October 10, 2025

Recent Advances in Systemic Therapy for Gastroesophageal Cancer

Haeseong Park, MD MPH
Associate Professor of Medicine
Division of Gastrointestinal Oncology
Center for Cancer Therapeutic Innovation
Dana-Farber Cancer Institute
Harvard Medical School

Disclosures

Research grant to my institution:

Exelixis, Mirati/BMS, Tizona, Mersana, Bolt Biotherapeutics, StrataPATH, Chugai, Huaota, D3Bio, Incyte, Idience, Amgen, Pfizer, Alterome, Yuhan

Consulting/Advisory Board: Merck, Astellas, Daiichi Sankyo

Learning Objectives

- Assemble existing clinical evidence for systemic therapy of gastroesophageal cancer
- Understand therapeutic indications for immunotherapy and targeted therapy for patients with advanced gastroesophageal cancer
- Examine novel therapeutic approaches in advanced gastroesophageal cancer

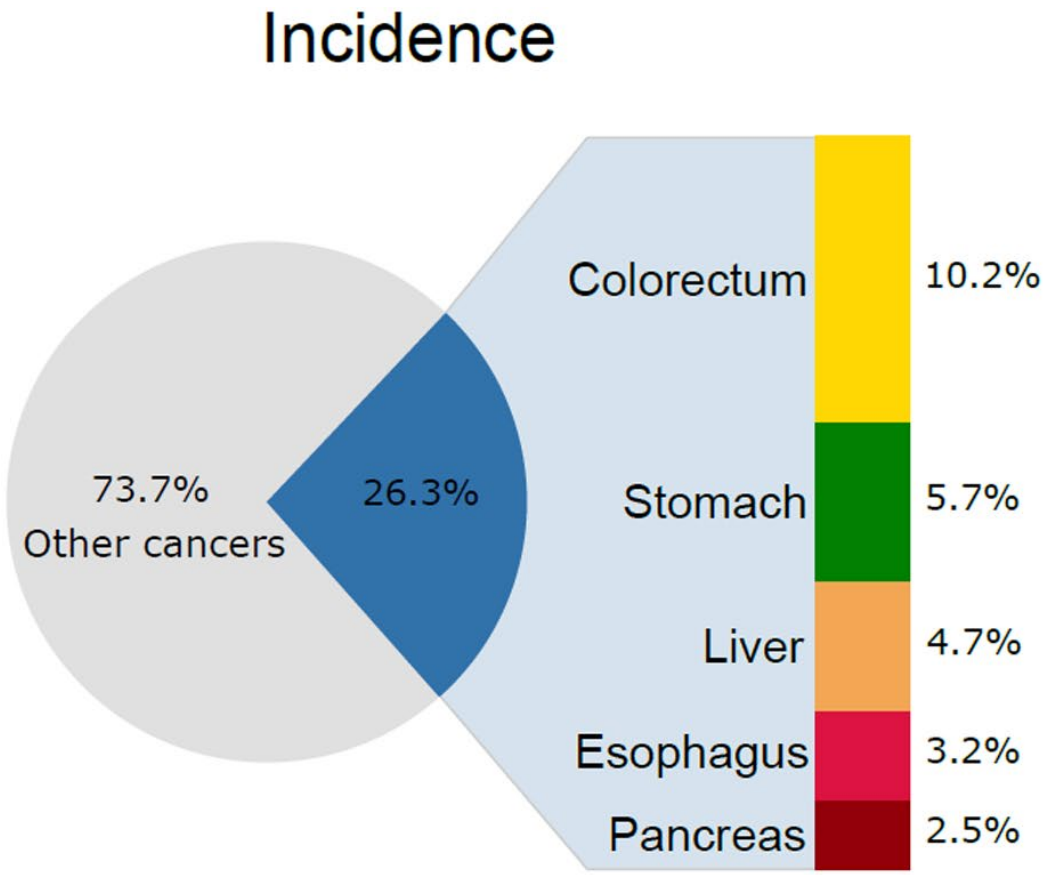
Overview

- Epidemiology, presentation and diagnostic work up
- Potential therapeutic targets in gastroesophageal cancer
- Targets, evidence, ongoing trials
  - PD-L1
  - HER2
  - CLDN18.2
  - VEGF
  - FGFR2b
- Novel therapeutic targets and clinical trials

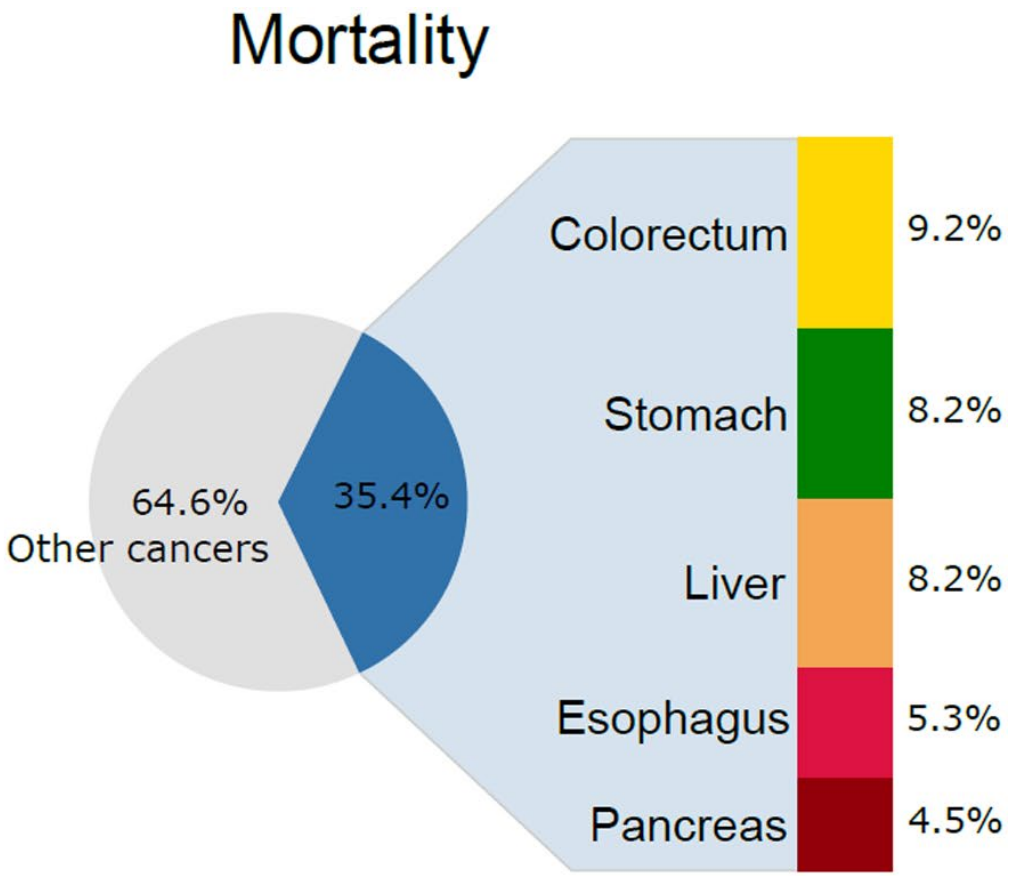
Overview

- **Epidemiology, presentation and diagnostic work up**
- Potential therapeutic targets in gastroesophageal cancer
- Targets, evidence, ongoing trials
  - PD-L1
  - HER2
  - CLDN18.2
  - VEGF
  - FGFR2b
- Novel therapeutic targets and clinical trials

Global disease burden: major GI cancers



Number of GI cancer cases: 4.8 million

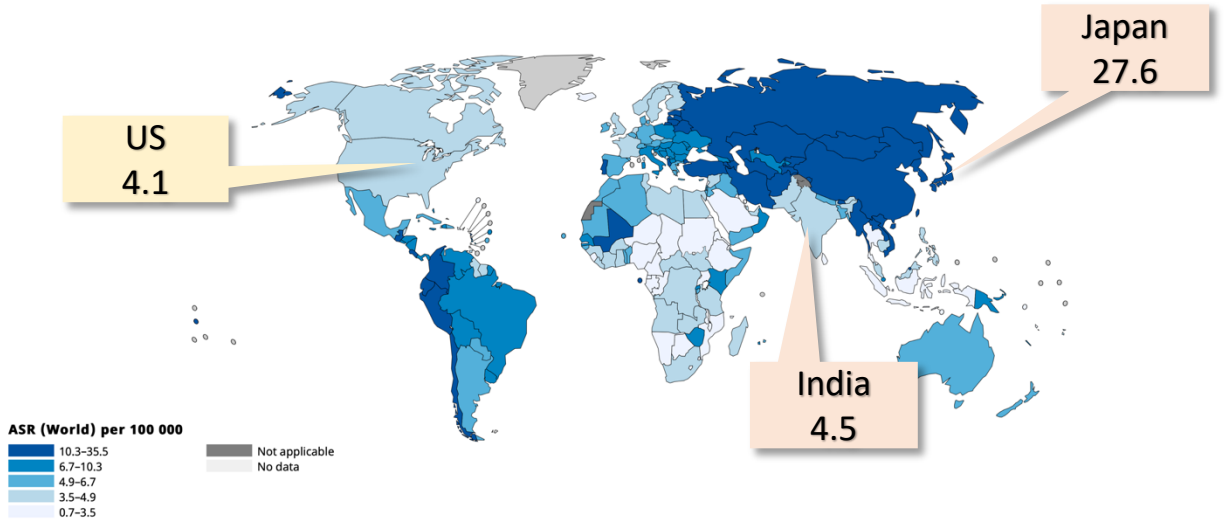


Number of GI cancer deaths: 3.4 million

GLOBOCAN 2018

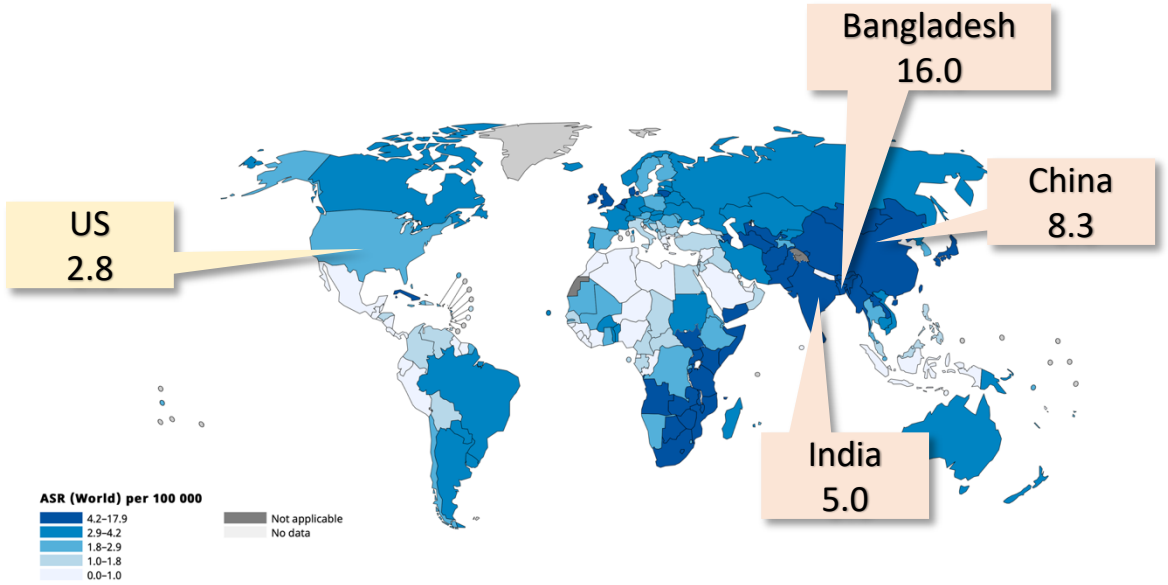
Global disease burden: gastric and esophageal cancers

Incidence of stomach cancer



	Location of gastric ca
Global	Cardia ~15% Non-cardia ~85%
West	Cardia 30-40% Non-cardia 60 -70%

Incidence of esophageal cancer

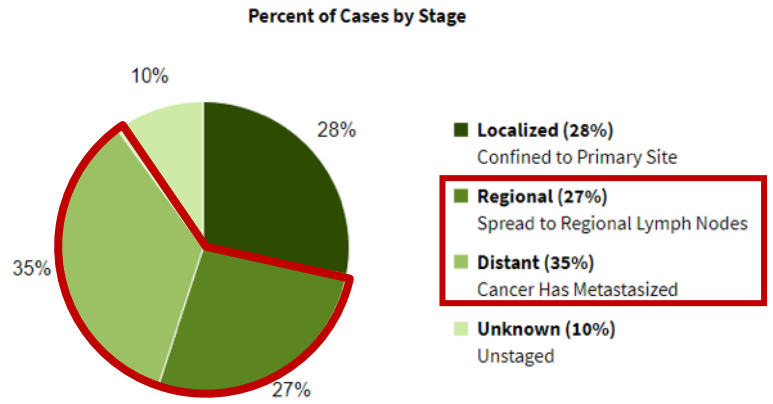


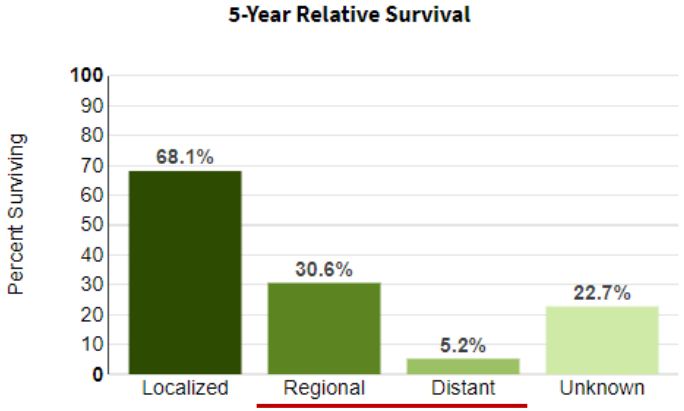
	Histology of esoph ca
Global	Squamous ~85% Adeno ~15%
West	Squamous 30-50% Adeno 50-70%

GLOBOCAN 2022
Arnold et al., Gut 2020

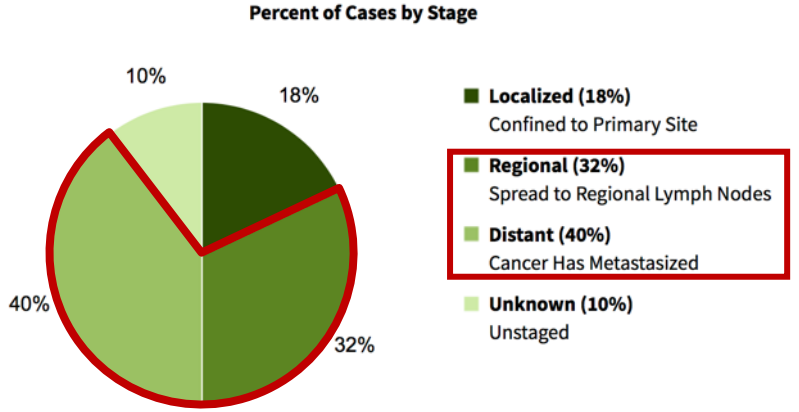
Stage and survival

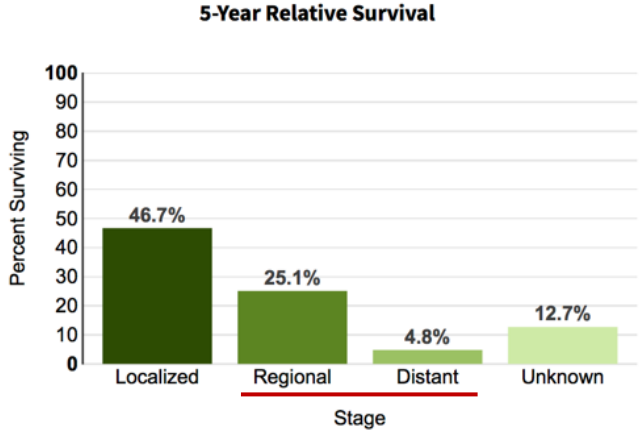
Gastric





Esophagus



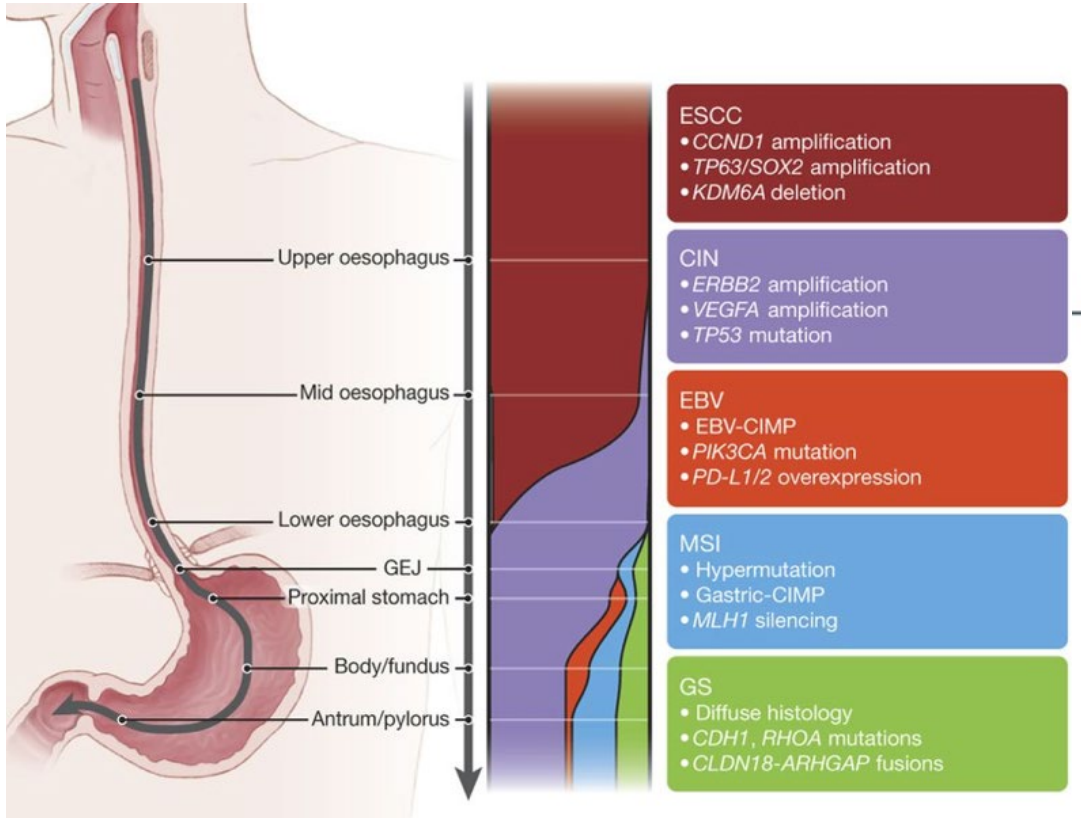


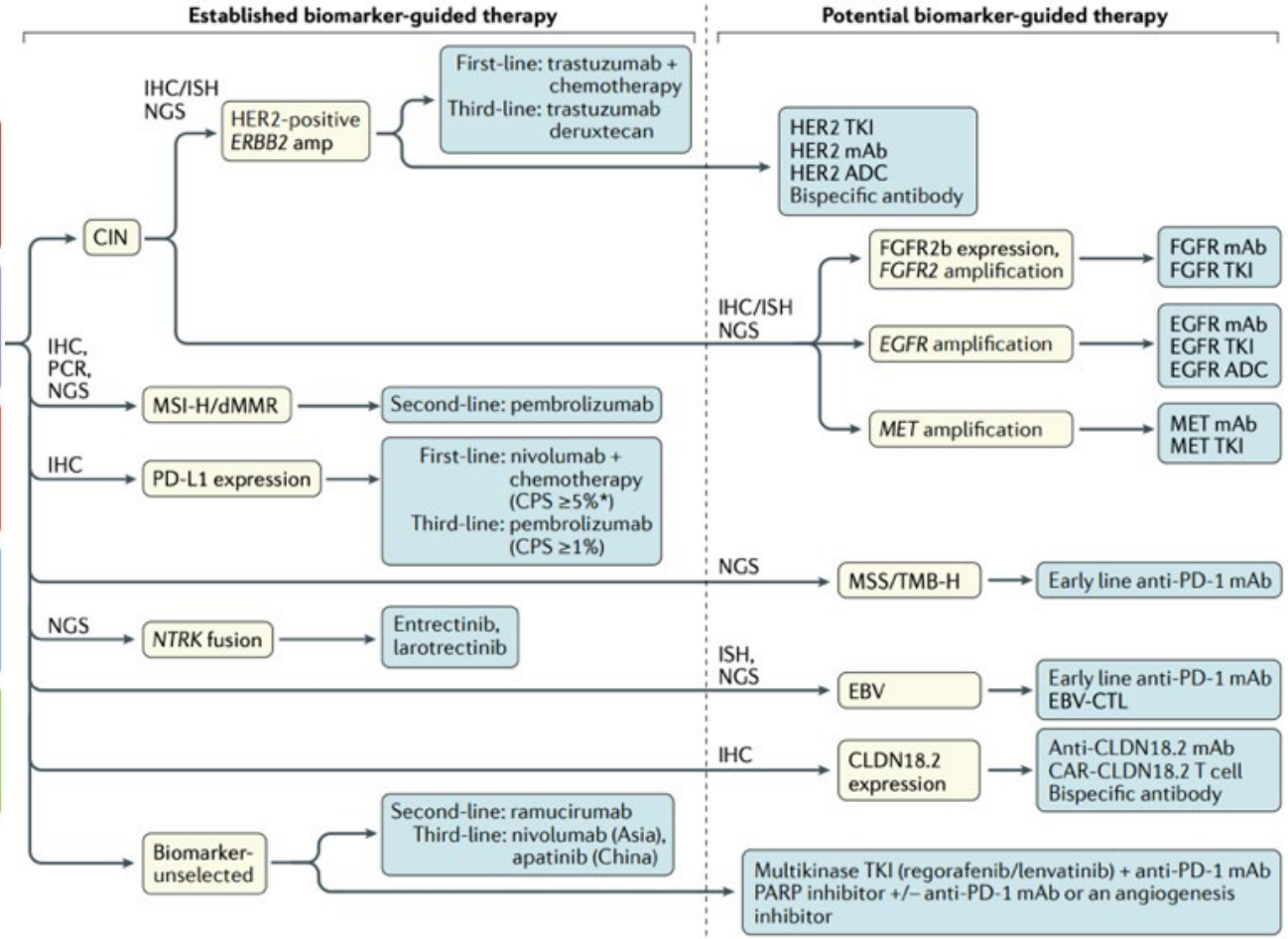
SEER Database

Overview

- Epidemiology, presentation and diagnostic work up
- **Potential therapeutic targets in gastroesophageal cancer**
- Targets, evidence, ongoing trials
  - PD-L1
  - HER2
  - CLDN18.2
  - VEGF
  - FGFR2b
- Novel therapeutic targets and clinical trials

Potential Therapeutic Targets in GEC

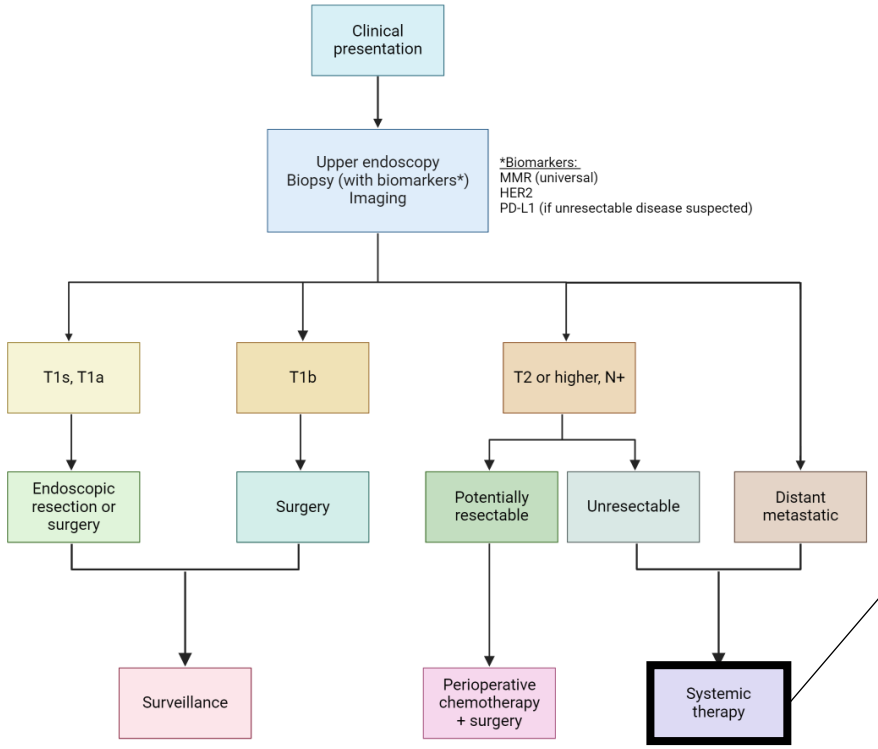




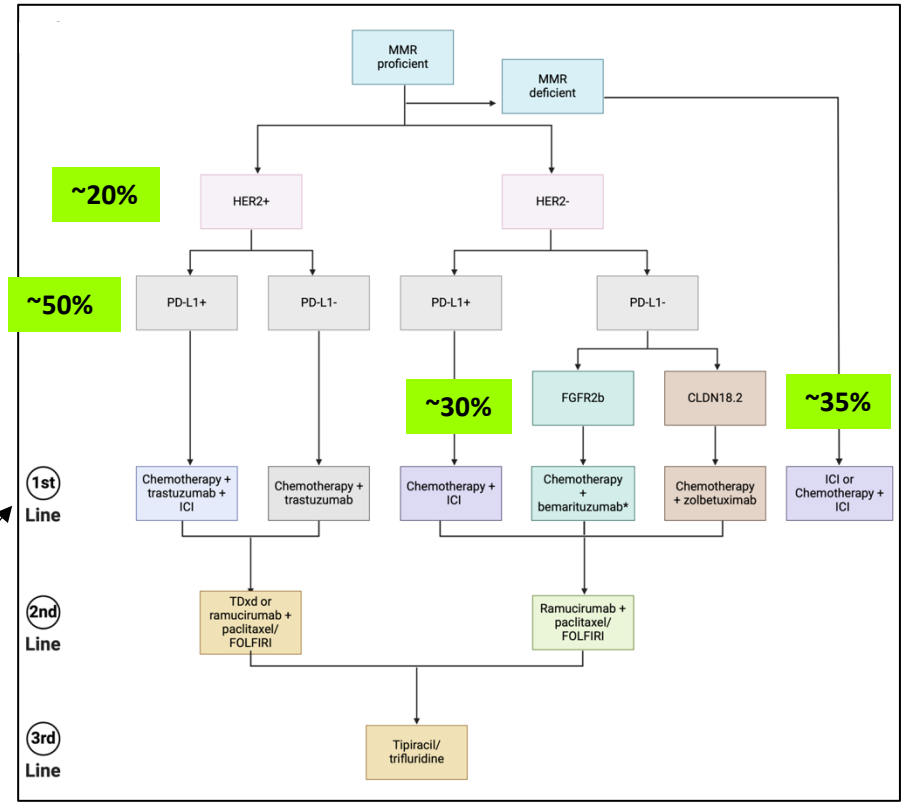
TCGA, *Nature* 2017

Nat Rev Clin Oncol. 2021 Aug;18(8):473-487.

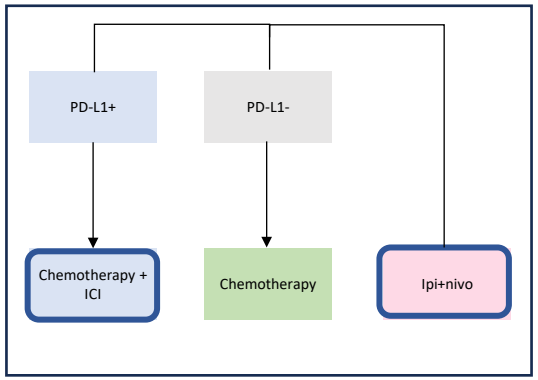
Work up, staging, and simplified therapeutic strategy



Adenocarcinoma



Squamous



Clinical practice guidelines

Dana-Farber Cancer Institute

FREE ACCESS | ASCO SPECIAL ARTICLES | January 05, 2023

Immunotherapy and Targeted Therapy for Advanced Gastroesophageal Cancer: ASCO Guideline

Authors: Manish A. Shah, MD, Erin B. Kennedy, MHSc, Ashley E. Alarcon-Rozas, MD, MBA, Thierry Alcindor, MD, Angela N. Bartley, MD, Aubrey Belk Malowany, BS, Nishin A. Bhadkamkar, MD, ... SHOW ALL ..., and Lakshmi Rajdev, MD | AUTHORS INFO & AFFILIATIONS

Publication: Journal of Clinical Oncology • Volume 41, Number 7 • https://doi.org/10.1200/JCO.22.02331

Journal of Clinical Oncology
An American Society of Clinical Oncology Journal

NCCN National Comprehensive Cancer Network®

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

F. Lordick[1], F. Carneiro[2,3,4], S. Cascinu[5], T. Fleitas[6], K. Haustermans[7], G. Piessen[8,9,10,11], A. Vogel[12] & E. C. Smyth[13], on behalf of the ESMO Guidelines Committee*

SPECIAL ARTICLE

Oesophageal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

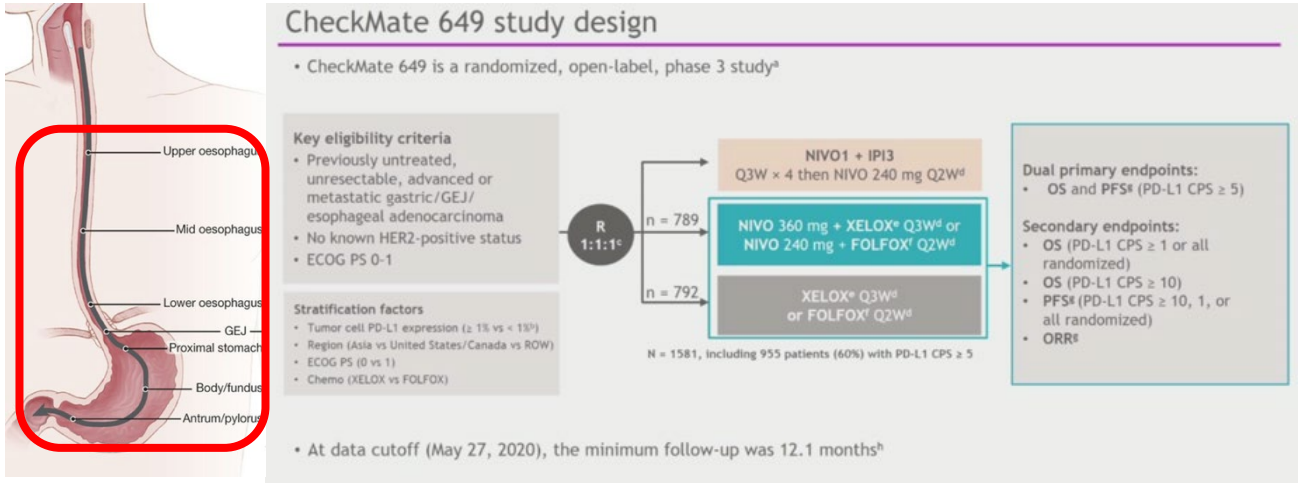
R. Obermannová[1], M. Alsina[2,3], A. Cervantes[4,5], T. Leong[6], F. Lordick[7], M. Nilsson[8,9], N. C. T. van Grieken[10], A. Vogel[11] & E. C. Smyth[12], on behalf of the ESMO Guidelines Committee*

Overview

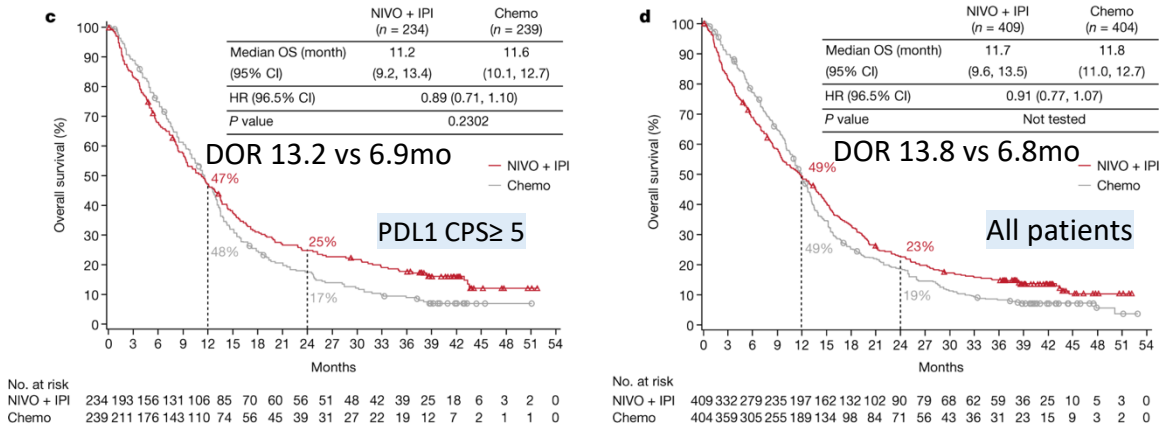
- Epidemiology, presentation and diagnostic work up
- **Potential therapeutic targets in gastroesophageal cancer**
- Targets, evidence, ongoing trials
  - PD-L1
  - HER2
  - CLDN18.2
  - VEGF
  - FGFR2b
- Novel therapeutic targets and clinical trials

Immunotherapy in metastatic gastroesophageal cancer: 1st line

CheckMate649

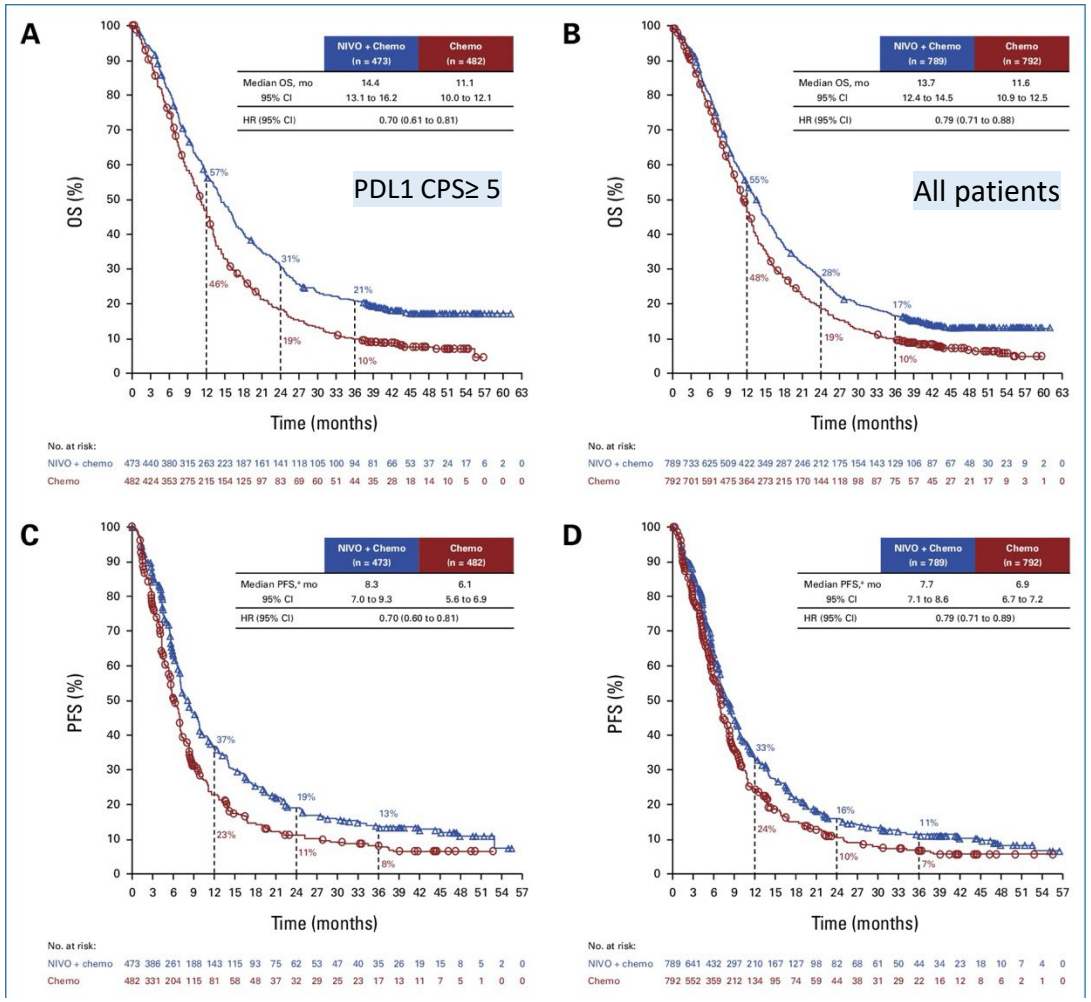


Nivo+ipi vs chemo



Nivo + FOLFOX as standard 1st line

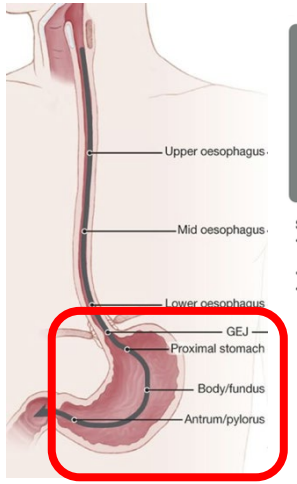
Nivo+chemo vs chemo



Lancet 2021; Nature 2022; JCO 2024

Immunotherapy in metastatic gastroesophageal cancer: 1st line

KN859 and KN590



KN859

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

N = 1579, R 1:1

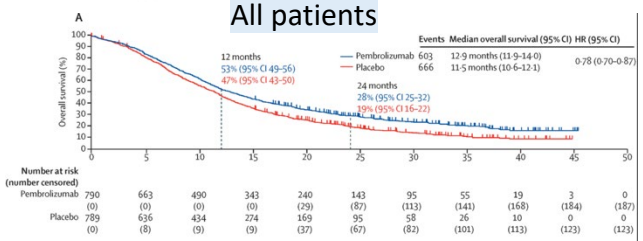
n = 790: Pembrolizumab 200 mg IV Q3W for ≤35 cycles (~2 years) + Chemotherapy (FP or CAPOX)[a]

n = 789: Placebo IV Q3W for ≤35 cycles (~2 years) + Chemotherapy (FP or CAPOX)[a]

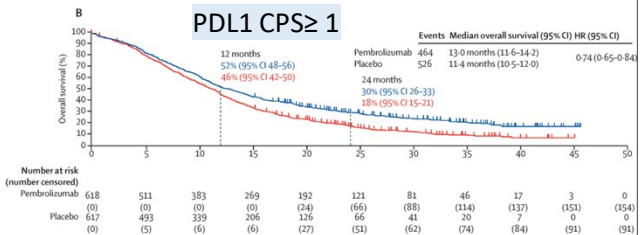
Stratification Factors
- Geographic region (Asia vs Australia/Europe/Israel/North America vs rest of world)
- PD-L1 CPS (<1 vs ≥1)
- Choice of chemotherapy (FP vs CAPOX)[a]

End Points
- Primary: OS
- Secondary: PFS, ORR, and DOR (all per RECIST v1.1 by BICR) and safety

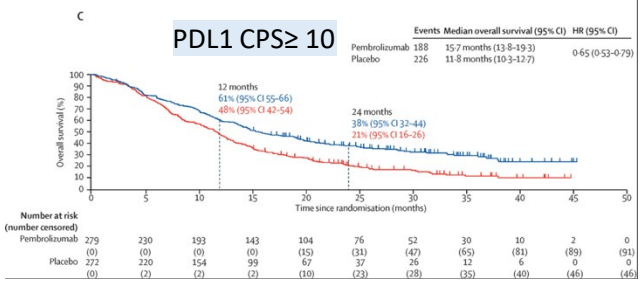
All patients



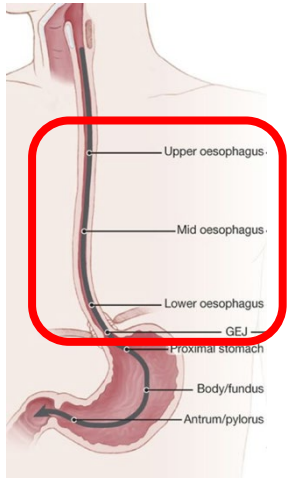
PDL1 CPS≥ 1



PDL1 CPS≥ 10



Pembro + chemo as standard 1st line, CPS ≥1



KN590

Key Eligibility Criteria
- Locally advanced/metastatic esophageal adenocarcinoma, ESCC, or Siewert type I GEJ adenocarcinoma
- Measurable disease per RECIST v1.1
- No prior treatment
- ECOG PS 0 or 1

N = 749, R 1:1

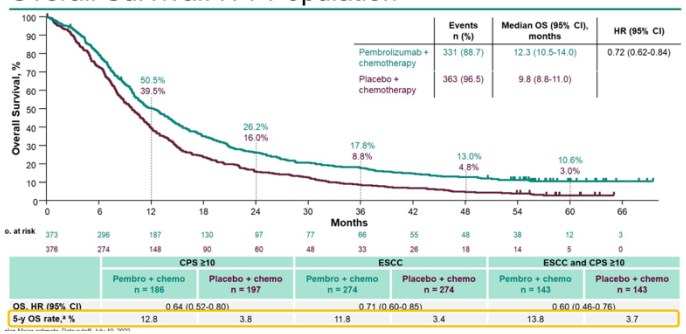
n = 373: Pembrolizumab 200 mg IV Q3W for ≤35 cycles (~2 years) + Chemotherapy[a] (FP)

n = 376: Placebo IV Q3W for ≤35 cycles (~2 years) + Chemotherapy[a] (FP)

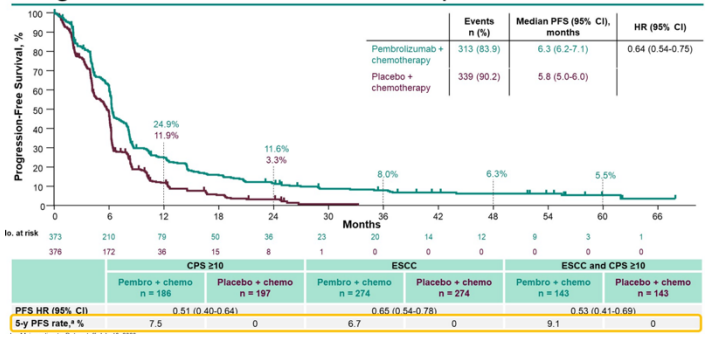
Stratification Factors
- Geographic region (Asia vs rest of world)
- Histology (adenocarcinoma vs squamous cell carcinoma)
- ECOG PS (0 vs 1)

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

Overall Survival: ITT Population



Progression-Free Survival: ITT Population

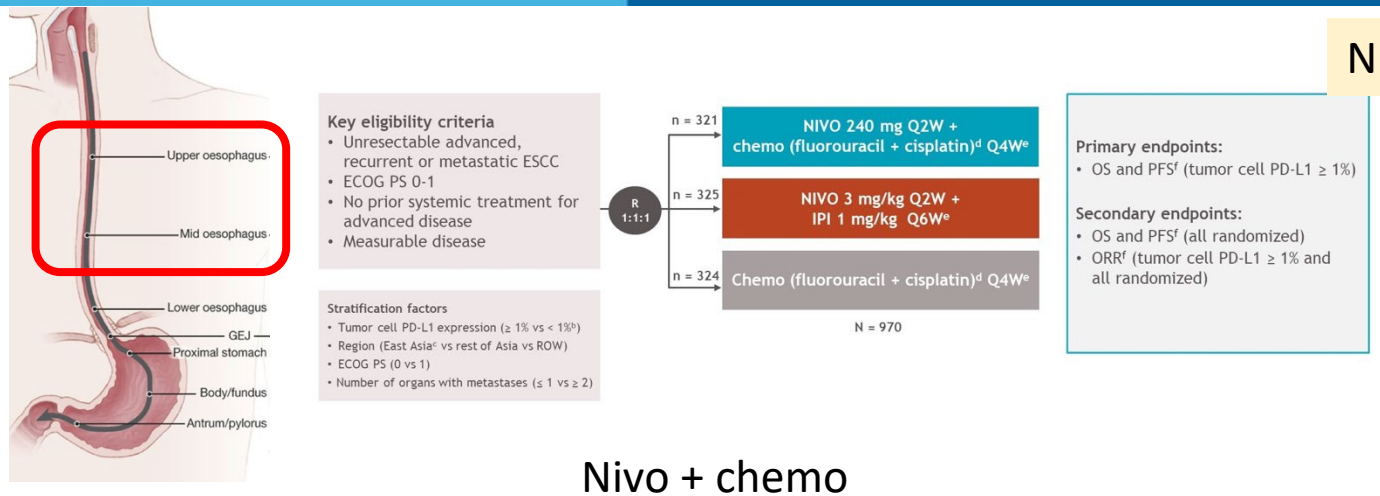


Lancet Oncol 2023; ASCO GI 2024

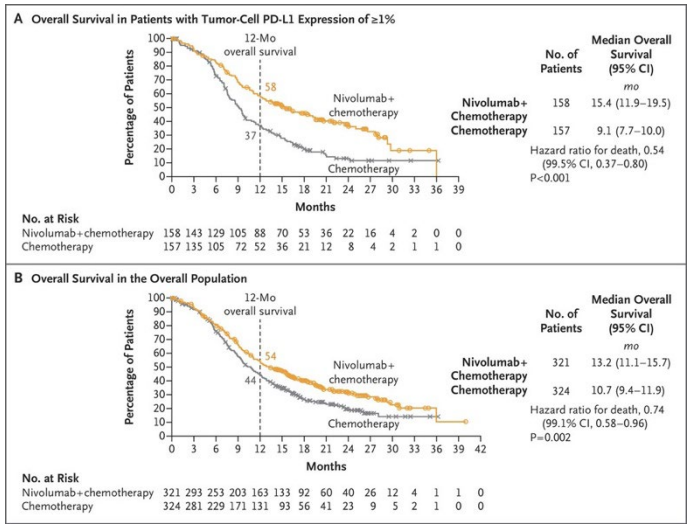
Immunotherapy in metastatic gastroesophageal cancer: 1st line

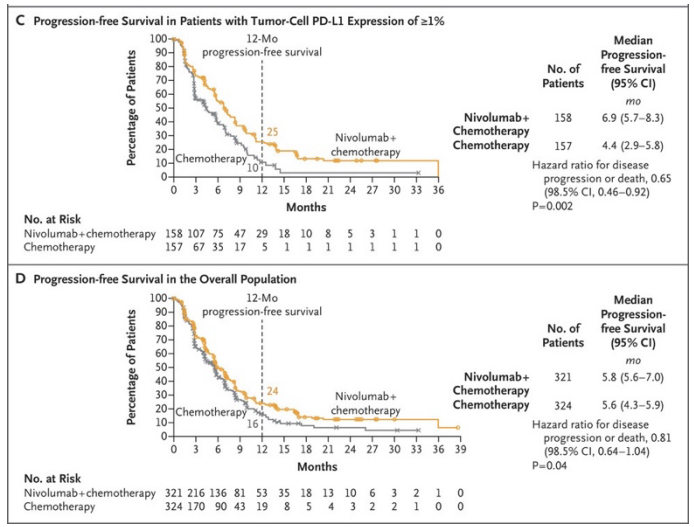
CheckMate648: ESCC

Nivo + chemo or nivo+ipi as standard 1st line for squamous

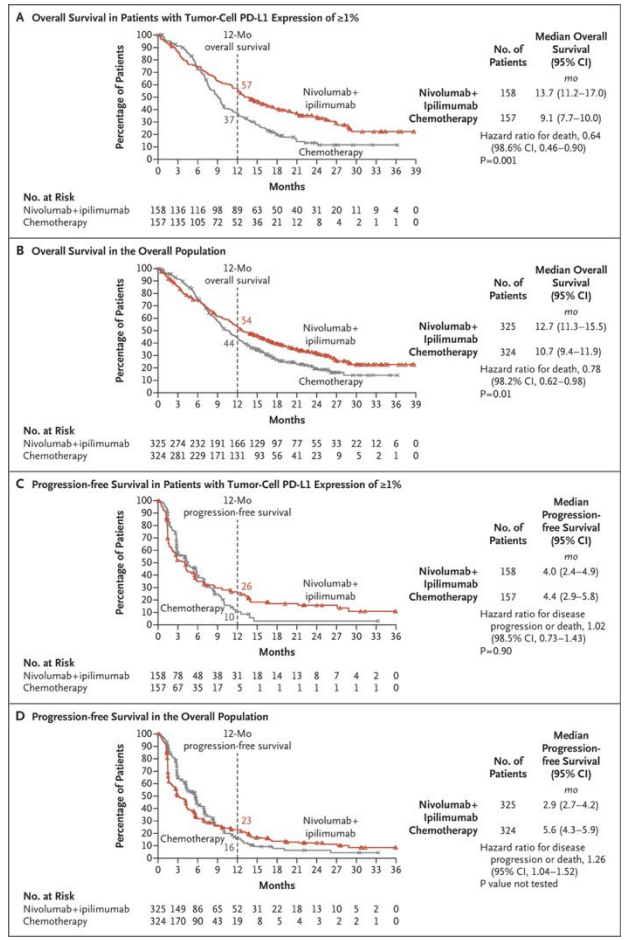


Nivo + chemo





Nivo + ipi



ASCO 2021, Doki et al., NEJM 2022

Immunotherapy in metastatic gastroesophageal cancer: 1st line

KN811

Patients
- Advanced G/GEJ adenocarcinoma
- No prior therapy in advanced setting
- HER2-positive

Stratification Factors
- Geographic region
- PD-L1 CPS
- Chemotherapy choice

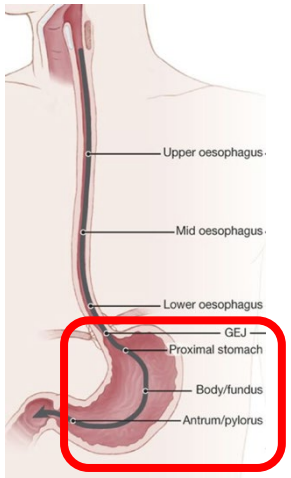
R 1:1
N ≈ 692

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

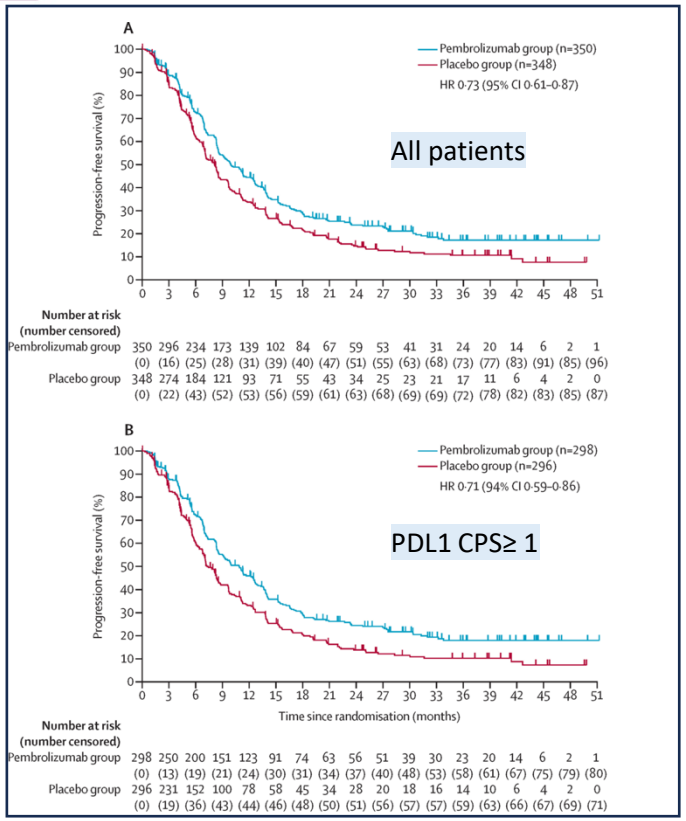
Placebo IV Q3W + Trastuzumab and FP or CAPOX[a] for up to 35 cycles

Dual Primary End Points
- OS
- PFS (RECIST v1.1 per BICR)

Secondary End Points
- ORR (RECIST v1.1 per BICR)
- DOR (RECIST v1.1 per BICR)
- Safety

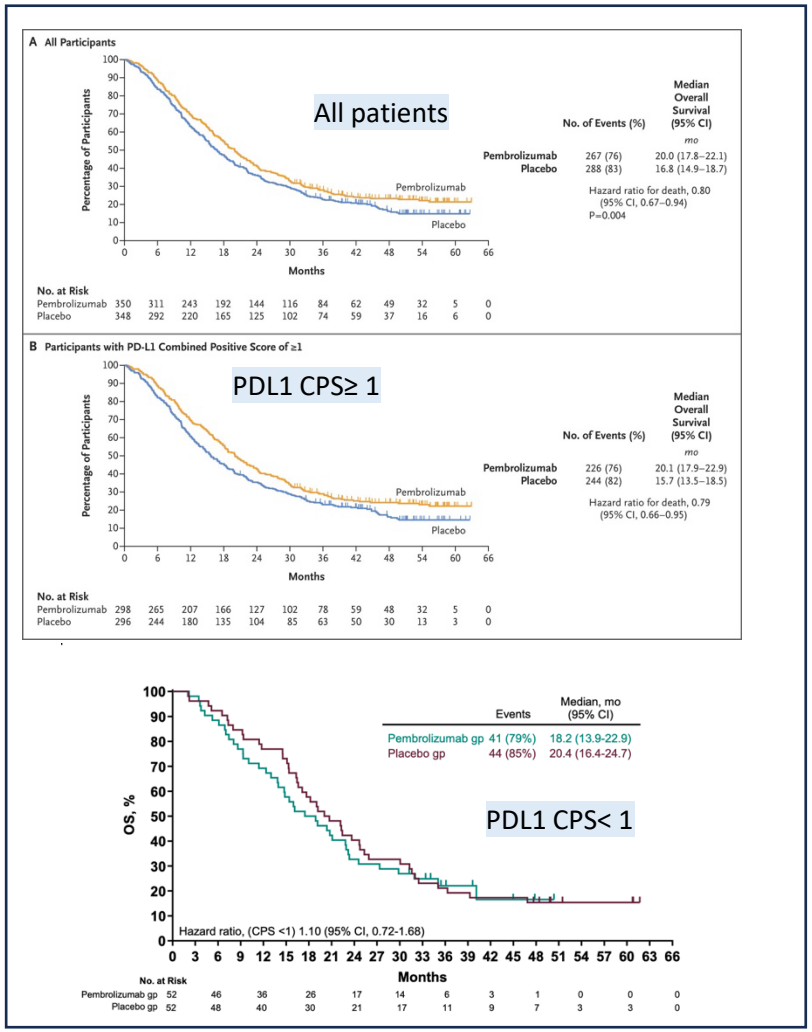


PFS



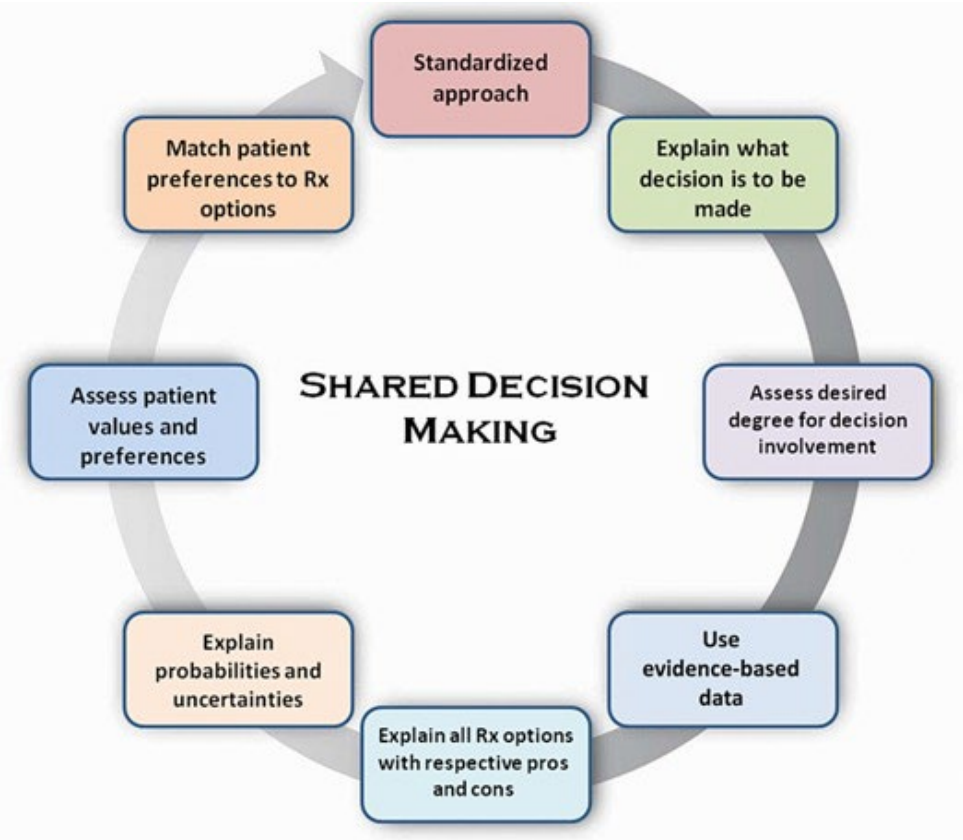
Pembro + tras + chemo if HER2+ and PDL1 CPS≥ 1

OS



Lancet 2023; NEJM 2024

What can we tell our patients?



- The median OS improvement is 2-3 months with the addition of PD-1 (ITT)
- The PFS is 6-7 months for most frontline therapies for HER2 negative disease
- There are clear differences in outcomes based on PD-L1 expression
- The addition of anti-PD-1 agents introduces new toxicities (~20%)

Immunotherapy in locally advanced gastroesophageal cancer

CheckMate577: Nivolumab for adjuvant therapy following trimodality therapy

RESEARCH SUMMARY

Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer

Kelly RJ et al. DOI: 10.1056/NEJMoa2032125

CLINICAL PROBLEM

For patients with locally advanced esophageal or gastroesophageal junction cancer, neoadjuvant chemoradiotherapy followed by surgery is a standard treatment. However, the risk of recurrence is high, especially among the 70 to 75% of patients without a pathological complete response, and clinicians lack proven adjuvant therapies for these patients.

CLINICAL TRIAL

A phase 3, double-blind, randomized, placebo-controlled trial to evaluate the efficacy of the checkpoint inhibitor nivolumab as adjuvant treatment after standard therapy.

794 adults who had received standard therapy for stage II or III esophageal or gastroesophageal junction cancer but had residual pathological disease were assigned within 4 to 16 weeks after surgery to intravenous nivolumab (30-minute infusions of 240 mg every 2 weeks for 16 weeks and then 480 mg monthly) or placebo for a maximum of 1 year. Median follow-up was 24.4 months.

RESULTS

Efficacy:

Median disease-free survival was 22.4 months with nivolumab and 11.0 months with placebo. Adjuvant nivolumab was also associated with longer metastasis-free survival.

Safety:

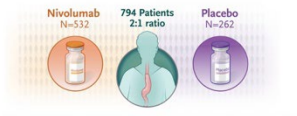
The safety profile of nivolumab was similar to that seen in other types of solid tumors. The most common high-grade nivolumab-related adverse events with potential immunologic cause were pneumonitis and rash.

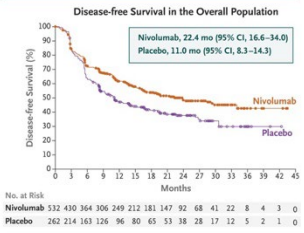
REMAINING QUESTIONS

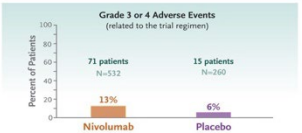
Further study is required to understand the following:

- The longer-term effects of nivolumab on overall survival
- Whether standard chemotherapy would be more effective if given with checkpoint inhibitors

Links: Full article | NEJM Quick Take | Editorial







CONCLUSIONS

Adjuvant nivolumab significantly prolonged disease-free survival among patients with an incomplete pathological response after standard therapy for esophageal or gastroesophageal junction cancer.

- 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 vs adenocarcinoma)
- Pathologic lymph node status (≥ ypN1 vs ypN0)
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[c])

N = 794 → R 2:1

- n = 532 → Nivolumab 240 mg Q2W × 16 weeks then 480 mg Q4W
- n = 262 → Placebo Q2W × 16 weeks then Q4W

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

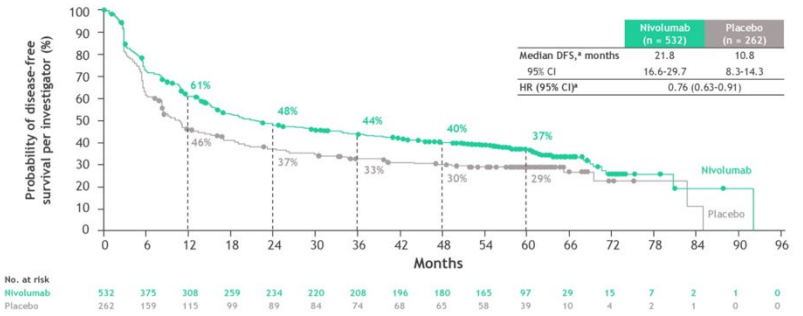
- Median follow-up was 24.4 months (range, 6.2-44.9)[g]
- Geographical regions: Europe (38%), US and Canada (32%), Asia (13%), rest of the world (16%)

FDA approves nivolumab for resected esophageal or GEJ cancer

On May 20, 2021, the Food and Drug Administration approved nivolumab (Opdivo, Bristol-Myers Squibb Company) for patients with completely resected esophageal or gastroesophageal junction (GEJ) cancer with residual pathologic disease who have received neoadjuvant chemoradiotherapy.

Efficacy was evaluated in CHECKMATE-577 (NCT02743494), a randomized, multicenter, double-blind trial in 794 patients with completely resected (negative margins) esophageal or GEJ cancers who had residual pathologic disease following concurrent chemoradiotherapy. Patients were randomized (2:1) to receive either nivolumab 240 mg or placebo every 2 weeks for 16 weeks followed by 480 mg of nivolumab or placebo every 4 weeks beginning at week 17 for up to one year of treatment.

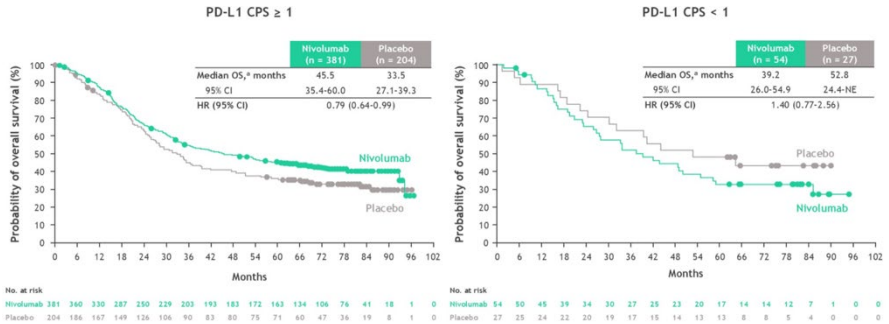
Disease-free survival



- Clinically meaningful improvement in DFS with nivolumab vs placebo was maintained with longer follow-up

[a]Median (range) follow-up, 78.3 (60.1-96.6) months.

Overall survival by PD-L1 CPS



- Improvement in OS with nivolumab vs placebo was enriched in patients with PD-L1 CPS ≥ 1

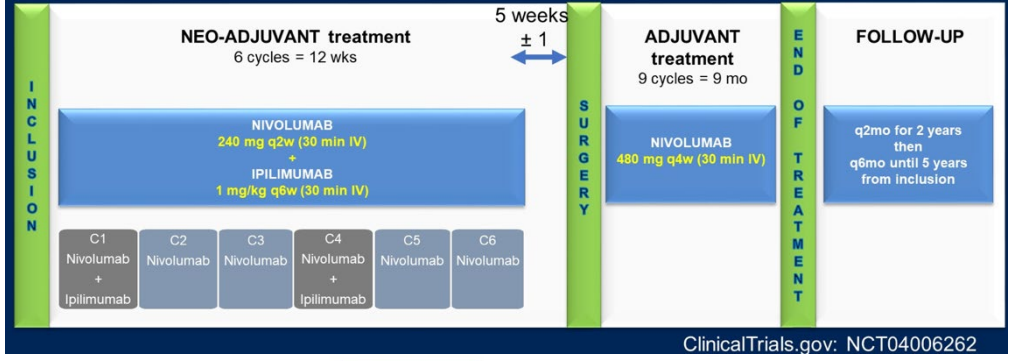
[a]Median (range) follow-up, 78.3 (60.1-96.6) months.

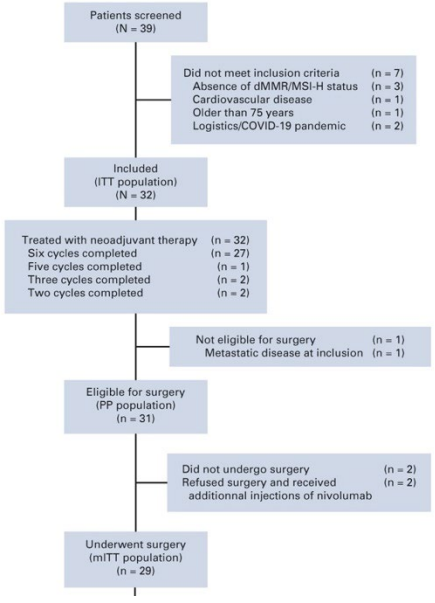
Kelly et al., NEJM 2021, ASCO 2025

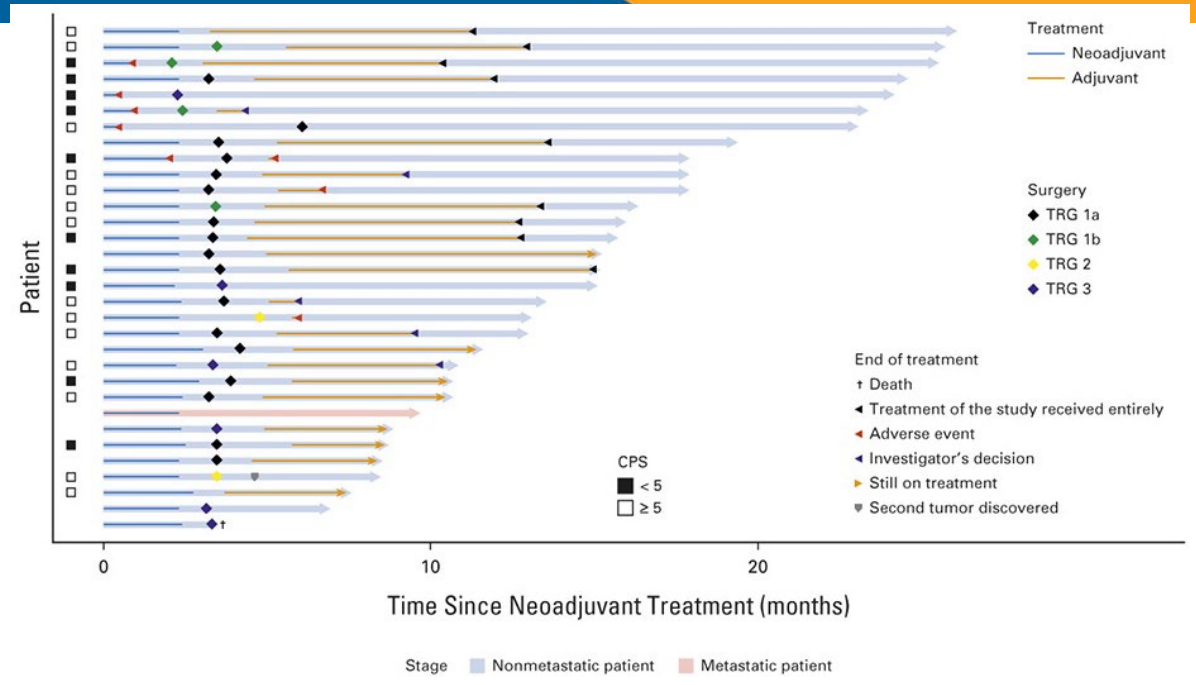
Immunotherapy in locally advanced gastroesophageal cancer

NEONIPIGA: MSI-H/dMMR

- 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).







TRG Becker	
TRG 1a: complete tumor regression without residual tumor	17 (59)
TRG 1b: < 10% residual tumor per tumor bed	4 (14)[a]
TGR 2: 10% to 50% residual tumor	2 (7)
TRG 3: > 50% residual tumor cells	6 (21)

TRG Mandard	
TRG 1: complete regression/fibrosis without tumor cells	17 (59)
TRG 2: fibrosis with scattered tumor cells	4 (14)[a]
TRG 3: fibrosis and tumor cells with a dominance of fibrosis	2 (7)
TRG 4: fibrosis and tumor cells with dominance of tumor cells	4 (14)
TRG 5: tumor without evidence of regression	2 (7)

pCR=17/29 (58.6%)

JCO 2023

Immunotherapy in locally advanced gastroesophageal cancer

MATTERHORN

MATTERHORN is a global, Phase 3, randomized, double-blind, placebo-controlled 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%*

Randomized (1:1) N=948

Pre-operative		Post-operative (1-year duration)	
2 doses of durvalumab or placebo 4 doses FLOT		2 doses of durvalumab or placebo 4 doses FLOT	10 doses of durvalumab or placebo
Durvalumab plus FLOT	SURGERY	Durvalumab† plus FLOT	Durvalumab
Placebo plus FLOT		Placebo† plus FLOT	Placebo

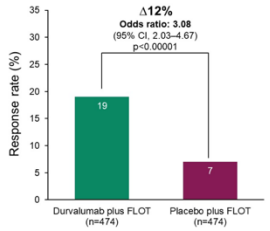
Primary objective:
- EFS

Key secondary objectives:
- Central review of pathological complete response by modified Ryan criteria
- OS

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

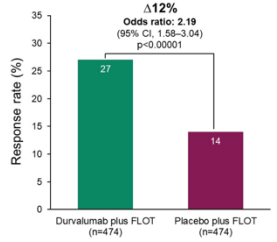
Pathological complete response

Durvalumab plus FLOT showed statistically significant improvement in pathological complete response

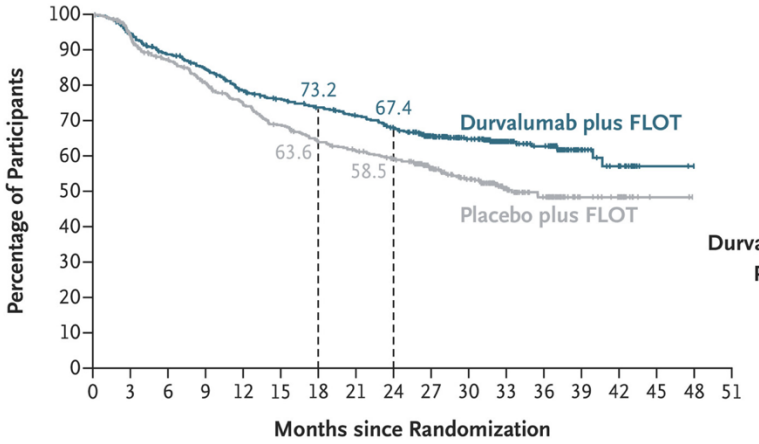


Combined complete and near-complete pathological response

Durvalumab plus FLOT showed improvement in combined complete and near-complete pathological response



Near-complete pathological response = single cells or rare small groups of cancer cells at the time of resection, per modified Ryan criteria

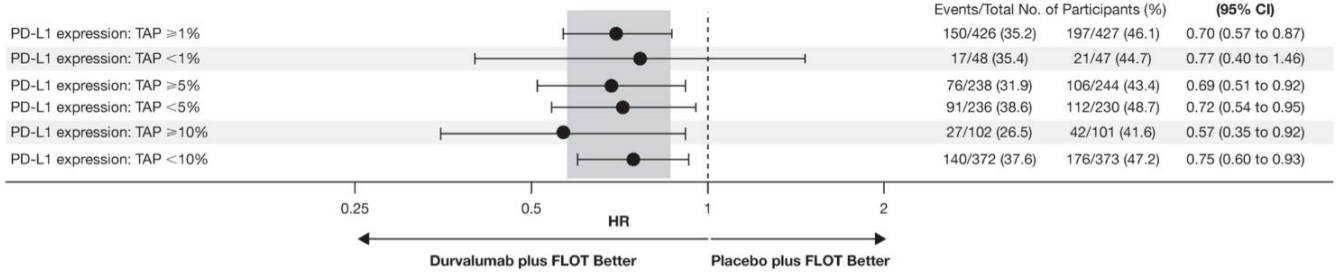


	No. of Participants with Event/ Total No. of Participants (%)	Median Event-free Survival (95% CI)
		mo
Durvalumab plus FLOT	167/474 (35.2)	NR (40.74–NR)
Placebo plus FLOT	218/474 (46.0)	32.8 (27.86–NR)

Stratified hazard ratio for event or death, 0.71 (95% CI, 0.58–0.86)
P<0.001 by stratified log-rank test

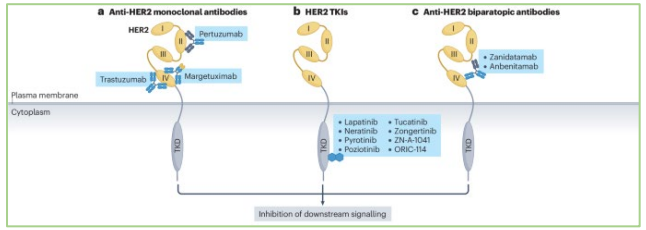
No. at Risk

Durvalumab plus FLOT	474	436	404	381	351	334	320	307	288	234	187	107	88	33	20	2	1	0
Placebo plus FLOT	474	429	392	360	329	302	278	264	249	202	160	89	65	26	21	2	1	0



ASCO GI 2024
Janjigian et al., NEJM 2025

HER2: 1st line



~20% of GEC

ToGA

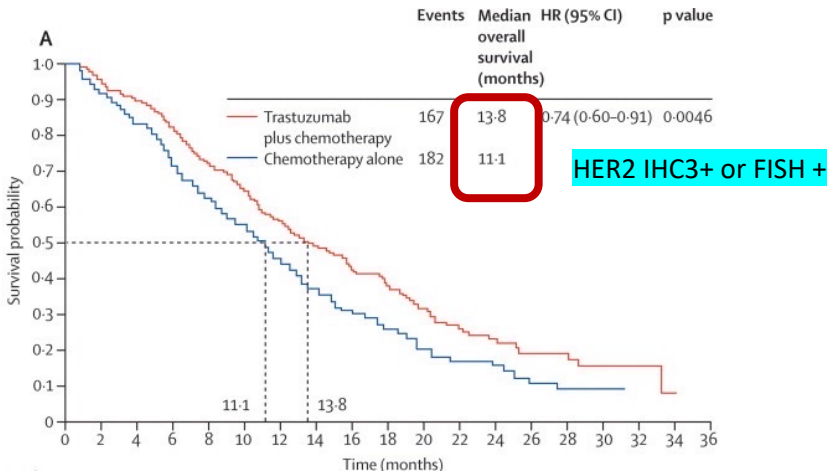
HER2+ advanced gastric cancer (N=584)

R

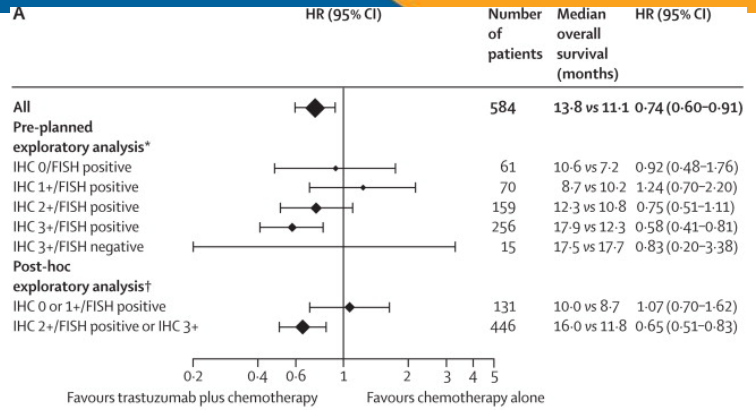
5-FU/capecitabine + cisplatin (N=290)

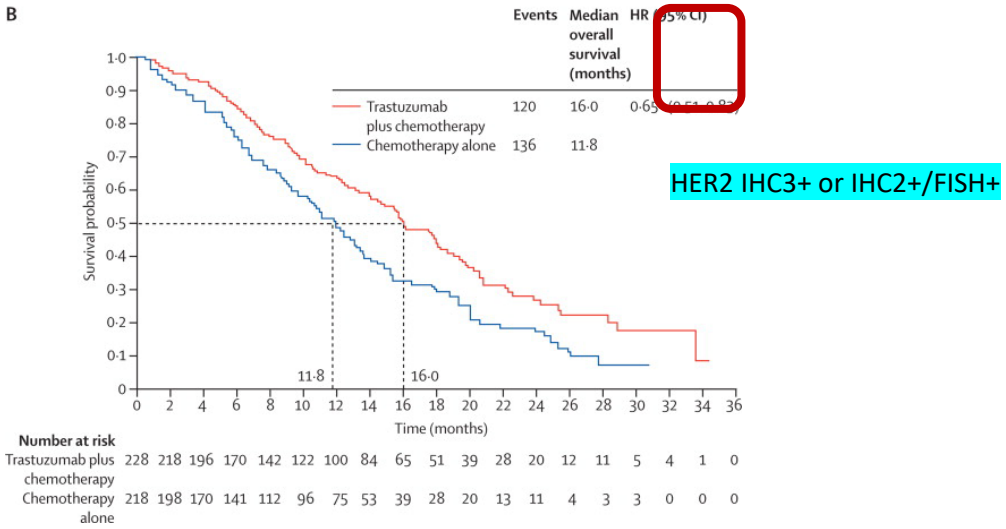
5-FU/capecitabine + cisplatin + trastuzumab (N=294)

*HER2 IHC3+ or FISH positive



HER2 IHC3+ or FISH +





HER2 IHC3+ or IHC2+/FISH+

Trastuzumab+ chemo

Lancet. 2010

HER2: 1st line

Patients
- Advanced G/GEJ adenocarcinoma
- No prior therapy in advanced setting
- HER2-positive

R 1:1
N ≈ 692

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
- Chemotherapy choice

KN811

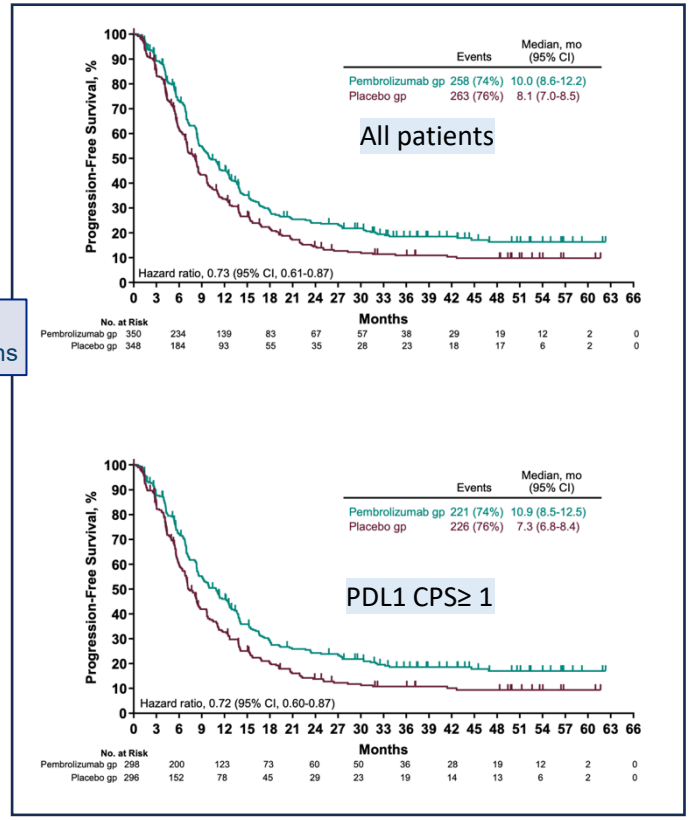
Dual Primary End Points
- OS
- PFS (RECIST v1.1 per BICR)

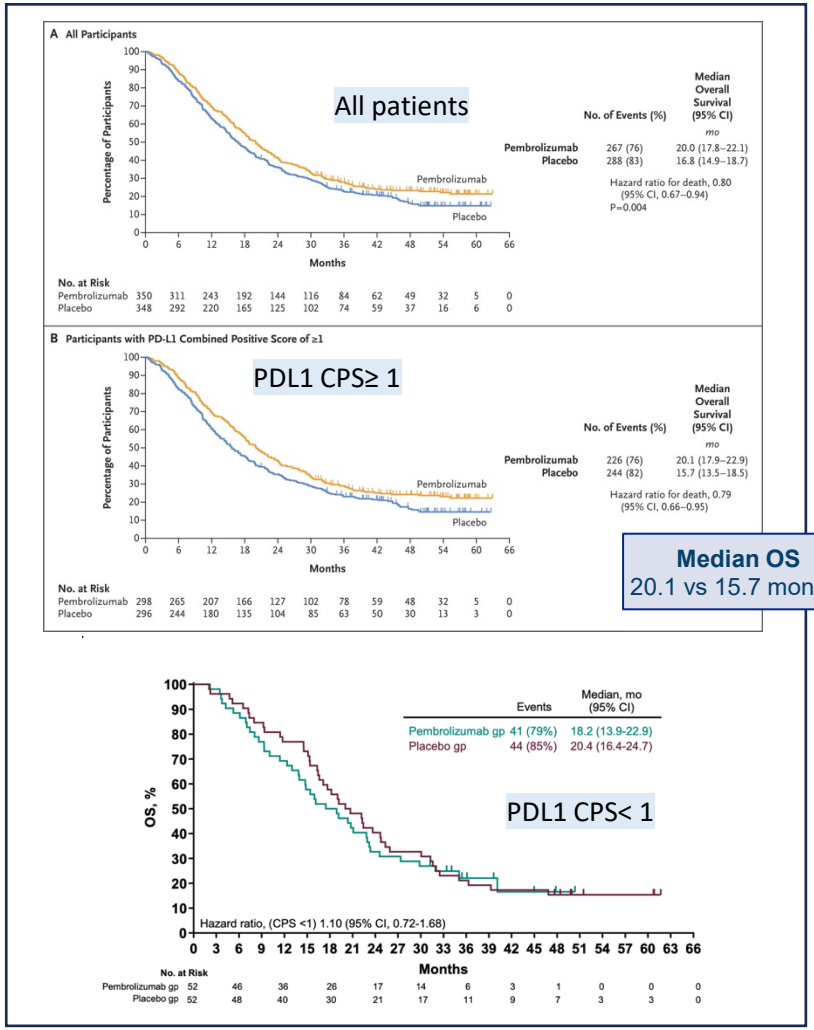
Secondary End Points
- ORR (RECIST v1.1 per BICR)
- DOR (RECIST v1.1 per BICR)
- Safety

ORR
72.6% vs 59.8%

PFS

Median PFS
10.9 vs 7.3 months





Median OS
20.1 vs 15.7 months

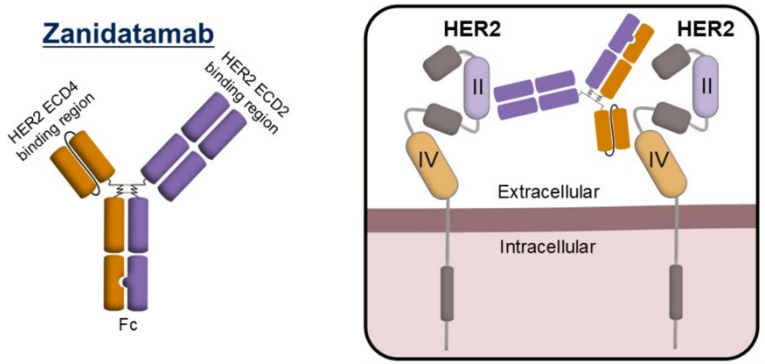
Pembro + trastuzumab + chemo if HER2+ and PDL1 CPS ≥1

Lancet. 2023; *NEJM.* 2024

HER2: 1st line

Dana-Farber Cancer Institute

Investigational



Eligibility criteria

- Aged ≥18 years at the time of signing informed consent
- HER2-expressing advanced or metastatic GEA
  - Part 1: IHC 3+ or IHC 2+ regardless of FISH status **per local or central assessment**
  - Part 2: IHC 3+ or IHC 2+/FISH+ **per central assessment**
- Measurable disease per RECIST v1.1[1]
- Baseline ECOG PS 0 or 1
- No prior HER2-targeted treatment

Single arm trial: Zanidatamab + clinician's choice of chemotherapy

Zanidatamab[a,b] IV Q3W + CAPOX[c]

Zanidatamab[a,b] IV Q3W + FP[d]

Zanidatamab[b,e] IV Q2W + mFOLFOX6[f]

After the first 25 patients were enrolled and treated, antidiarrheal prophylaxis[g] was added for all subsequent patients

CT/MRI scans Q6W per RECIST v1.1[1]

Plasma ctDNA samples at baseline and on treatment using NGS testing (Guardant360)

Primary endpoint

- Investigator-assessed confirmed ORR

Select secondary endpoints

- DOR
- PFS
- OS
- Rate and severity of AEs

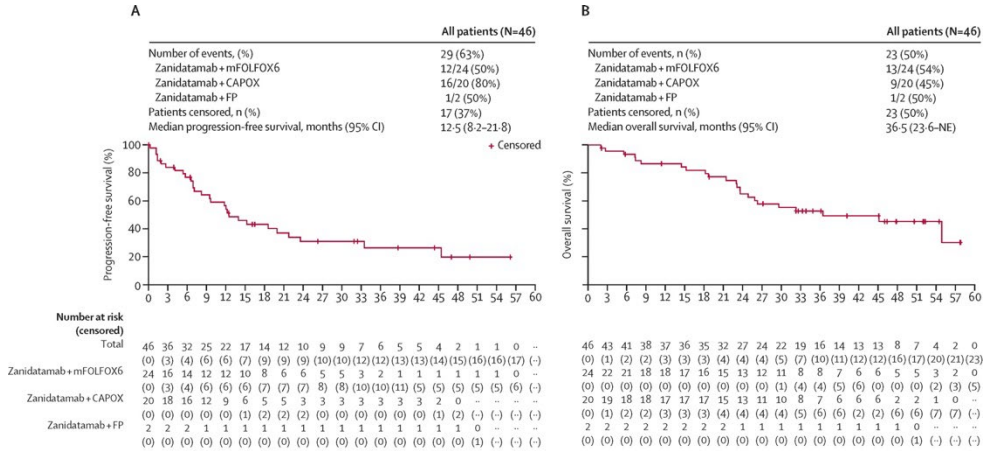
Exploratory endpoint

- Potential biomarkers for prognostic prediction

ORR
76%

Median PFS
12.5 mo

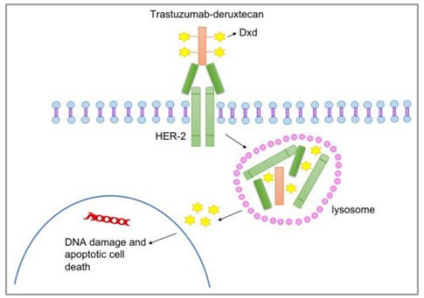
Median OS
36.5 mo



Global phase III, HERIZON-GEA-01 ongoing: zanidatamab + chemo +/- immunotherapy

ASCO 2025; Elimova et al., Lancet Oncol 2025

HER2: 2nd line



DESTINY-Gastric01

Study population
— HER2-expressing advanced gastric or GEJ adenocarcinoma
— ≥ 2 Prior regimens; must include fluoropyrimidine and a platinum agent

Stratification factors (primary cohort)
— Region (Japan or Korea)
— ECOG PS (0 or 1)
— HER2 status (IHC 3+ or IHC 2+/ISH+)

REGISTRATION

R 2:1

Primary cohort (HER2 positive [IHC 3+ or IHC 2+/ISH+])
- Progressed on trastuzumab-containing regimen

T-DXd (n = 120)
6.4 mg/kg, 3-week cycle

Physician's choice
(irinotecan or paclitaxel) (n = 60)

Exploratory cohorts (HER2 low)
- Anti–HER2 treatment naive

Cohort 1: HER2 (IHC 2+/ISH–)
T-DXd (N ≈ 20)

Cohort 2: HER2 (IHC 1+)
T-DXd (N ≈ 20)

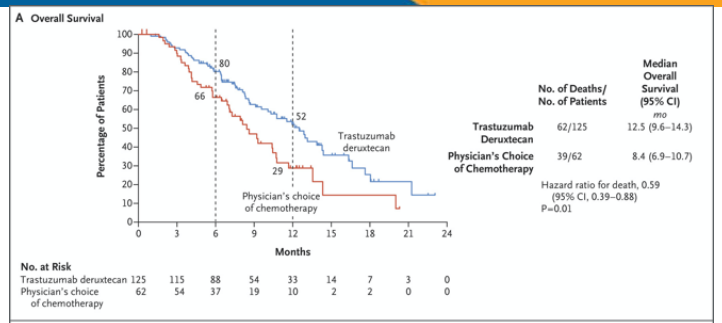
DESTINY-Gastric02

Key eligibility criteria
- Pathologically documented, unresectable or metastatic gastric or GEJ cancer
- Centrally confirmed HER2 positive disease (defined as IHC 3+ or IHC 2+/ISH+) on biopsy after progression on first-line trastuzumab-containing regimen
- ECOG PS 0 or 1

T-DXd
6.4 mg/kg Q3W
N = 79[a]

Primary endpoint
- Confirmed ORR by ICR

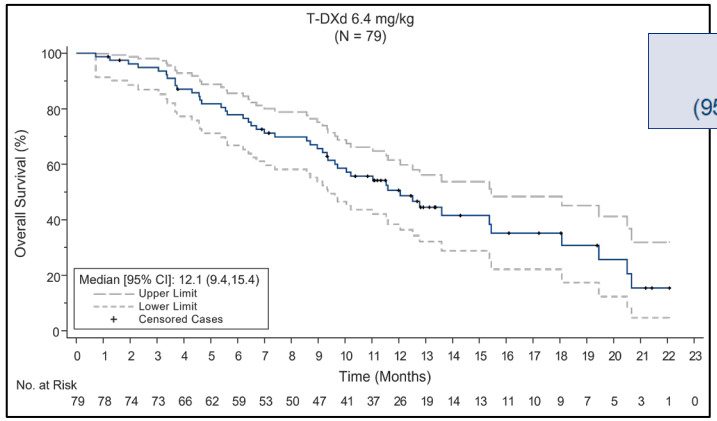
Secondary endpoints[b]
- PFS by ICR
- OS
- DoR
- Safety
- Patient-reported outcomes



Median OS
12.5 vs 8.4 months

ORR
51 vs 14%

Median PFS
5.6 vs 3.5 months



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

ORR 38%

Int J Mol Sci. 2021; *NEJM.* 2020; *Lancet Oncol.* 2023

HER2: 2nd line

DESTINY-Gastric04

Patient Population

- HER2+ (IHC 3+ or IHC 2+/ISH+)[a] GC/GEJA
- HER2 status confirmed locally or centrally[b] on a recent biopsy obtained after progression on trastuzumab
- ECOG PS 0 or 1
- No clinically active CNS metastases[c]

R 1:1

- T-DXd 6.4 mg/kg Q3W
- RAM + PTX[d]

Stratification factors

- HER2 status (IHC 3+ vs IHC 2+/ISH+)
- Geography (Asia [excluding mainland China] vs Western Europe vs mainland China/rest of world)
- Time to progression on 1L therapy (<6 months vs ≥6 months)

Primary Endpoint

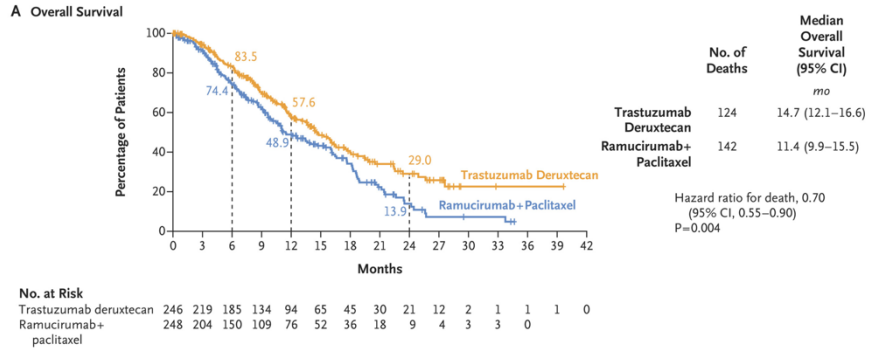
- OS

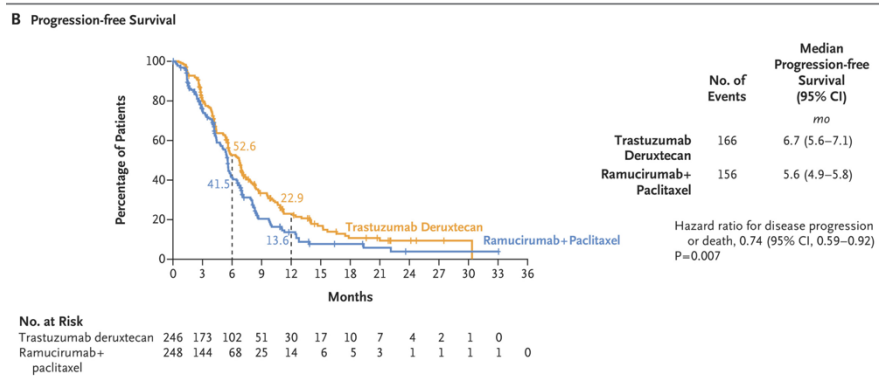
Secondary Endpoints

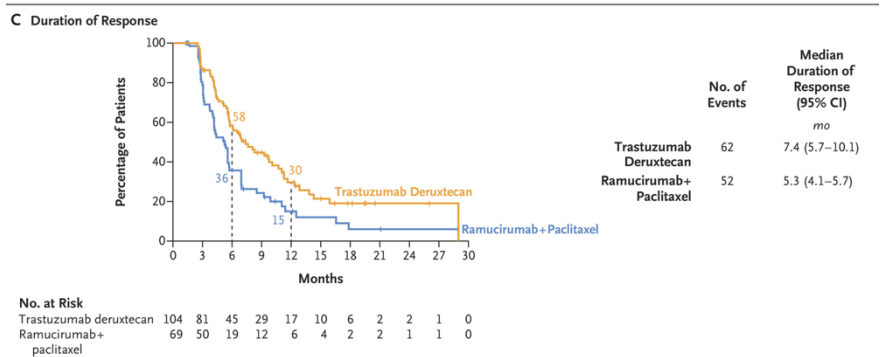
- PFS (INV)[e]
- Confirmed ORR (INV)[e]
- DCR (INV)[e]
- DOR (INV)[e]
- Safety

Exploratory Endpoints

- PROs[f]







Median OS
14.7 vs 11.4 months

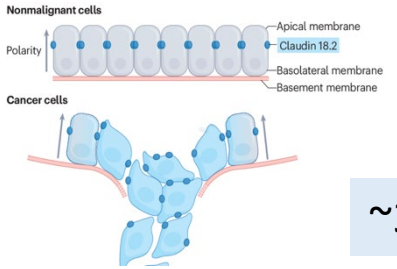
ORR 44%

Median PFS
6.7 vs 5.6months

Median DoR
7.4 vs 5.3months

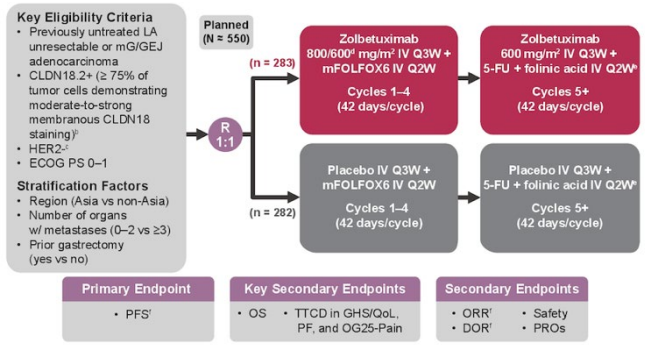
ASCO 2025; Shitara et al., NEJM 2025

CLDN 18.2

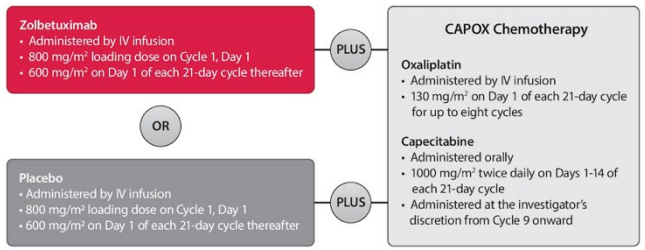


~35% of GEC

SPOTLIGHT



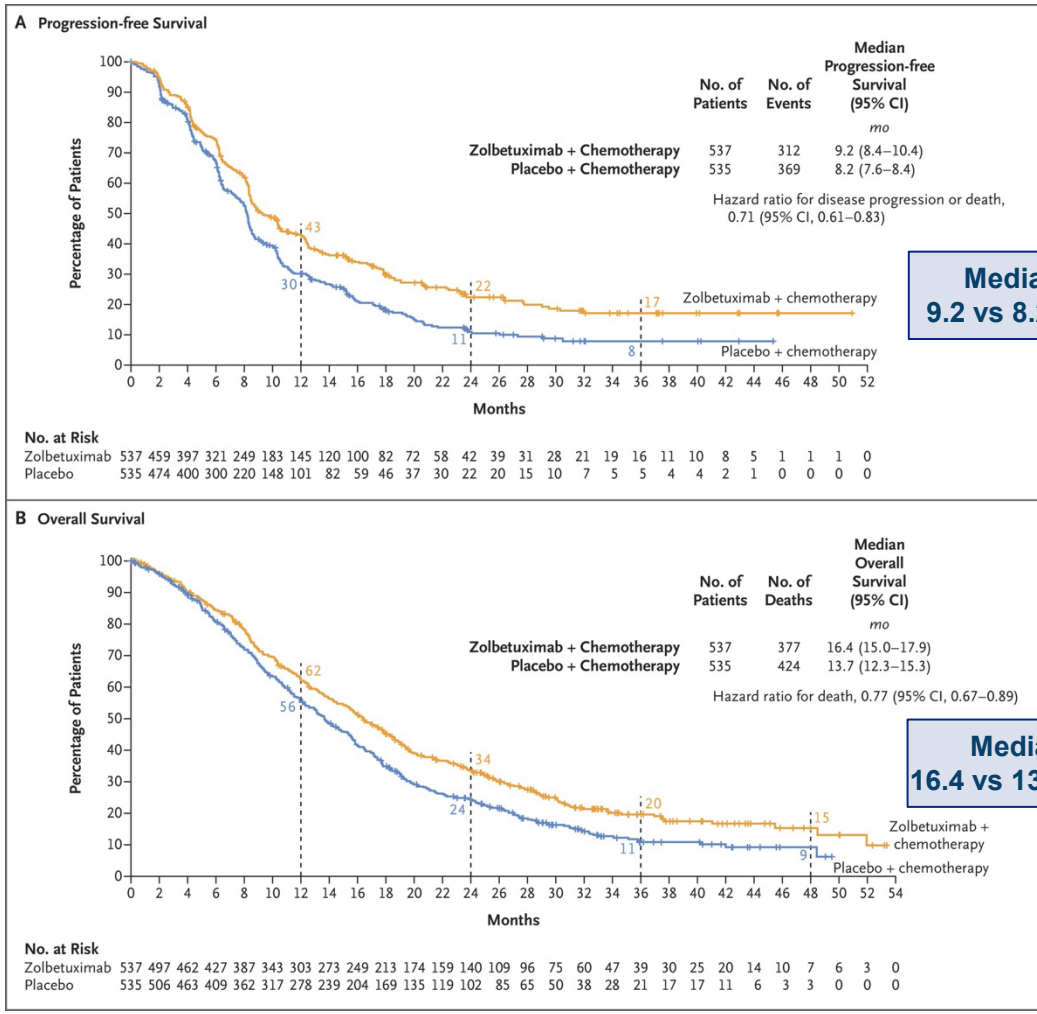
GLOW



FDA approves zolbetuximab-clzb with chemotherapy for gastric or gastroesophageal junction adenocarcinoma

On October 18, 2024, the Food and Drug Administration approved zolbetuximab-clzb (Vyloy, Astellas Pharma US, Inc.), a claudin 18.2 (CLDN18.2)-directed cytolytic antibody, with fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of adults with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors are CLDN18.2 positive, as determined by an FDA-approved test.

Today, FDA also approved the VENTANA CLDN18 (43-14A) RxDx Assay (Ventana Medical Systems, Inc./Roche Diagnostics) as a companion diagnostic device to identify patients with gastric or GEJ adenocarcinoma who may be eligible for treatment with zolbetuximab.



Median PFS
9.2 vs 8.2 months

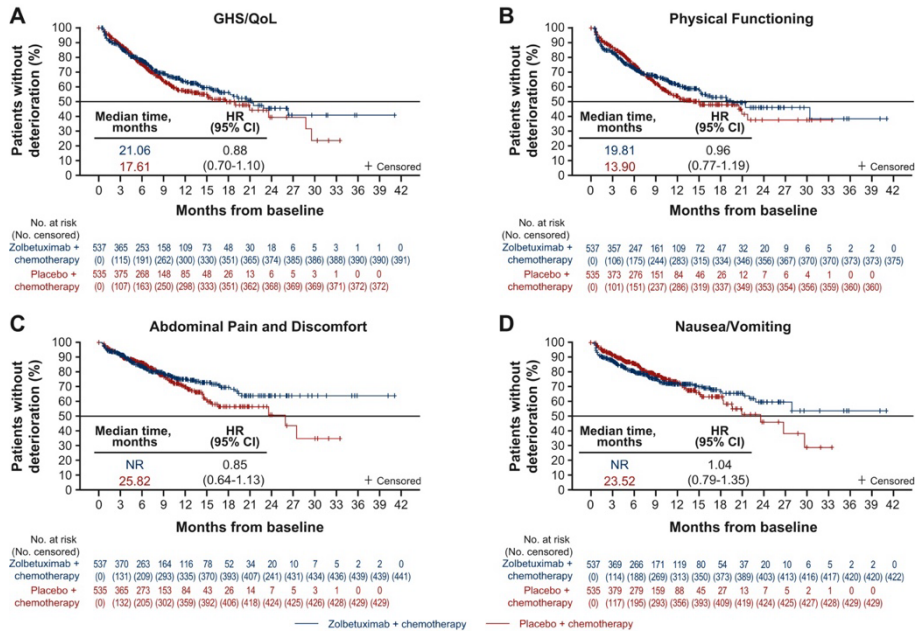
Median OS
16.4 vs 13.7 months

Nat Rev Clin Oncol. 2024; *NEJM*. 2024

CLDN 18.2: AE's

Table S10. Adverse Events in the Safety Analysis Set in SPOTLIGHT and in GLOW

Event – no. (%)	SPOTLIGHT		GLOW	
	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)
Treatment-emergent adverse events				
All	278 (99.6)	277 (99.6)	251 (98.8)	244 (98.0)
Grade ≥3	244 (87.5)	219 (78.8)	186 (73.2)	175 (70.3)
Serious	133 (47.7)	129 (46.4)	123 (48.4)	126 (50.6)
Treatment-related adverse events				
Leading to dose interruption of any study drug	217 (77.8)	130 (46.8)	168 (66.1)	108 (43.4)
Leading to dose interruption of zolbetuximab or placebo	172 (61.6)	61 (21.9)	114 (44.9)	39 (15.7)
Leading to discontinuation of any study drug	108 (38.7)	83 (29.9)	56 (22.0)	40 (16.1)
Leading to discontinuation of zolbetuximab or placebo	38 (13.6)	7 (2.5)	18 (7.1)	11 (4.4)
Leading to death	5 (1.8)	5 (1.8)	6 (2.4)	7 (2.8)
Treatment-emergent adverse events by preferred terms†				
	All grade	**Grade ≥3**	**All grade**	**Grade ≥3**	**All grade**	**Grade ≥3**	**All grade**	**Grade ≥3**
Nausea	230 (82.4)	45 (16.1)	171 (61.5)	19 (6.8)	175 (68.9)	22 (8.7)	125 (50.2)	6 (2.4)
Vomiting	188 (67.4)	45 (16.1)	101 (36.3)	17 (6.1)	168 (66.1)	31 (12.2)	79 (31.7)	9 (3.6)
Decreased appetite	136 (48.7)	17 (6.1)	97 (34.9)	9 (3.2)	105 (41.3)	17 (6.7)	86 (34.5)	4 (1.6)
Anemia	106 (38.0)	24 (8.6)	107 (38.5)	26 (9.4)	93 (36.6)	29 (11.4)	92 (36.9)	28 (11.2)
Diarrhea	114 (40.9)	12 (4.3)	125 (45.0)	10 (3.6)	83 (32.7)	15 (5.9)	87 (34.9)	18 (7.2)
Neutrophil count decreased	96 (34.4)	69 (24.7)	91 (32.7)	69 (24.8)	71 (28.0)	26 (10.2)	59 (23.7)	24 (9.6)

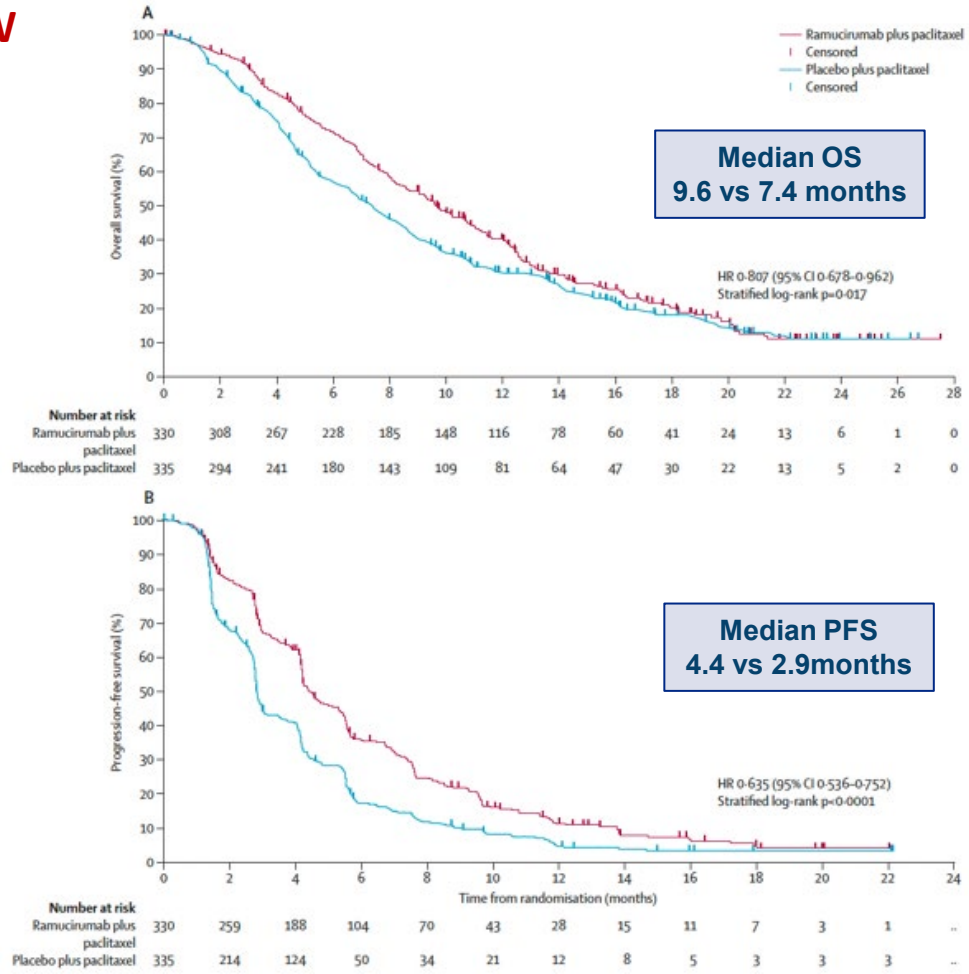


- Change from baseline trends for key PRO domains were similar with zolbetuximab + chemotherapy and placebo + chemotherapy.
- Nausea/vomiting worsened in early cycles but later returned to baseline levels without clinically meaningful deterioration.

ESMO Open 2024; *NEJM.* 2024

VEGF/angiogenesis

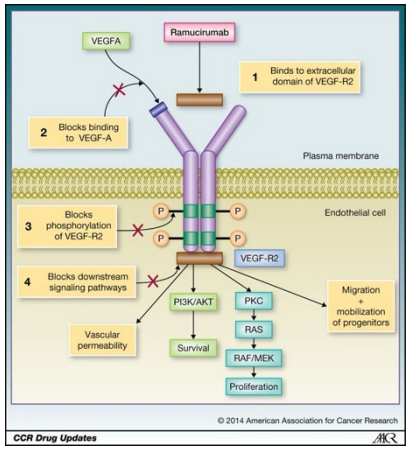
RAINBOW

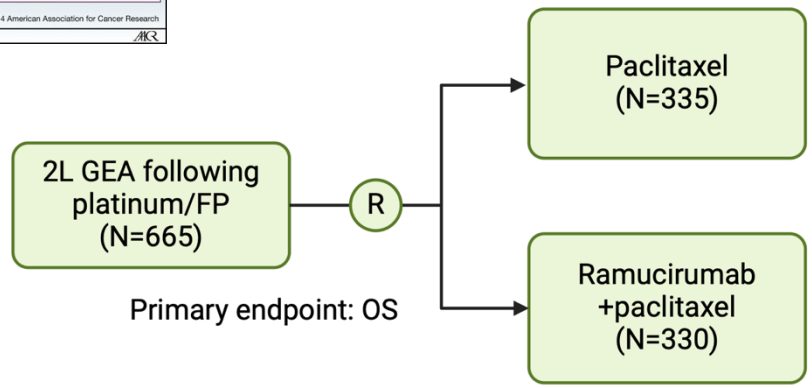


Median OS
9.6 vs 7.4 months

Median PFS
4.4 vs 2.9months

ORR
27 vs 16%



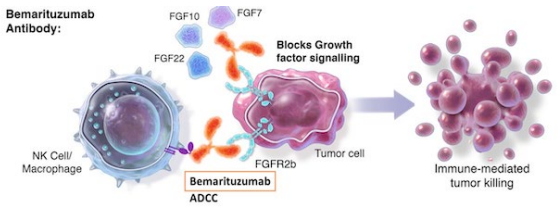


- No survival benefit in 1L
- 2L FOLFIRI-Ram: RAMIRIS Phase II/III ongoing

Lancet Oncol. 2014;15:1224-35

FGFR2b

~30% of GEC



Dana-Farber Cancer Institute

Investigational

FIGHT Trial Design

Key Eligibility Criteria
- No prior therapy for unresectable locally advanced or metastatic gastric/GEJ adenocarcinoma
- RECIST v1.1 evaluable disease
- FGFR2b overexpression by IHC and/or *FGFR2* gene amplification by ctDNA[1]
- ECOG 0/1
- HER2 not positive
- May receive 1 dose of mFOLFOX6

Stratification Factors
- Geographic region
- Single dose of mFOLFOX6 during screening
- Prior adjuvant or neo-adjuvant chemotherapy

R 1:1

Double blind, placebo controlled

Bema + mFOLFOX6 (n = 77)

VS

Placebo + mFOLFOX6 (n = 78)

Treatment Q2W[2]

Primary endpoint
- Investigator-Assessed Progression-Free Survival

Secondary endpoints
- Overall Survival
- Response Rate

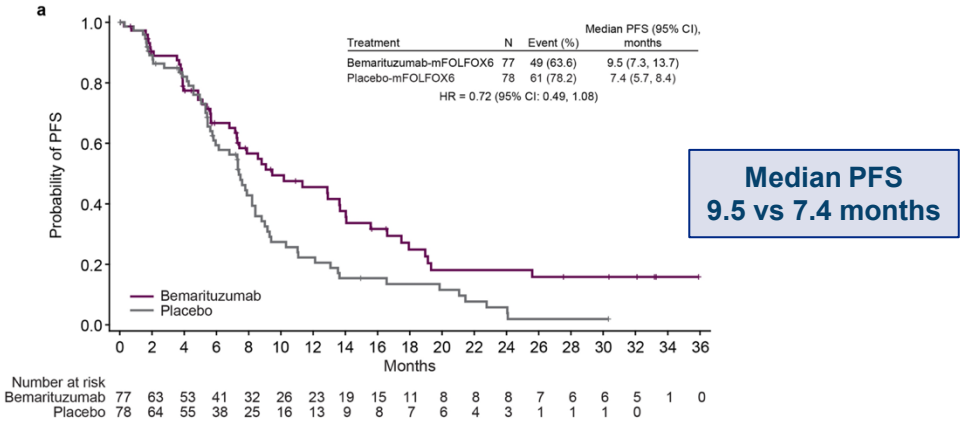
Statistical Plan

Trial initially designed as registrational Phase 3 (n=548) with 2-sided α 0.05
Amended after enrolling n = 155 to a proof-of-concept Phase 2 with pre-specified statistical assumptions of:
- Hierarchical sequential testing: PFS, then OS/ORR
- ≥84 events to demonstrate benefit at a HR≤0.76 for PFS at 2-sided α of 0.2

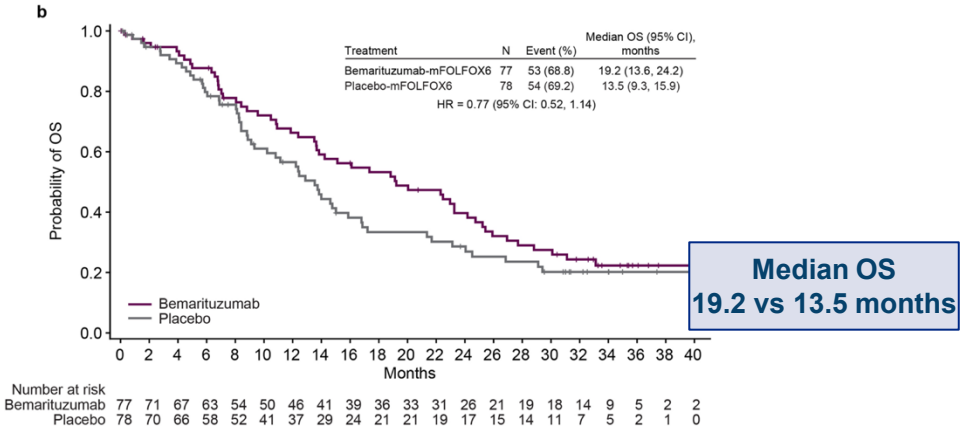
1 Central testing: Immunohistochemical stain (Ventana): cut-off any 2+/3+; circulating tumor DNA (PGDx): cut-off 1.5X
2 15mg/kg Q2W with a single 7.5mg/kg dose on Cycle 1 Day 8[2]

Summary

- The FIGHT trial is the first study to evaluate targeting overexpression of FGFR2b
- ~ 30% of 1L advanced non-HER2+ GC/GEA overexpress FGFR2b+ by a centrally performed IHC test
- Bemarituzumab, added to mFOLFOX6 chemotherapy, led to clinically meaningful and statistically significant improvements in PFS, OS and ORR
- Bemarituzumab was associated with an increase in corneal adverse events and stomatitis, the majority of which were reversible
- The FIGHT trial results support
  - A prospective randomized phase 3 study in gastric/gastroesophageal adenocarcinoma
  - The evaluation of bemarituzumab to treat other FGFR2b+ tumor types



Median PFS
9.5 vs 7.4 months



Median OS
19.2 vs 13.5 months

Awaiting phase III (FORTITUDE 101/102) results

AMGEN ANNOUNCES POSITIVE TOPLINE PHASE 3 RESULTS FOR BEMARITUZUMAB IN FIBROBLAST GROWTH FACTOR RECEPTOR 2b (FGFR2b) POSITIVE FIRST-LINE GASTRIC CANCER

At an Interim Analysis, Bemarituzumab Plus Chemotherapy Significantly Improved Overall Survival in People With FGFR2b Overexpression Compared to Chemotherapy Alone

Lancet Oncol. 2022; *Gastric Cancer.* 2024

Overview

- Epidemiology, presentation and diagnostic work up
- Potential therapeutic targets in gastroesophageal cancer
- Targets, evidence, ongoing trials
  - PD-L1
  - HER2
  - CLDN18.2
  - VEGF
  - FGFR2b
- **Novel therapeutic targets and clinical trials**

Ongoing clinical trials

14010 - Trastuzumab deruxtecan (T-DXd) monotherapy and combinations in patients (pts) with advanced/metastatic HER2-positive (HER2+) esophageal, gastric or gastroesophageal junction adenocarcinoma (GEJA): DESTINY-Gastric03 (DG-03)

Date

14 Sep 2024

Presenters

Yelena Janjigian

HER2

Zanidatamab, a HER2-targeted bispecific antibody, in combination with tislelizumab and chemotherapy as first-line therapy for patients with advanced HER2-positive gastric/gastroesophageal junction adenocarcinoma: Preliminary results from a Phase 1b/2 study

Abstract No: 4032, presented at ASCO, Chicago, IL, June 2022

VEGF

LEAP-014: AN OPEN-LABEL, RANDOMIZED, PHASE 3 STUDY OF FIRST-LINE LENVATINIB PLUS PEMBROLIZUMAB PLUS CHEMOTHERAPY IN ESOPHAGEAL SQUAMOUS CELL CARCINOMA

Other targets

nature medicine

Article https://doi.org/10.1038/s41591-024-03037-z

Claudin18.2-specific CAR T cells in gastrointestinal cancers: phase 1 trial final results

CLDN18.2

CLARITY-PanTumor01: A Phase 2 trial of the claudin 18.2-specific antibody-drug conjugate AZD0901 (CMG901) in patients with CLDN18.2-expressing advanced solid tumors

NCT06219941

2024 ASCO ANNUAL MEETING

Updated Results from EDGE-Gastric Arm A1: Phase 2 Study of Domvanalimab, Zimberelimab, and FOLFOX in First-Line Advanced Gastroesophageal Cancer

A Phase 2 clinical trial including some combination of quemliclustat, domvanalimab, zimberelimab, and chemotherapy, for people with an upper gastrointestinal tract (GI) cancer (cancer of the stomach or esophagus) that cannot be removed with surgery (unresectable) that has spread to other parts of the body (metastasized).

EDGE-Gastric

In Partnership With: GILEAD

TPS4202

Telisotuzumab Adizutecan (ABBV-400; Temab-A) in Combination With Fluorouracil, Leucovorin, and Budigalimab in Locally Advanced/Metastatic Gastric, Gastroesophageal Junction, or Esophageal Adenocarcinoma

Predictive role of homologous recombination deficiency (HRD) for irinotecan in combination with venadaparib, a novel PARP1/2 inhibitor as third- or fourth-line treatment in patients with advanced gastric cancer

Study/Phase	Indications*	Key Overview	ClinicalTirals.gov reference
FORTITUDE-101 Phase 3 Study (NCT05052801)	Untreated advanced gastric and GEJ cancer	**Bemarituzumab + mFOLFOX6 vs mFOLFOX6 alone** **Primary outcome:** Efficacy assessed by OS **Secondary outcomes:** Efficacy assessed by PFS and OR; safety and tolerability	https://clinicaltrials.gov/ct2/show/NCT05052801
FORTITUDE-102 Phase 1b/3 Study (NCT05111626)	Untreated advanced gastric and GEJ cancer	**Bemarituzumab + mFOLFOX6 + nivolumab (Part 2: comparison with mFOLFOX6 + nivolumab alone)** **Part 1 (phase 1b):** DLTs, TEAEs, clinically significant changes **Part 2 (phase 3):** Efficacy assessed by OS, PRS, OR	https://clinicaltrials.gov/ct2/show/NCT05111626

FGFR2b

1471TiP MK-2870-015: A phase III study of trophoblast antigen 2 (TROP2)-directed antibody-drug conjugate (ADC) sacituzumab tirumotecan (sac-TMT) vs treatment of physician's choice (TPC) for previously treated metastatic gastroesophageal adenocarcinoma (GEA)

Z.A. Wainberg · E. Van Cutsem · K. Shitara · ... · S. Bhaumik · P. Bhagia · J. Tabernero ... Show more

Enfortumab vedotin in previously treated gastric/esophageal cancers cohorts of EV-202

A Phase 2, Open-label Study of Amivantamab in Patients with Previously Treated Advanced or Metastatic Gastric and Gastroesophageal Junction Cancer or Esophageal Cancer

ESMO 2024, 2021. ASCO GI 2024, 2023, 2022. ASCO AM 2025, 2024, 2022. *Nature Med*. 2024

Can we enhance chemotherapy backbone?

ALLIANCE A022102: RANDOMIZED PHASE III TRIAL OF mFOLFIRINOX +/- NIVOLUMAB VS. FOLFOX +/- NIVOLUMAB FOR FIRST-LINE TREATMENT OF METASTATIC HER2-NEGATIVE GASTROESOPHAGEAL ADENOCARCINOMA (GEA)

Haeseong Park[1], Susan Geyer[2], Kelsey Klute[3], Jonathan Bleeker[4], Daniel King[5], Matthew Strickland[6], Austin Goodrich[2], Destin Carlisle[7], Ardaman Shergill[7], Eileen M. O'Reilly[8], Jeffrey Meyerhardt[1], Manish A. Shah[9]

[1]Dana-Farber Cancer Institute, Boston MA, [2]Alliance Statistics and Data Management Center, Mayo Clinic, Rochester, MN, [3]University of Nebraska, Omaha, NE, [4]Sanford Health, Sioux Falls, SD, [5]Northwell Health, New Hyde Park, NY, [6]Massachusetts General Hospital, Boston, MA, [7]Alliance Protocol Operations Office, University of Chicago, Chicago, IL , [8]Memorial Sloan Kettering, New York, NY, [9]Weill Cornell Medicine, New York, NY

ASCO2023 TPS4175

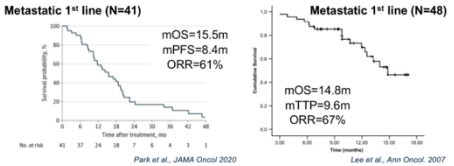
Background

Challenging the current standard: mFOLFIRINOX vs FOLFOX

- Doublet chemotherapy with FOLFOX has been preferred standard first line therapy
- Upfront triplet strategy allows exposure to more active agents in a population where the majority (>80%) do not receive all effective agents
- Prior triplet regimens were developed in an era when there were no third-line treatment options, and few patients received second-line therapy
- Recent studies (CheckMate649 or KEYNOTE-590) established immune checkpoint inhibitor (ICI) + doublet chemotherapy as standard first line therapy: ICIs are approved in the US independent of bioomarker, but subgroup analyses indicate greater benefit in tumors with higher PD-L1 expression (CPS ≥ 5)

Why FOLFIRINOX?

- More manageable toxicity than taxane-based triplet
- Promising activity in multiple phase II trials (overall survival shown below)
- Efficacy and safety established across other GI cancers



Study Schema, Eligibility and Treatment Plans

Patients with newly diagnosed, advanced HER2 negative gastric, GEJ, esophageal adenocarcinoma

R* 1:1

Arm 1. mFOLFIRINOX +/- nivolumab#

5-FU infusion 2400mg/m² IV over 44-46h
Leucovorin 400mg/m² IV
Oxaliplatin 85mg/m² IV
Irinotecan 150mg/m² IV
(Nivolumab 240mg IV)

Arm 2. mFOLFOX6 +/- nivolumab#

5-FU bolus 400mg/m² IV
5-FU infusion 2400mg/m² IV over 44-46h
Leucovorin 400mg/m² IV
Oxaliplatin 85mg/m² IV
(Nivolumab 240mg IV)

Key Eligibility Criteria

- HER2 negative gastroesophageal adenocarcinoma, known PD-L1 CPS
- Measurable or non-measurable, but evaluable disease by RECIST 1.1
- No prior treatment for metastatic disease
- ECOG 0 or 1
- Prior or concurrent malignancy that does not interfere with the safety or efficacy of the regimen allowed
- No known UGT1A1*28 polymorphism
- No concurrent uncontrolled medical condition that would make this protocol unreasonably hazardous for the patient
- No active autoimmune disease requiring systemic therapy

** Stratification factors include tumor location (gastric, GEJ, esophagus), measurable disease (yes vs no), PD-L1 expression (CPS ≥5 vs <5), and nivolumab use (yes vs no)*
\# Patients whose tumors have PD-L1 CPS ≥5 MUST receive nivolumab, unless there are contraindications to immunotherapy use. Patients whose tumors have PD-L1 CPS <5 may receive nivolumab with chemotherapy. The use of nivolumab in this patient population is not mandated by the protocol and is left at the discretion of the treating physician.

ASCO 2023

Unanswered questions

- Who are the responders? Cell-free DNA, better chemo and IO biomarkers, expanding the pool (EBV+, high PD-L1, MSI, etc)
- Optimal 2nd line + therapy after IO+chemo? Do we continue IO?
- Optimal chemo backbone?
- How do we incorporate additional therapeutic targets: EGFR, FGFR2, CLDN18.2, TMB, HRD, MET, etc

Take-home messages

- Global incidence and mortality rates of gastroesophageal cancers are high
- Incorporation of novel biomarkers have led to advances in therapeutic effectiveness
- Multiple biomarkers of therapeutic implications exist and should be identified before treatment planning
  - HER2, PDL1, MMR/MSI, CLDN18.2
- Addition of immune checkpoint inhibitors improve survival in metastatic HER2 positive or negative gastroesophageal cancer
- Immune checkpoint inhibitors are beneficial in selected population for treatment of locally advanced gastroesophageal cancer
- Future directions: mechanism of resistance, managing toxicities, better combinations