Esophageal and Gastric Cancer: Moving to a More Personalized Approach

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OBJECTIVES

BIOMARKERS:

- *Review*

IMMUNOTHERAPY:

- Matterhorn study
- Keynote 585
- Infinity

CLAUDIN 18.2 TARGETED THERAPY

- Glow Study

HEUR 2 TARGETED THERAPY

- Keynote 811
- Destiny Gastric 03

FGFR INHIBITORS

- Fight Trial

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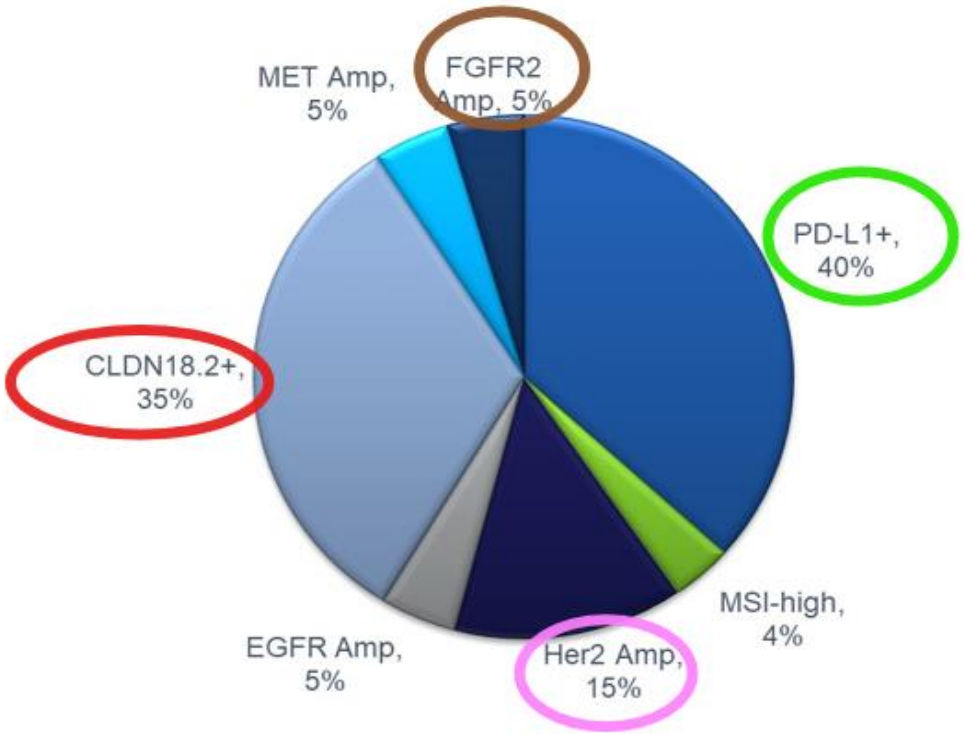
Key Biomarkers for Treatment in Gastroesophageal Cancer



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

PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

ADENOCARCINOMA

First-Line Therapy

- Oxaliplatin is preferred over cisplatin due to lower toxicity.

Preferred Regimens

- HER2 overexpression positive[d]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and trastuzumab[a]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, trastuzumab[a] and pembrolizumab for PD-L1 CPS ≥1 (category 1)[e,g,23,24]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), cisplatin, and trastuzumab (category 1)[a,25]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), cisplatin, trastuzumab[a] and pembrolizumab for PD-L1 CPS ≥1 (category 1)[e,g,23,24]
- HER2 overexpression negative[f]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and nivolumab (category 1 for PD-L1 CPS ≥ 5; category 2B for PD-L1 CPS <5)[e,g,26]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and pembrolizumab for PD-L1 CPS ≥ 1 (category 1 for PD-L1 CPS ≥ 10; category 2B for PD-L1 CPS 1 to <10)[e,g,27,28]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin and zolbetuximab-clzb for CLDN18.2 positive[d] (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)[29,30]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin[31-33]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), cisplatin, and pembrolizumab for PD-L1 CPS ≥ 1 (category 1 for PD-L1 CPS ≥ 10; category 2B for PD-L1 CPS 1 to <10)[e,g,27,28]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin[31,34-36]
- MSI-H/dMMR tumors (independent of PD-L1 status)[f]
  - Pembrolizumab[e,g,37-39]
  - Dostarlimab-gxly[e,g,40]
  - Nivolumab and ipilimumab[e,g,26]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and nivolumab[e,g,26]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and pembrolizumab[e,g,27]

Other Recommended Regimens

- Fluorouracil[b,h] and irinotecan[i,41]
- Paclitaxel with or without carboplatin or cisplatin [i,42-46]
- Docetaxel with or without cisplatin[i,47-50]
- Fluoropyrimidine[i,35,51,52] (fluorouracil[b] or capecitabine)
- Docetaxel, cisplatin or oxaliplatin, and fluorouracil[b,i,53,54]

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2024
Esophageal and Esophagogastric Junction Cancers

NCCN Guidelines Index
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Discussion

PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

ADENOCARCINOMA

Second-Line or Subsequent Therapy

- Dependent on prior therapy and PS

Preferred Regimens

- Ramucirumab and paclitaxel (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)[56]
- Fam-trastuzumab deruxtecan-nxki for HER2 overexpression positive[e,f]
- Docetaxel (category 1)[40,50]
- Paclitaxel (category 1)[45,46,58]
- Irinotecan (category 1)[58-61]
- Fluorouracil[b,h] and irinotecan[59,62,63]
- Trifluridine and tipiracil for third-line or subsequent therapy for EGJ adenocarcinoma (category 1)[64]

Other Recommended Regimens

- Ramucirumab (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)[65]
- Irinotecan and cisplatin[32,66]
- Fluorouracil and irinotecan + ramucirumab[b,h,67]
- Irinotecan and ramucirumab[68]
- Docetaxel and irinotecan (category 2B)[69]

Useful in Certain Circumstances[d]

- Entrectinib, larotrectinib, or repotrectinib[j] for *NTRK* gene fusion-positive tumors[70-72]
- Pembrolizumab[e,g] for MSI-H/dMMR tumors[37-39]
- Nivolumab and ipilimumab[e,g] for MSI-H/dMMR tumors[26]
- Pembrolizumab[e,g] for TMB high (≥10 mutations/megabase) tumors[73]
- Dostarlimab-gxly[e,g,k] for MSI-H/dMMR tumors[40]
- Dabrafenib and trametinib for *BRAF* V600E mutated tumors[74]
- Selpercatinib for *RET* gene fusion-positive tumors[75]

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IMMUNOTHERAPY IN THE ADJUVANT SETTING

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 1, 2021 VOL. 384 NO. 13

Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer

R.J. Kelly, J.A. Ajani, J. Kuzdzal, T. Zander, E. Van Cutsem, G. Piessen, G. Mendez, J. Feliciano, S. Motoyama, A. Lièvre, H. Uronis, E. Elimova, C. Grootscholten, K. Geboes, S. Zafar, S. Snow, A.H. Ko, K. Feeney, M. Schenker, P. Kocon, J. Zhang, L. Zhu, M. Lei, P. Singh, K. Kondo, J.M. Cleary, and M. Moehler, for the CheckMate 577 Investigators*

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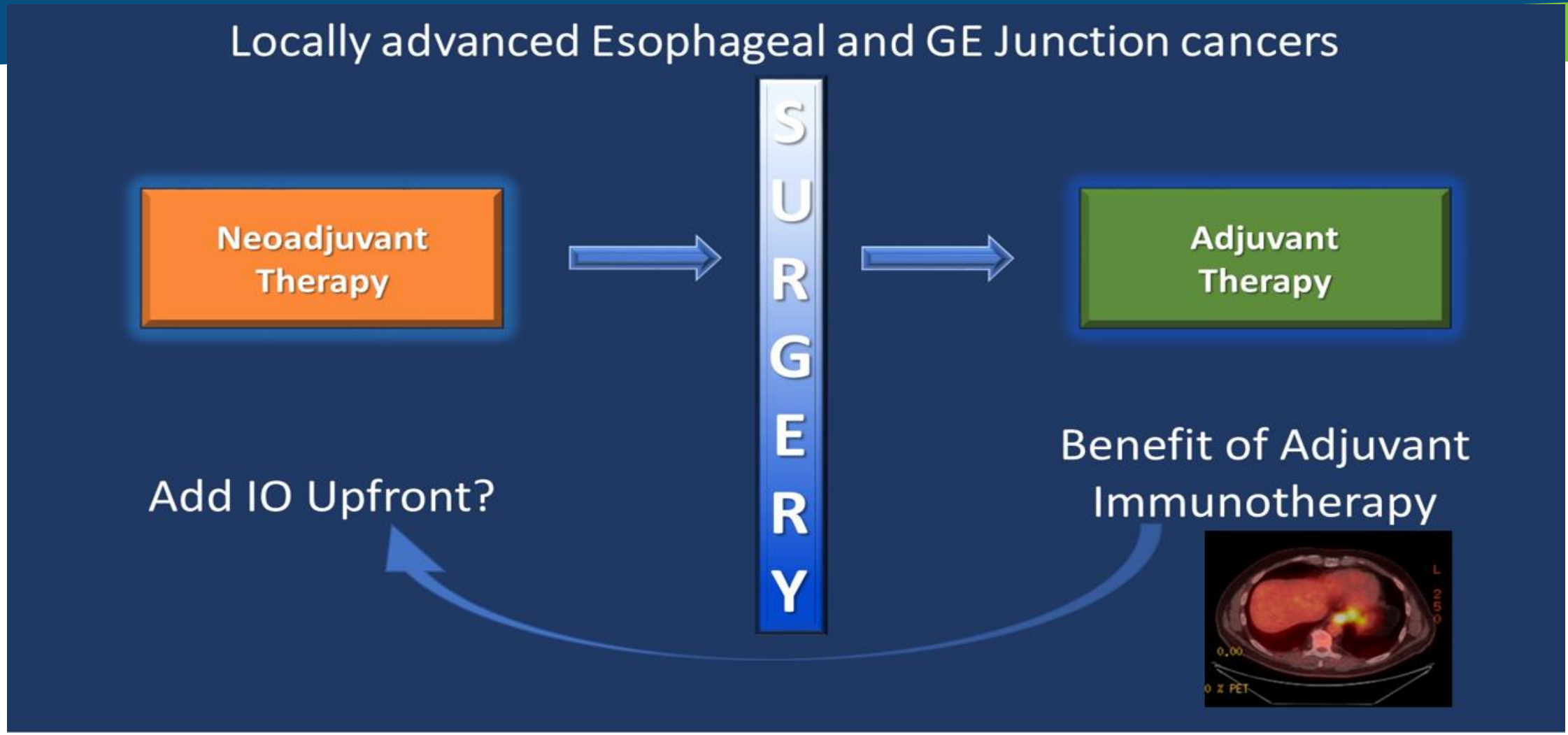
Immunotherapy for Locally Advanced GE Cancers



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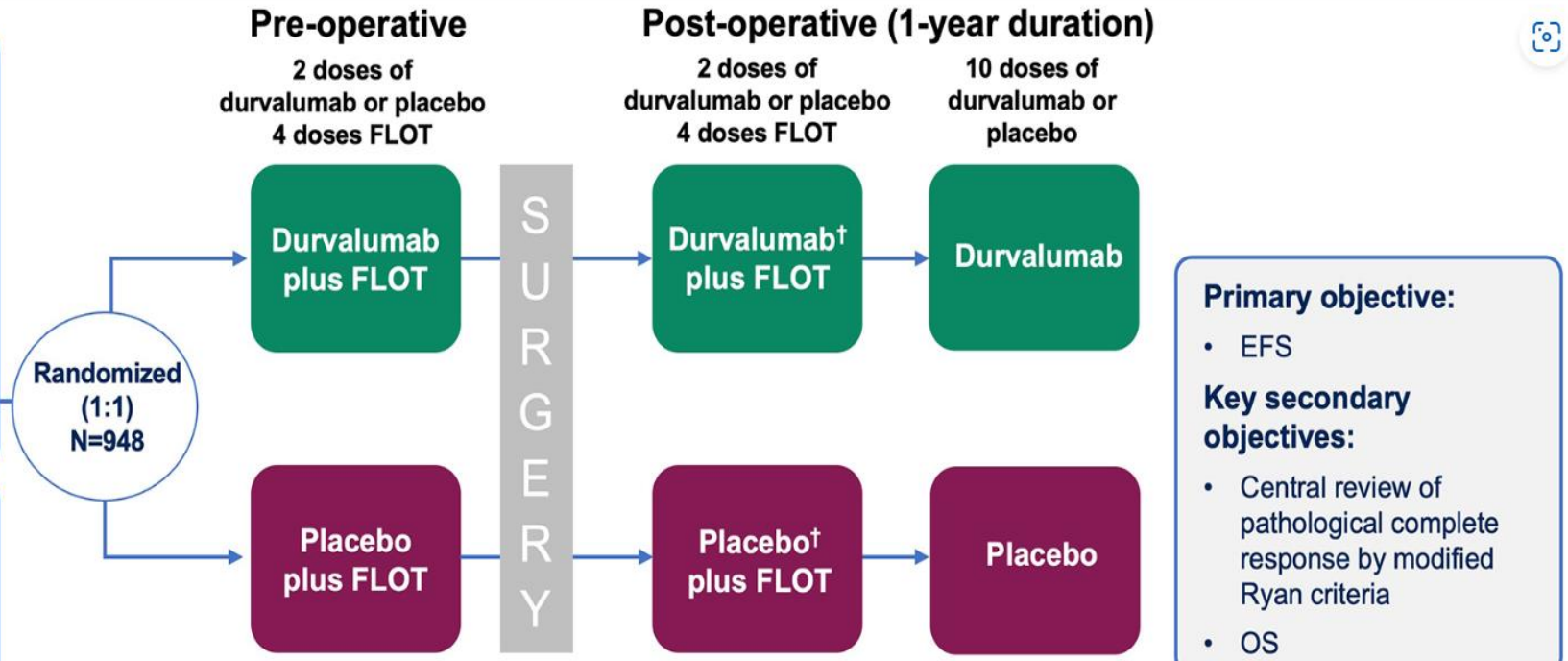
MATTERHORN STUDY

Study population

- Gastric and GEJ adenocarcinoma
- Stage II, III and IVA (>T2 N0-3 M0 or T0-4 N1-3 M0)
- No evidence of metastasis
- No prior therapy
- ECOG PS 0 or 1
- Global enrolment from Asia, Europe, North America, and South America

Stratification factors

- Geographic region: Asia versus non-Asia
- Clinical lymph node status: positive versus negative
- PD-L1 status: TAP <1% versus TAP ≥1%*



Durvalumab 1500 mg or placebo Q4W (Day 1) plus FLOT Q2W (Days 1 and 15) for 4 cycles (2 doses of durvalumab or placebo plus 4 doses of FLOT pre- and post-operative), followed by durvalumab or placebo Q4W (Day 1) for 10 further cycles

Primary objective:

- EFS

Key secondary objectives:

- Central review of pathological complete response by modified Ryan criteria
- OS

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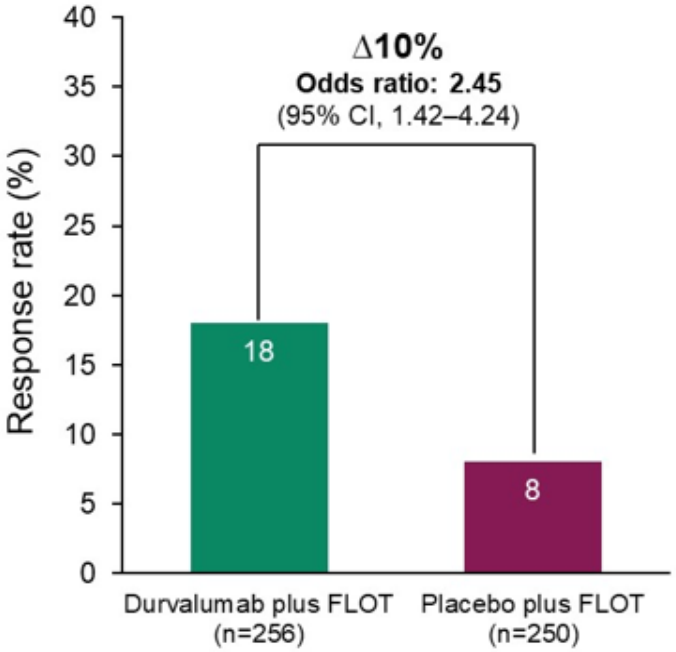
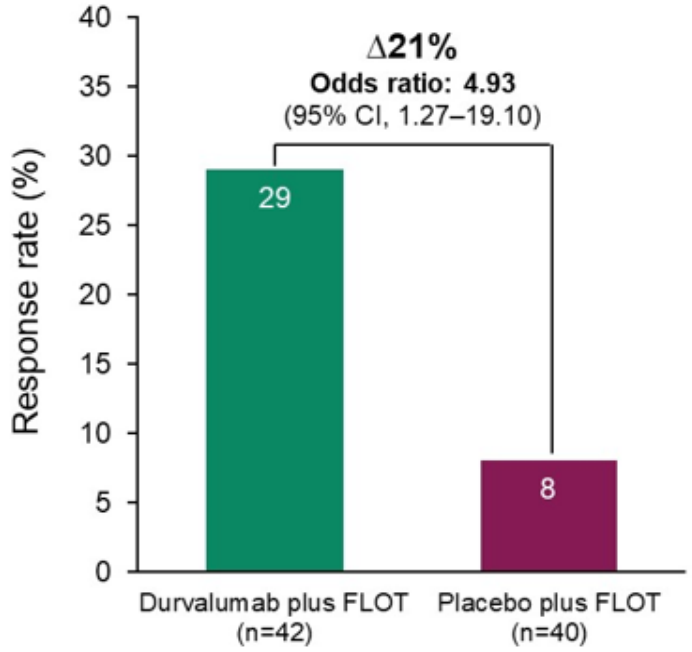
Pathological complete response by region (non-Asia)

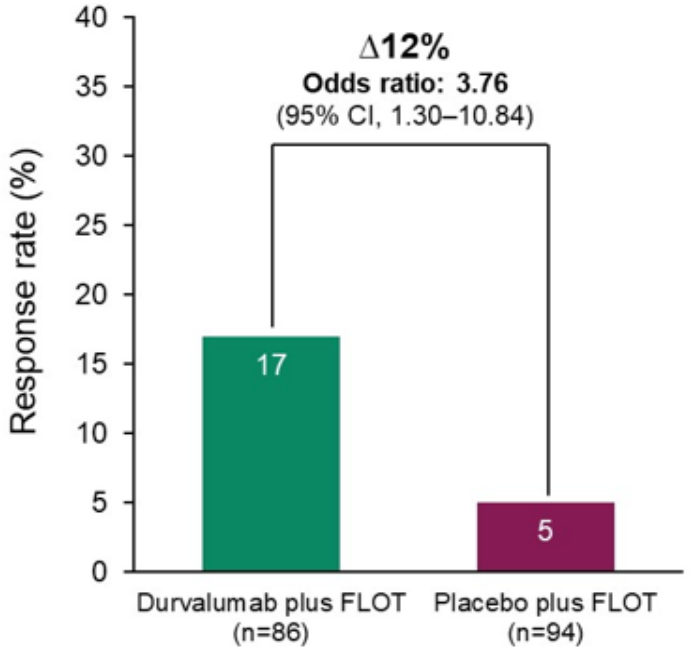
Europe (n=506)



North America (n=82)

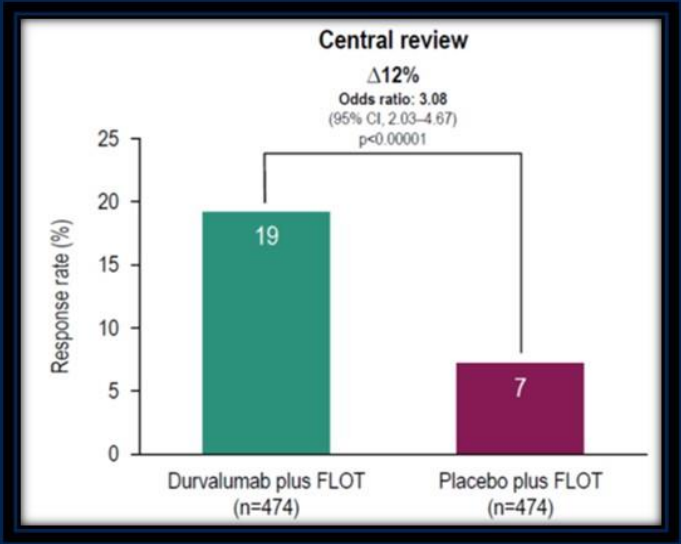


South America (n=180)



Participants achieve pathological complete response if there is no residual viable tumor cells found at primary tumor and resected lymph nodes at the time of resection, meaning a pathological regression of 100%, based on central assessment. Central review of pathological complete response was scored using modified Ryan criteria.
CI, confidence interval; FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel.

MATTERHORN reported superior pCR with EFS data yet pending

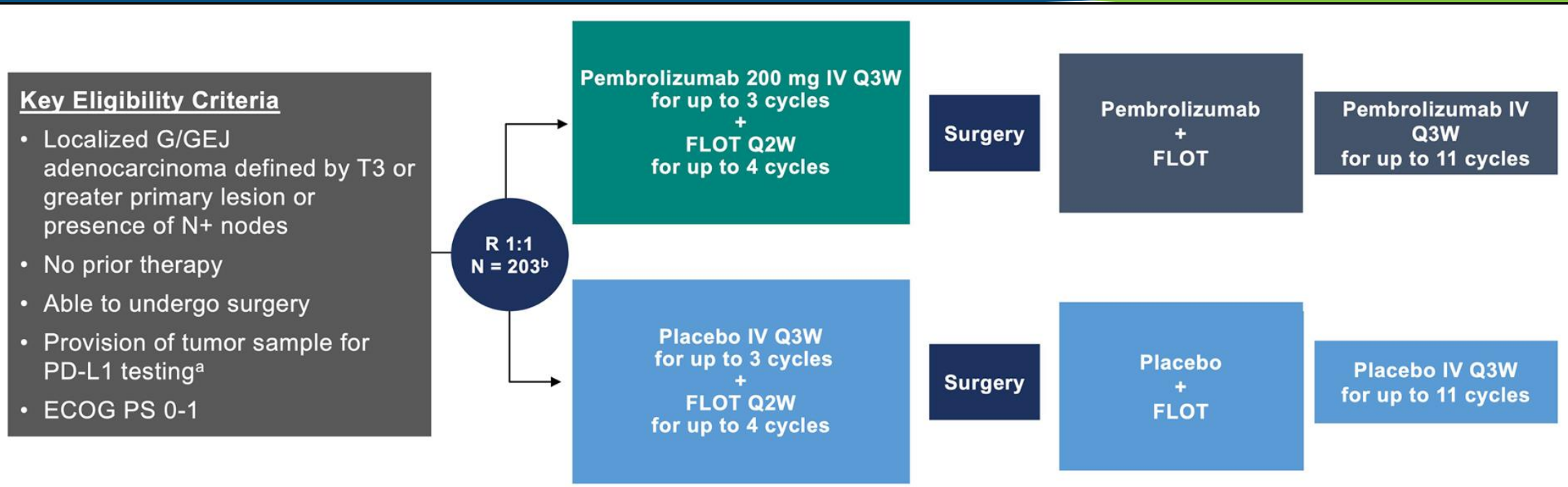


Pathological response subgroup analysis (central review)

	Durvalumab plus FLOT, N	Placebo plus FLOT, N	Pathological complete response Odds ratio (95% CI)	Combined complete and near-complete pathological response Odds ratio (95% CI)
All participants	474	474	3.08 (2.03–4.67)	2.19 (1.58–3.04)
Sex				
Male	326	356	3.35 (2.07–5.41)	2.22 (1.54–3.22)
Female	148	118	2.53 (1.09–5.89)	2.47 (1.18–5.18)
Age group				
<65 years	291	265	2.71 (1.53–4.79)	2.16 (1.39–3.37)
≥65 years	183	209	3.70 (2.01–6.84)	2.29 (1.41–3.73)
Location at screening				
GC	324	316	2.56 (1.50–4.38)	1.69 (1.12–2.55)
GEJC	150	158	4.20 (2.14–8.21)	3.50 (2.01–6.07)
TNM classification				
T4	117	117	2.81 (1.18–6.67)	2.14 (1.07–4.26)
Non-T4	357	357	3.16 (1.96–5.09)	2.20 (1.52–3.19)
Clinical lymph node status				
Positive	334	333	3.23 (1.97–5.30)	2.14 (1.45–3.18)
Negative	137	140	2.62 (1.20–5.74)	2.26 (1.25–4.08)
PD-L1 expression at baseline				
<1%	48	47	0.98 (0.19–5.11)	1.94 (0.60–6.29)
≥1%	426	427	3.33 (2.15–5.13)	2.21 (1.57–3.11)
<5%	236	230	2.25 (1.11–4.57)	2.30 (1.35–3.92)
≥5%	238	244	3.79 (2.25–6.39)	2.20 (1.44–3.35)
Region				
Asia	90	90	3.96 (1.39–11.26)	2.41 (1.14–5.06)
Non-Asia	384	384	2.92 (1.85–4.61)	2.13 (1.48–3.07)
Country				
Germany	47	70	2.88 (1.13–7.35)	2.72 (1.21–6.12)
Non-Germany	427	404	3.34 (2.08–5.36)	2.21 (1.54–3.18)

pCR in the German subgroup 30% vs. 13%

KEYNOTE 585 DESIGN



Stratification factors
- Geographic region (Asia versus non-Asia)
- Tumor staging (II vs III vs IVa)
- Chemotherapy backbone (XP/FP vs FLOT)

Endpoints:
- Primary: safety
- Key secondary: pathCR rate per BICR, EFS per investigator, OS

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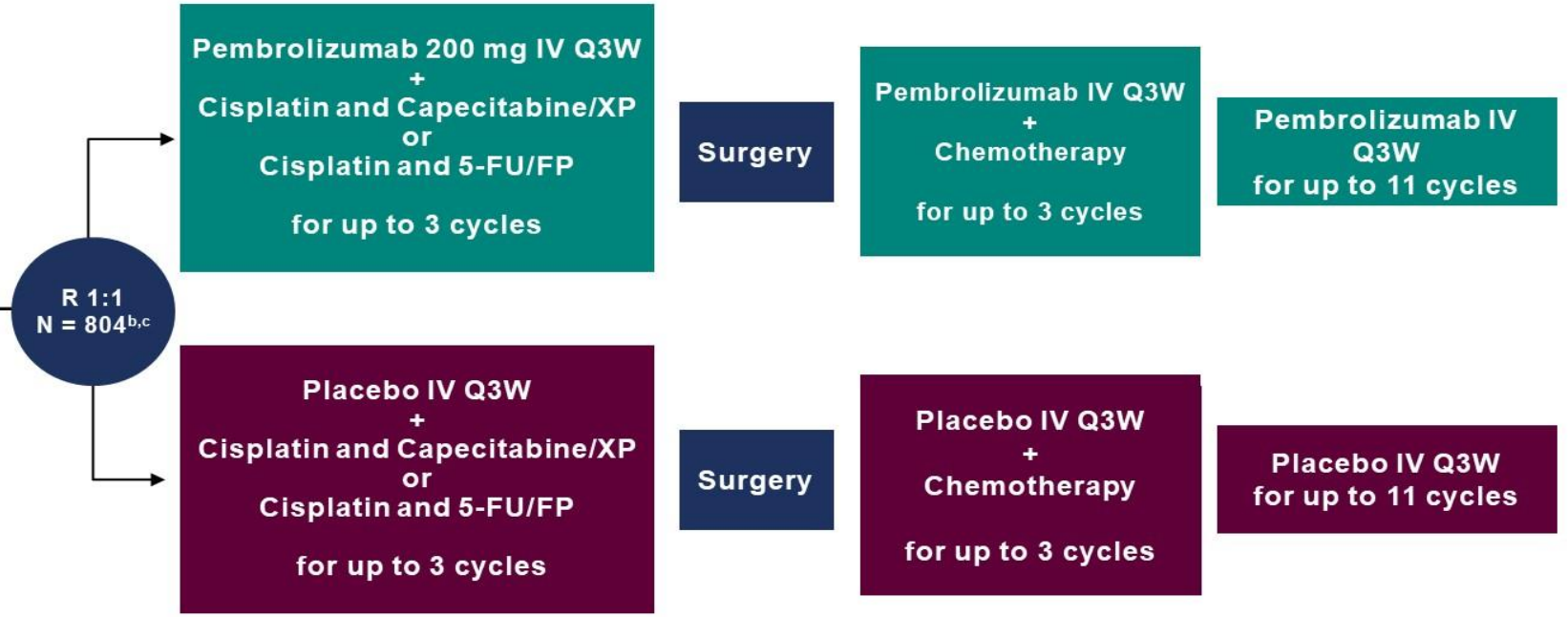
KEYNOTE-585 Study Design

Randomized, Double-Blind, Phase 3 Trial of Neoadjuvant and Adjuvant Pembrolizumab Plus Chemotherapy Versus Placebo Plus Chemotherapy in G/GEJ Adenocarcinoma (**Main Cohort**)

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



Stratification factors

- Geographic region (Asia versus non-Asia)
- Tumor staging (II vs III vs IVa)
- Chemotherapy backbone (XP/FP vs FLOT)

Endpoints:

- Primary: pathCR rate per BICR, EFS per investigator, OS (main cohort), safety (FLOT)
- Key secondary: safety (main cohort), safety, OS, EFS (main plus FLOT cohort)

[a]PD-L1 status was centrally assessed; [b]Main cohort. [c]An additional 203 patients were randomized 1:1 to a separate FLOT cohort evaluating pembrolizumab + FLOT vs placebo + FLOT (5-FU 2600 mg/m^2, leucovorin 200 mg/m^2, oxaliplatin 85 mg/m^2, docetaxel 50 mg/m^2) Q2W for up to 4 cycles in the neoadjuvant and adjuvant phases. XP: cisplatin 80 mg/m^2 IV on d1 and capecitabine 1000 mg/m^2 orally BID from d1 – d14. FP: cisplatin 80 mg/m^2 IV on d1 and 5-FU 800 mg/m^2 IV from d1 – d5 up to 4000 mg/m^2.

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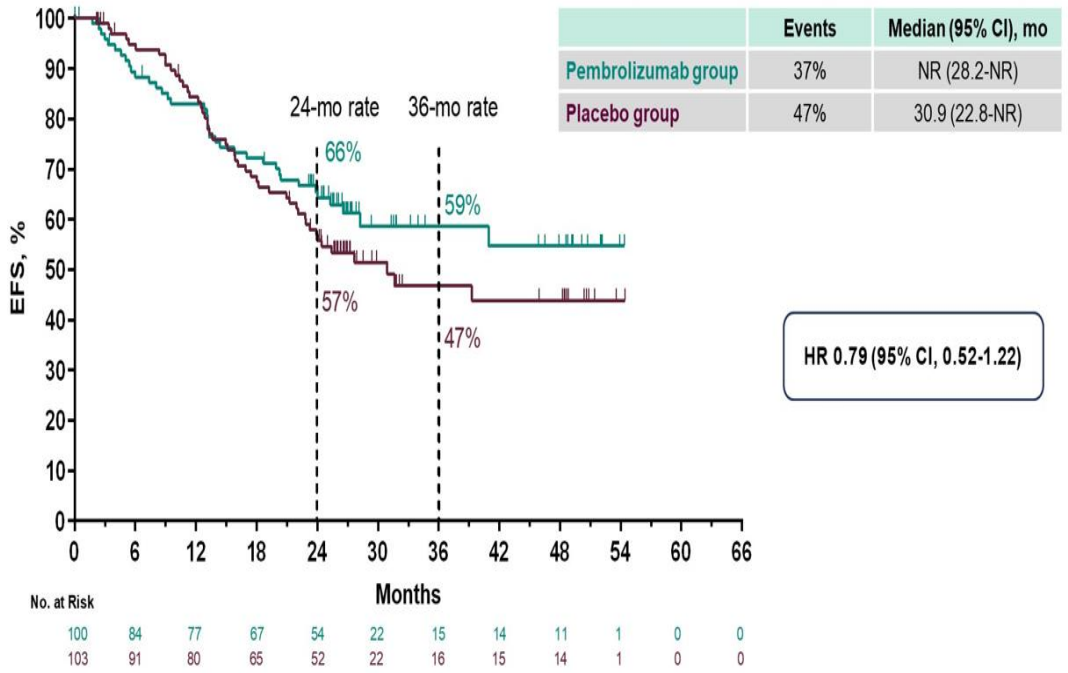
KEYNOTE 585 EFS, OS

Event-Free Survival: FLOT Cohort

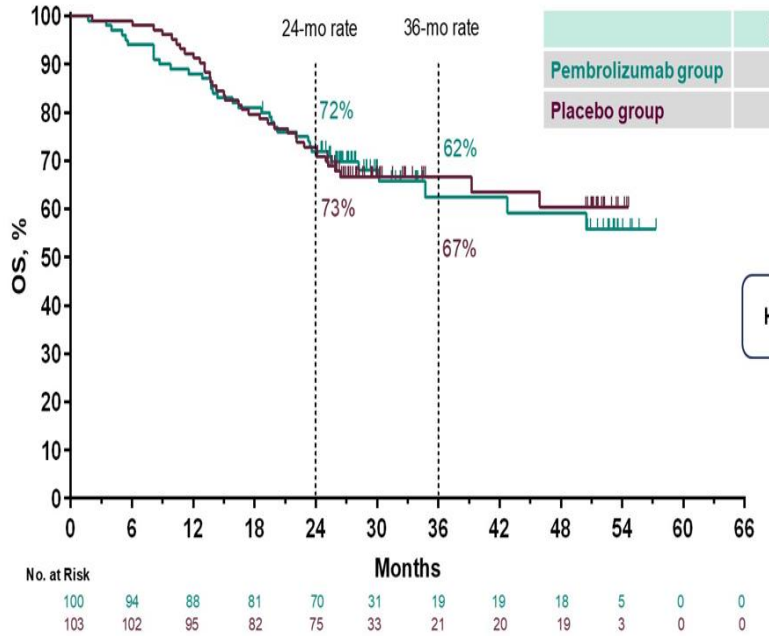


	Events	Median (95% CI), mo
Pembrolizumab group	37%	NR (28.2-NR)
Placebo group	47%	30.9 (22.8-NR)

HR 0.79 (95% CI, 0.52-1.22)

Data cutoff date: 09 Feb 2023. Median Follow-Up*: 31.6 months (range, 24.5-57.6). EFS defined as time from randomization to first occurrence of radiographic disease progression per RECIST v1.1, local or distant recurrence as assesses by CT scan or biopsy if indicated, clinical progression, or death due to any cause per investigator assessment. NR, not reached.

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)

Data cutoff date: 09 Feb 2023. Median Follow-Up: 31.6 months (range, 24.5-57.6).

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MATTERHORN STUDY VS KEYNOTE 585 STUDY

Table: LBA73

	D + FLOT (n=474)	P + FLOT (n=474)
pCR		
n; % (95% CI)	91; 19 (15.8–23.0)	34; 7 (5.0–9.9)
OR (95% CI)	3.08 (2.03–4.67); p<0.00001	
pCR/pnCR		
n; % (95% CI)	127; 27 (22.9–31.0)	68; 14 (11.3–17.8)
OR (95% CI)	2.19 (1.58–3.04); p<0.00001	
Surgery performed		
n; % (95% CI)	411; 87 (83.3–89.6)	399; 84 (80.6–87.4)
OR (95% CI)	1.23 (0.85–1.76)	
R0 resection*		
n; % (95% CI)	369; 86 (82.2–89.0)	362; 86 (82.1–89.0)
OR (95% CI)	1.00 (0.68–1.48)	
AE†, n (%)	470 (99)	463 (99)
Grade 3/4	326 (69)	317 (68)
TRAE	452 (95)	441 (94)
Grade 3/4 TRAE	275 (58)	264 (56)

*In pts with surgery: D + FLOT, n=430, P + FLOT, n=422. †In safety analysis set: D + FLOT, n=475, P + FLOT, n=469. TRAE, treatment-related AE.

Table: LBA74 Outcomes in main + FLOT cohort

Efficacy	Pembro + chemo N = 502	Pbo + chemo N = 505	Treatment difference (95% CI)
Path CR[a], %	13.0 (10.2-16.3)	2.4 (1.3-4.2)	10.6% (7.4-14.0) P<0.0001
Median EFS, mo (95% CI)	45.8 (35.9-NR)	[illegible]	HR 0.81 (0.68-0.97) P=0.011
Median OS, mo (95% CI)	60.7 (51.5-NR)	NR (45.7-NR)	HR 0.93 (0.76-1.12)
Safety	Pembro + chemo N = 498	[illegible] N = 503	NA
Grade ≥ 3 drug-related AEs	67%	63%	NA

[a]In first 987 pts randomized; HR, hazard ratio; NA, not applicable; NR, not reached

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Do MATTERHORN and KEYNOTE meet the goal for successful Neoadjuvant therapy?

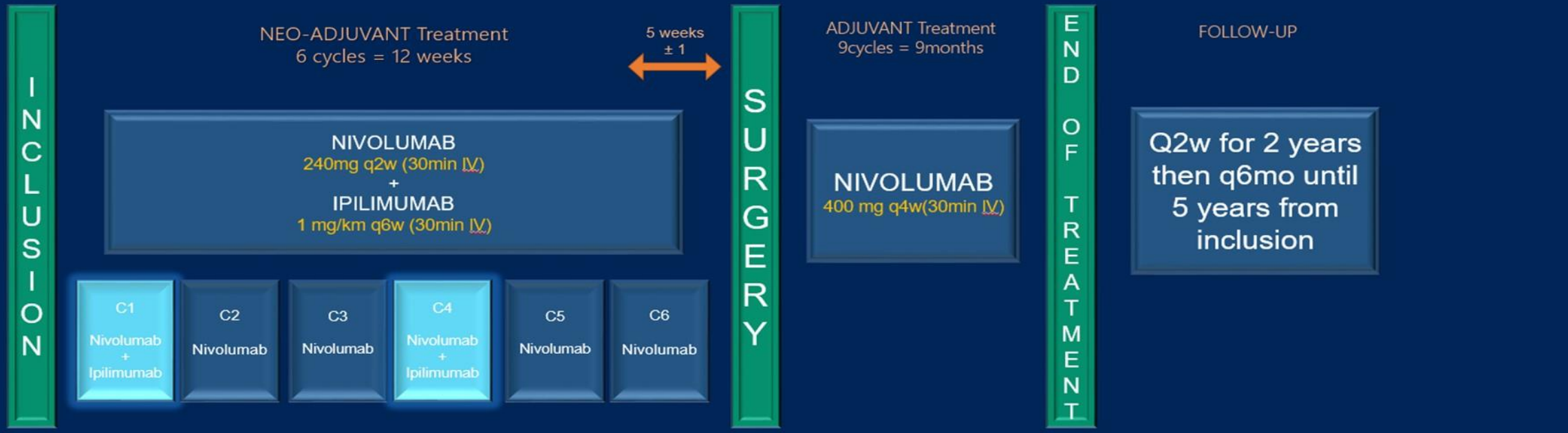
YES, equal rates of resection in control and experimental arms but toxicity is not trivial (KN 585 11% Grade 3-4 AEs experimental arm)

YES, unequivocal improvements in pCR rate for both trials Control arm pCR underperformed in both studies (advanced tumours)

MAYBE, but probably only for immunologically hot tumors

Microsatellite Unstable Esophageal and GE-Junction tumors

NEONIPIGA

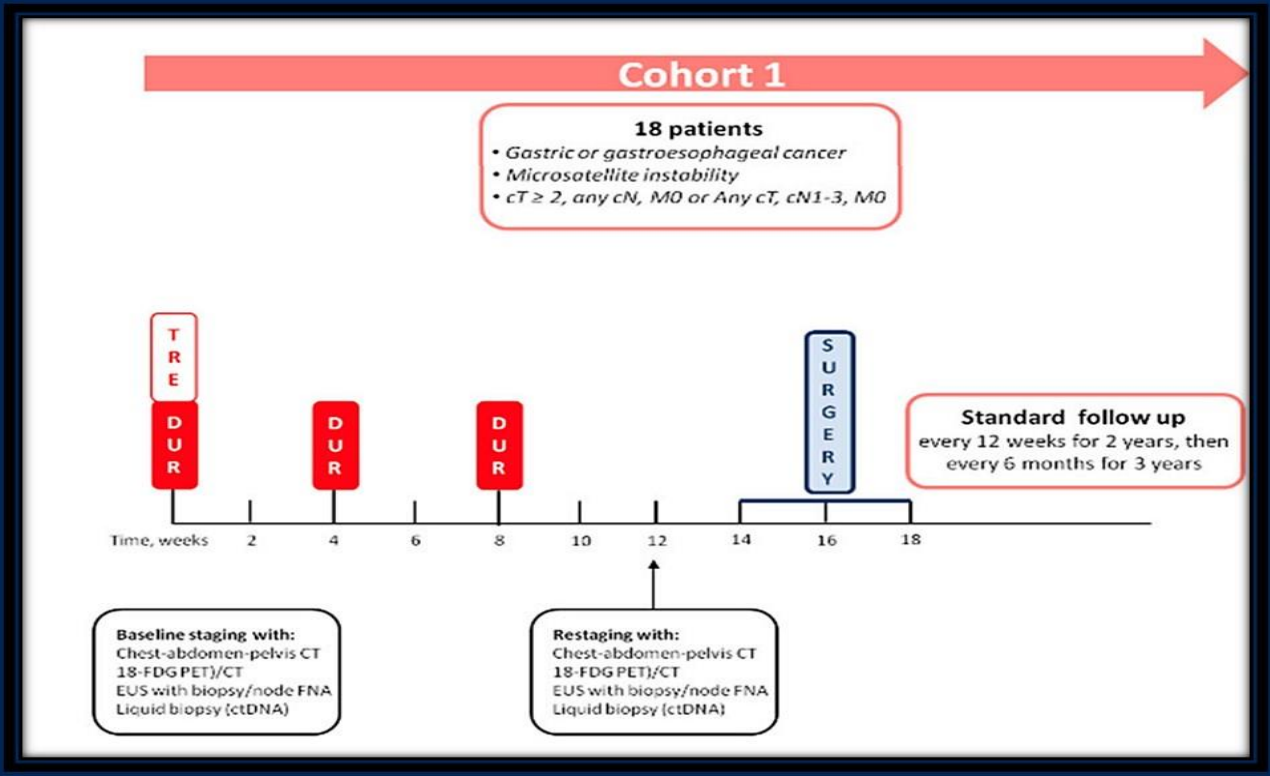


Treatment protocol:	Surgical outcome:	Pathologic complete response (pCR):	Survival at 12-month follow-up:
12 weeks neoadjuvant nivolumab + low-dose (1 mg) ipilimumab. Surgery followed by 9 months adjuvant nivolumab.	Almost all patients (except 1) underwent surgery.	58.6% achieved pCR	93.7% of patients alive without relapse.

Thierry et al. J Clin Oncol 2023 Jan 10;41(2):255-265

IMMUNOTHERAPY NEOADJUVANT MSI-H WITHOUT CHEMORx

INFINITY:

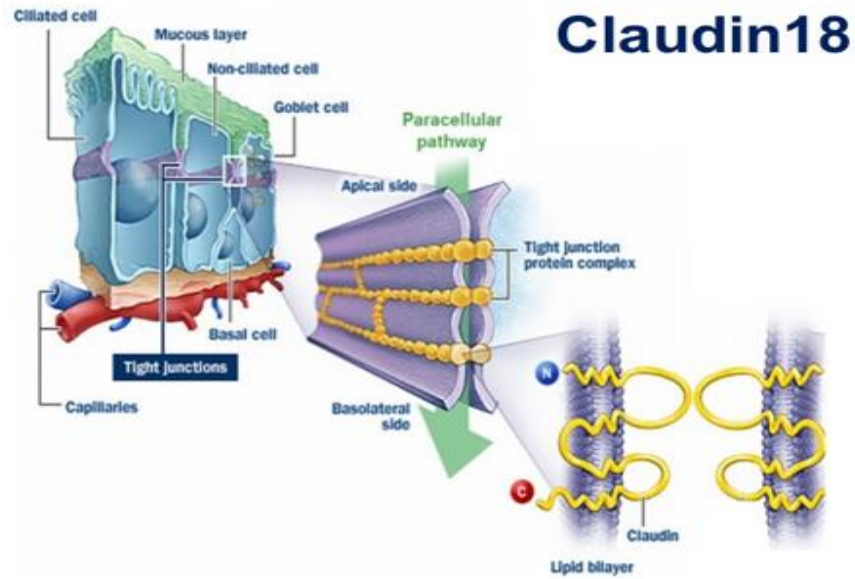


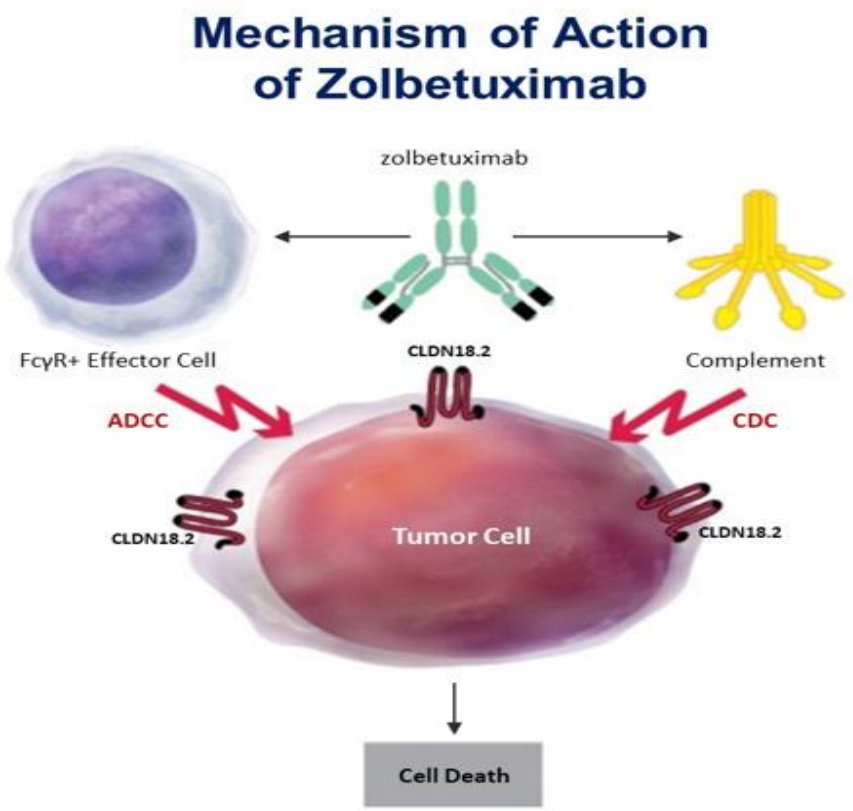
- **Single-Arm, Multi-Cohort, Phase II INFINITY Study for microsatellite instability-high (MSI) resectable gastric or gastroesophageal junction adenocarcinoma.**

Cancers (Basel) . 2021 Jun 7;13(11):2839.

NOVEL BIOMARKER PATHWAY

Claudin18.2
A Novel Target





- 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

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

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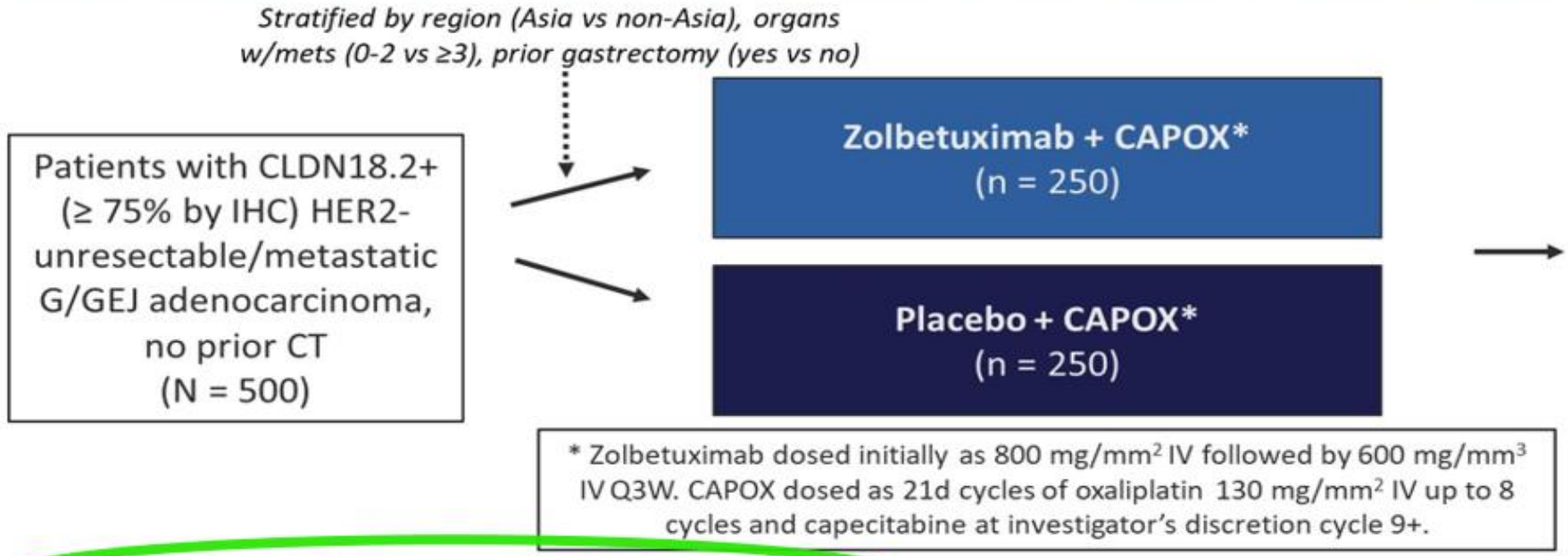
GLOW: Zolbetuximab + CAPOX in CLDN18.2+ G/GEJ Cancer

- Global, double-blind, placebo-controlled, randomized phase III study



Primary endpoint: IRC-assessed PFS

Secondary endpoints: OS, ORR, DOR, safety, PK, QoL

Shah. et al. Nat Med 2023.

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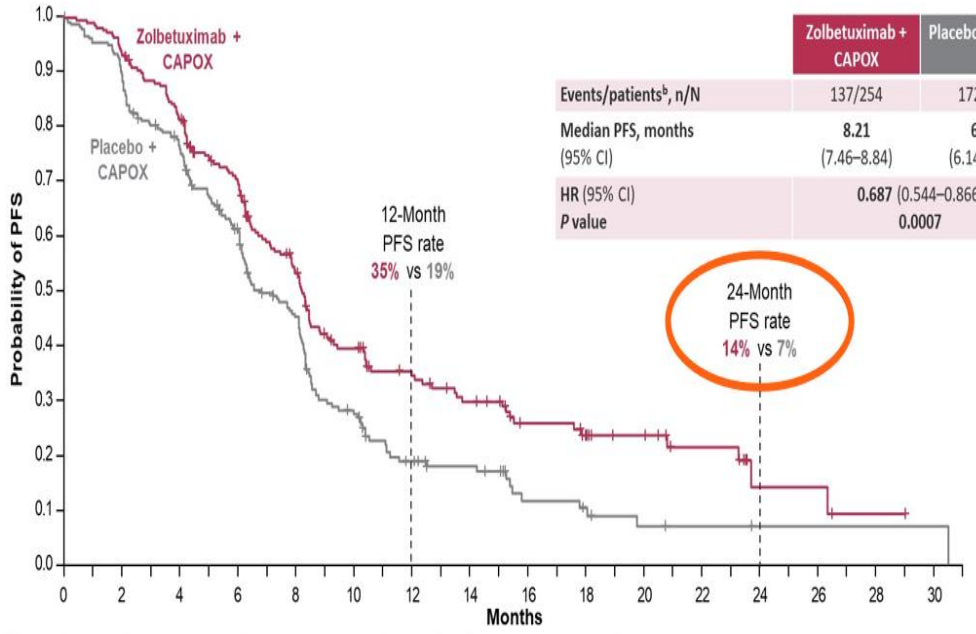
GLOW: Zolbetuximab + CAPOX in CLDN18.2+ G/GEJ Cancer

- Global, double-blind, placebo-controlled, randomized phase III study

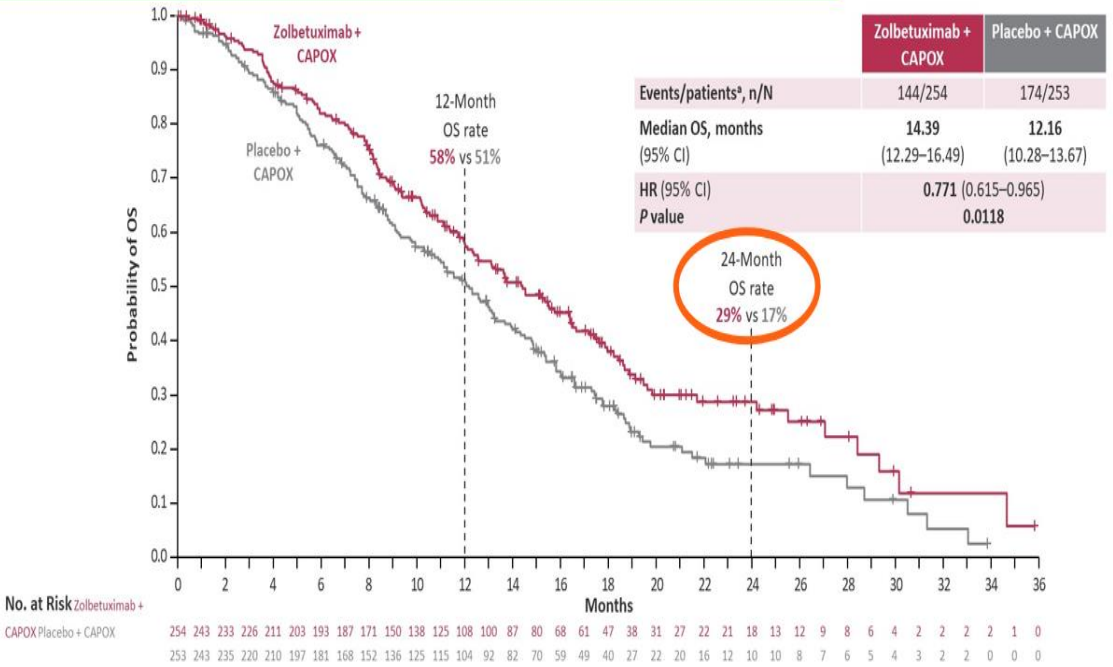
Primary End Point: PFS by Independent Review Committee



	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	

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

Key Secondary End Point: OS



	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	

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

Subsequent anticancer therapies were administered to 47% of patients in the zolbetuximab arm and 55% in the placebo arm

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SPOTLIGHT and GLOW

	SPOTLIGHT (n=550)	GLOW (n=500)
Control	FOLFOX	CapeOX
Countries	Global	Global (~50% from China)
CPS≥5	13%	22%
mPFS	10.6 vs 8.7 **+1.9** **HR 0.75**	8.2 vs 6.8 **+1.4** **HR 0.69**
mOS	18.2 vs 15.5 **+2.7** **HR 0.75**	14.4 vs 12.2 **+2.2** **HR 0.77**
ORR	61% vs 62% -1%	54% vs 49% +5%
Nausea Vomiting	81% vs 61% 65% vs 35%	69% vs 50% 66% vs 31%
Discontinuation of zolbe/pbo by AE	14% vs 2%	7% vs 4%

Shitara K et al. Presented at: ASCO-GI 2023. Abstract LBA 292
Xu RH et al. Presemted at: ASCO Plenary 2023. Abstract 40573

KEYNOTE-811 Study Design (NCT03615326)

Phase 3 Randomized, Placebo-Controlled

Key Eligibility Criteria

- Advanced, unresectable G/GEJ adenocarcinoma
- No prior systemic therapy in advanced setting
- HER2+ by central review (IHC 3+ or IHC 2+ ISH+)
- ECOG PS 0 or 1

R 1:1
N=698

Pembrolizumab 200 mg IV Q3W + Trastuzumab and FP or CAPOX[a]
for up to 35 cycles

Placebo IV Q3W + Trastuzumab and FP or CAPOX[a]
for up to 35 cycles

Stratification Factors

- Geographic region
- PD-L1 CPS <1 vs CPS ≥1
- Chemotherapy choice

Endpoints

- Dual primary: OS, PFS
- 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.

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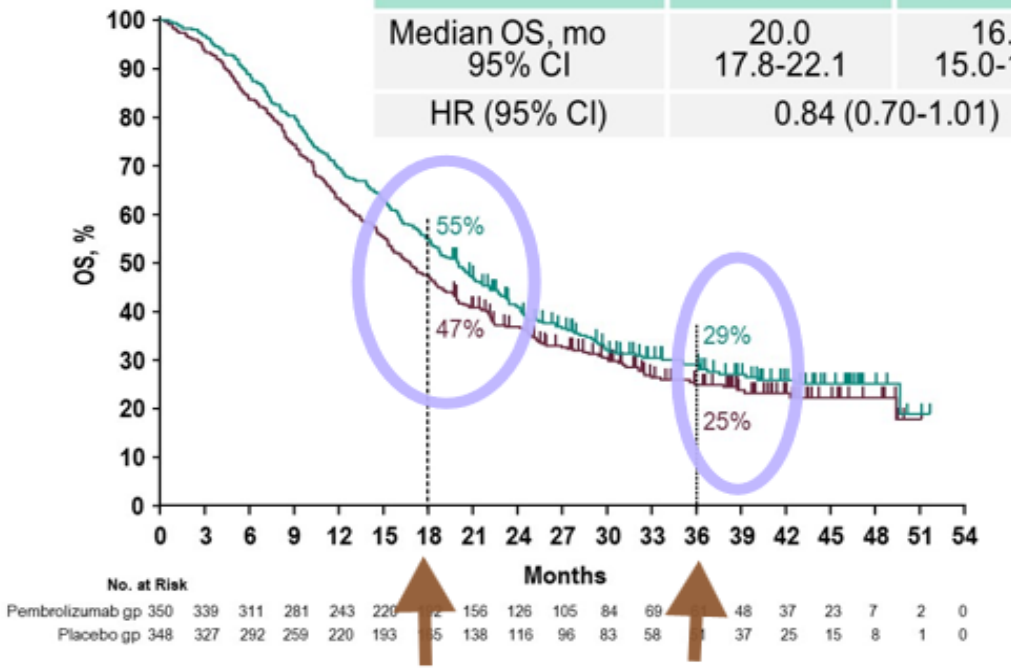
Overall Survival at IA3

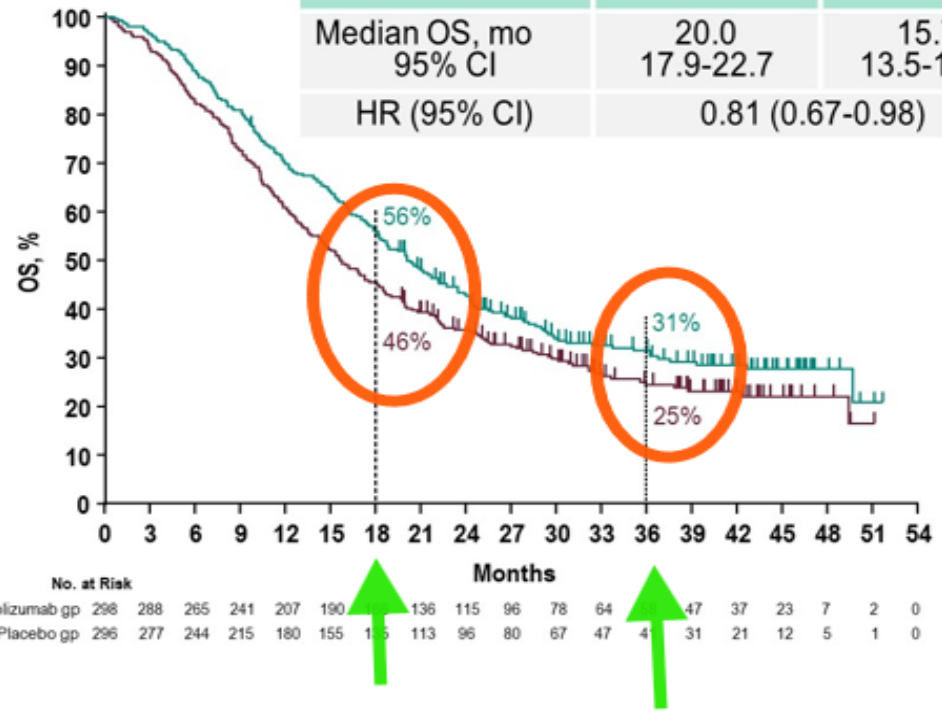
All patients

	Pembro	Placebo
Median OS, mo 95% CI	20.0 17.8-22.1	16.8 15.0-18.7
HR (95% CI)	0.84 (0.70-1.01)	



PD-L1 CPS ≥1[a]

	Pembro	Placebo
Median OS, mo 95% CI	20.0 17.9-22.7	15.7 13.5-18.5
HR (95% CI)	0.81 (0.67-0.98)	



Data cut-off: March 29, 2023. OS did not meet the prespecified criteria for significance at IA3 and will be retested at final analysis. [a]Not a prespecified endpoint.

Janjigian Lancet 2023

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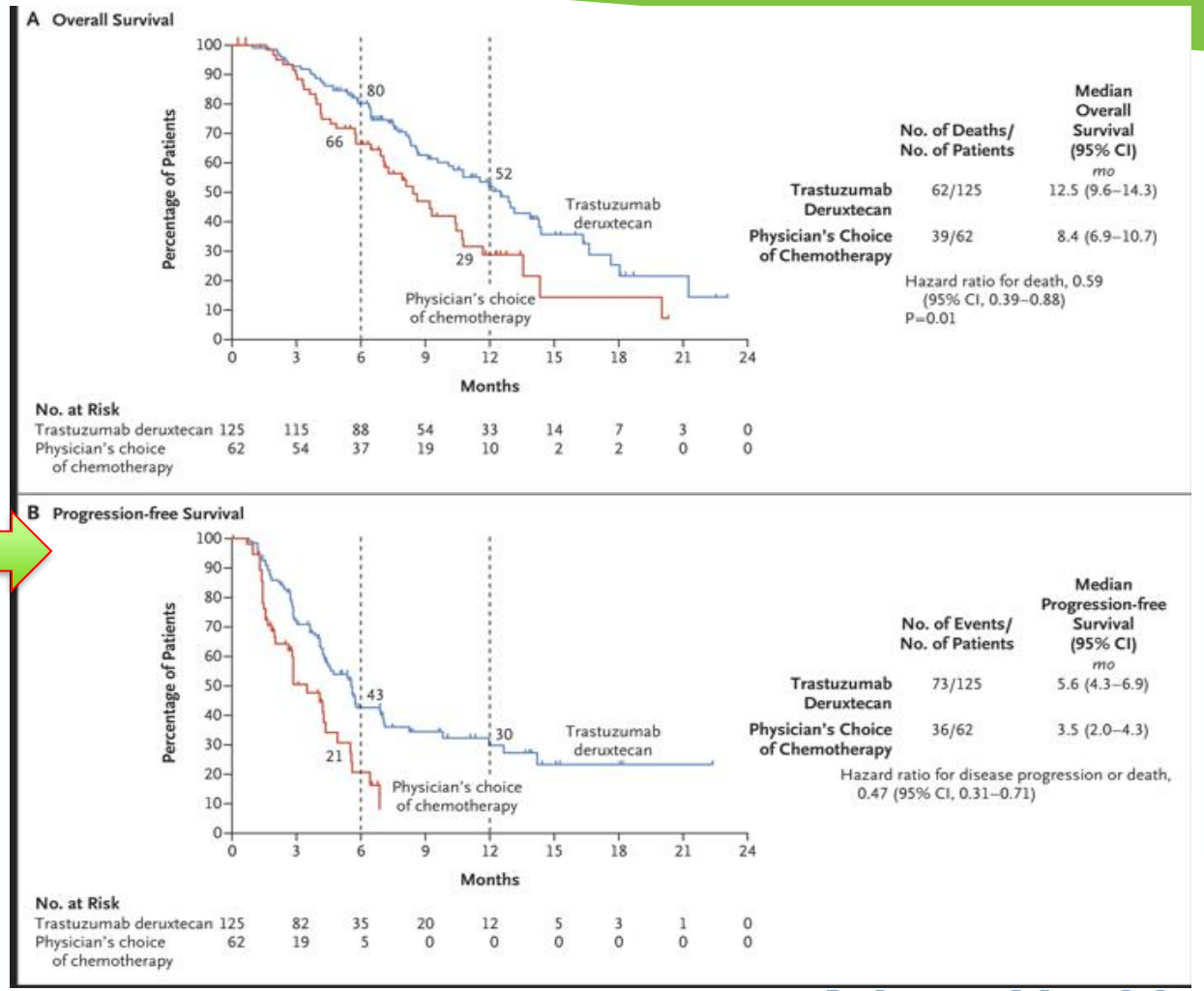
HEUR 2 NEU TARGETED THERAPY

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer

K. Shitara, Y.-J. Bang, S. Iwasa, N. Sugimoto, M.-H. Ryu, D. Sakai, H.-C. Chung, H. Kawakami, H. Yabusaki, J. Lee, K. Saito, Y. Kawaguchi, T. Kamio, A. Kojima, M. Sugihara, and K. Yamaguchi, for the DESTINY-Gastric01 Investigators*



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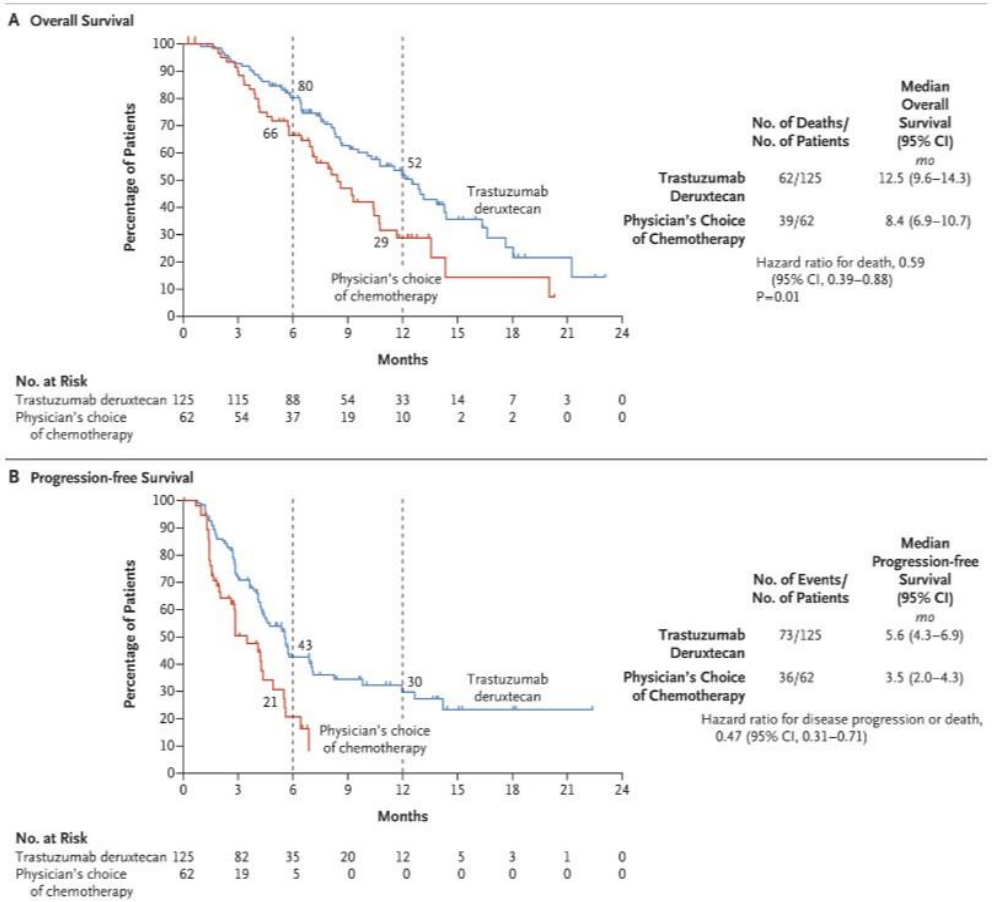
T-DXd for Gastric/GEJ Cancer



- DESTINY-Gastric01:
- HER2+ advanced/metastatic G/GEJ adenoca
- ≥2 prior regimens, including trastuzumab
- T-DXd 6.4 mg/kg vs irinotecan or paclitaxel
- cORR was 40.5% with T-DXd vs 11.3%

- FDA approved for advanced/metastatic HER2+ gastric/GEJ adenoca who have received a prior trastuzumab-based regimen.

Shitara NEJM, 2020

BARCELONA 2024 ESMO congress

DESTINY-Gastric03

Trastuzumab deruxtecan monotherapy and combinations in patients with advanced/metastatic HER2-positive esophageal, gastric or gastroesophageal junction adenocarcinoma: DESTINY-Gastric03 (DG-03)

Yelena Y Janjigian,[1] Hanneke van Laarhoven, Sun Young Rha, Vadim Kozlov, Do-Youn Oh, Adriano Gravina, Liane Rapatoni, Hirokazu Shoji, Ralf-Dieter Hofheinz, Li-Tzong Chen, Hugo Ford, Maxime Chénard-Poirier, Saeed Raoufmoghaddam, Caron Lloyd, Cuihong Zhang, Carla Mateo Mohedano, Jeeyun Lee

[1]Memorial Sloan Kettering Cancer Center, New York, NY, US

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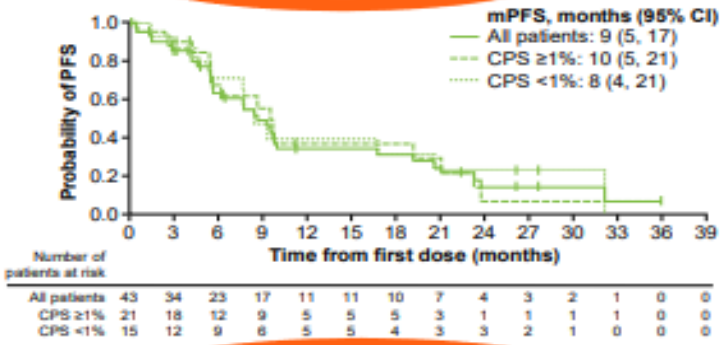
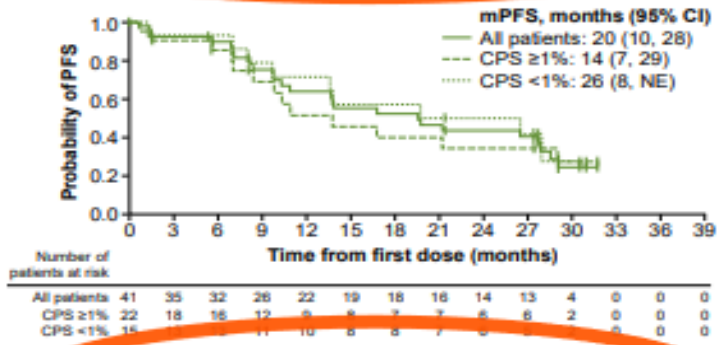
DESTINY-Gastric03

Progression-free survival in all patients and by PD-L1 status

T-DXd 6.4 mg/kg n=43

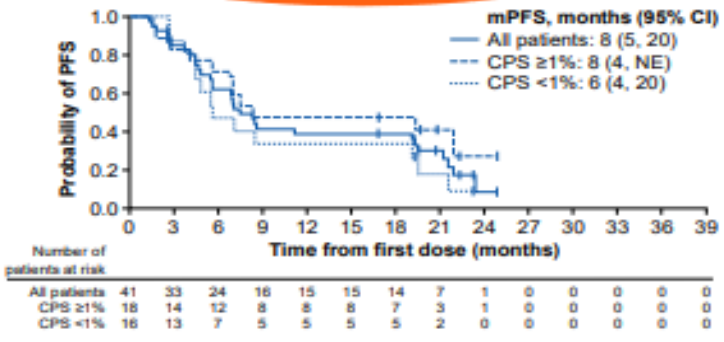


T-DXd 6.4 mg/kg + 5-FU/cape 1000 mg/m² n=41

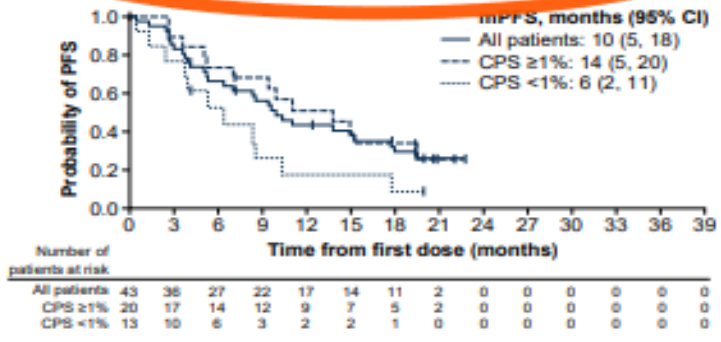


Data for arm T-DXd 5.4 mg/kg + 5-FU/cape 750 mg/m² + pembro are immature

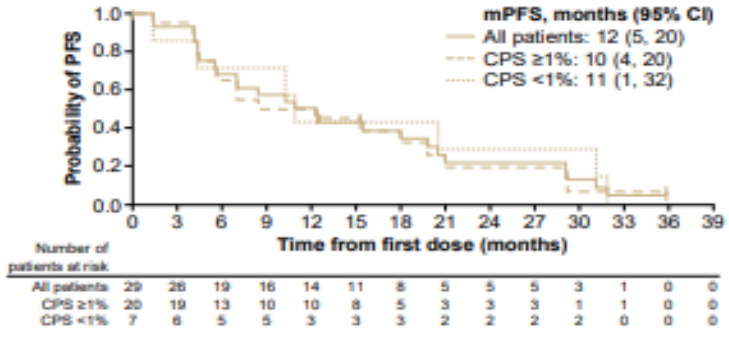
T-DXd 6.4 mg/kg + pembro n=41



T-DXd 6.4 mg/kg + 5-FU/cape 1000 mg/m² + pembro n=43



SOC - trastuzumab + 5-FU/cape + cisplatin/oxaliplatin n=29



For PFS analyses (assessed by investigator per RECIST 1.1), patients without progression or who died, or who had progression or died after two or more missed visits, were censored at the latest evaluable RECIST assessment, or at Day 1 (randomization/treatment assignment) if there were no evaluable visits or no baseline assessment (unless the patient died within 13 weeks of baseline assessment). PD-L1 status was centrally assessed. Patients with CPS missing/pending status were not included in the PFS subgroup analyses.

DESTINY 03 ESMO 2024

DESTINY-Gastric03

Conclusions

- T-DXd 6.4 mg/kg demonstrated antitumor activity as a first-line treatment for HER2+ GC/GEJA, with a confirmed ORR of 49%, a median PFS of 9 months, and a median OS of 18 months
- Combining T-DXd 6.4 mg/kg with fluoropyrimidine showed a confirmed ORR of 78%, a median PFS of 20 months, and a median OS of 23 months, with a manageable safety profile in HER2+ GC/GEJA, irrespective of PD-L1 status
- T-DXd 6.4 mg/kg with full-dose fluoropyrimidine and pembrolizumab demonstrated antitumor activity in HER2+ GC/GEJA, specifically in tumors with a PD-L1 CPS ≥1%; however, it was associated with a high level of toxicities, including ILD, leading to treatment discontinuations
- T-DXd 5.4 mg/kg and reduced-dose fluoropyrimidine with pembrolizumab has a manageable safety profile, with promising early antitumor activity in HER2+ GC/GEJA
- Studies evaluating the combination of T-DXd with fluoropyrimidine and immunotherapy are planned for patients with HER2+ CPS ≥1% GC/GEJA

First-line T-DXd combinations with fluoropyrimidine and/or pembrolizumab demonstrated promising antitumor activity in metastatic HER2+ GC/GEJA

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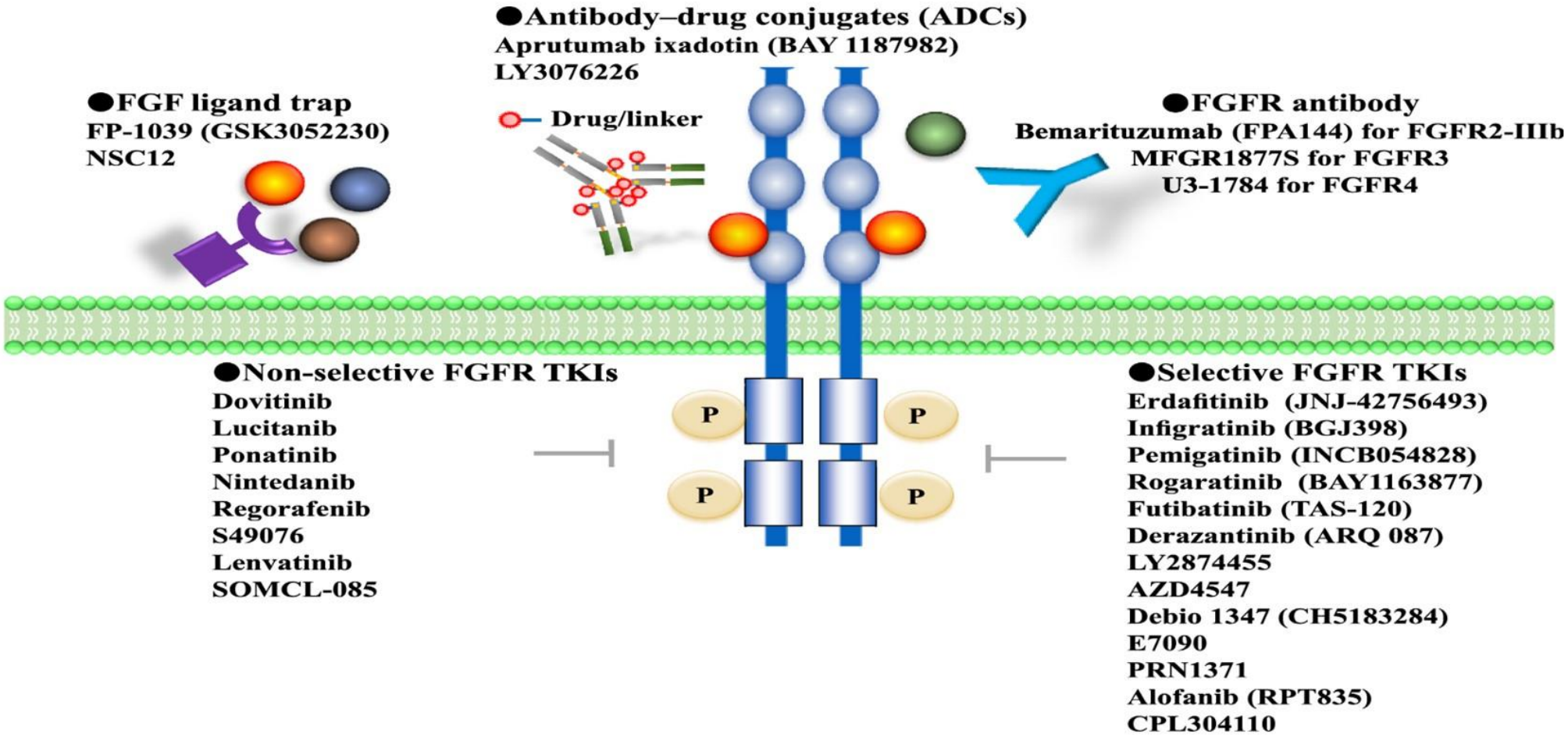
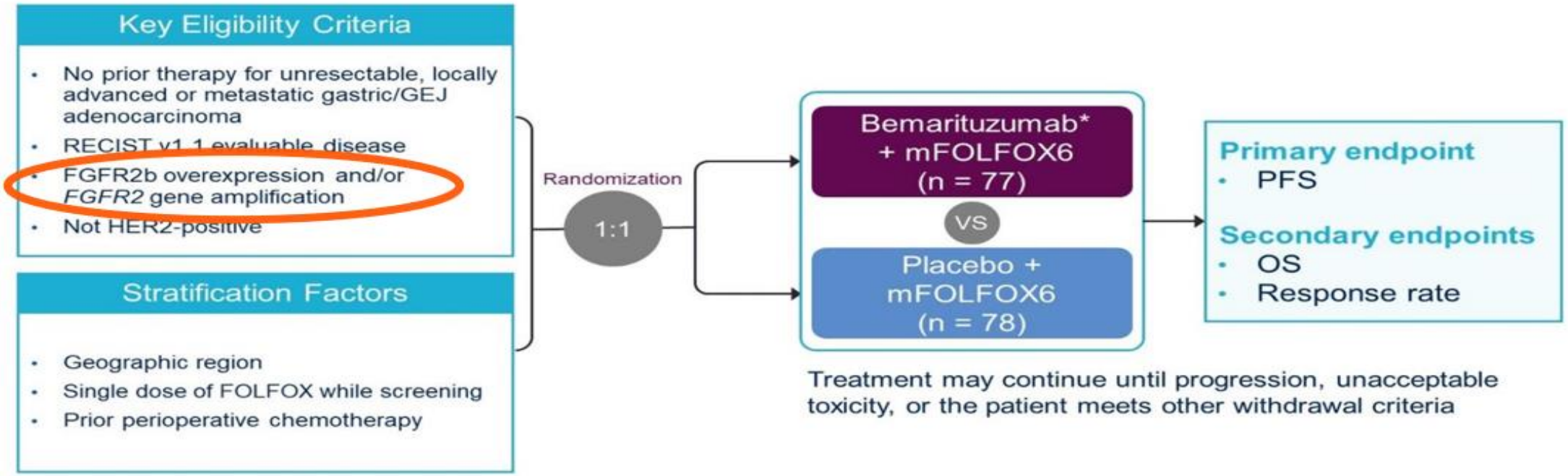
FGFR Pathway Inhibitors



Ooki A et al. *Gastric Cancer*. 2021;24(6):1169-1183.

FIGHT Phase II Study Design



*Bemarituzumab dosing: 15 mg/kg Q2W beginning cycle 1 day 1 (plus 1 dose of 7.5 mg/kg on day 8 of cycle 1 only). FOLFOX6 dosing: standard fixed doses Q2W.
FGFR2b, fibroblast growth factor receptor 2b.

Catenacci D. Presented at: ASCO 2021 Annual Meeting. Abstract 4010.

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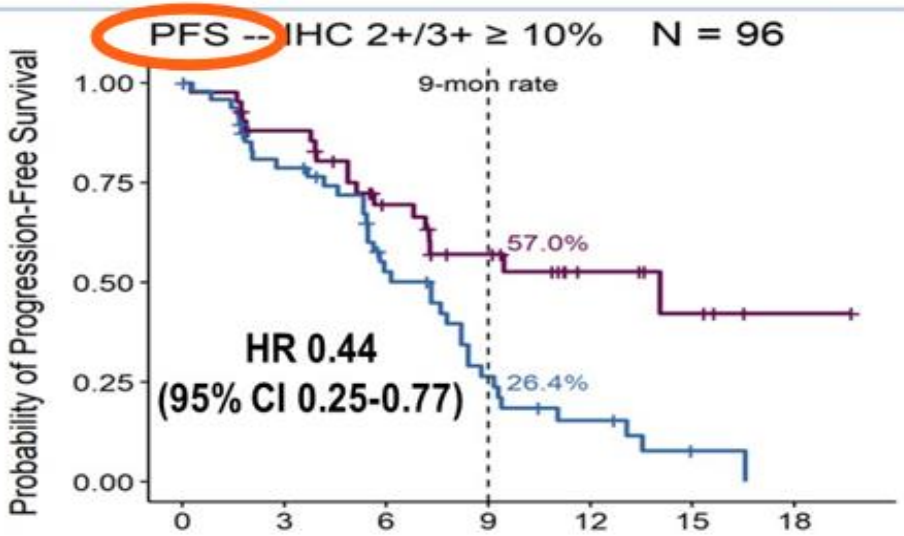
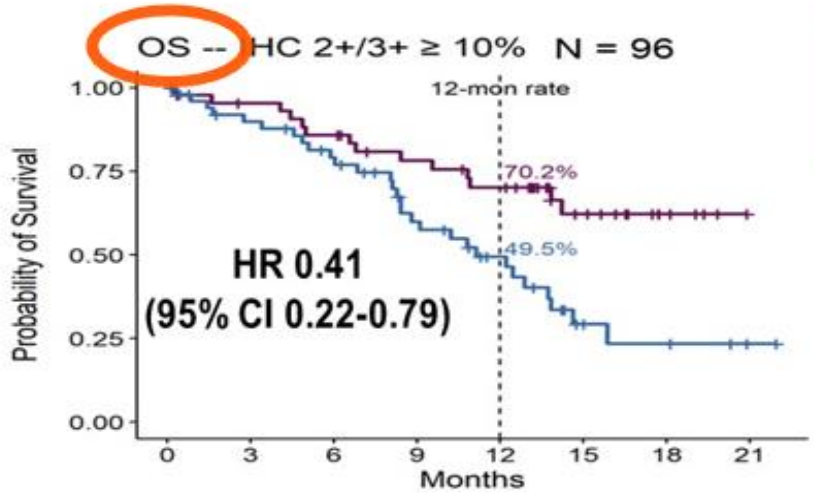
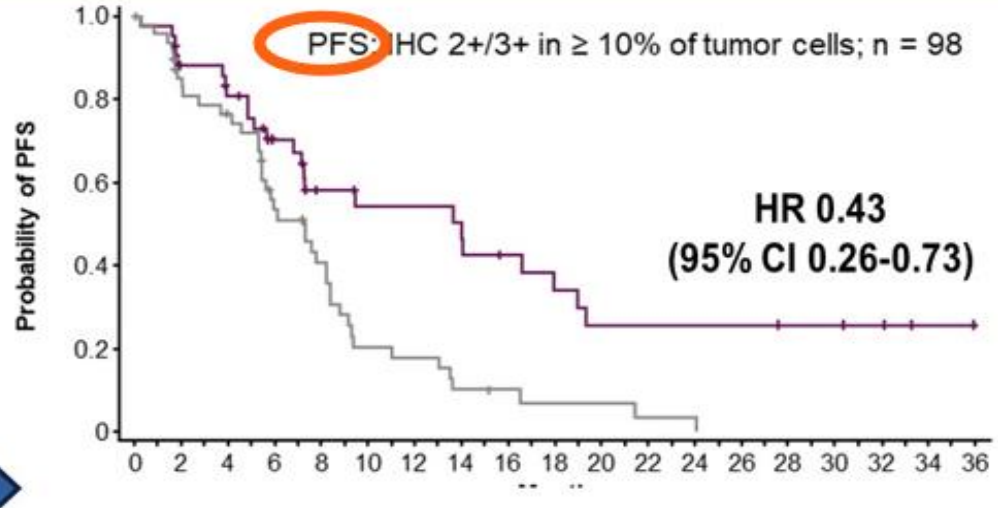
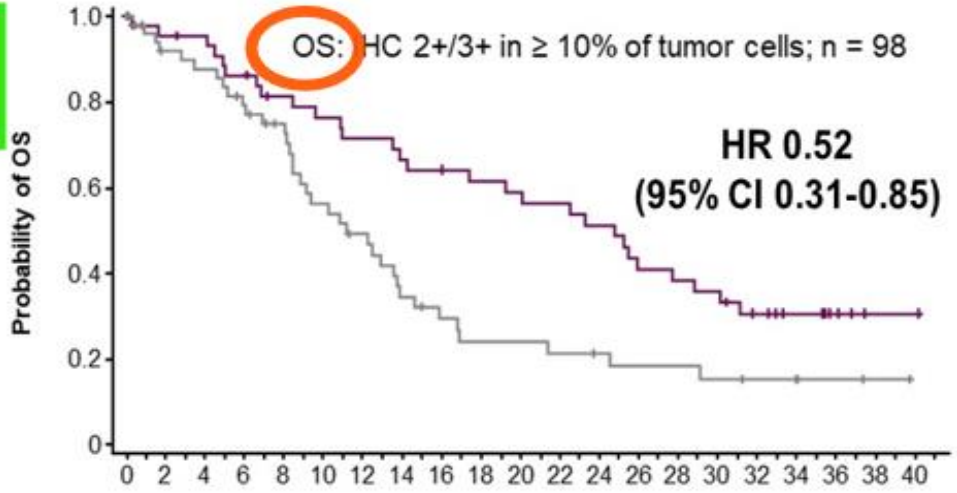
FIGHT: *Update of Main Results (FGFR ≥10% Population)*





Extra follow up
+ around 20ms





Wainberg ZA et al. Presented at: ASCO-GI 2021 Abstract 160; Presented at: ESMO-GI 2023 Abstract SO-11.

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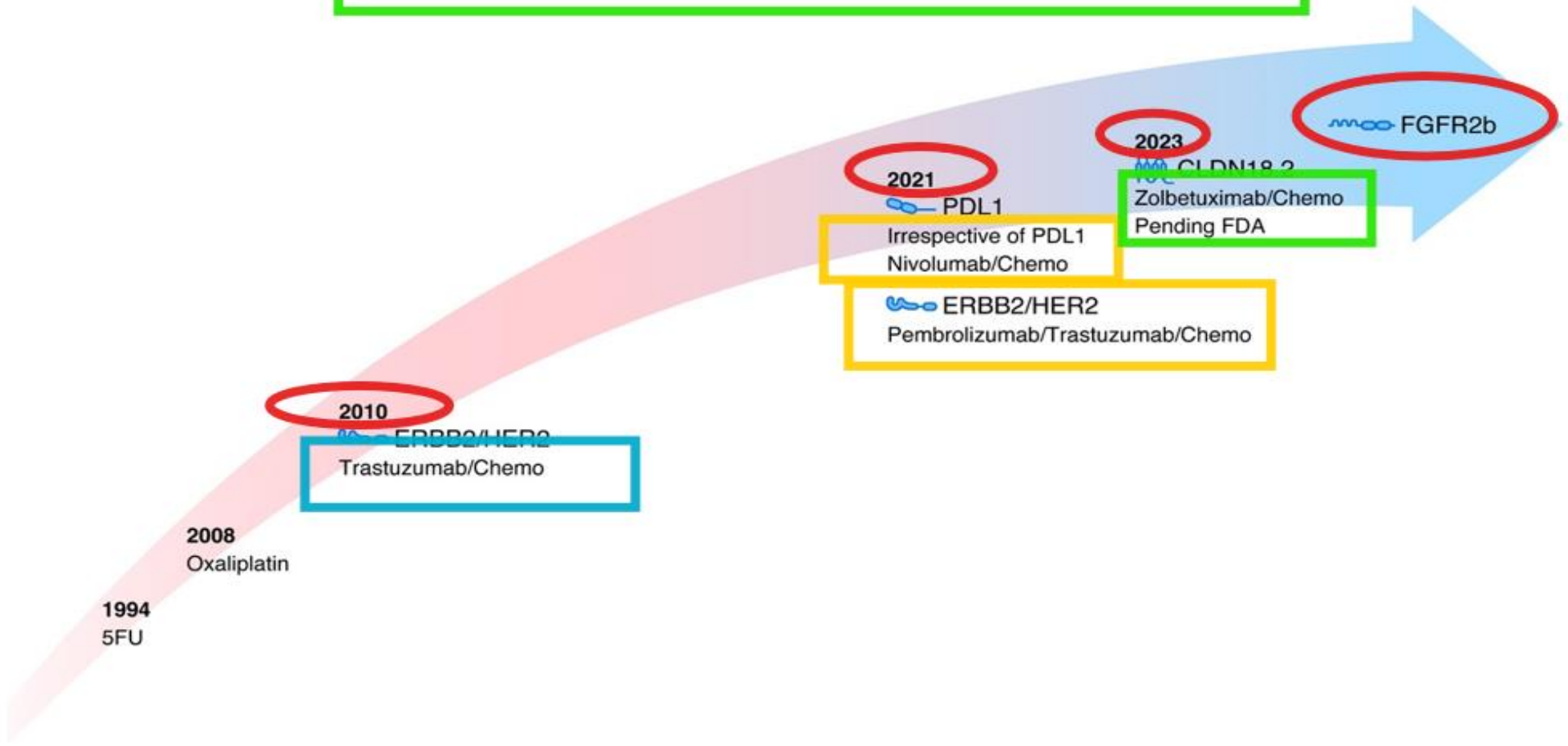
Evolution of first-line therapy



Scheithauer et al Ann Hematol 1994; Al-Batran *et al* J. Clin Oncolo 2008; Bang *et al* Lancet 2010;
Janjigian YY, Shitara K *et al* Lancet 2021; Janjigian YY Nature 2021; Shitara 2023 ASCO GI; Xu RH 2023 ASCO Plenary Series Virtual

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BIOMARKER DIRECTED THERPAY FOR ESOPH- GASTRIC CA

Biomarker	Prevalence in metastatic gastric cancer	Therapeutic agent(s)
ERBB2/HER2	**20%**	Trastuzumab and Pembrolizumab
MSI-high	**5%** in Stage IV **20%** in Stage I-III	Pembrolizumab or Nivolumab
EBV-positive	**3%**	Pembrolizumab or Nivolumab
PD-L1 CPSBio	**80%** CPS ≥ 1 **60%** CPS ≥ 5	Pembrolizumab and Nivolumab
FGFR2b overexpression	**30%**	Bemarituzumab
CLDN18.2	**35%**	Zolbetuximab
TCAG Tumor sequencing	NTRACK, EGFR, MET, RAS amplification	Larotrectinib, Afatinib, etc.
Plasma DNA	Monitoring for response and resistance	Broad application

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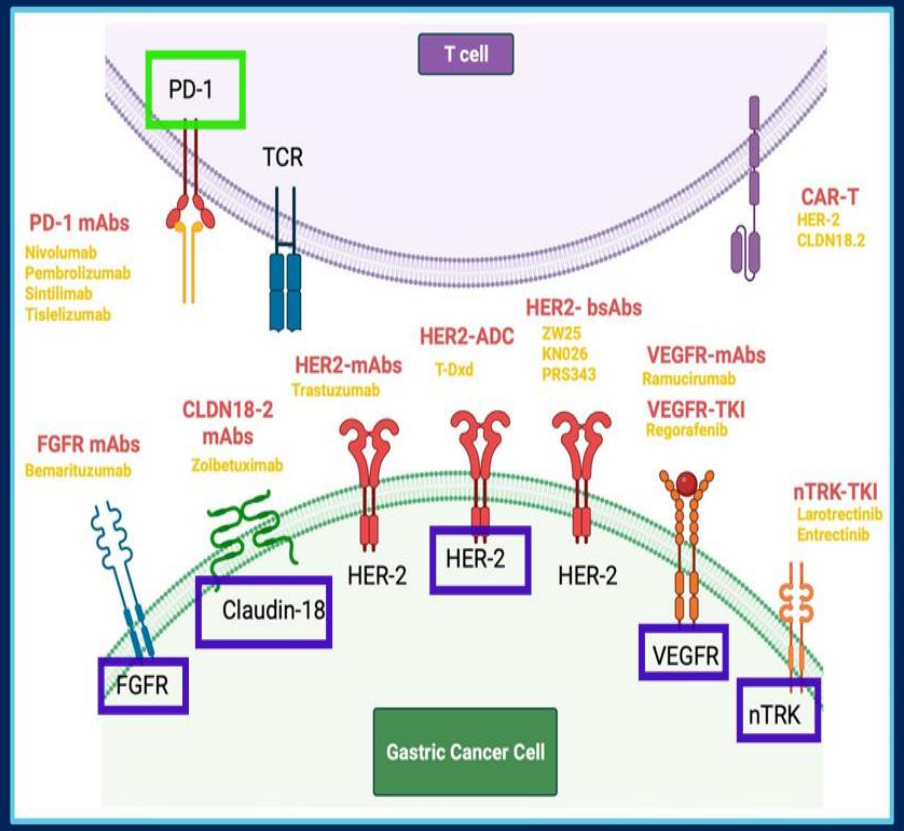
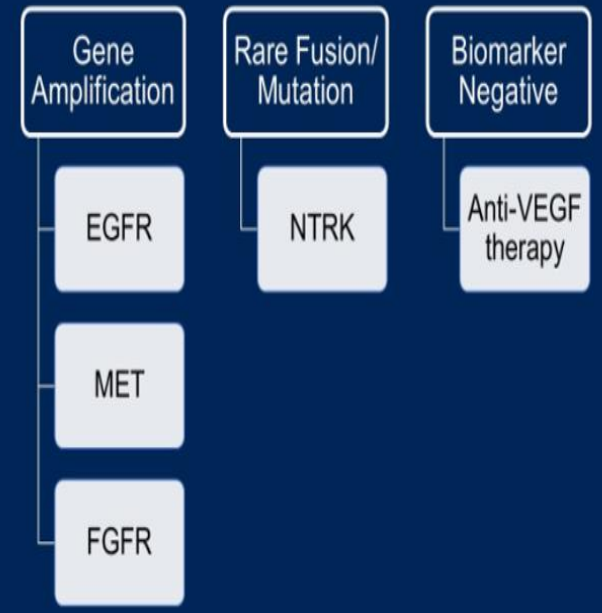
BIMARKER TESTING IN GASTRO-ESOPHAGEAL CANCERS

Gastroesophageal Biomarkers



Cancers 2023, 15, 5075

Gastroesophageal Biomarkers – Other



CONCLUSION

- The landscape of Gastro-Esophageal Cancer management had evolved to a personalized biomarker selected pathways.
- Biomarkers identification at diagnosis is critical initial step in this new paradigm

- Anti-PDL1 for metastatic Esophageal and Gastric cancers improve survival
  - Will there be a role in the perioperative management
- Optimizing targeted therapies with Anti- CLDN 12.8 will maximize patients outcomes

- ADC had emerged important therapeutic class → Moving TDX , Anti-Her-2 Neu therapy from 2nd Line treatment option to upfront
- Integration of ctDNA in the future as MRD and prognostic tool.

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