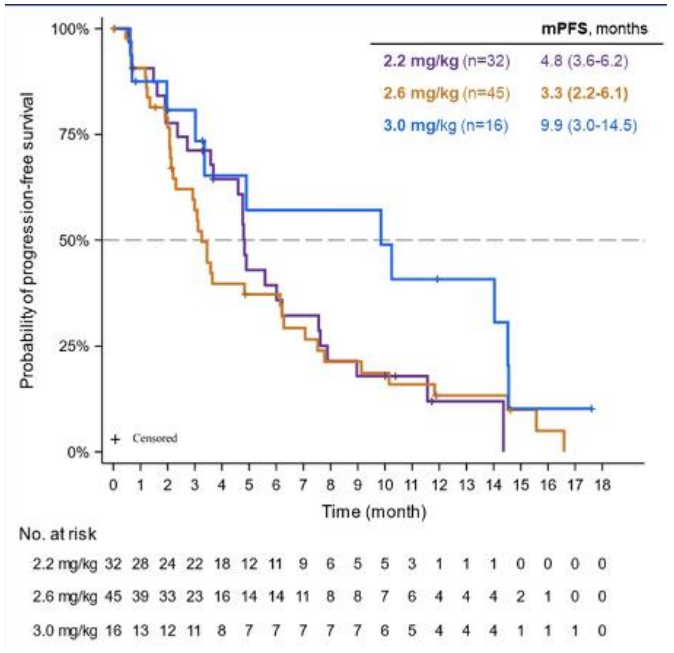
- Pathologically confirmed advanced solid tumor, evaluable by RECIST v1.1
- Refractory/intolerant to standard therapies
- ECOG PS ≤1
- Part A dose escalation:
  - CLDN18.2 expression not required
- Part B dose expansion:
  - CLDN18.2 expression of ≥2+ membrane staining intensity in ≥5% tumor cells required



Primary Endpoints
Part A: Adverse events and DLT
Part B: ORR[a] and RP2D

Focus on the 113 patients with G/GEJ cancer dosed at 2.2-3.0 mg/kg (107 patients from part B plus 6 patients from part A).

Data cut-off: February 24, 2024



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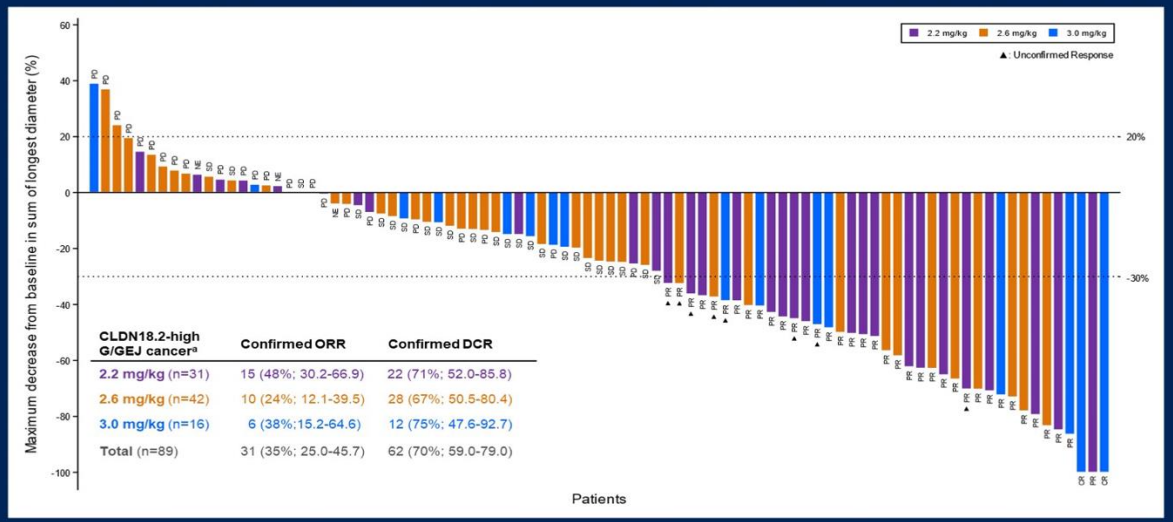

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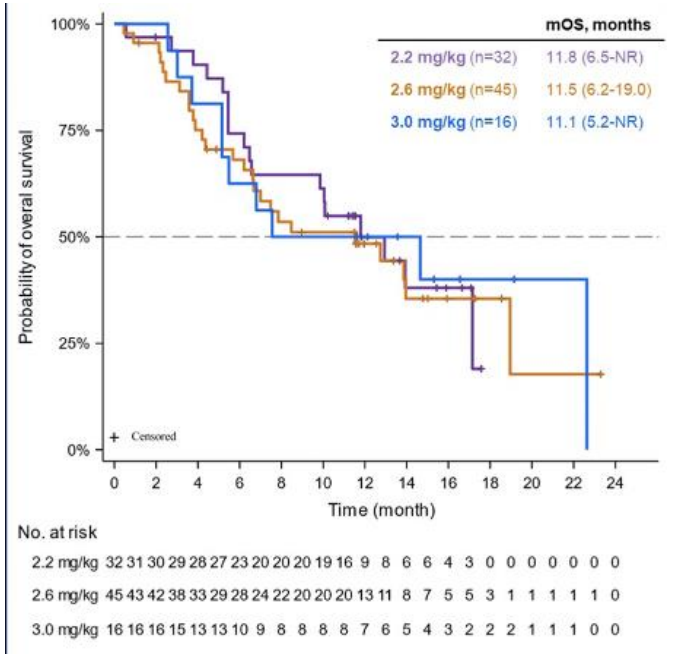


CLDN 18.2 Summary

- Zolbetuximab with mFOLFOX6 and CAPOX with improvement in PFS and OS
- Toxicity profile includes GI toxicity – nausea/vomiting – but appears to be tolerable and manageable
- Awaiting FDA approval
- Claudin ADC
- Target for cell therapy, antibody drug conjugates and other trials

Fruquintinib

FRUTIGA

Key Eligibility Criteria:
- Advanced G/GEJ adenocarcinoma
- Progressed on fluoropyrimidine- or platinum-containing chemotherapy
- ECOG PS 0-1

R 1:1

N=703

Fruquintinib + paclitaxel group (F+PTX)
- Fruquintinib: 4mg, QD, 3w on/1w off, po
- Paclitaxel: 80mg/m^2, Day1/8/15, IV 4w/cycle

Placebo + paclitaxel group (PBO+PTX)
- Placebo: 4mg, QD, 3w on/1w off, po
- Paclitaxel: 80mg/m^2, Day1/8/15, IV 4w/cycle

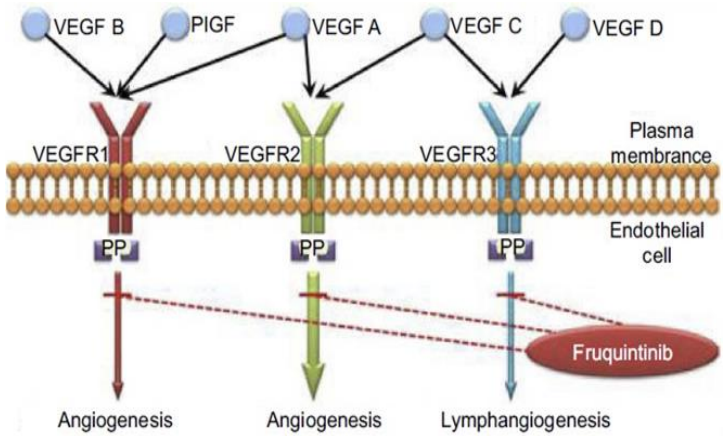
Treatment continued until
- **PD per RECIST 1.1 or**
- **Intolerable toxicity**

Stratification Factors:
- *GEJ vs Stomach;*
- *Peritoneal metastasis Y vs N;*
- *ECOG PS 0 vs 1*

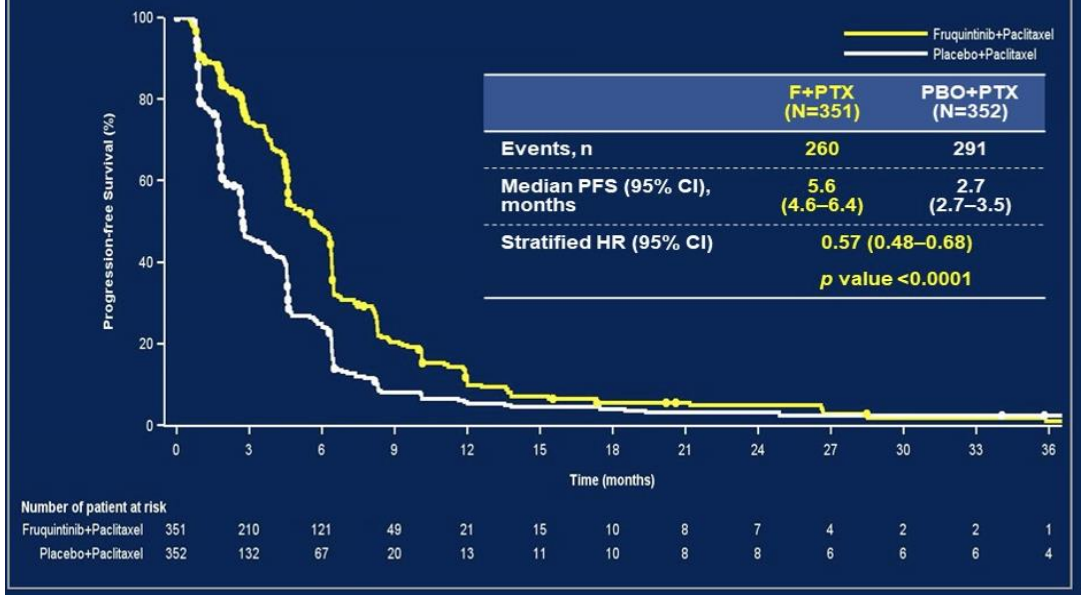
Dual Primary Endpoints*: PFS and OS

* Alpha allocation and recycling were used to control type I error for the final analysis of the dual primary endpoints

Secondary Endpoints: ORR, DCR, DoR, Safety, QoL



Progression-free survival

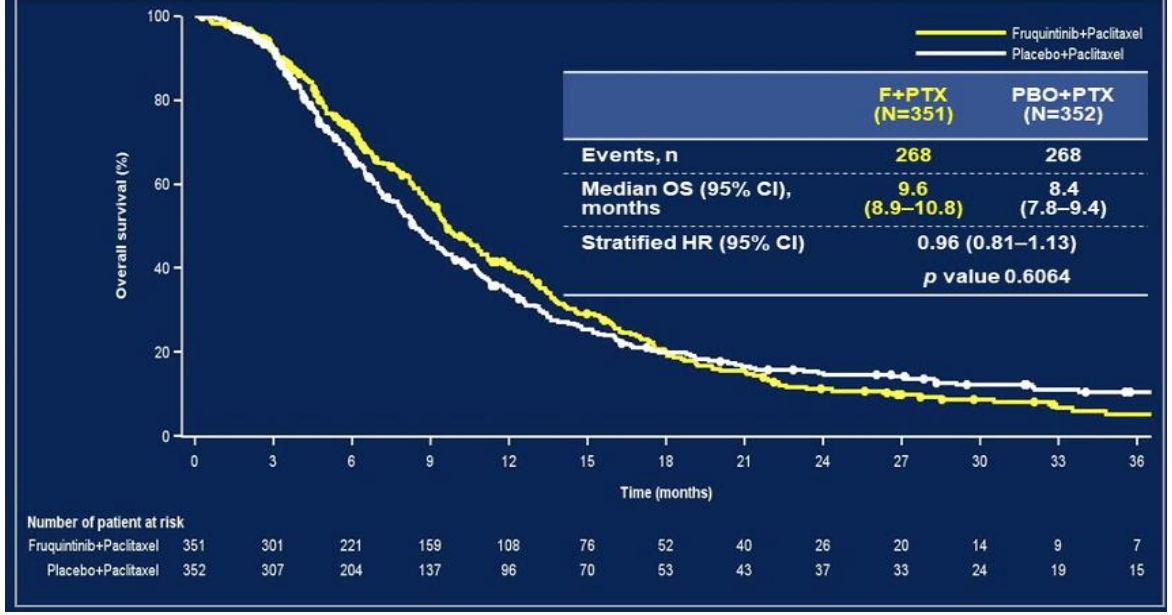


	F+PTX (N=351)	PBO+PTX (N=352)
Events, n	260	291
Median PFS (95% CI), months	5.6 (4.6–6.4)	2.7 (2.7–3.5)
Stratified HR (95% CI)	0.57 (0.48–0.68)	
	p value <0.0001	

Number of patient at risk

Fruquintinib+Paclitaxel	351	210	121	49	21	15	10	8	7	4	2	2	1
Placebo+Paclitaxel	352	132	67	20	13	11	10	8	8	6	6	6	4

Overall survival



	F+PTX (N=351)	PBO+PTX (N=352)
Events, n	268	268
Median OS (95% CI), months	9.6 (8.9–10.8)	8.4 (7.8–9.4)
Stratified HR (95% CI)	0.96 (0.81–1.13)	
	p value 0.6064	

Number of patient at risk

Fruquintinib+Paclitaxel	351	301	221	159	108	76	52	40	26	20	14	9	7
Placebo+Paclitaxel	352	307	204	137	96	70	53	43	37	33	24	19	15

Improved outcomes in non-diffuse subtypes and with nodal involvement

Thank you!