ESMO ON AIR

ESMO Webinar:

Advanced Gastric Cancer

Filippo Pietrantonio

Chair

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY

Programme

12 March 2025

5 minutes	**Introduction and Welcome** Filippo Pietrantonio
15 minutes	**Navigating the therapeutic landscape & exploring unmet needs in advanced gastric cancer** Sylvie Lorenzen
15 minutes	**Optimal biomarker workup for patients with advanced gastric cancer: diagnosis, prognostication, and personalised treatment** Filippo Pietrantonio
15 minutes	**Preventing and managing adverse events in patients with advanced gastric cancer in the era of precision oncology** Tanja Fleitas Kanonnikoff
10 minutes	**Live discussion, Q&A and Conclusions** All speakers

Filippo Pietrantonio
Chair
GI Medical Oncologist at Fondazione IRCCS Istituto Nazionale dei Tumori, Milan

Sylvie Lorenzen
Speaker
Klinikum rechts der Isar Department of Hematology and Oncology
Technical University Munich

Tania Fleitas Kanonnikoff
Speaker
University Hospital of Valencia, INCLIVA

Learning Objectives

- Improving treatment decisions for gastric cancer in the rapidly evolving treatment landscape.
- Improving identification and differentiation of key biomarkers in gastric cancer and understanding their impact on diagnosis, personalised treatment, and clinical outcomes.
- Improving awareness of potential adverse events associated with current and emerging gastric cancer treatments.

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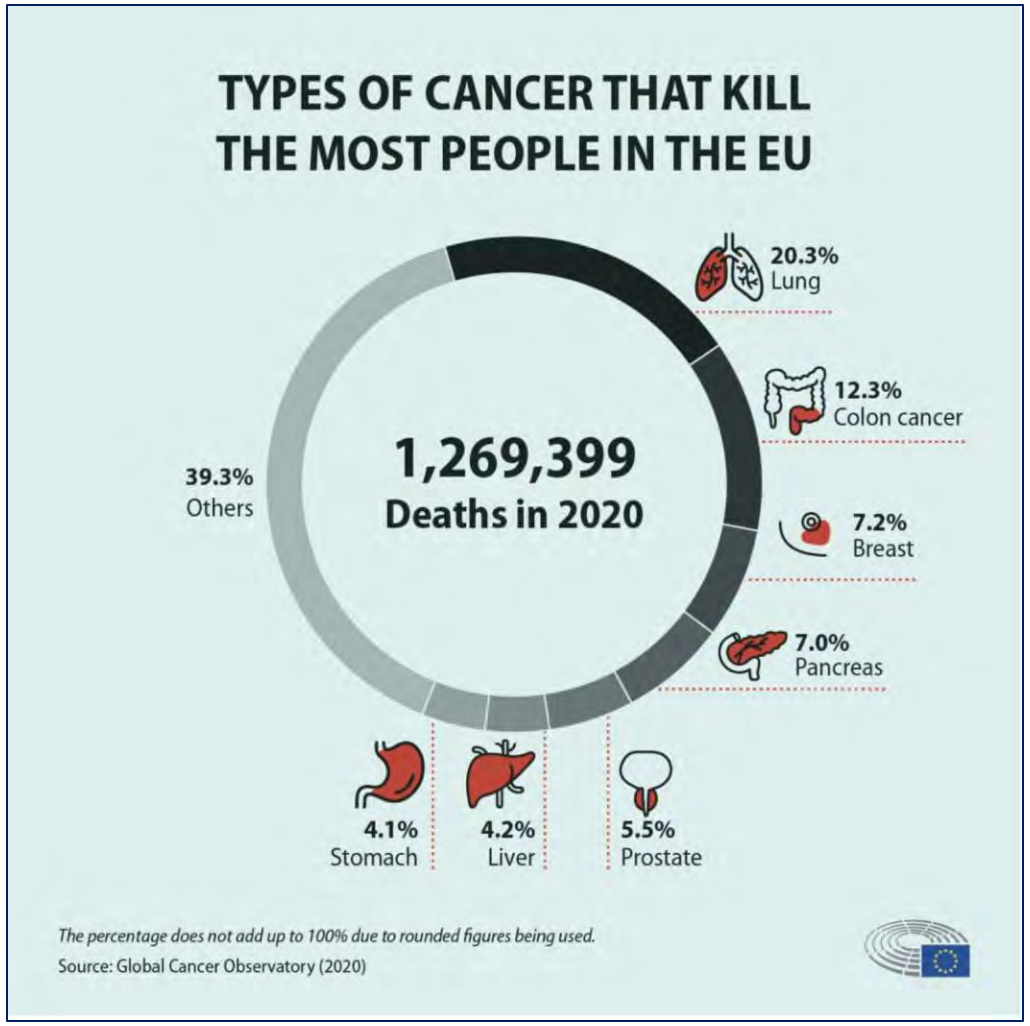
ESMO Webinar "Advanced Gastric Cancer: Navigating the therapeutic landscape & exploring unmet needs

Sylvie Lorenzen

12. March 2025

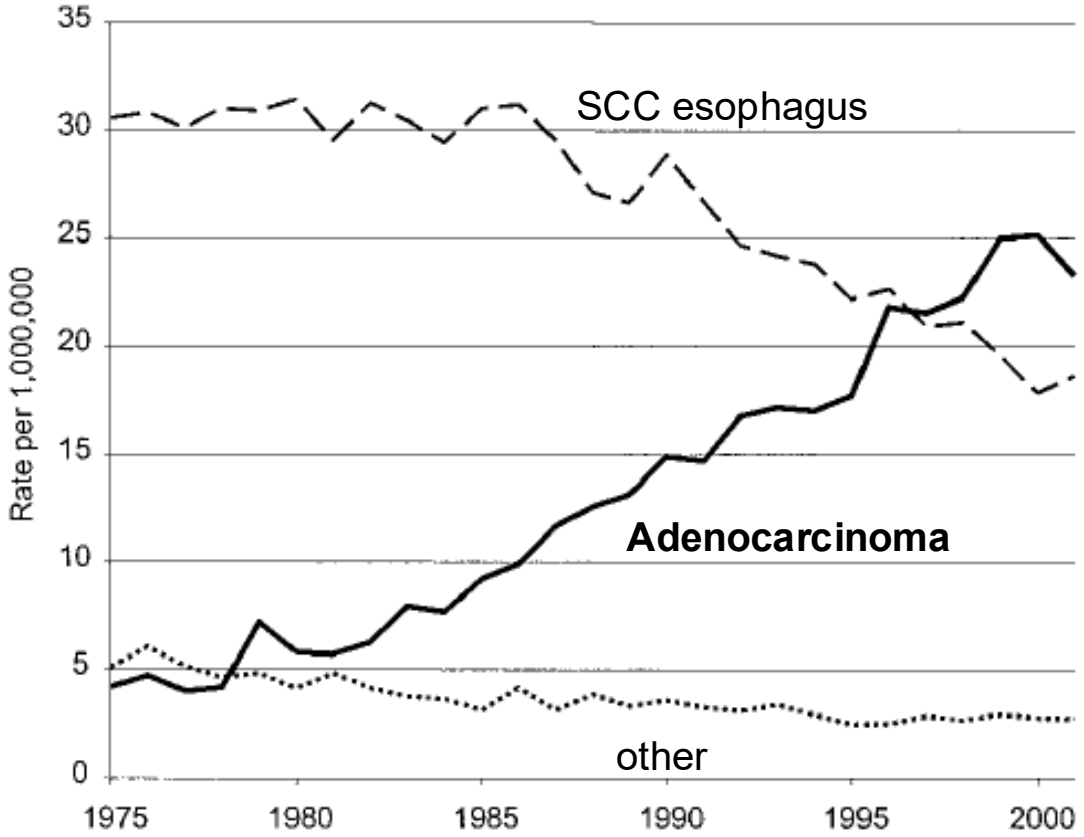
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY

Epidemiology – Cancer related cause of death in Europe 2020

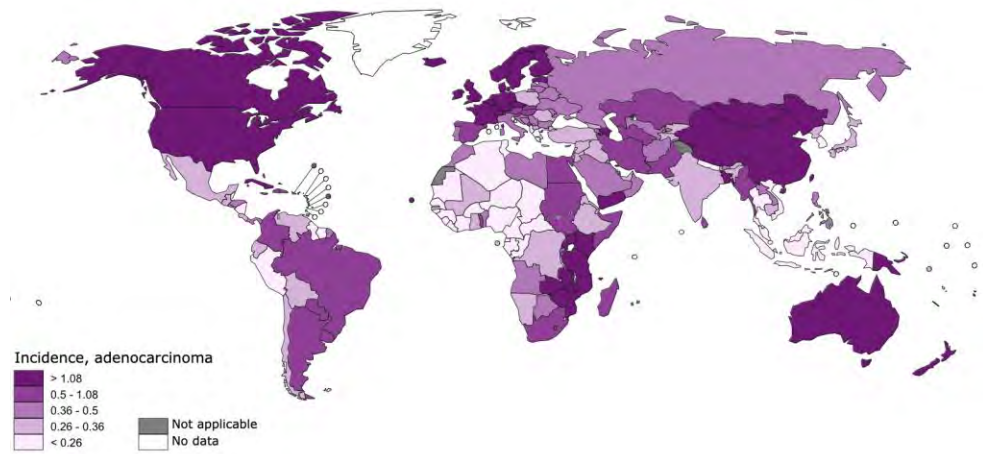


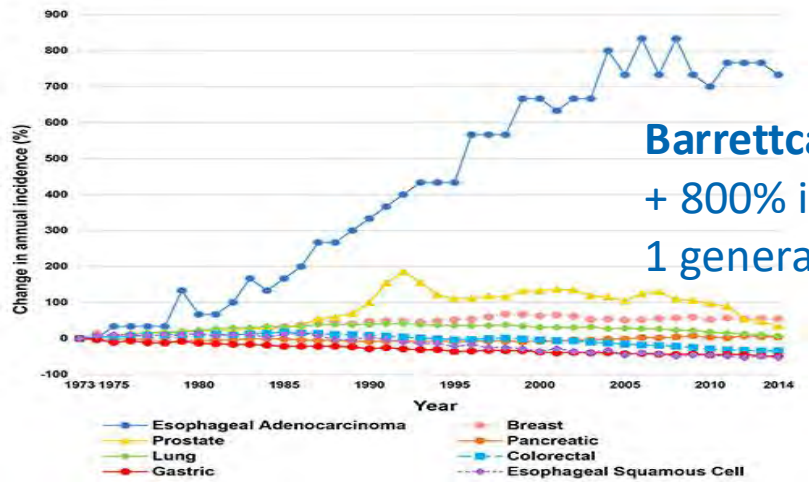
Gastrointestinal Cancers Nr. 1

Gastroesophageal junction cancer on the rise!



Pohl & Welch. *J Natl Canc Inst* 2005

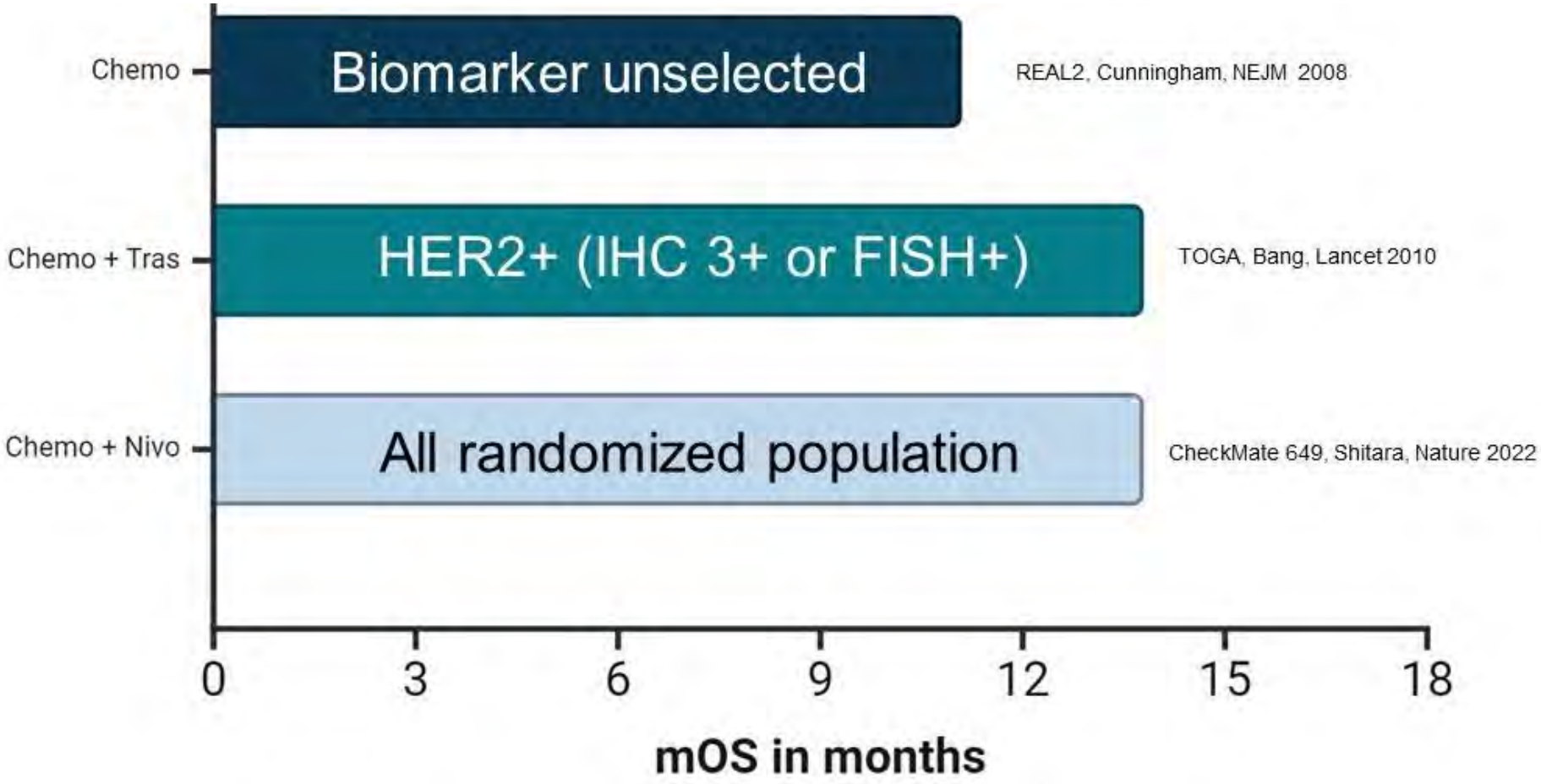




Barrettcarcinoma
+ 800% increase within
1 generationeneration

Morgan et al, Gastroenterology 2022;163:649–658,; Pohl & Welch. J Natl Cancer Inst. 2005 Jan 19;97(2):142-6

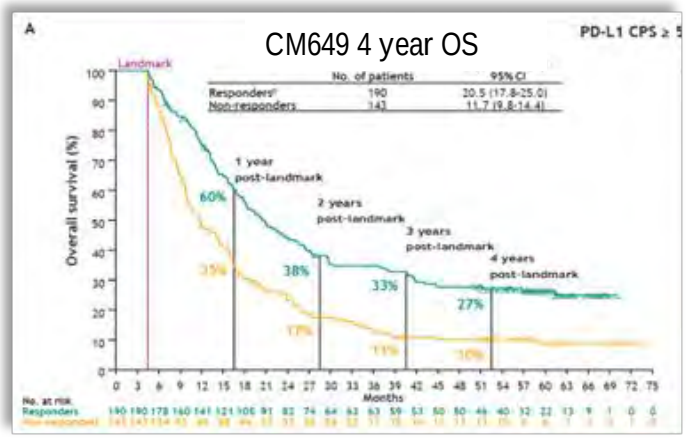
The Broad Reality in Advanced Disease

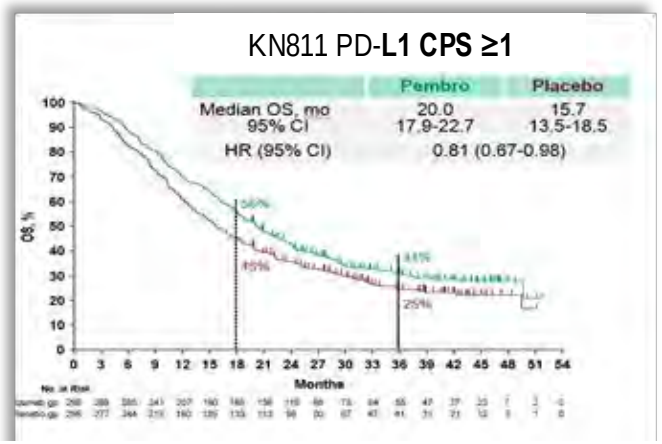


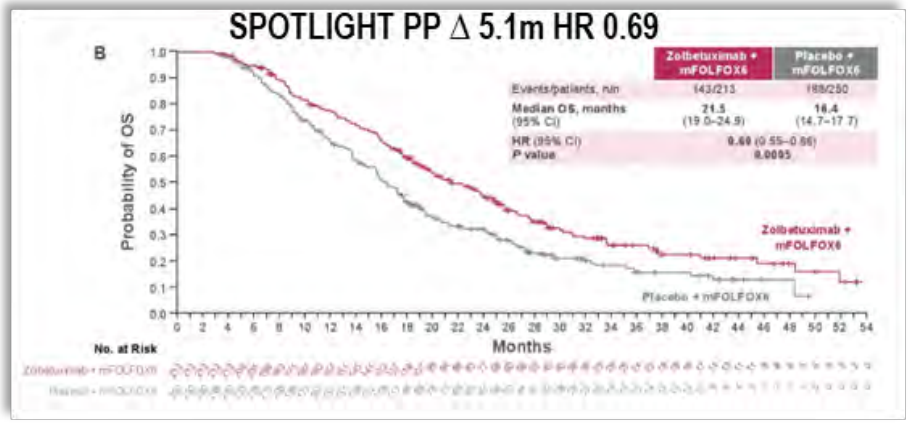
- Objective response rates ~45-60%
- Median progression free survival ~6 months
- Median overall survival ~11-14 months

Treatment of advanced GASTRIC CANCER in 2025

Wins for targeted therapy in biomarker selected populations







Trial	mAb	Cohort	Median OS
CM649	Nivolumab	CPS ≥ 5 responding patients	20.5m
KN811	Trastuzumab + pembrolizumab	HER2+ PD-L1 CPS≥1	20.0m
SPOTLIGHT	Zolbetuximab	CLD 18.2+ PP analysis	21.5m

Janjigian et al, ASCO GI 2024
Jangigian et al, Lancet 2023
Shitara et al, ASCO 2024

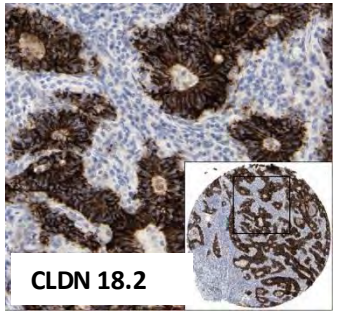
Diagnostik: Which Biomarker do we need in 2025?

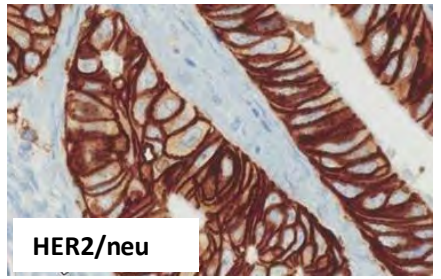
First-line

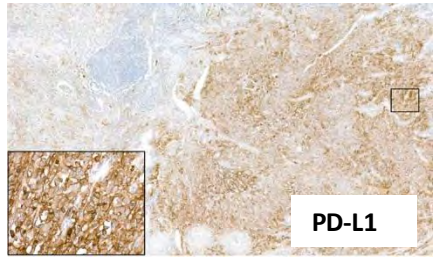
- HER2
- PD-L1 (CPS)
- MSI
- CLDN 18.2

Second/Third-Line

- NGS?

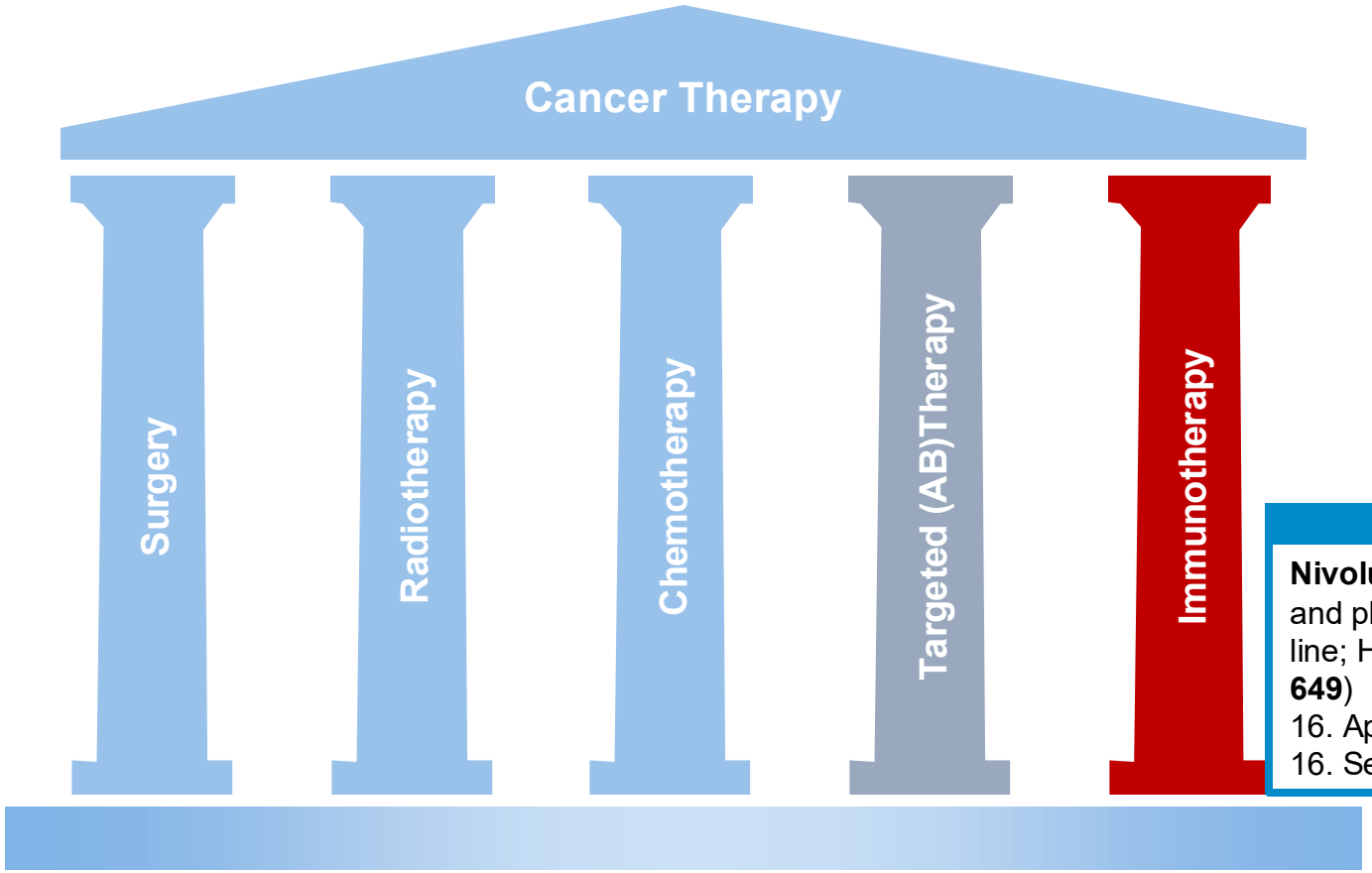




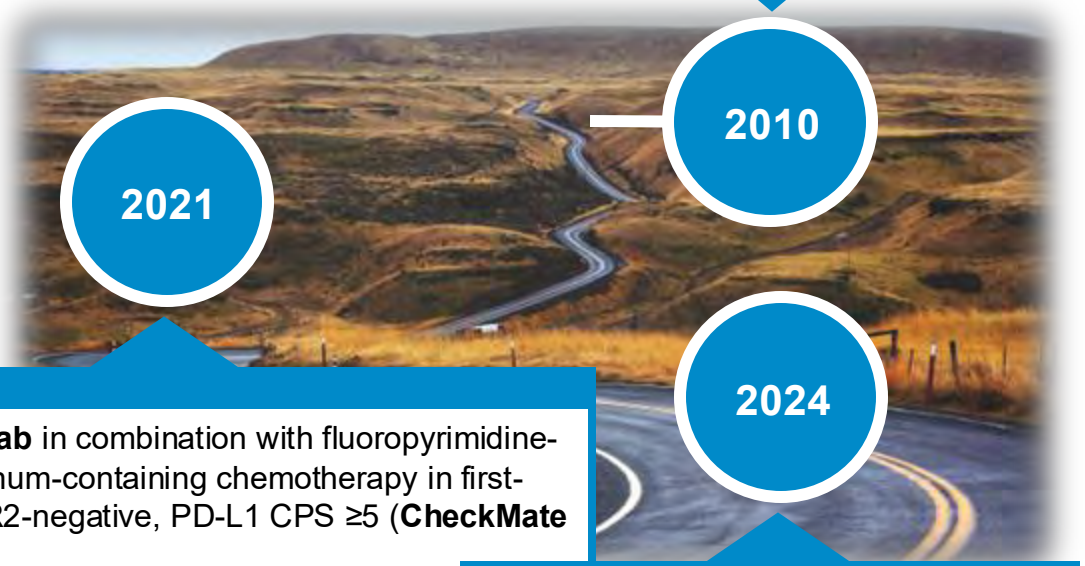


Arnold et al., Clin Transl Oncol. 2020 (CLDN 18.2 IHC); Rüschoff et al., Mod Pathol. 2012 (HER2/neu IHC); Ahn et al., Mod Pathol. 2021 (PD-L1 IHC)

Individualised therapy as the cornerstone of adenocarcinoma of the stomach and gastroesophageal junction



Trastuzumab in combination with fluoropyrimidine- and platinum-containing chemotherapy in first-line; HER2-positive (**ToGA**)
2. February **2010: EMA approval**
20. October **2010: FDA approval**



Nivolumab in combination with fluoropyrimidine- and platinum-containing chemotherapy in first-line; HER2-negative, PD-L1 CPS ≥5 (**CheckMate 649**)
16. April **2021: FDA approval**
16. September **2021: EMA approval**

Zolbetuximab in combination with fluoropyrimidine- and platinum-containing chemotherapy in first-line;; CLDH18.2 +
(SPOTLIGHT)
19. September **2024 EMA approval**

Bang YJ, et al. Lancet. 2010;376(9742):687–97; Shitara et al., Nature Medicine volume 29, pages 2133–2141 (2023);
Janjigian YY, et al. Lancet. 2021;398(10294):27–4; Shitara et al., Nature Medicine 2023

First-Line Therapies 2024/25

ToGA[1]
Phase III RCT
1L HER2 pos.
Addition of trastuzumab to chemotherapy improved OS

CheckMate 649[2]
Phase III RCT
1L non-HER2 pos.
Addition of nivolumab to chemotherapy improved OS, PFS in PD-L1 CPS ≥5

KEYNOTE-811[3]
Phase III RCT
1L HER2 pos.
Addition of pembrolizumab to trastuzumab and chemotherapy improved ORR in PD-L1 CPS ≥1

KEYNOTE-859[4]
Phase III RCT
1L HER2 neg.
Addition of pembrolizumab to chemotherapy improved OS, PFS, ORR, DOR in PD-L1 CPS ≥1

GLOW[5]**/SPOTLIGHT**[6]
Phase III RCTs
1L HER2 neg.
CLDN18.2 positive
Addition of zolbetuximab to CAPOX/mFolfox6 improved PFS, OS in

RATIONALE-305[7]
Phase III RCT
1L HER2 neg.
In PD-L1 TAP score ≥5% addition of tislelizumab to CAPOX or FP improved PFS, OS

[1]**Trastuzumab** in combination with fluoropyrimidine- and platinum-containing chemotherapy in 1st line; HER2-positive
2. Febuary **2010: EMA approval** 20. October **2010: FDA approval**

[2]**Nivolumab** in combination with fluoropyrimidine- and platinum-containing chemotherapy in 1st line; HER2-negative, PD-L1 CPS ≥5
16. April **2021: FDA approval**
16. September **2021: EMA approval**

[3]**Pembrolizumab** in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy in 1st line; HER2-positive, PD-L1 CPS ≥1
5. May **2021: FDA approval**
29. August **2023: EMA approval**

[4]**Pembrolizumab** in combination with fluoropyrimidine- and platinum-containing chemotherapy in 1st line; HER2-negative, PD-L1 CPS ≥1
2023: FDA approval
13. October **2023: EMA approval**

[5, 6]**Zolbetuximab** in combination with [5]CAPOX or [6]mFOLFOX6 in 1st line; HER2-negative, CLDN18.2 positive (moderate-to-high) mGEA
EMA approval 25.09.2024
FDA approval 18.10.2024

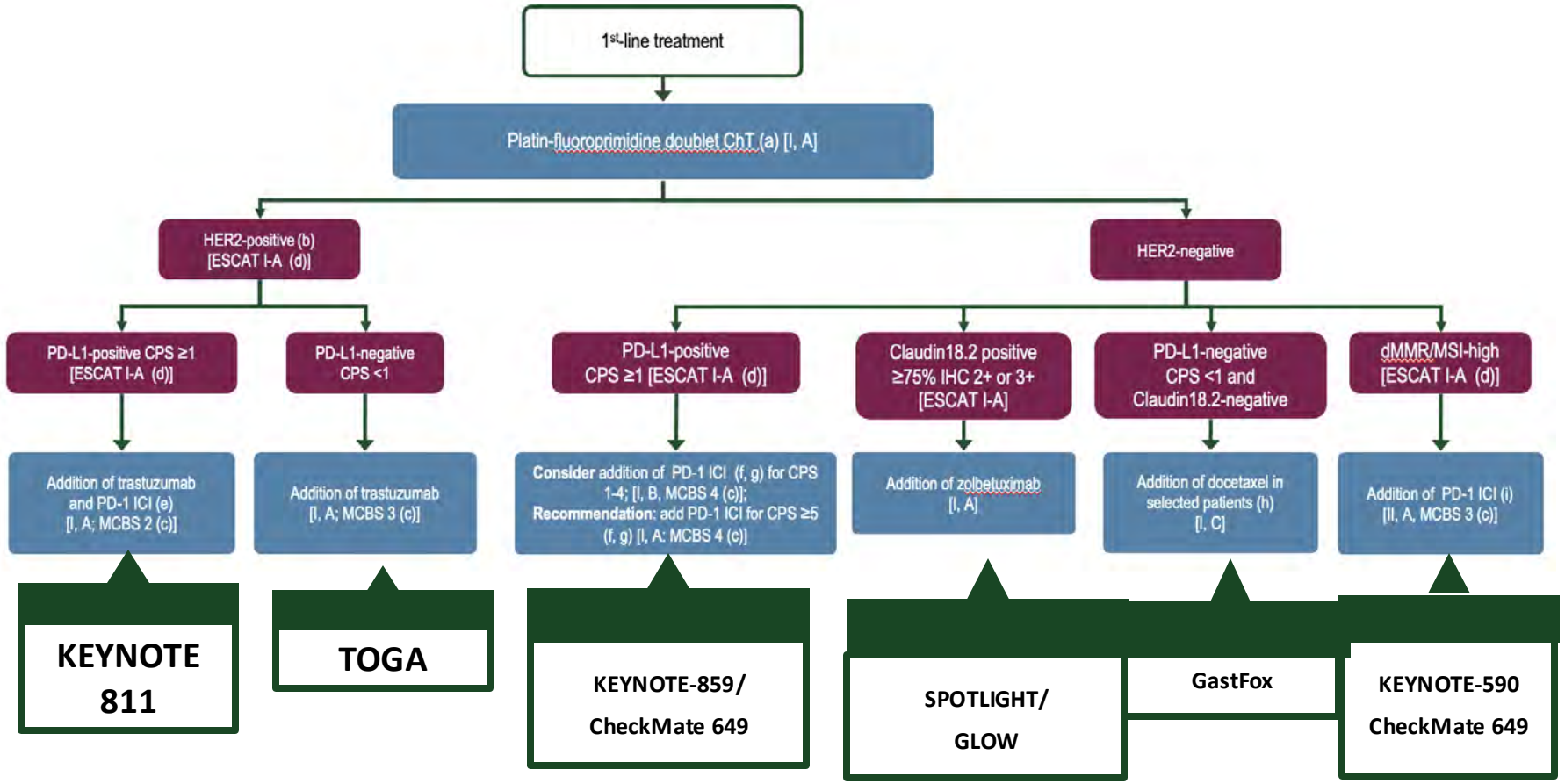
[7]**Tislelizumab** in combination with CAPOX (or FP) in 1st line; HER2-negative, PD-L1 positive (TAP score ≥5%) mGEA

FDA approval pending,
EMA approval 26.11.2024

1Bang et al., Lancet. 2010; 2Janjigian et al., Lancet. 2021; 3Janjigian et al., Lancet. 2023; 4Rha et al., Lancet Oncology. 2023
5Shah et al., Nat. Med. 2023; 6Shitara et al., Lancet. 2023; 7Moehler et al., 2023 ASCO GI Cancers Symposium (Abstract 286). 2023

ESMO Living Guidelines Update Sept 2024

v1.4 – September 2024



Lordick F et al. Ann Oncol 2022 Oct;33(10):1005-1020; ESMO Gastric Cancer Living Guideline, v1.4 September 2024

Metastatic Gastric Cancer – Case presentation

Patient

- 63 years, female, ECOG 0

Current Problem

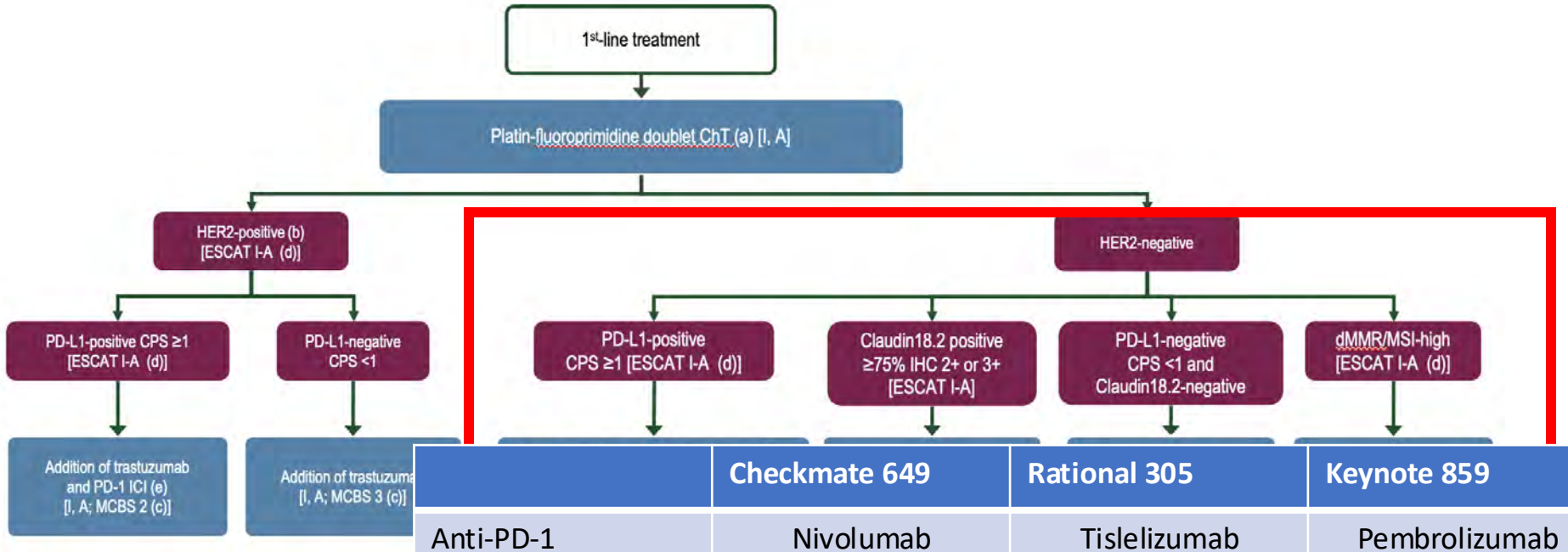
- Weight loss 10 kg /6 months, Pain right abdomen
- Endoscopy: Cancer at Antrum
- Histology: Adenocarcinoma G3, intestinal Type according to Lauren, **HER2 -, MSI, PD-L1 CPS 4, CLDN 18.2-** CT Thorax/Abdomen: suspicious peritumoral Lymphnodes, Livermetastases Seg II, IV, VII

Staging uT3, N+, M1 (Lymph, Liver)

Treatment recommendation?

Principles of immune checkpoint inhibitor therapy in metastatic disease

v1.4 – September 2024



	Checkmate 649	Rational 305	Keynote 859
Anti-PD-1	Nivolumab	Tislelizumab	Pembrolizumab
OS	All HR 0.80 CPS ≥1 HR 0.77 CPS ≥ 5 HR 0.71 CPS ≥ 10 HR 0.66	TAP ≥ 5 HR 0.74	All HR 0.78 CPS ≥1 HR 0.73 CPS ≥10 HR 0.64

Equivalence anti-PD1 antibodies in global clinical trials for PD-L1 high patients

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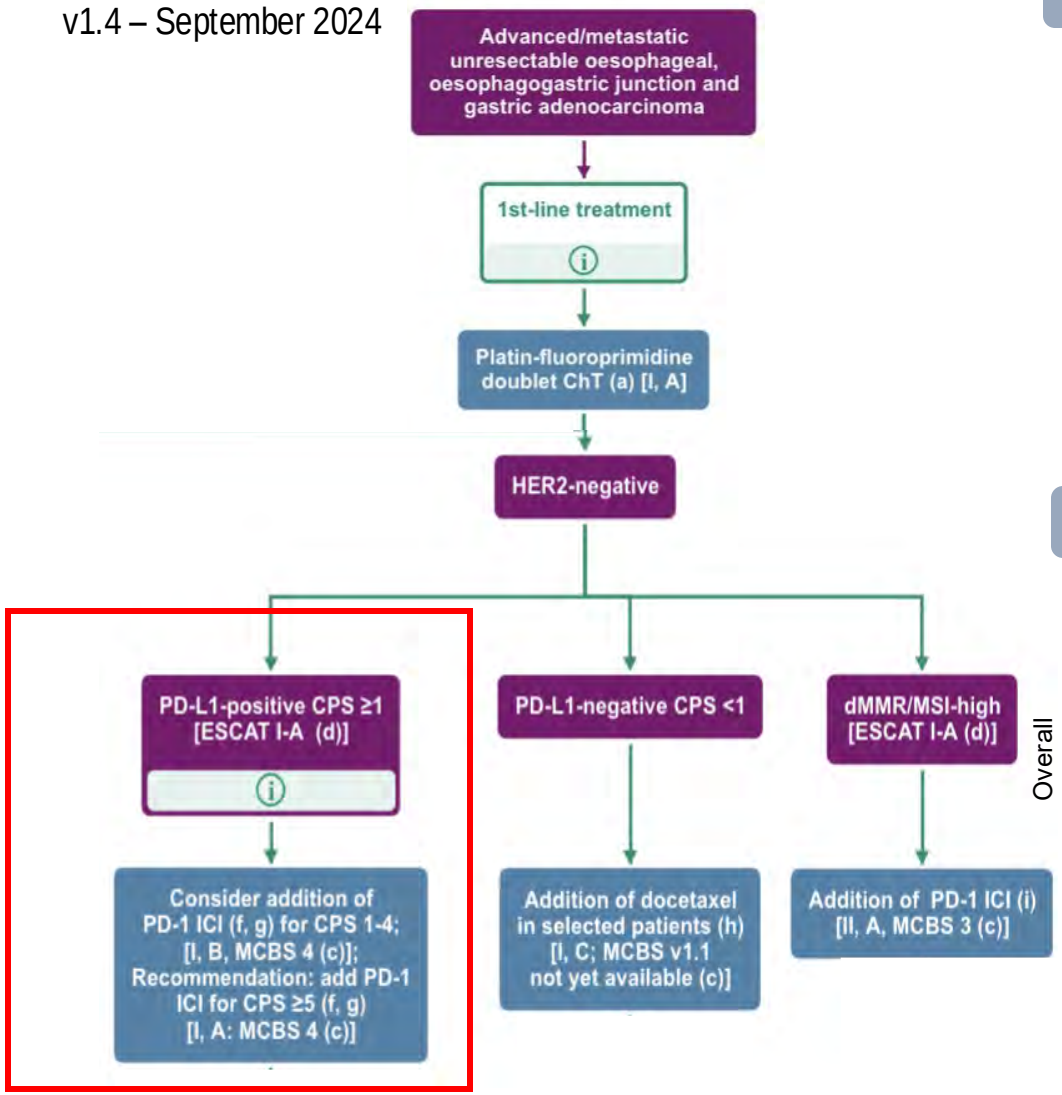
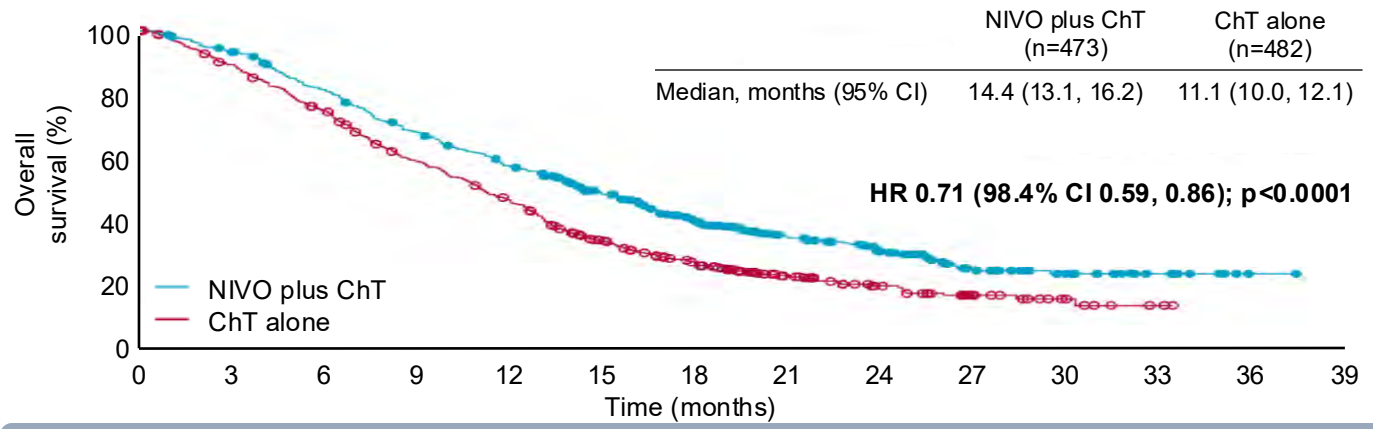
Lordick F et al. Ann Oncol 2022 Oct;33(10):1005-1020; ESMO Gastric Cancer Living Guideline, v1.4 September 2024

CM649 & KN859: 1L– HER2 negative, PD-L1 +

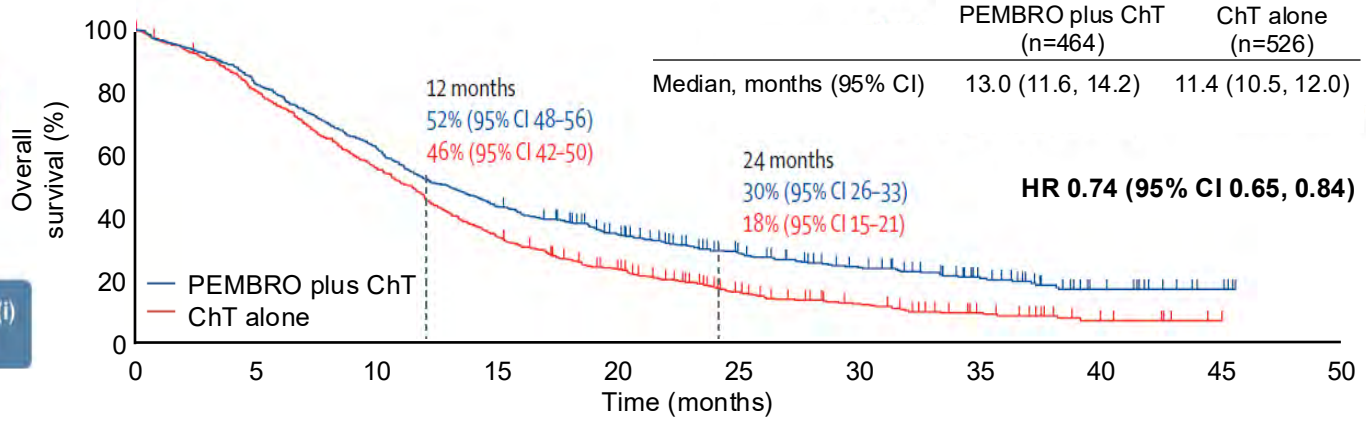
v1.4 – September 2024



CHECKMATE-649, PD-L1 CPS ≥5[2]



KN 859, PD-L1 CPS ≥1[3]

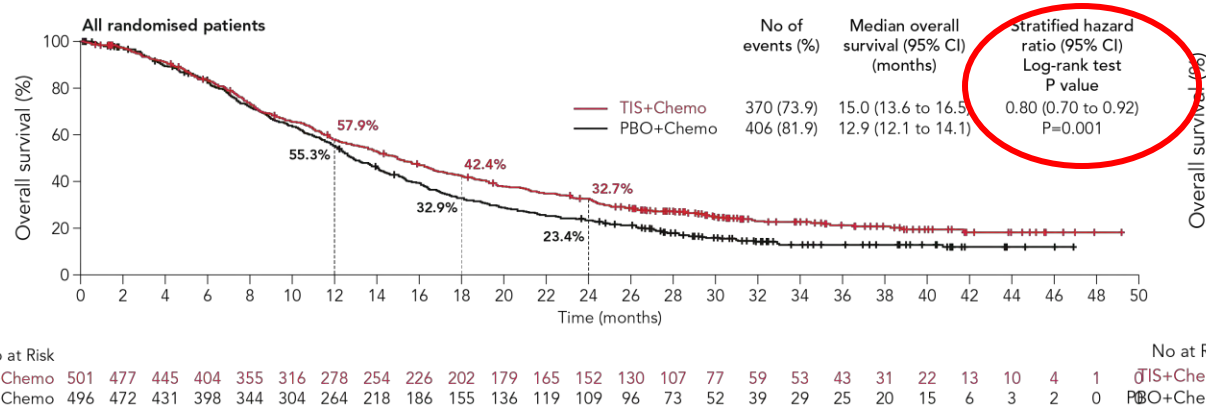


In the absence of head-to-head studies, cross-trial comparisons cannot be made as trials differ in design, size, time period of recruitment, location of study sites, etc

Janjigian YY, et al. Lancet. 2021;398(10294):27–40; Rha SY, et al. Lancet Oncol. 2023;24:1181–95.

RATIONALE-305: 1L– HER2 negativ

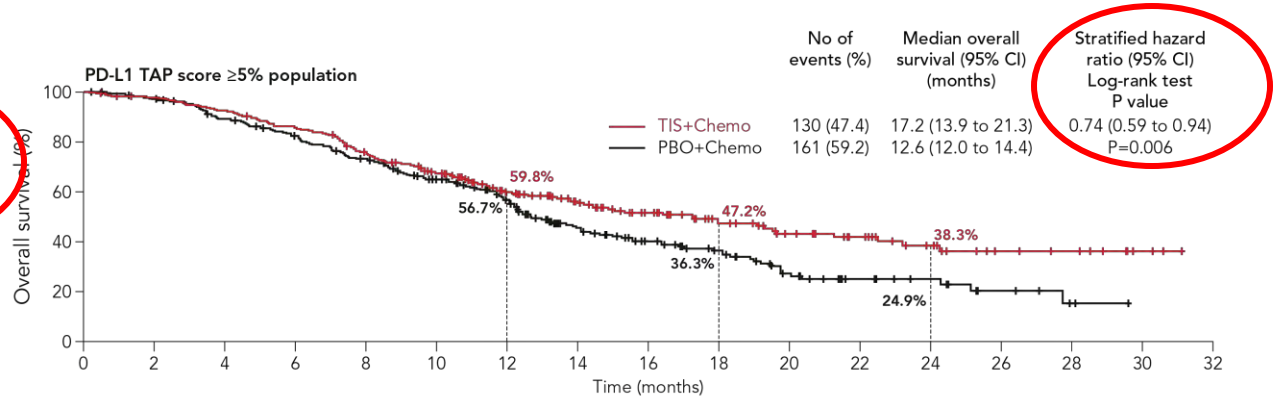
ITT Population



No at Risk

TIS+Chemo	501	477	445	404	355	316	278	254	226	202	179	165	152	130	107	77	59	53	43	31	22	13	10	4	1	0
PBO+Chemo	496	472	431	398	344	304	264	218	186	155	136	119	109	96	73	52	39	29	25	20	15	6	3	2	0	

PD-L1 Score ≥5% Population[1]



No at Risk

TIS+Chemo	274	262	246	227	196	167	122	93	70	52	38	30	19	11	9	3	0								
PBO+Chemo	272	261	237	215	189	156	118	80	57	44	26	16	12	6	2	0	0								

- Tislelizumab + chemo as first-line treatment of advanced GC/GEJC demonstrated a statistically significant and clinically meaningful improvement in **OS (ITT and TAP ≥5%)** over placebo + chemo **at the final analysis**

Qiu M-Z, et al. BMJ 2024; 385:e078876: 2 Moehler M et al. ASCO-GI 2023 abstract no. 286 Jan19-21, 2023

Checkpoint-Inhibitors and low PD-L1 Expression

PD-L1 CPS 1-9 (HR 0.84) PD-L1 CPS 1-4 (HR 0.86) PD-L1 CPS 5-9 (HR 0.86)

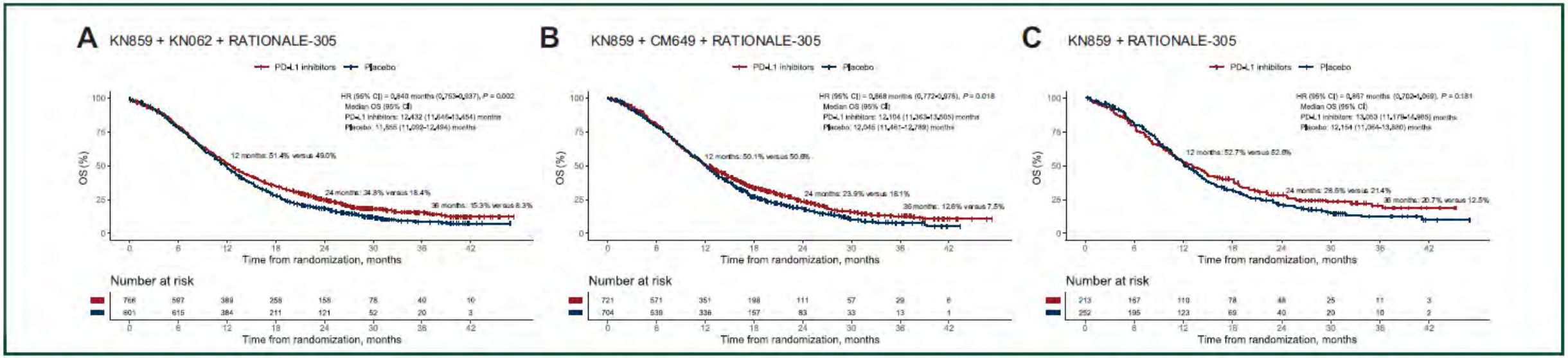


Figure 4. Pooled analysis of PD-L1$_{low}$ subgroups in human epidermal growth factor receptor 2 (HER2)-advanced GEAC. (A) OS outcomes for the PD-L1 CPS 1-9 subgroup comprising KEYNOTE-859, KEYNOTE-062, and RATIONALE-305. (B) OS outcomes for the PD-L1 CPS 1-4 subgroup comprising KEYNOTE-859, CHECKMATE-649, and RATIONALE-305. (C) OS outcomes for the PD-L1 CPS 5-9 subgroup comprising KEYNOTE-859 and RATIONALE-305.
CI, confidence interval; CPS, combined positive score; GEAC, gastroesophageal adenocarcinoma; HR, hazard ratio; OS, overall survival; PD-L1, programmed death-ligand 1.

Leone AG et al., ESMO Open. 2024 Nov;9(11):103962.

There are more biomarkers available!: CLDN18.2

Metastatic Gastric Cancer – Case presentation

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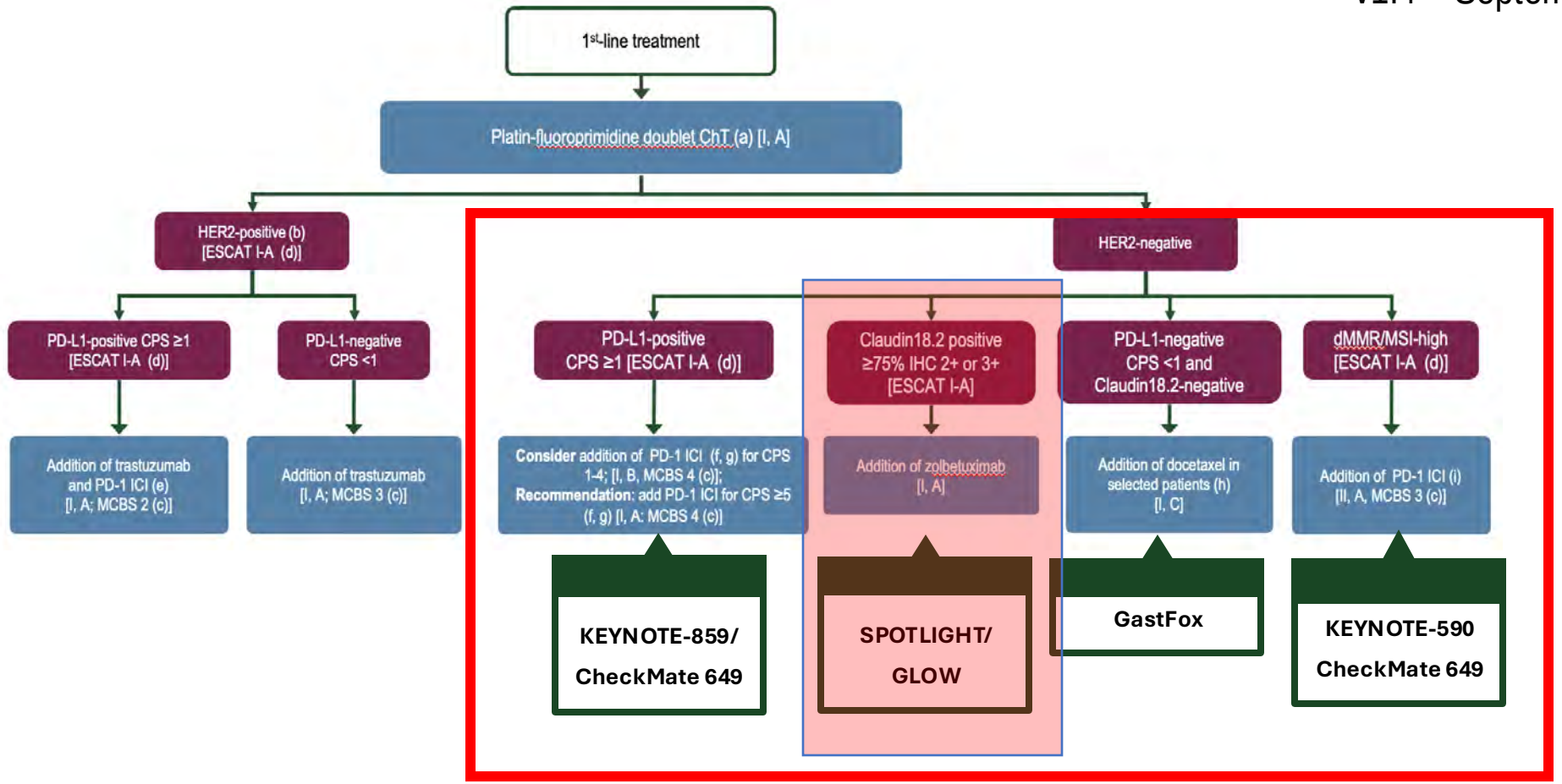
Staging uT3, N+, M1 (Lymph, Liver)

Treatment recommendation?

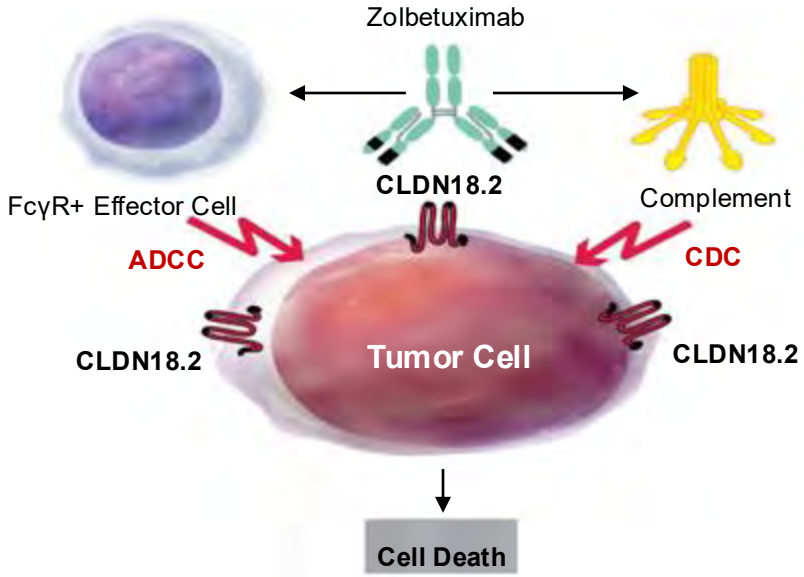
Update ESMO Living Guideline September 2024

v1.4 – September 2024



Lordick F et al. Ann Oncol 2022 Oct;33(10):1005-1020; ESMO Gastric Cancer Living Guideline, v1.4 September 2024

New Target: CLAUDIN 18.2



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

Claudin 18.2 in normal and transformed cells

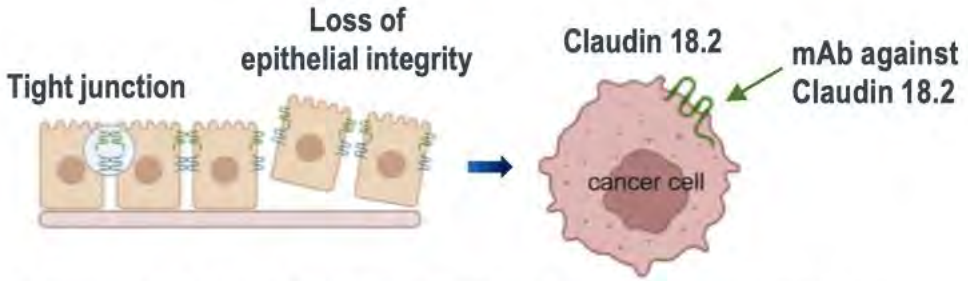


Figure reproduced with permission from Wei W et al., Development and comparison of 68Ga/18F/64Cu-labeled nanobody tracers probing Claudin18.2.; *Mol Ther Oncolytics.* 2022;27:305–314.

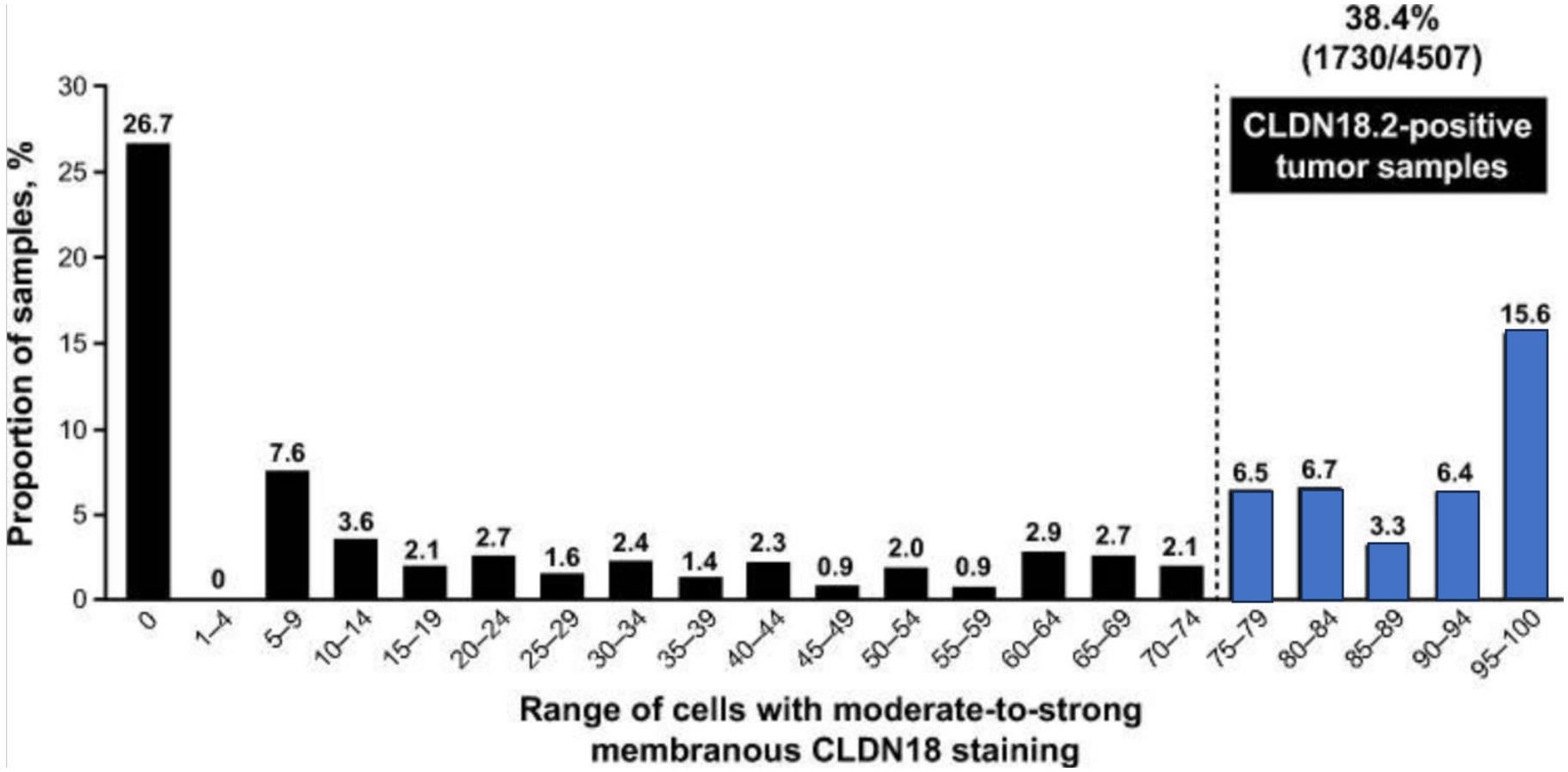
Claudin 18.2 Gastric Ca (IHC 2-3+ >75%)
- All clin. Subgroups 30-45%
- Trend towards clustering in diffuse type

More likely with low CPS

Not prognostic (vs. CLDN fusion -> prognostically unfavourable)

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

Claudin 18.2 positivity

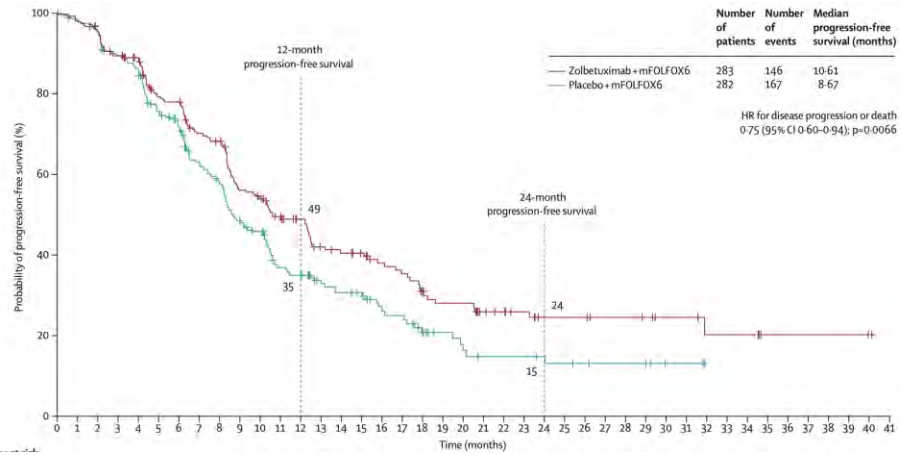


Shitara et al, Gastric Cancer 2024

SPOTLIGHT – Phase III 1st-Line-Trial FOLFOX ± Zolbetuximab (IMAB 362) in Claudin 18.2-positive gastroesophageale Cancer

Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicentre, randomised, double-blind, phase 3 trial

Kohei Shitara, Florian Lordick, Yung-Jue Bang, Peter Enzinger, David Ilson, Manish A Shah, Eric Van Cutsem, Rui-Hua Xu, Giuseppe Aprile, Jianming Xu, Joseph Chao, Roberto Pazo-Cid, Yoon-Koo Kang, Jianning Yang, Diarmuid Moran, Pranob Bhattacharya, Ahsan Arozullah, Jung Wook Park, Mok Oh, Jaffer A Ajani



N=550

Gastric/GEJ
Stage IV
1st-line HER2 – CLDN18.2
≥ 75% of tumour cells (≥2+)

R A N D O M

Zolbetuximab + mFolfox
until progression

1:1
Primary Endpoint: PFS

Placebo + mFolfox
until progression

FOLFOX-based
68.7% outside Asia
Asian patients mainly from Japan

Median Follow-up 12,9 Months

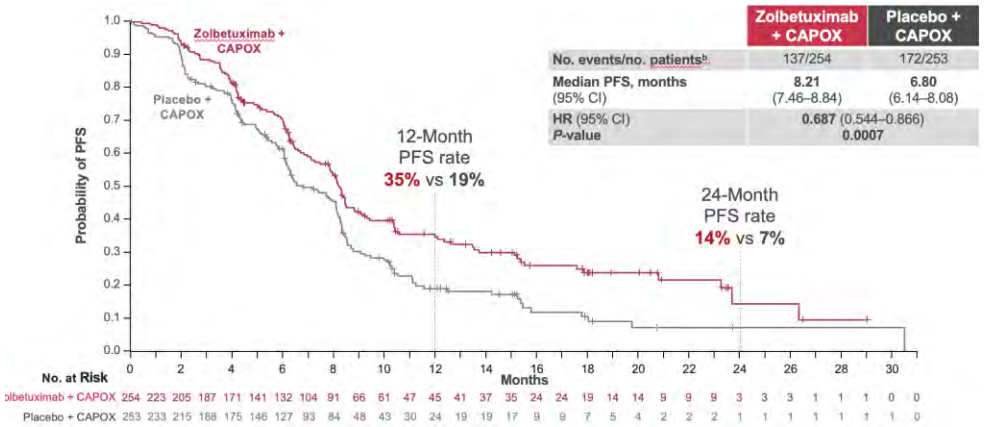
ClinicalTrials.gov. NCT03504397

GLOW – Phase III 1st-Linien-Trial CAPOX ± Zolbetuximab in Claudin 18.2-positive gastroesophageal Cancer

nature medicine

Article https://doi.org/10.1038/s41591-023-02465-7

Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial



	Zolbetuximab + CAPOX	Placebo + CAPOX
No. events/no. patients[b]	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	

Median Follow-up 12,6 Months

N=507

Gastric/GEJ
Stage IV
1st-line HER2 – CLDN18.2
≥ 75% of tumour cells (≥2+)

R A N D O M

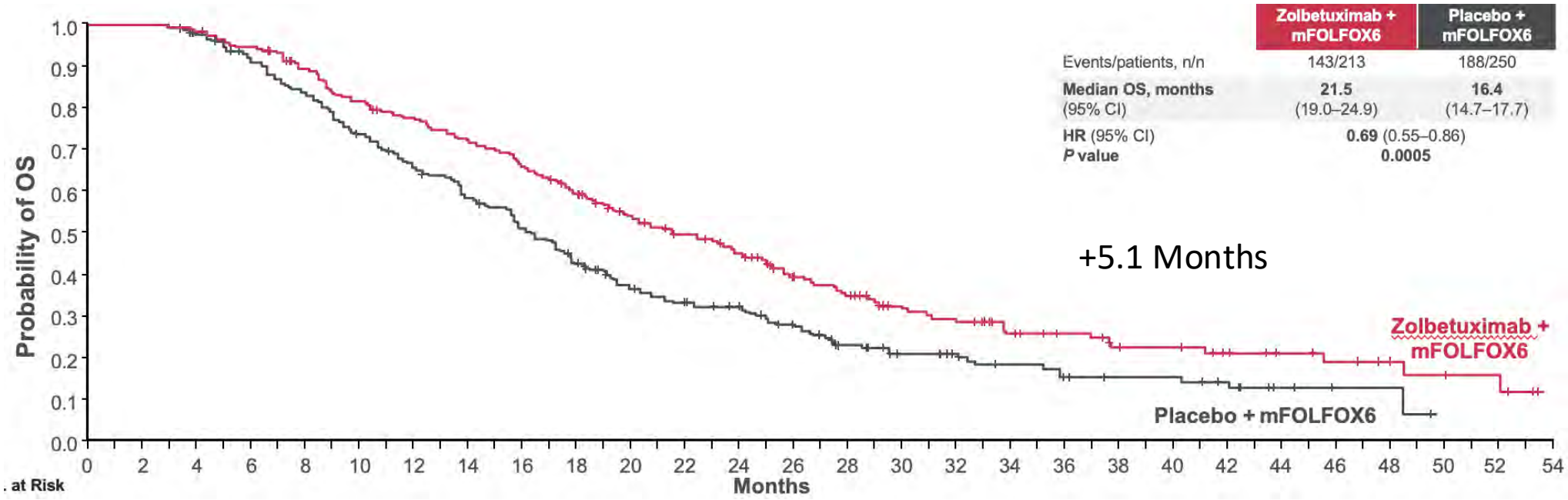
Zolbetuximab + CAPOX
until progression

1:1
PrimaryEndpoint: PFS

Placebo + CAPOX
until progression

CAPOX-based
63.2% from Asia, mainly China

OS in PP-Population in Zolbetuximab vs Placebo-Group signifikantly improved!- Final Analysis

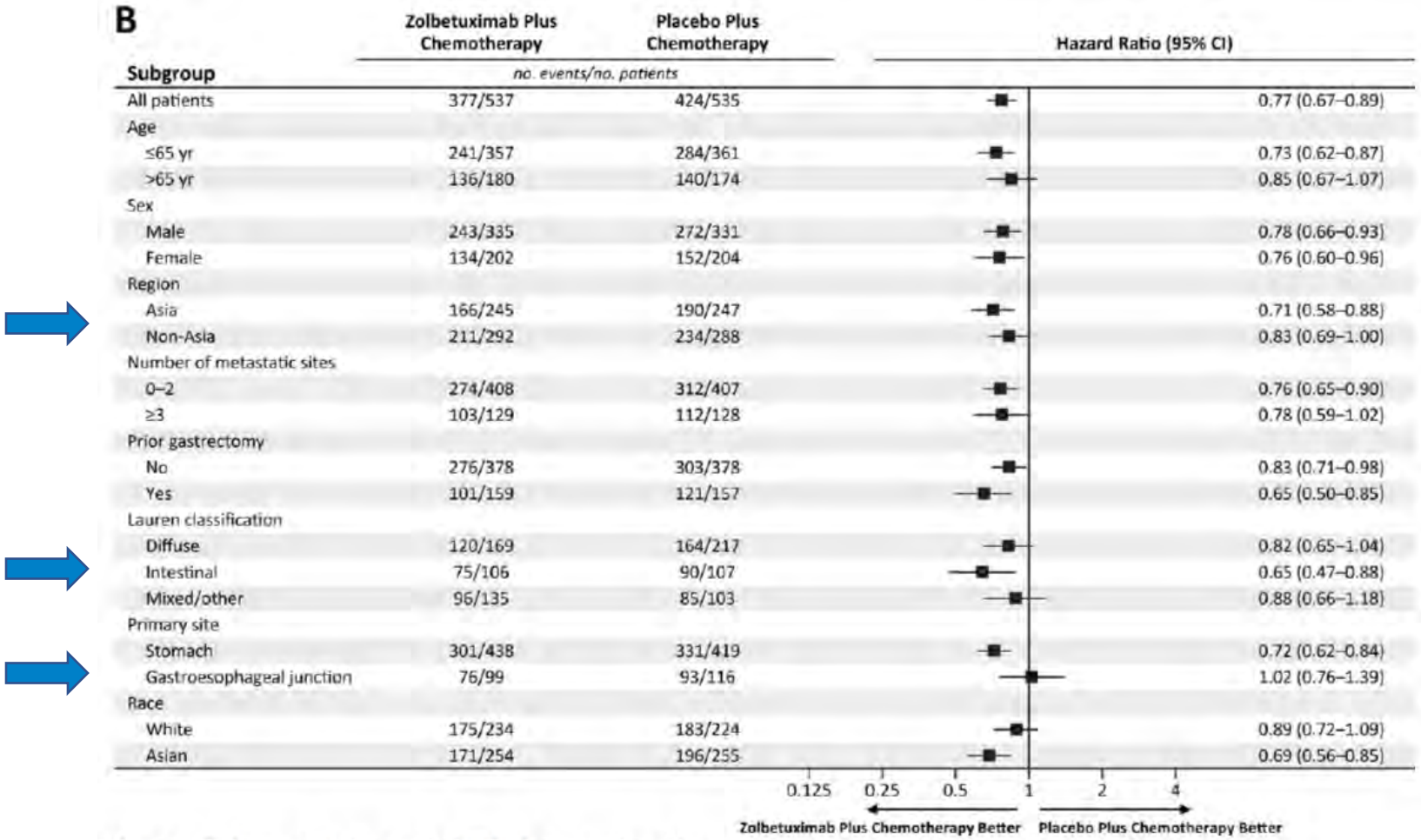


	Zolbetuximab + mFOLFOX6	Placebo + mFOLFOX6
Events/patients, n/n	143/213	188/250
Median OS, months (95% CI)	**21.5** (19.0–24.9)	**16.4** (14.7–17.7)
HR (95% CI)	**0.69** (0.55–0.86)	
***P* value**	**0.0005**	

PPS population: Defined as excluding all randomly assigned patients who did not receive study treatment or lacked sufficient study drug exposure and/or who lacked an imaging assessment – this excluded patients who were not adherent to the study protocol, which excluded the majority of patients with early withdrawals.

Data cutoff date: September 8, 2023.

Zolbetuximab (SPOTLIGHT) – Survival in subgroups



B

Subgroup	Zolbetuximab Plus Chemotherapy	Placebo Plus Chemotherapy	Hazard Ratio (95% CI)
	no. events/no. patients		
All patients	377/537	424/535	0.77 (0.67–0.89)
Age			
≤65 yr	241/357	284/361	0.73 (0.62–0.87)
>65 yr	136/180	140/174	0.85 (0.67–1.07)
Sex			
Male	243/335	272/331	0.78 (0.66–0.93)
Female	134/202	152/204	0.76 (0.60–0.96)
Region			
Asia	166/245	190/247	0.71 (0.58–0.88)
Non-Asia	211/292	234/288	0.83 (0.69–1.00)
Number of metastatic sites			
0–2	274/408	312/407	0.76 (0.65–0.90)
≥3	103/129	112/128	0.78 (0.59–1.02)
Prior gastrectomy			
No	276/378	303/378	0.83 (0.71–0.98)
Yes	101/159	121/157	0.65 (0.50–0.85)
Lauren classification			
Diffuse	120/169	164/217	0.82 (0.65–1.04)
Intestinal	75/106	90/107	0.65 (0.47–0.88)
Mixed/other	96/135	85/103	0.88 (0.66–1.18)
Primary site			
Stomach	301/438	331/419	0.72 (0.62–0.84)
Gastroesophageal junction	76/99	93/116	1.02 (0.76–1.39)
Race			
White	175/234	183/224	0.89 (0.72–1.09)
Asian	171/254	196/255	0.69 (0.56–0.85)

CI, confidence interval; HR, hazard ratio.

Shitara K et al. N Engl J Med. 2024 Sep 26;391(12):1159-1162

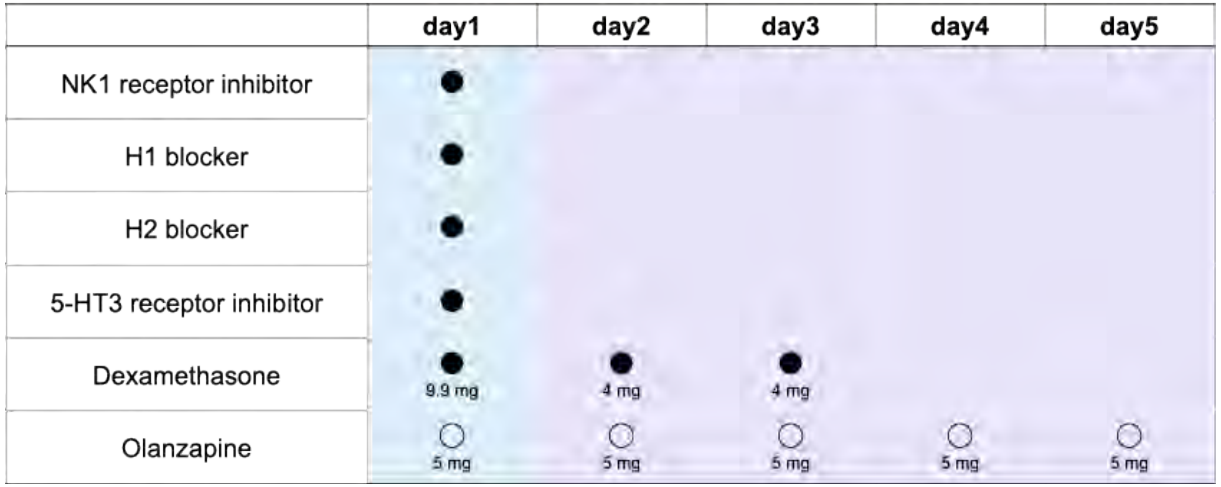
Zolbetuximab (SPOTLIGHT) – Adverse events

Table S9. Treatment-Emergent Adverse Events*,† in the Safety Analysis Set in the Combined Analysis

Event – no. (%)	Zolbetuximab + chemotherapy (n = 533)		Placebo + chemotherapy (n = 527)	
	All grade	Grade ≥3	All grade	Grade ≥3
Nausea	405 (76.0)	67 (12.6)	296 (56.2)	25 (4.7)
Vomiting	356 (66.8)	76 (14.3)	180 (34.2)	26 (4.9)
Decreased appetite	241 (45.2)	34 (6.4)	183 (34.7)	13 (2.5)
Anemia	199 (37.3)	53 (9.9)	199 (37.8)	54 (10.2)
Diarrhea	197 (37.0)	27 (5.1)	212 (40.2)	28 (5.3)
Neutrophil count decreased	167 (31.3)	95 (17.8)	150 (28.5)	93 (17.6)
Peripheral sensory neuropathy	164 (30.8)	13 (2.4)	175 (33.2)	21 (4.0)
Neutropenia	152 (28.5)	97 (18.2)	129 (24.5)	72 (13.7)
Constipation	141 (26.5)	3 (0.6)	166 (31.5)	4 (0.8)
Fatigue	118 (22.1)	25 (4.7)	136 (25.8)	24 (4.6)
Aspartate aminotransferase increased	113 (21.2)	10 (1.9)	122 (23.1)	16 (3.0)
Abdominal pain	111 (20.8)	15 (2.8)	143 (27.1)	11 (2.1)
Asthenia	108 (20.3)	28 (5.3)	96 (18.2)	10 (1.9)
Weight decreased	108 (20.3)	7 (1.3)	81 (15.4)	4 (0.8)
Hypoalbuminemia	103 (19.3)	20 (3.8)	53 (10.1)	6 (1.1)
Platelet count decreased	102 (19.1)	22 (4.1)	111 (21.1)	27 (5.1)
White blood cell count decreased	102 (19.1)	13 (2.4)	86 (16.3)	26 (4.9)
Pyrexia	95 (17.8)	2 (0.4)	73 (13.9)	1 (0.2)
Hypokalemia	88 (16.5)	30 (5.6)	80 (15.2)	27 (5.1)
Alanine aminotransferase increased	83 (15.6)	4 (0.8)	103 (19.5)	17 (3.2)

*The all-grade events reported here occurred in ≥15% of patients in either treatment group in the combined analysis.
†Preferred terms were defined according to the Medical Dictionary for Regulatory Activities terminology version 25.0.

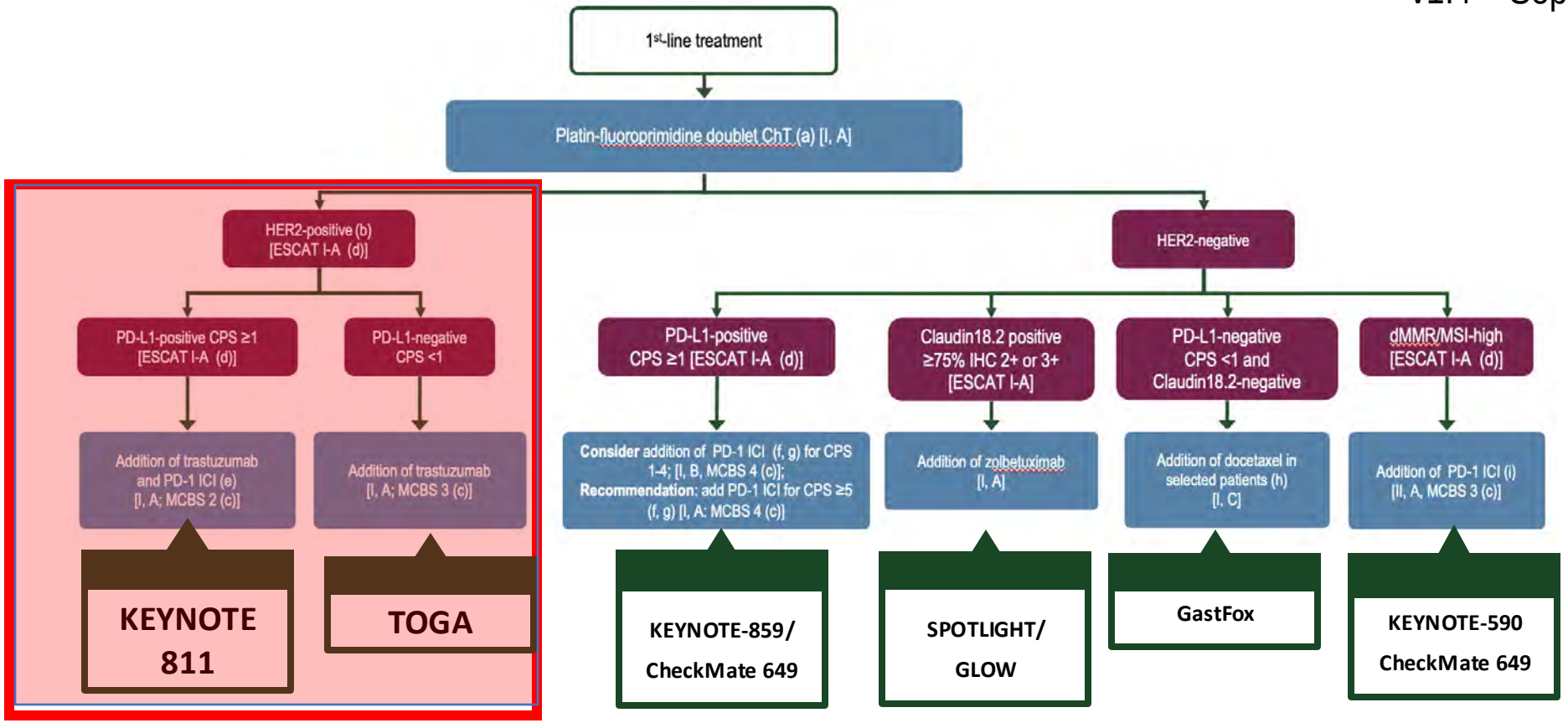
Shitara K et al. N Engl J Med. 2024 Sep 26;391(12):1159-1162



Shimozaki et al, ESMO GastroIntestinal Oncology 2025

Update ESMO Living Guideline September 2024

v1.4 – September 2024



Lordick F et al. Ann Oncol 2022 Oct;33(10):1005-1020; ESMO Gastric Cancer Living Guideline, v1.4 September 2024

Metastatic Gastric Cancer – Case presentation

Patient

- 63 years, female, ECOG 0

Current Problem

- Weight loss 10 kg /6 months, Pain right abdomen
- Endoscopy: Cancer at Antrum
- Histology: Adenocarcinoma G3, intestinal Type according to Lauren, **HER2 +, MSI, PD-L1 CPS 4, CLDN 18.2+** CT Thorax/Abdomen: suspicious peritumoral Lymphnodes, Livermetastases Seg II, IV, VII

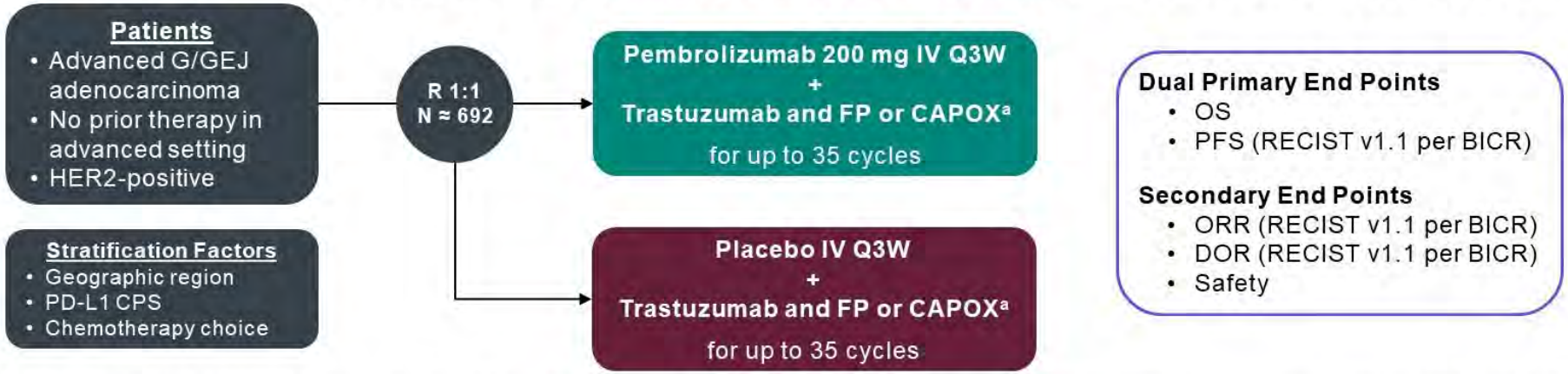
Staging uT3, N+, M1 (Lymph, Liver)

Treatment recommendation?

Immunotherapy 1st-line: HER2-pos.

KEYNOTE-811: Randomisierte globale Phase III
First-line fortgeschrittenes HER2-positives Magen-Ca/ AEG

Double-Blind Phase 3 Study of Pembrolizumab + Trastuzumab and Chemotherapy vs Placebo + Trastuzumab and Chemotherapy as First-Line Therapy For HER2-Positive Unresectable or Metastatic G/GEJ Cancer (NCT03615326)



[a]Trastuzumab dose: 6 mg/kg IV Q3W following an 8 mg/kg loading dose. FP dose: 5-fluorouracil 800 mg/m² IV on D1-5 Q3W + cisplatin 80 mg/m² IV Q3W. CAPOX dose: capecitabine 1000 mg/m² BID on D1-14 Q3W + oxaliplatin 130 mg/m² IV Q3W.
BICR, blinded independent central review; CPS, combined positive score (number of PD-L1–staining cells [tumor cells, lymphocytes, macrophages] divided by the total number of viable tumor cells, multiplied by 100).

Janjigian YY et al., Lancet. 2023; 402(10418):2197–2208

KEYNOTE- 811: Survival benefit in HER2 and PD-L1 positive patients

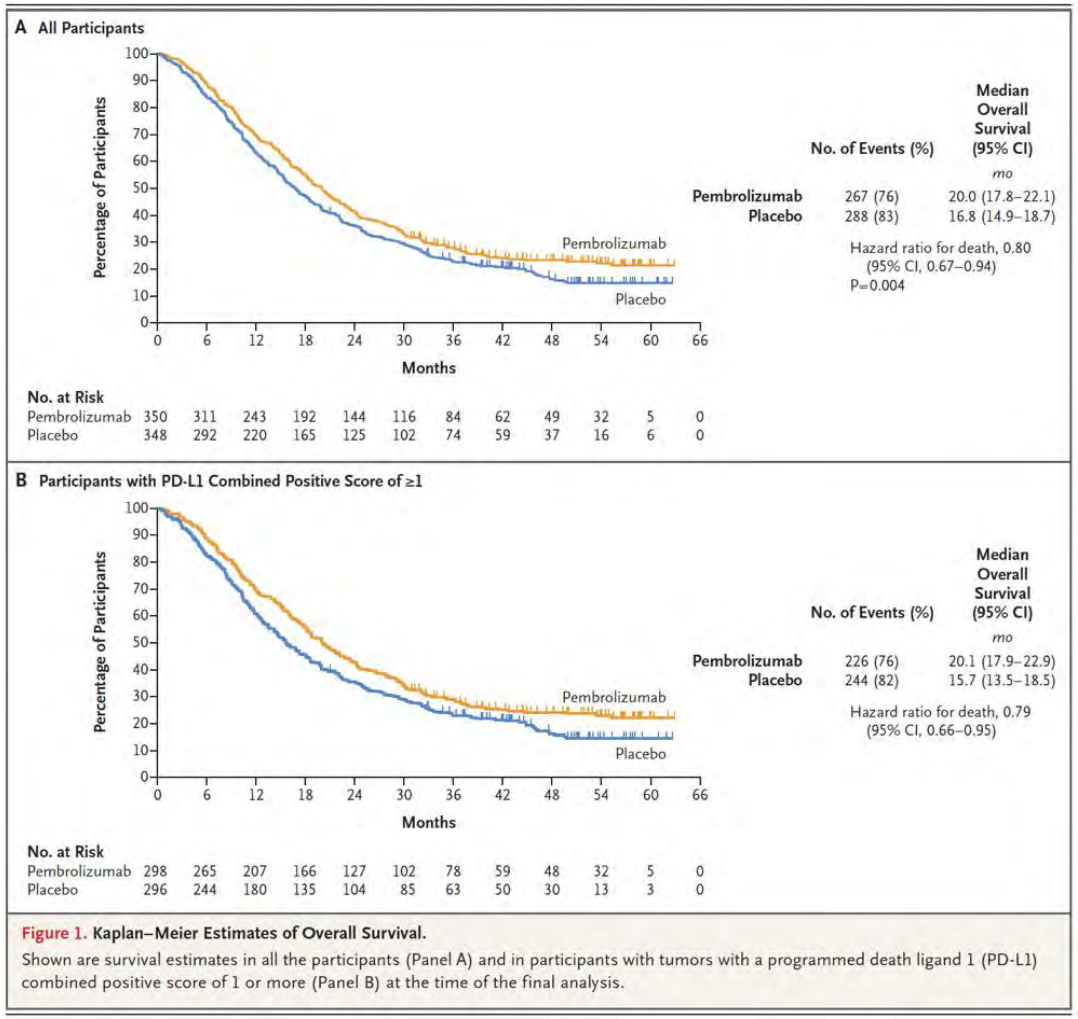


Figure 1. Kaplan–Meier Estimates of Overall Survival.
Shown are survival estimates in all the participants (Panel A) and in participants with tumors with a programmed death ligand 1 (PD-L1) combined positive score of 1 or more (Panel B) at the time of the final analysis.

1. HER2+ in 18-30% of GEA
2. As with PD-L1 – the grade of HER2-Expression/Amplification matters
3. IO plus 5FU/Platin/Trastuzumab improves PFS **and OS** in HER2+ (> in PD-L1+)

	PD-**L1 CPS ≥1**		PD-L1 CPS <1	
	Pembrolizumab Group N = 298	Placebo Group N = 296	Pembrolizumab Group N = 52	Placebo Group N = 52
PFS, median	10.9	7.3	9.5	9.5
HR (95% CI)	0.72 (0.60-0.87)		0.99 (0.62-1.56)	
OS, median	20.1	15.7	18.2	20.4
HR (95% CI)	0.79 (0.66-0.95)		1.10 (0.72-1.68)	

Janjigian et al, ESMO 2024, Rha et al, ESMO Asia 2024

Metastatic Gastric Cancer – Case presentation

Patient

- 63 years, female, ECOG 0

Current Problem

- Weight loss 10 kg /6 months, Pain right abdomen
- Endoscopy: Cancer at Antrum
- Histology: Adenocarcinoma G3, intestinal Type according to Lauren,
  HER2-, MSI high, PD-L1 CPS 10

CT Thorax/Abdomen: suspicious peritumoral Lymphnodes,
Livermetastases Seg II, IV, VII

Staging uT3, N+, M1 (Lymph, Liver)

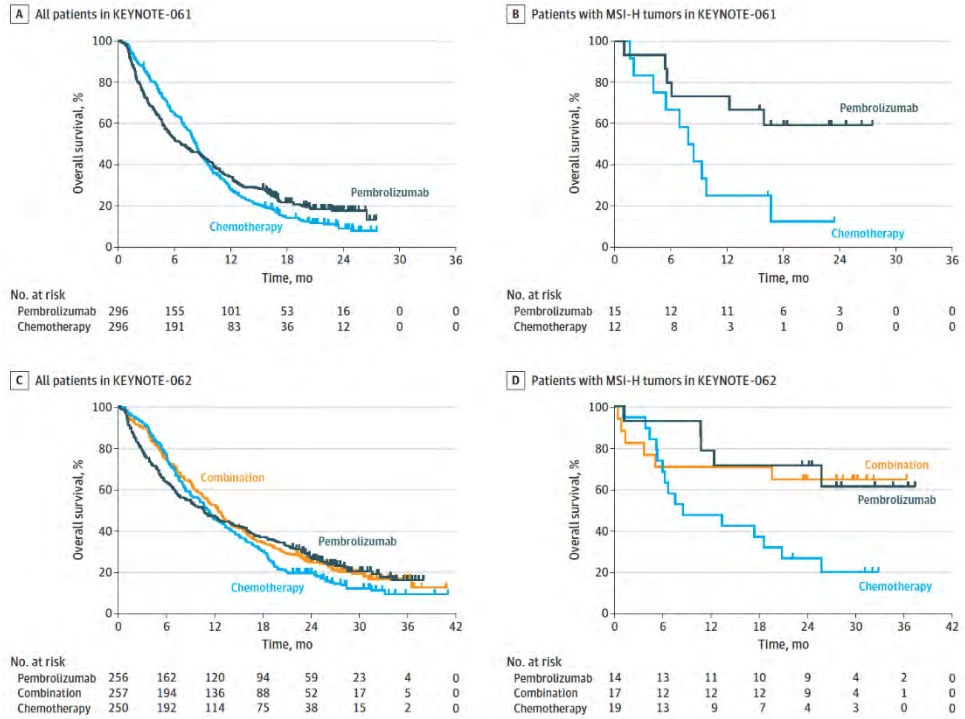
Treatment recommendation?

MSI-high is predictive for response Immunotherapy

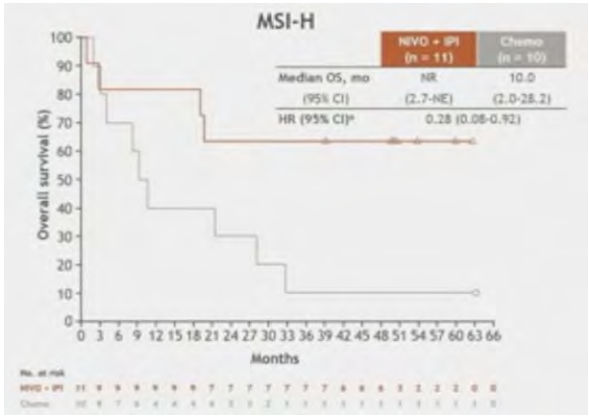
JAMA Oncology | Brief Report

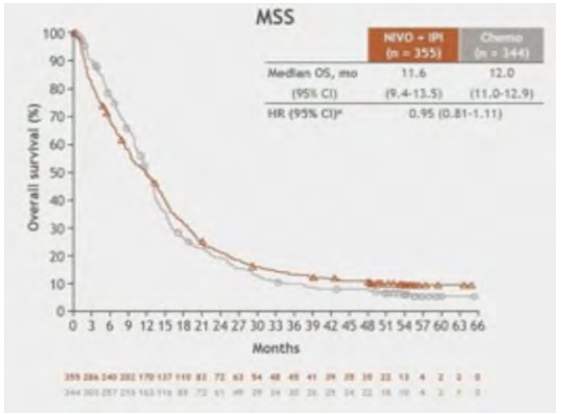
Assessment of Pembrolizumab Therapy for the Treatment of Microsatellite Instability–High Gastric or Gastroesophageal Junction Cancer Among Patients in the KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062 Clinical Trials

Joseph Chao, MD; Charles S. Fuchs, MD; Kohei Shitara, MD; Josep Tabernero, MD; Kei Muro, MD; Eric Van Cutsem, MD; Yung-Jue Bang, MD; Ferdinando De Vita, MD; Gregory Landers, MD; Chia-Jui Yen, MD; Ian Chau, MD; Anneli Elme, MD; Jeeyun Lee, MD; Mustafa Özgüroğlu, MD; Daniel Catenacci, MD; Harry H. Yoon, MD; Erluo Chen, MPH; David Adelberg, MD; Chie-Schin Shih, MD; Sukrut Shah, PhD; Pooja Bhagia, MD; Zev A. Wainberg, MD



CM 649: OS according to MSI Status



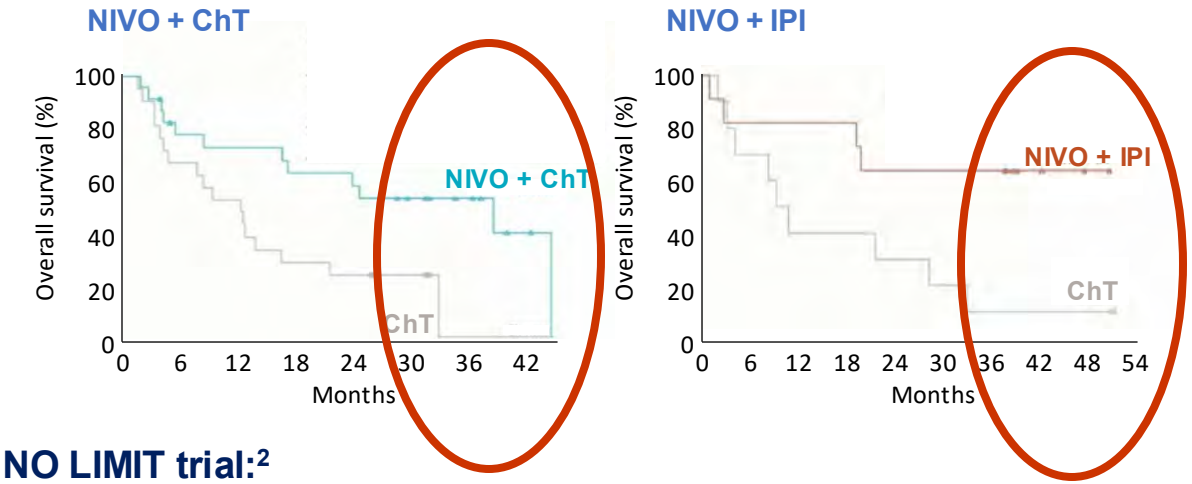


MSI-H Status should be routinely assessed in advanced gastroesophageal cancer. Efficacy independent of treatment line!

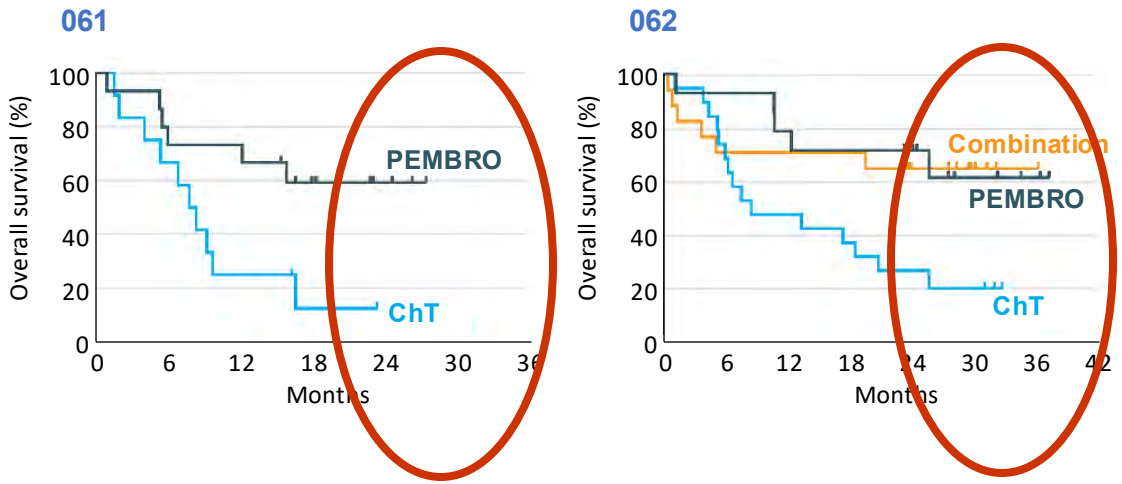
Chao J et al. Jama Oncol 2021; 7(6): 895-902

MSI is predictive for response to Immunotherapy

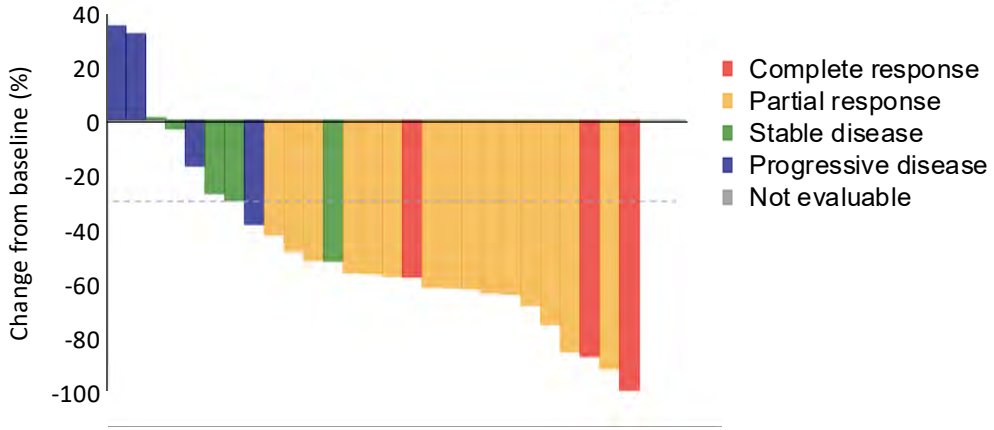
CheckMate 649:[1]
NIVO + IPI und NIVO + ChT vs ChT alleine



KEYNOTE-061 und -062:[3]
PEMBRO + ChT vs ChT alleine



NO LIMIT trial:[2]
NIVO + low dose IPI als 1L Therapie im MSI Magenkarzinom

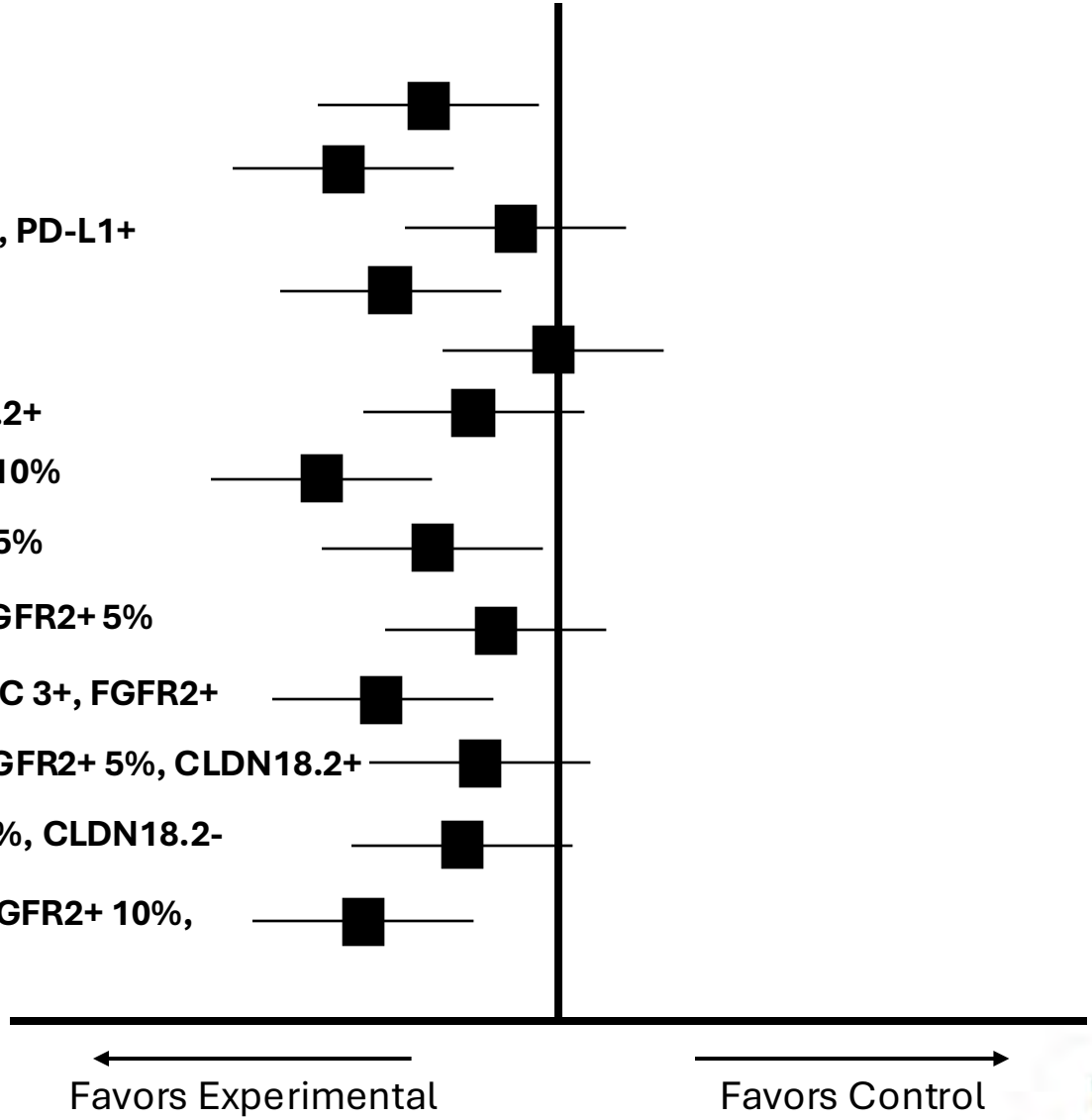


MSI status should always be determined by default

Effectiveness of immunotherapy depends on the line of therapy

1.Jangjigian YY, et al. Lancet1.. 2021 2. Muro K, et al. Ann Oncol. 2023; 3. Figures angepasst von Chao J, et al. JAMA Oncol. 2021

The future of 1L is complicated, but hopeful



Conclusions metastatic gastric- and GEJ cancer I

- ICI are currently part of the SoC of metastatic G/GEJ cancer patients
  - PD-L1 is a challenging biomarker and enriches for response!
- Chemotherapy is still required for all G/GEJ cancer patients, to avoid early progression
  - Except for dMMR/MSI-H
- G/GEJ cancer is a heterogenic disease, with distinct driver biomarkers (temporal and spatial heterogeneity)
- Combinations of ICI + matched targeted therapy showed preliminary improvement in survival, but this may be dependent on immune context
- Addressing mechanisms of immune evasion (angiogenesis, WNT) may be helpful

Conclusion metastatic gastric- and GEJ cancer II

- Sequential therapy has been established!
- Immunotherapy is standard in first-line therapy for HER2- oesophageal and gastric cancer (CM 649, Rational 305, KN 859 ...) - efficacy depends on PD-L (1) expression!
- First-line therapy HER2-positive, PD-L1-positive: IO plus trastuzumab plus chemotherapy new standard (KN811)
- CLDN 18.2-positive: patients receive zolbetuximab from first of November! But still many questions unanswered: Testing, PD-L1-positive patients, toxicity management, subgroups ...
- New biomarkers (FGFR2) and treatments (BiTES, CAR-T, ADCs) on the horizon...

The future is bright
for esophagus and gastric cancer biomarker selected strategies

Thank you for your kind attention!

Sylvie.Lorenzen@mri.tum.de

ESMO ON AIR

Optimal biomarker workup for patients with advanced gastric cancer: diagnosis, prognostication, and personalized treatment

Filippo Pietrantonio, Milan (IT)

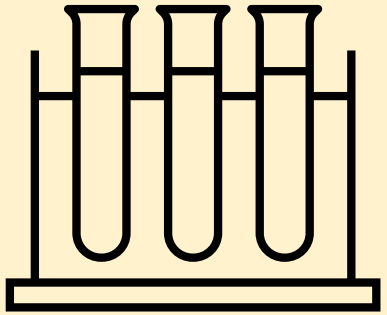
12 March 2025

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY

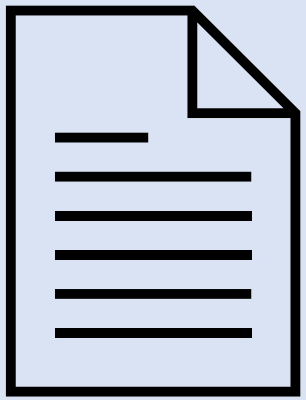
GEA BIOMARKERS TODAY

	HER2	PD-L1	MMR/ MSI	EBV	CLDN18	Fgfr2b
 IHC/ISH	✓	✓	✓	✓	✓	✓
 Molecular	✗	✗	✓	✗	✗	✗

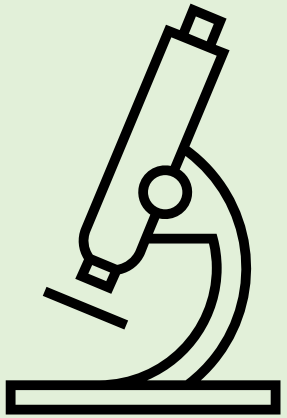
REAL WORLD ISSUES IN BIOMARKER TESTING IN GEA



The sample



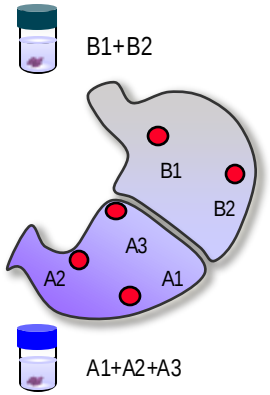
The methods of analysis

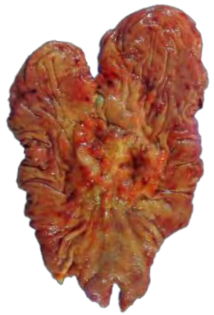


Staining interpretation

THE TISSUE IS THE TISSUE

Tissue-related influence on biomarker testing in GE cancers

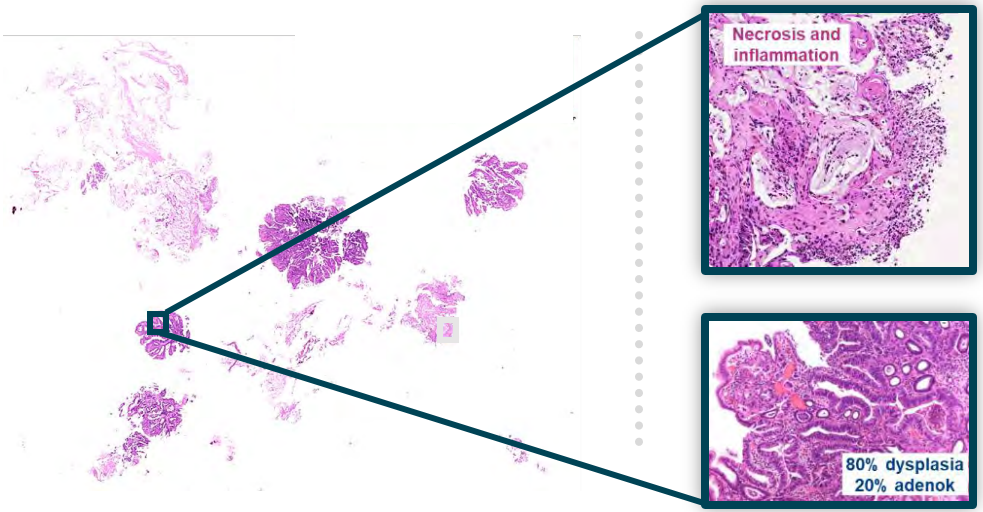




Biopsies ~70%

Surgery ~30%

Not all biopsies are adequate for molecular testing![1]



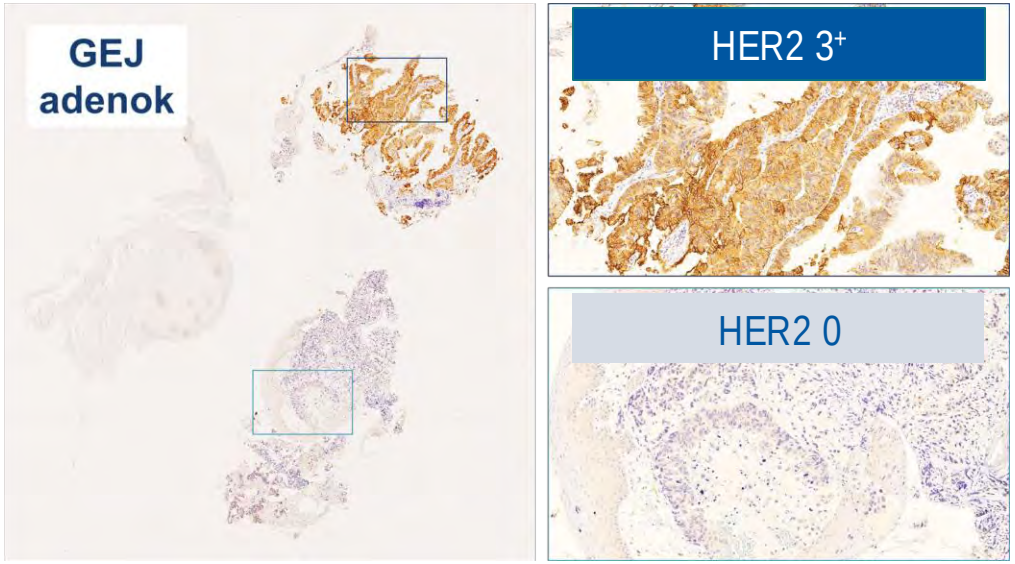
GASTROENTEROLOGIST

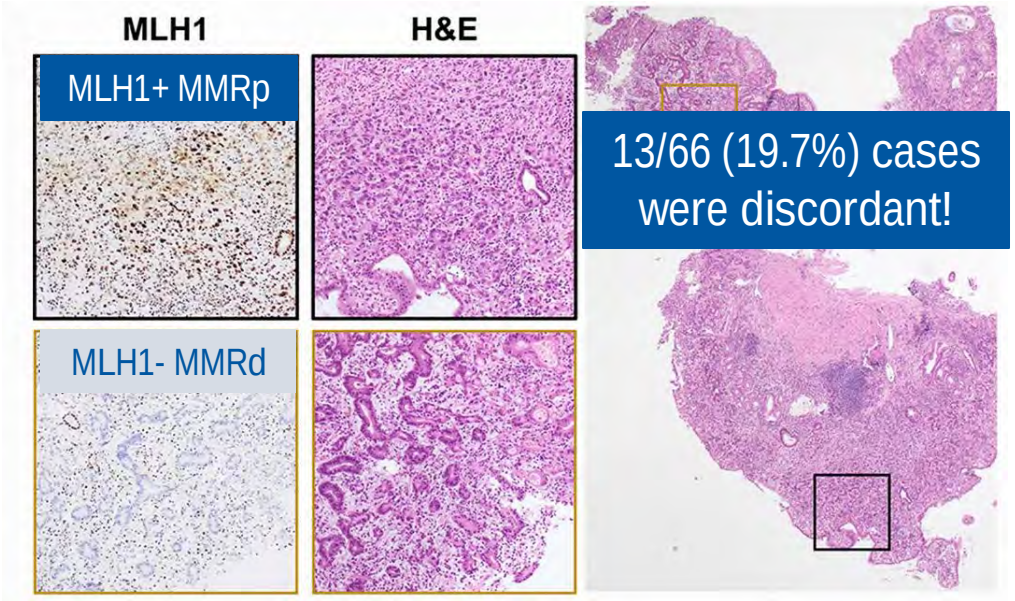
At least 6 endoscopic biopsy specimens
(to overcome tumor heterogeneity!)

Angerilli V, et al. J Clin Pathol. 2023;76(12):815–21.

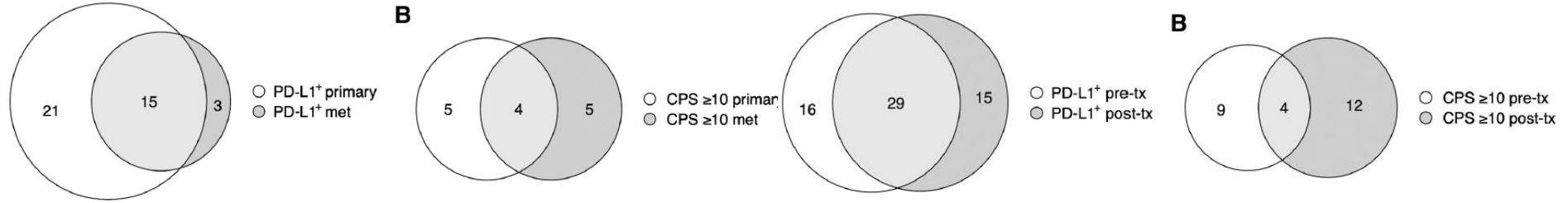
1. Parente P, et al. Expert Rev Mol Diagn 2023; 2. Yamashita K, et al. Br J Cancer 2019; 3. Zhou KI, et al. Clin Cancer Res 2020

GASTRIC CANCER IS A HETEROGENEOUS DISEASE



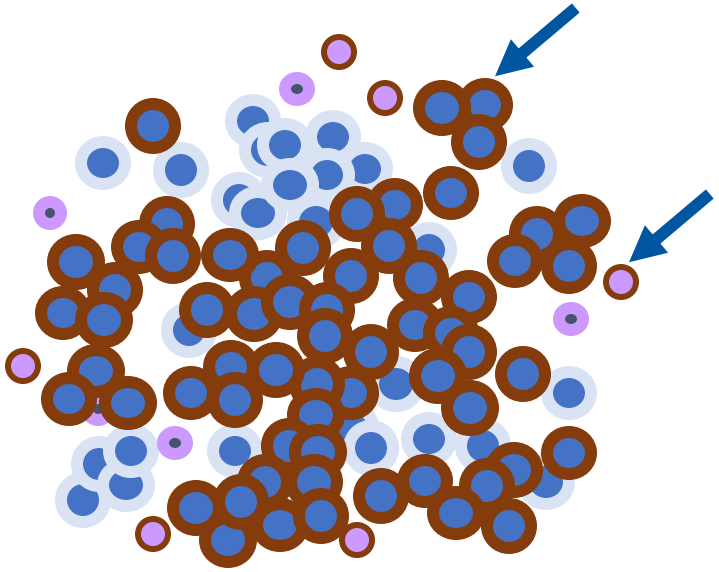


PD-L1 heterogeneity

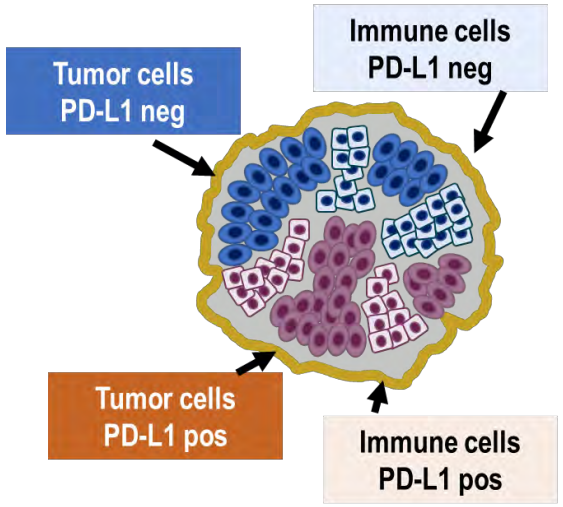


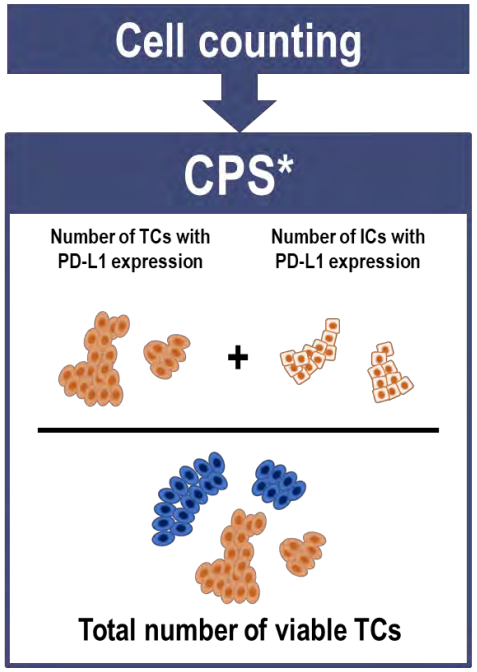
Businello G, *et al.* – Updates Surg 2023; *Fornaro L, et al. – Gastric Cancer 2023; Zhou KI, et al. – Clin Cancer Res 2020*

PD-L1 SCORING SYSTEMS

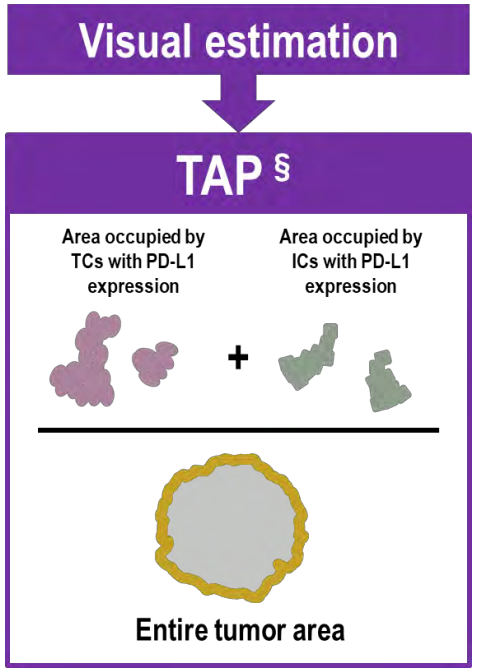


$$\text{CPS} = \frac{\text{PD-L1 staining} \begin{cases} \text{Tumour cells} \\ \text{Lymphocytes} \\ \text{Macrophages} \end{cases}}{\text{Viable tumour cells}} \times 100$$





*ICs= lymphocytes, macrophages

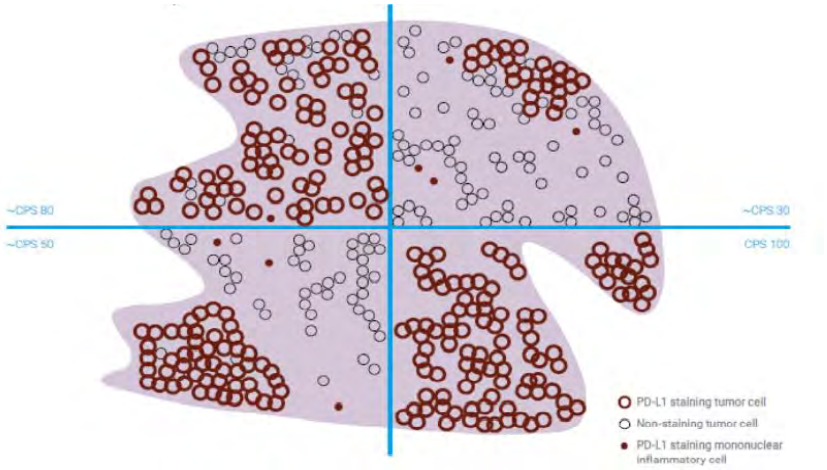


§ inclusive of all types of ICs

Unstained mononuclear cell PD-L1pos mononuclear cell Unstained tumour cell PD-L1pos tumour cell

Figure adapted from Sajjadi E, et al. Ecancermedicalscience 2020; Klempner MJ, *et al.* – JCO Prec Oncol 2024

PD-L1 STAINING INTERPRETATION

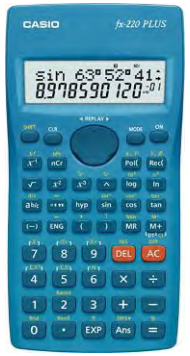


Heterogeneous PD-L1 Staining Area

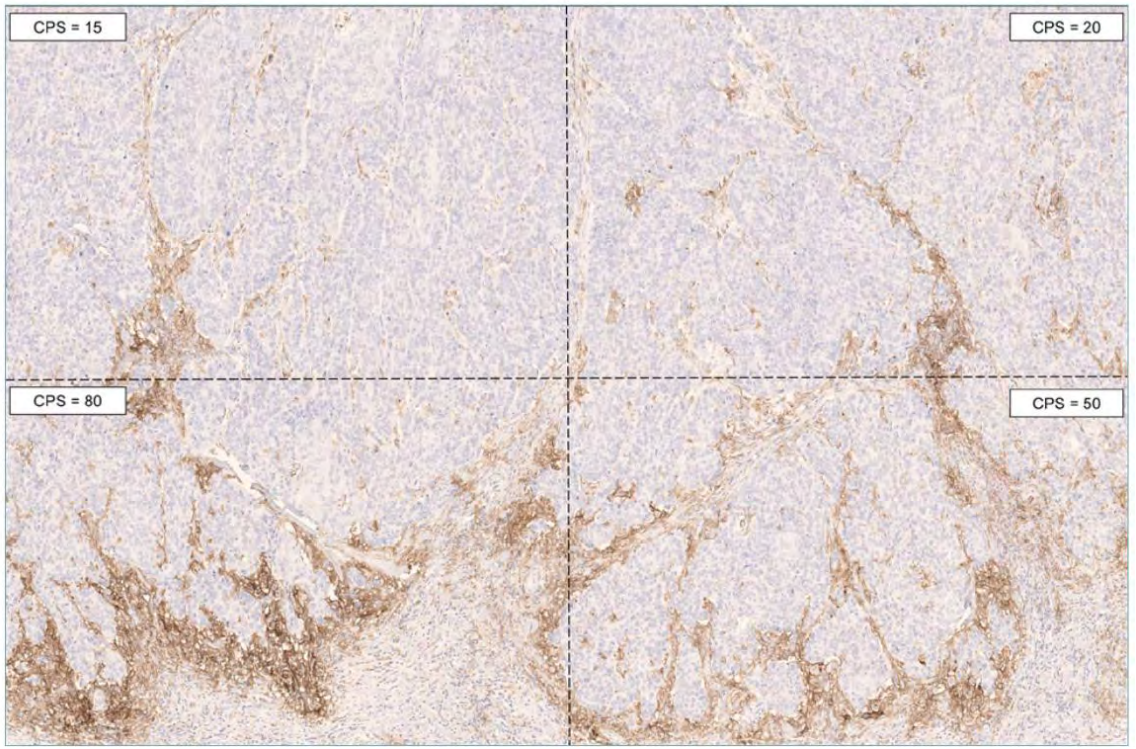
Combined Positive Score:

((80 + 30 + 50 + 100) / 4) ≅ 65

CPS 65, Clinical Interpretation: CPS≥10



It is <u>not</u> a hot-spot evaluation!

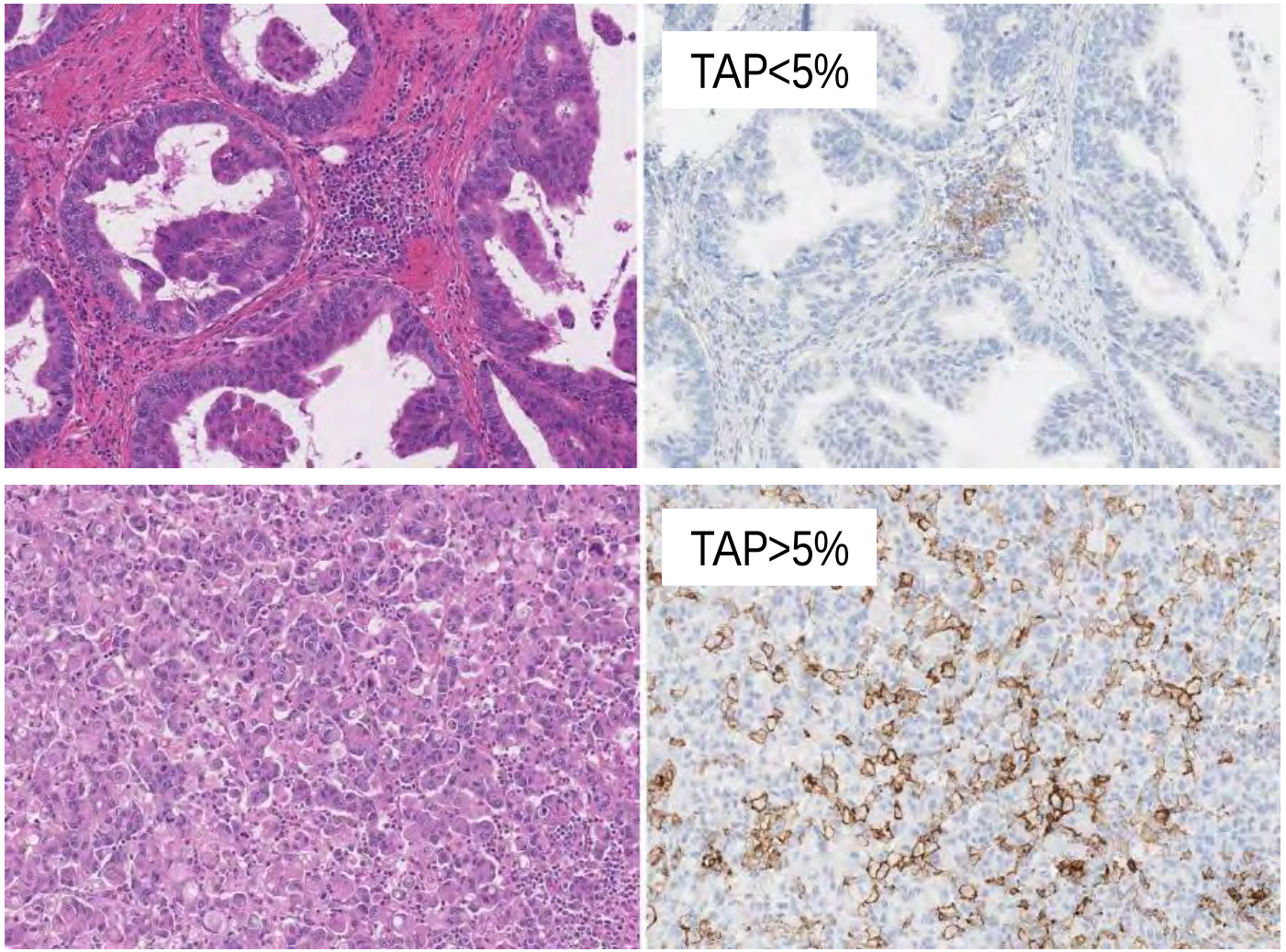


PD-L1 is still a imperfect biomarker with suboptimal interpathologist agreement rate, due interobserver and interlaboratory variability.

ESMO ON AIR

Robert et al, Mod Pathol 2023; Fernandez et al, Mod Pathol 2023

Tumor Area Positivity (TAP) score of PD-L1: a novel visual estimation method for combined tumor cell and immune cell scoring



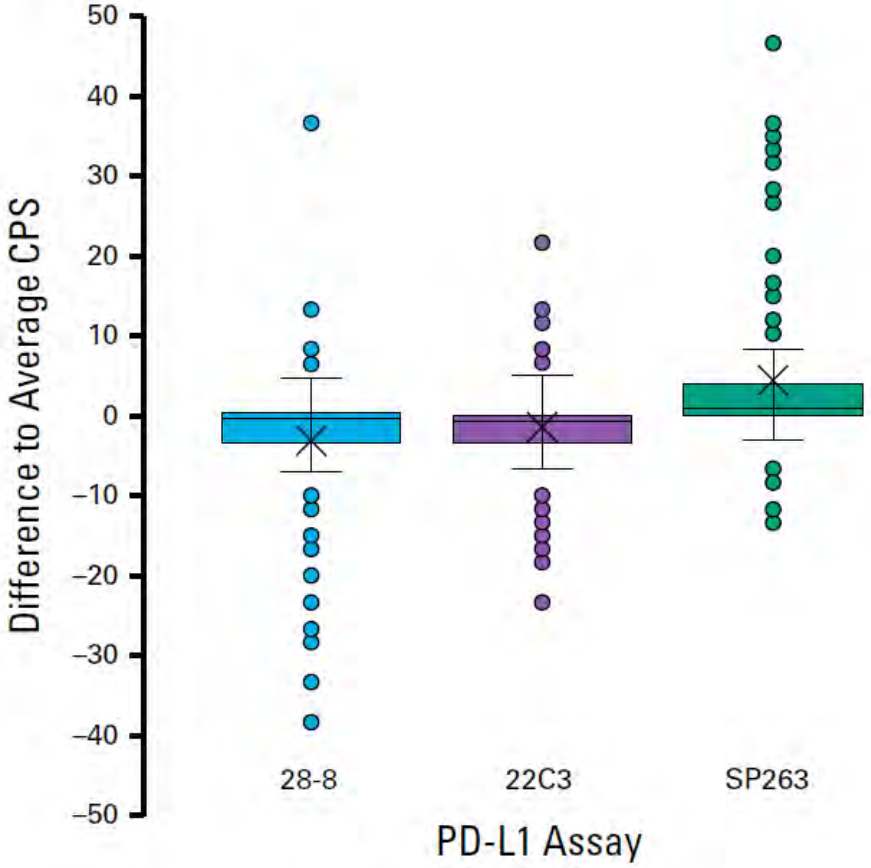
- The average positive agreement, average negative agreement, and overall percent agreement between and within readers were all above 85% for both internal and combined external reader precision studies.
- TAP score had high concordance rate at 5% cutoff compared with CPS at cutoff 1.
- TAP scoring method to be straightforward, significantly less time-consuming, and highly reproducible with a high concordance rate between TAP score and CPS.

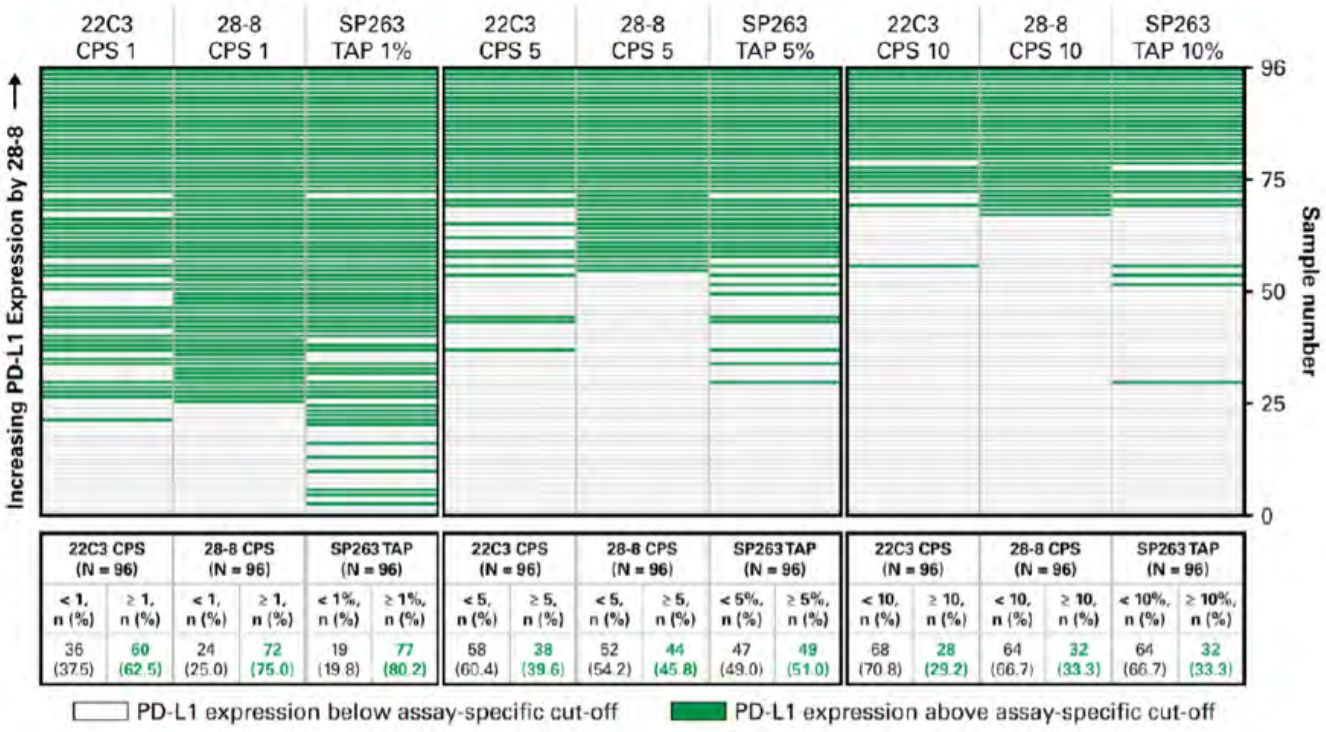
Liu C, et al. – Diagn Pathol 2023

IO in HER2-neg: CROSS TRIAL COMPARISON BASED ON PD-L1

	Checkmate 649	Keynote 859	Rationale 305
Anatomic Location	Gastric/GEJ/**esophageal adenocarcinoma**	Gastric/GEJ adenocarcinoma	Gastric/GEJ adenocarcinoma
HER2 status	**Not known to be positive**	Negative	Negative
PD-L1 expression	Any	Any	Any
PD-L1 assay	Agilent/Dako PD-L1 IHC **28-8 pharmDx assay** (Stratification by TPS; Endpoint Analysis by CPS)	Agilent PD-L1 IHC **22C3 pharmDx assay (CPS)**	Ventana PD-L1 IHC **SP263 CDx assay (TAP)**
PD-L1 Stratification factors	**PD-L1 TPS <1 vs. ≥1**	**PD-L1 CPS <1 vs. ≥1**	**PD-L1 TAP ≥ 5 vs < 5**
OS Endpoint Analysis	1. **PD-L1 CPS ≥5** 2. PD-L1 CPS ≥1 3. ITT	1. **PD-L1 CPS ≥10 and ITT** 2. PD-L1 CPS ≥1	1. **PD-L1 TAP ≥5** 2. ITT

PD-L1: concordance between different assays





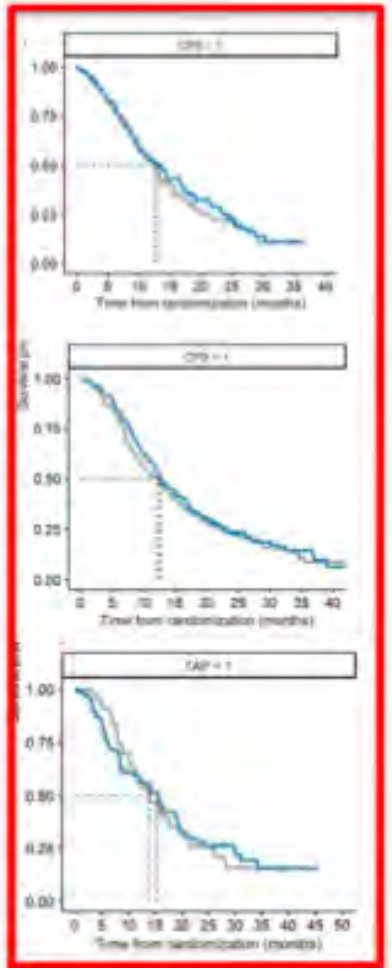
These results support cross-application flexibility of the different PD-L1 assays and scoring algorithms for PD-L1 expression

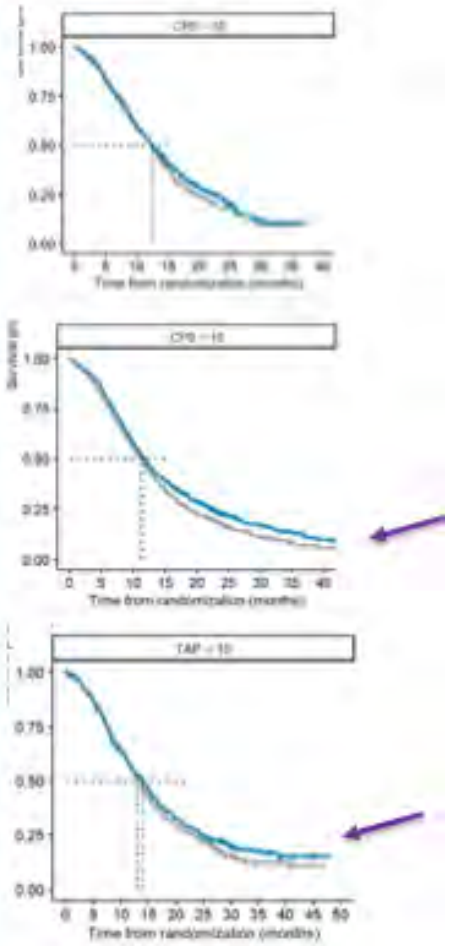
Klempner MJ, et al. – JCO Prec Oncol 2024

PD-L1 negative subgroup: clear no go signal

	All Patients		PD-L1 <1		PD-L1 <10	
CM649	**N+CHT**	**CHT**	**N+CHT**	**CHT**	**N+CHT**	**CHT**
N	**789**	**792**	**140**	**125**	**406**	**387**
mOS (95% CI)	13.8 (12.6, 14.6	11.6 (10.9, 12.5)	13.1 (9.8, 16.7)	12.5 (10.1, 13.8)	12.6 (11.1, 14.2)	12.5 (11.2, 13.3)
OS HR (95% CI)	**0.79 (0.70, 0.89)**		**0.92 (0.70, 1.23)**		**0.94 (0.80, 1.1)**	
KN859	**P+CHT**	**CHT**	**P+CHT**	**CHT**	**P+CHT**	**CHT**
N	**790**	**789**	**172**	**172**	**511**	**517**
mOS (95% CI)	12.9 (11.9, 14.0)	11.5 (10.6, 12.1)	12.7 (11.4, 15.0)	12.2 (9.5, 14.0)	11.7 (10.7, 12.8)	11.2 (10.0, 12.1)
OS HR (95% CI)	**0.77 (0.69, 0.86)**		**0.92 (0.73 ,1.17)**		**0.86 (0.75, 0.98)**	
RN306	**T+CHT**	**CHT**	**T+CHT**	**CHT**	**T+CHT**	**CHT**
N	**501**	**496**	**69**	**43**	**365**	**351**
mOS (95% CI)	15.0 (13.6, 16.5)	12.9 (12.1, 14.1)	15.4 (8.4, 19.2)	13.8 (10.2, 17.8)	14.0 (12.0, 15.3)	13.0 (12.1, 14.3)
OS HR (95% CI)	**0.80 (0.69, 0.92)**		**0.98 (0.64, 1.50)**		**0.91 (0.77, 1.07)**	

Exploratory FDA analyses (refer to briefing document for methodology)

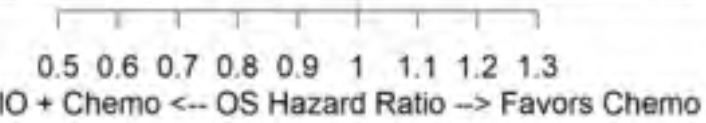




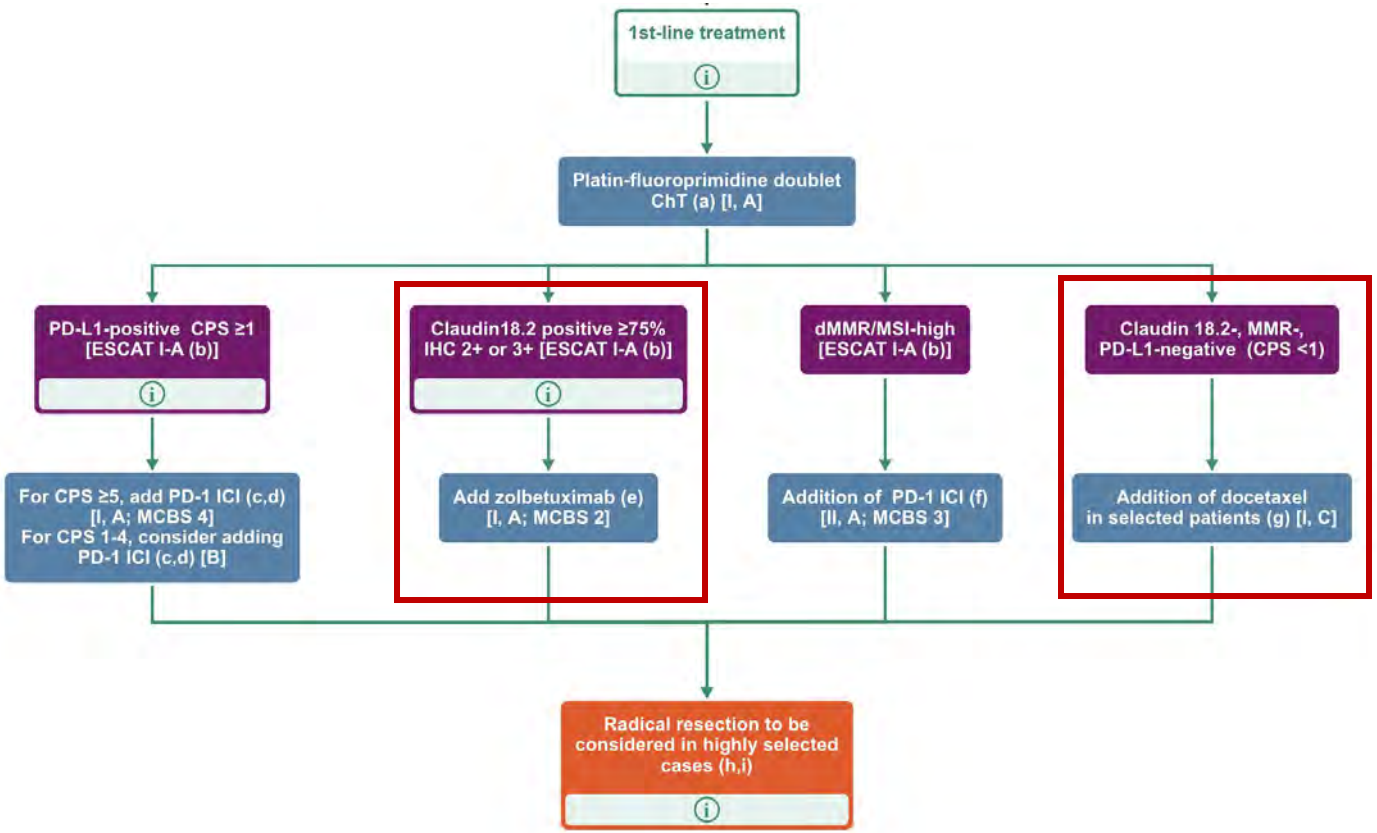
Intermediate PD-L1 subgroups: still unanswered question

FDA pooled analysis of KN-859, CM649 and RAT305 (MSS only)

	Subgroup	% of Pts	IO + Chemo Evt / N	Chemo Evt / N	HR (95% CI)	IO + Chemo Median (95% CI)	Chemo Median (95% CI)
	Overall	**100**	**1246/1684**	**1340/1664**	**0.8 (0.74 ,0.87)**	**13.8 (12.9, 14.4)**	**12 (11.4, 12.5)**
Intermediate	PDL1 1-<5	27	364/446	392/466	0.88 (0.76 ,1.02)	12.2 (11.1, 13.6)	11.8 (10.8, 12.6)
Intermediate	PDL1 5-<10	17	237/297	217/274	1.01 (0.84 ,1.22)	11.7 (10.4, 13)	13 (12.1, 14)
Intermediate	PDL1 1-<10	44	601/743	609/740	0.93 (0.83 ,1.04)	12 (11.1, 12.9)	12.3 (11.4, 12.9)



ESMO Living Guidelines in HER2-neg disease



CPS < 1

- ESMO/ASCO: Not recommended
- FDA approved (ODAC negative opinion)
- EMA not approved

CPS ≥ 5

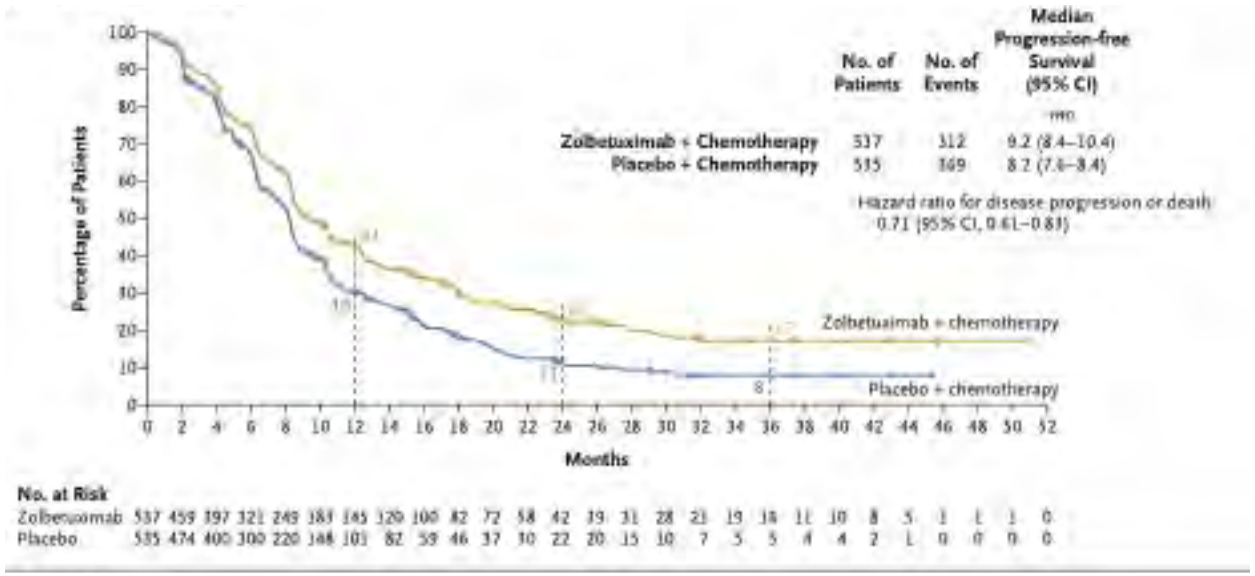
- ESMO/ASCO: Recommended
- FDA approved both nivo and pembro
- EMA approved nivo/pembro (tisle TAP 5%)

CPS 1-4

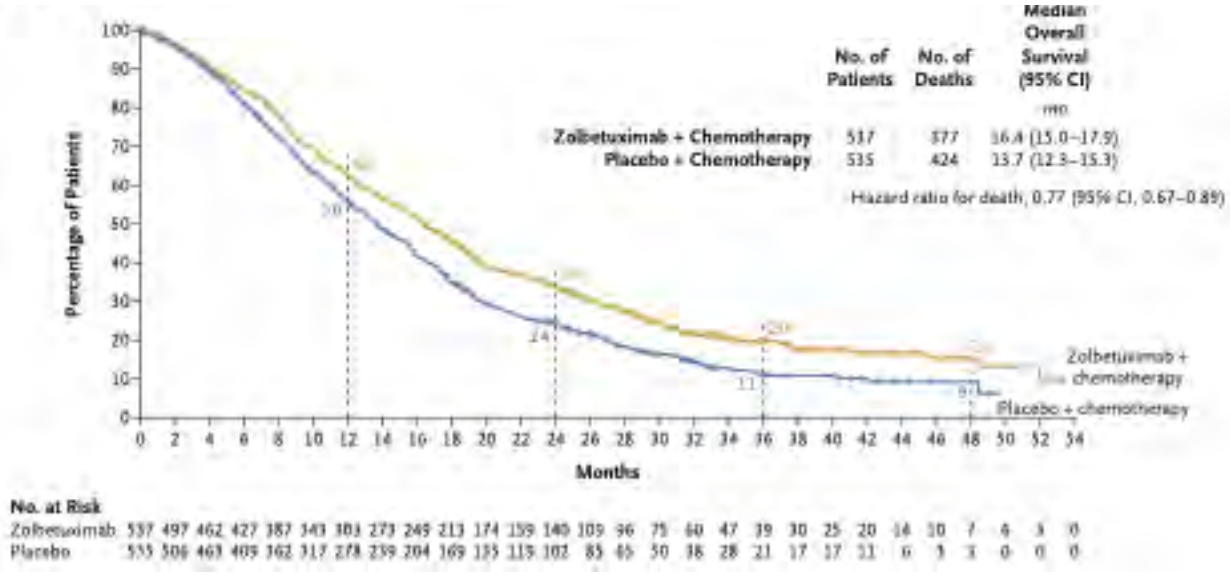
- ESMO/ASCO: Consider case-by-case
- FDA approved both nivo and pembro
- EMA only pembrolizumab approved

POOLED ANALYSIS OF SPOTLIGHT AND GLOW

Progression-free survival



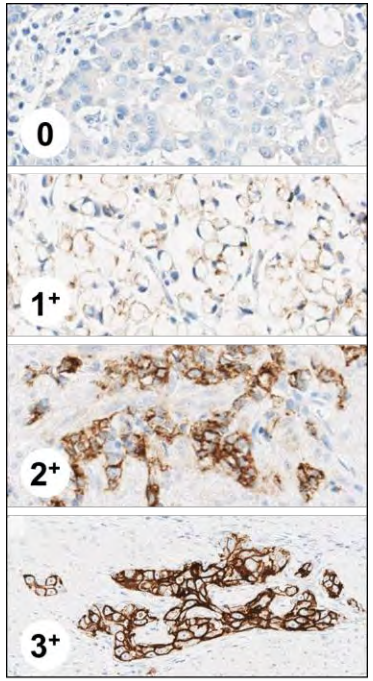
Overall survival



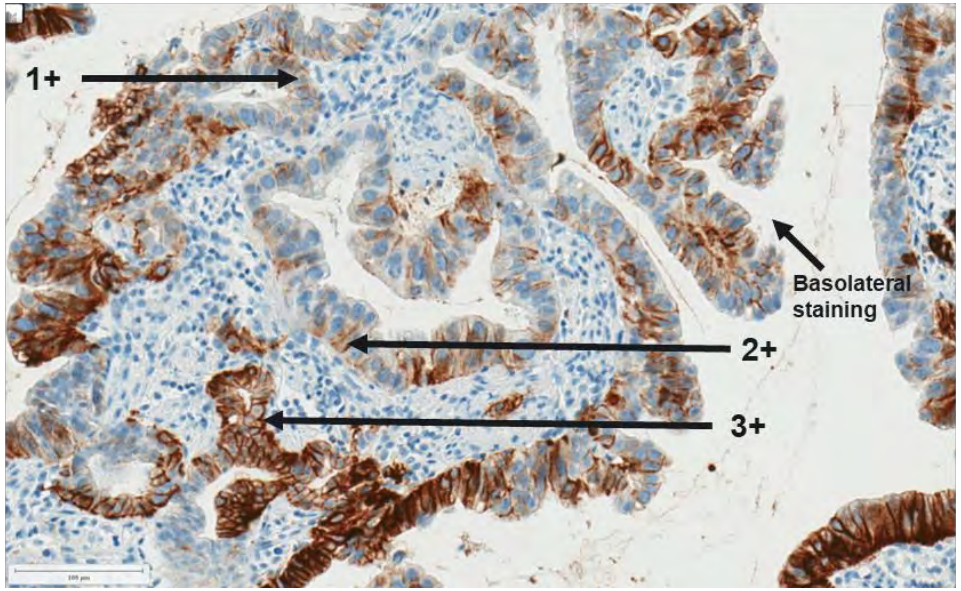
ESMO ON AIR

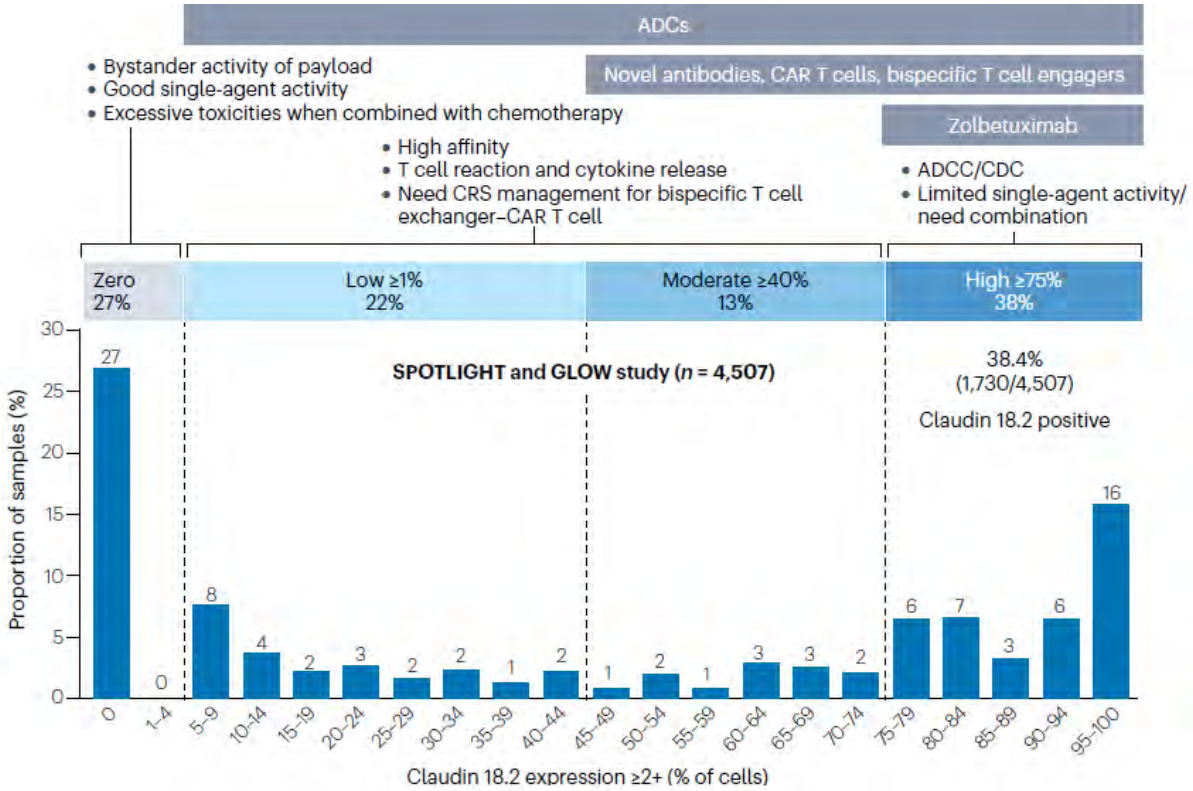
Shitara et al, NEJM 2024

HETEROGENEITY OF CLDN18 EXPRESSION
drug-dependent cut-offs?



1+, 2+ and 3+ CLDN18 staining intensities* (20X magnification). Incomplete basolateral staining may be present





ADCC, antibody-dependent cell cytotoxicity; CAR, chimeric antigen receptor; CDC, complement-dependent cytotoxicity; CLDN18.2, claudin 18.2; CRS, cytokine release syndrome.

Nakayama I, et al. Nat Rev Clin Oncol 2024;21(5):354–369.

NEXT STEP: TARGETED MoAB+IO

Trastuzumab+pembrolizumab (SOC based on KN-811)

Zanidatamab+tislelizumab?

TDX-d+pembrolizumab?

TDX-d+rilvegostomig?

Zolbetuximab+pembrolizumab?

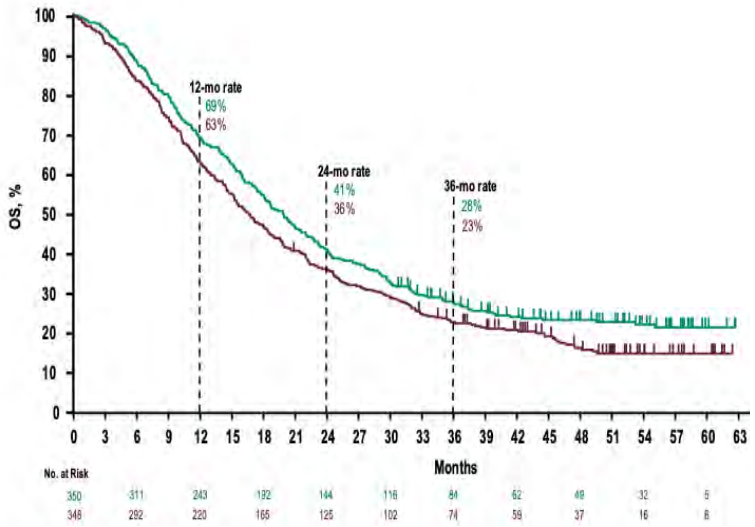
Anti-CLDN18.2 ADC+pembrolizumab?

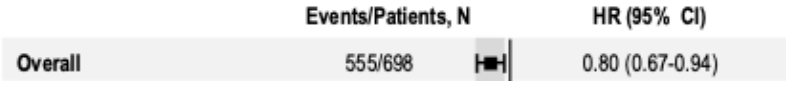
Bemarituzumab+nivolumab?

KEYNOTE-811 trial results based on PD-L1

KN-811 All comers

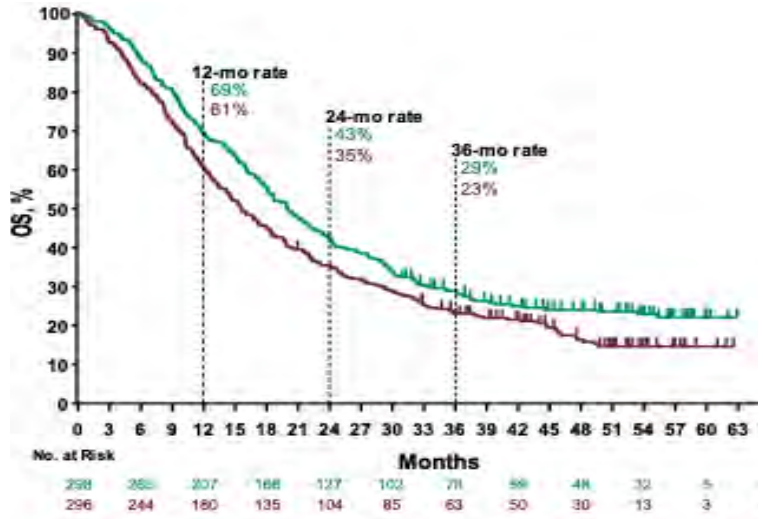
mOS: 20 vs 16.8 mos
(delta 3.2 mos)

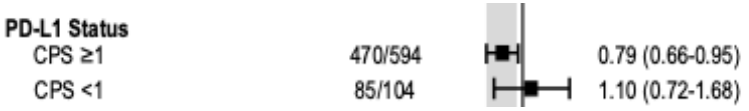




CPS ≥1 (KM pre-planned)

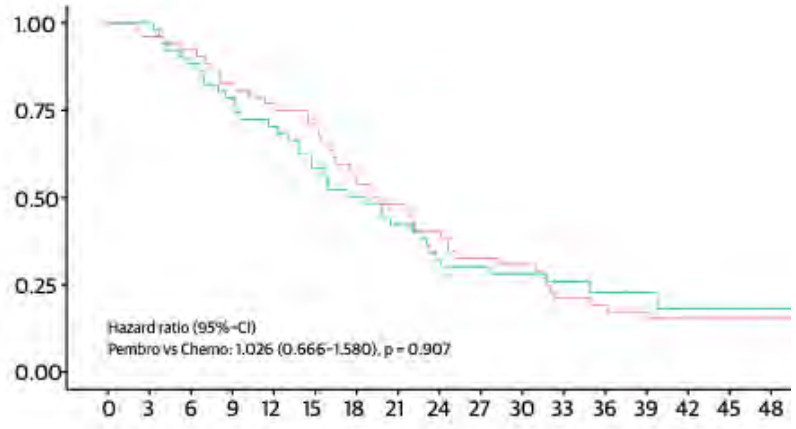
mOS: 20.1 vs 15.7 mos
(delta 4.4 mos)

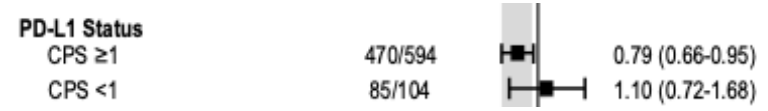




CPS <1 (KM Reconstructed)

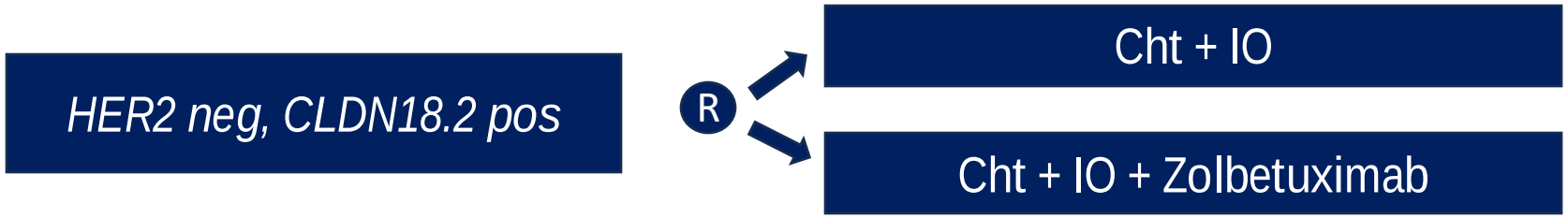
mOS: 18.2 vs 20.4 mos
(delta 2.2 mos in favor of placebo)





Janjigian et al, NEJM 2024; Leone et al, ESMO Open 2024

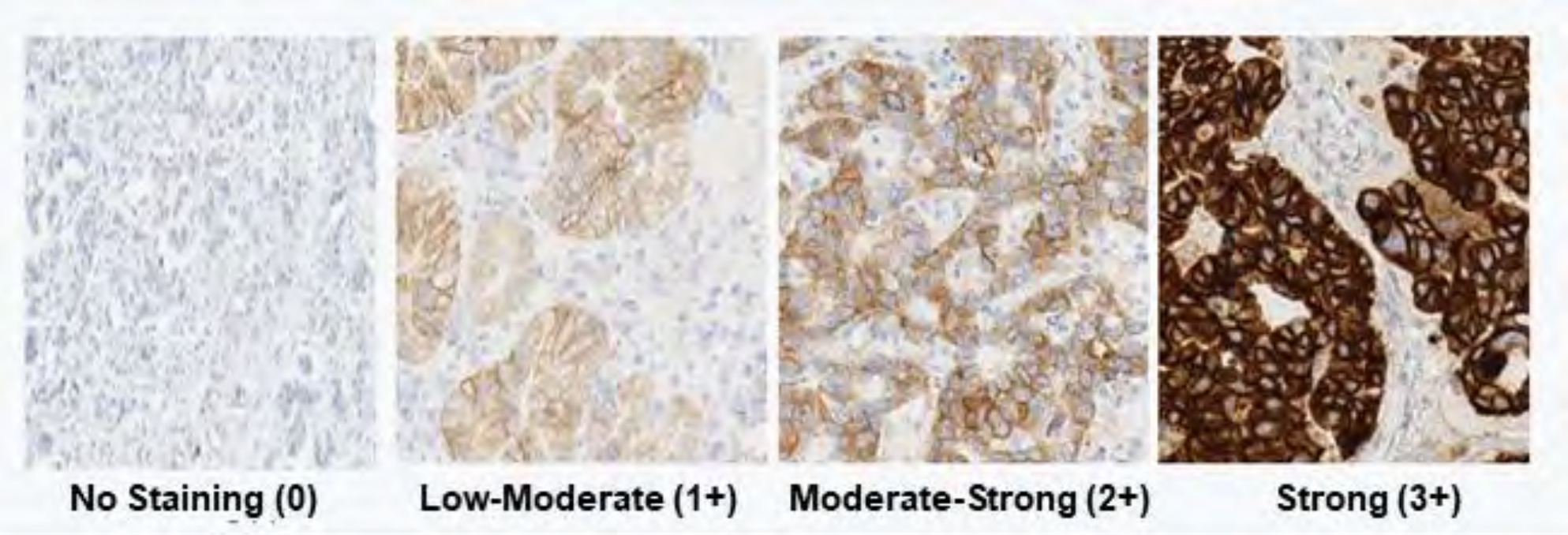
POTENTIAL COMBINATION OF ZOLBETUXIMAB + IO
Choosing wisely the next trials design



All comers including PD-L1 neg	**Target population CPS ≥1**	**CPS ≥5 or ≥10 (pre-planned)**
Unethical based on negative subgroup analyses both in HER2+ and -ve disease	Additive or synergistic effect?	Difficult to show positive results given the long-term benefit from IO in both arms Synergy may be needed

Characteristic	
Replication across multiple trials	Yes
Sample ascertainment	High
Biological plausibility	Yes
Study design	+/-

EMERGING BIOMARKERS
FGFR2b TESTING BY IHC

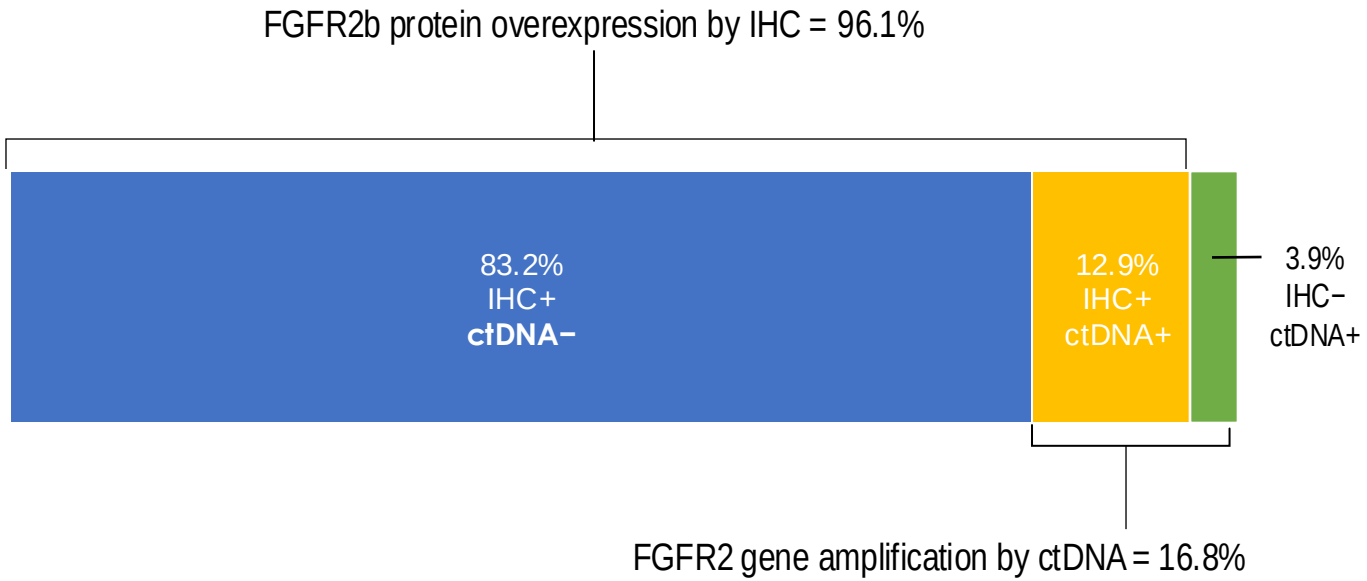


FGFR2b IHC+ defined as 2+/3+ staining

1. Wainberg ZA, et al. Lancet Oncol 2022; 2. Wainberg ZA, et al. Gastric Cancer 2024

FIGHT first-line ph. 2 RCT
PRESCREENING BY FGFR2b IHC or *FGFR2* amplification in ctDNA

FGFR2b overexpression and FGFR2 amplification status of enrolled patients (N=155)



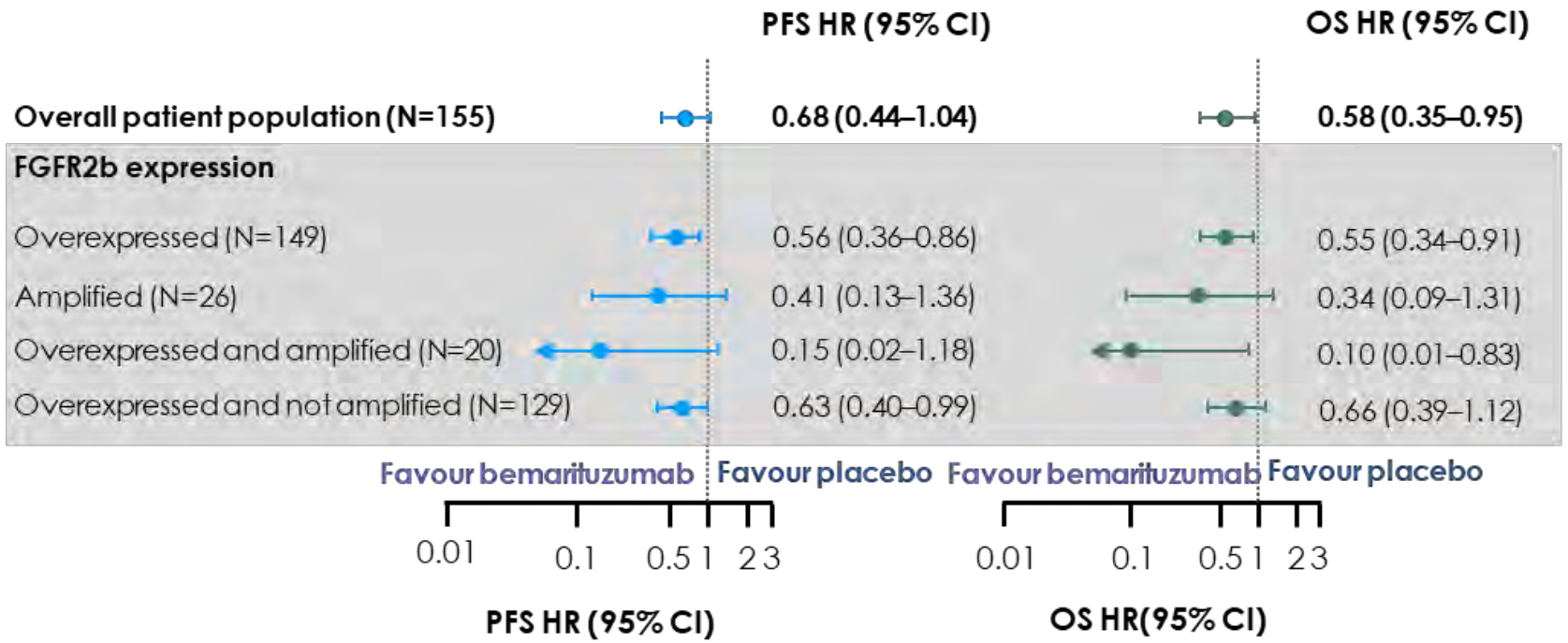
Legend:
IHC+ = FGFR2b protein overexpression
ctDNA+ = FGFR2 gene amplification

Most pre-screened patients were positive for FGFR2b overexpression by IHC rather than ctDNA analysis

Catenacci D, et al. Presented at ASCO 2021, abstract 4010.

FGFR2b PRE-SCREENING: FIGHT first-line ph. 2 RCT

FGFR2b overexpression and/or FGFR2 amplification



FGFR2b overexpression was associated with PFS and OS benefit irrespective of amplification status in ctDNA
In subsequent Phase 3 trials, patients are selected according to overexpression and by the 10% positive tumor cells cut-off

Wainberg ZA, et al. Lancet Oncol 2022;23:1430–40 (and suppl).

FGFR2b: Phase 3 FORTITUDE-101 trial, 1L setting

Study design

Randomised, multicentre, double-blind, placebo-controlled study

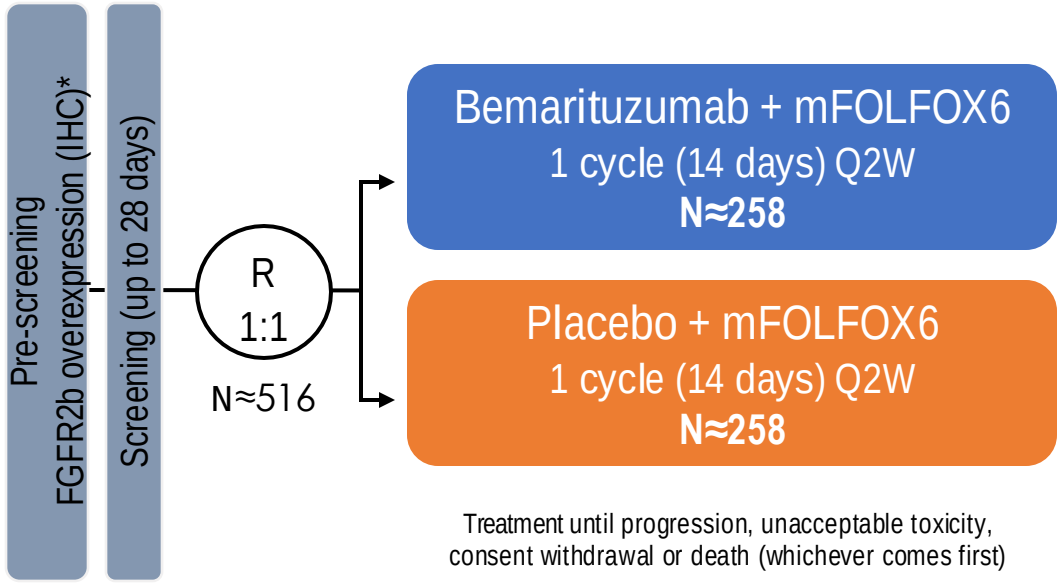
Key eligibility criteria

- Untreated, unresectable, locally advanced or metastatic G/GEJ cancer
- ECOG PS 0/1
- Measurable disease per RECIST v1.1
- HER2 negative
- FGFR2b 2+/3+ tumour cells determined by centrally performed IHC testing*

Stratification factors

- Geographic region (US/EU vs Asia vs ROW)
- ECOG PS (0 vs 1)
- Tumour cell and immune cell PD-L1 status (CPS) (≥5 vs <5 or indeterminate)

Study amended to enrol patients with FGFR2b ≥10% 2+/3+ tumour staining



Treatment until progression, unacceptable toxicity, consent withdrawal or death (whichever comes first)

Primary endpoints:

- OS (in patients with **≥10% 2+/3+** FGFR2b tumour cell staining)*

Secondary endpoints:

- PFS, ORR (in patients with ≥10% 2+/3+ FGFR2b tumour cell staining)*
- OS, PFS, ORR, DoR, DCR, HRQoL, PK, safety, immunogenicity, (all randomised patients)

**Centrally assessed during pre-screening by IHC on a tumour sample (either archival, obtained within 6 months/180 days prior to pre-screening or fresh biopsy).*
CPS, combined positive score; DCR, disease control rate; EU, Europe; HRQoL, health-related quality of life; PK, pharmacokinetics; ROW, rest of world; US, United States.
NCT05052801. Available at: https://www.clinicaltrials.gov/study/NCT05052801 (accessed June 2024); Smyth E, et al. Presented at ASCO 2022, poster TPS4164.

FGFR2b: Phase 1b/3 FORTITUDE-102, 1L setting

Study design

Double-blind, randomised, placebo-controlled study

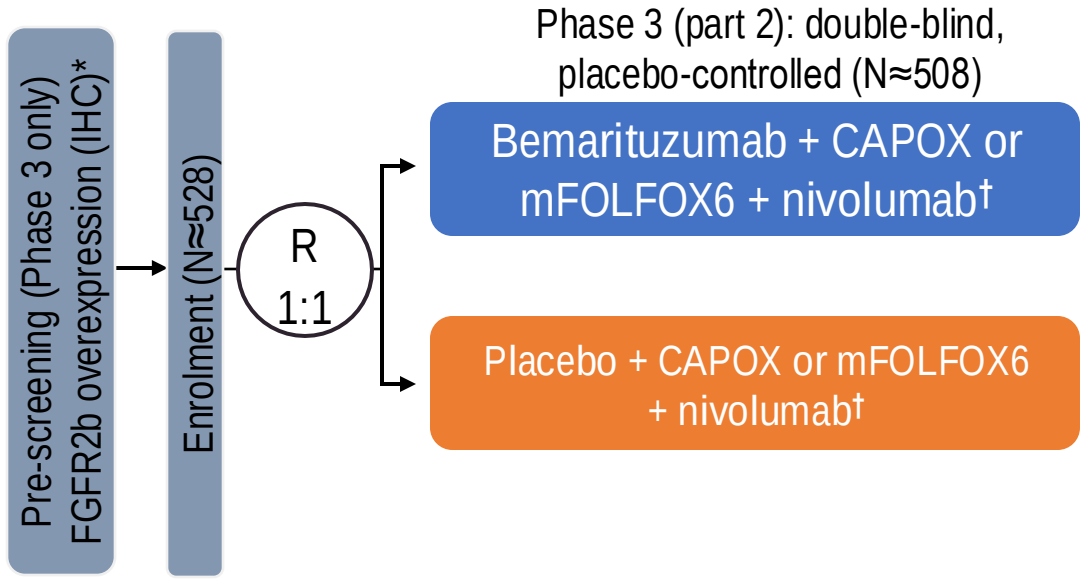
Key eligibility criteria

- Phase 1b: unresectable, locally advanced or metastatic G/GEJ cancer
- ECOG PS 0/1
- Measurable disease per RECIST v1.1
- Not known to be HER2 positive
- No chronic/systemic ophthalmologic disorders or corneal abnormalities

Additional for Phase 3:

- No prior treatment except for max. 1 dose chemotherapy ± nivolumab
- FGFR2b 2+/3+ tumour cells determined by centrally performed IHC testing*

Study amended to enrol patients with FGFR2b ≥10% 2+/3+ tumour staining



Primary endpoints:

- OS (in patients with ≥10% 2+/3+ FGFR2b tumour cell staining)*

Secondary endpoints:

- PFS, ORR, DoR, DCR, HRQoL (in patients with ≥10% 2+/3+ FGFR2b tumour cell staining)*
- OS, PFS, ORR, safety, PK (all patients)

**Centrally assessed during pre-screening by IHC on a tumour sample (either archival, obtained within 6 months/180 days prior to pre-screening or fresh biopsy);*
†Patients will be given FOLFOX6 and nivolumab on a 14-day cycle, or given CAPOX and nivolumab on a 21-day cycle.
NCT05111626. Available at: https://www.clinicaltrials.gov/study/NCT05111626 (accessed April 2024); Wainberg ZA, et al. ESMO Congress 2023, poster 1526P.

Thank you!

ESMO ON AIR

Preventing and managing adverse events in patients with advanced gastric cancer in the era of precision oncology

TANIA FLEITAS KANONNIKOFF

March 2025

Medical Oncology Department. Hospital Clínico Universitario de Valencia, INCLIVA, Valencia, Spain

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY

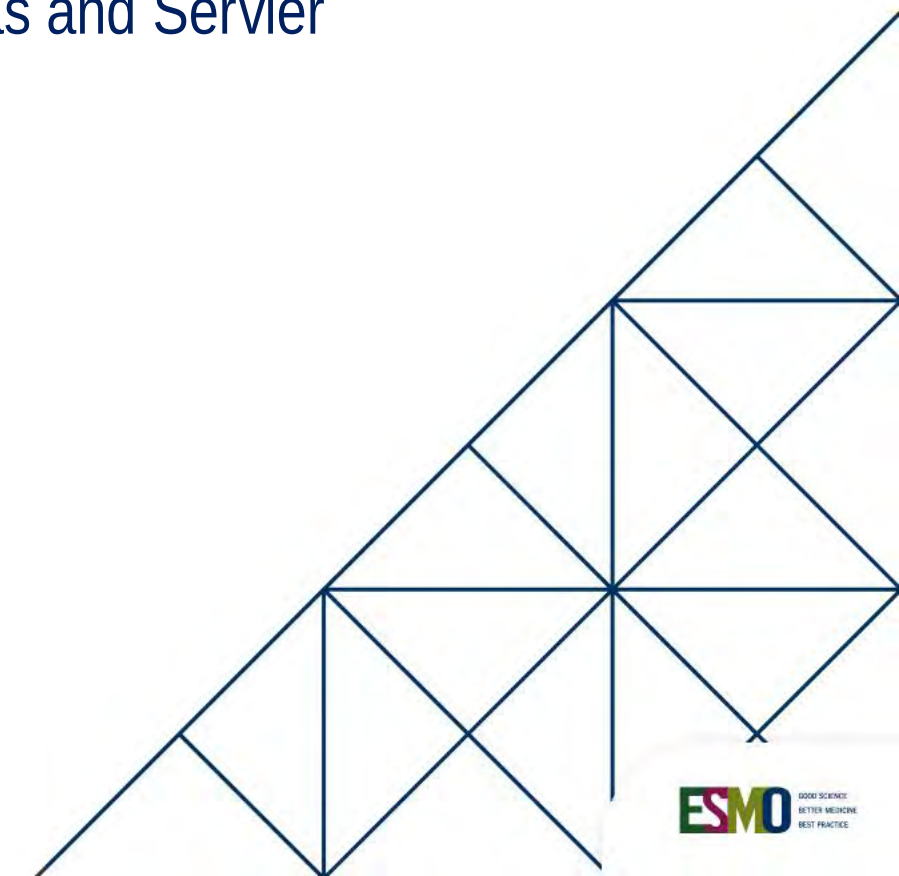
DECLARATION OF INTERESTS

Clinical trials and research funding: Genentech, Adapt immune, Roche, Beigene, Astelas, BMS, Daichii Sanyo, Amgen, Gilead.

Participation as speaker: Amgen, Bayer, BMS, Lilly, MSD, Astellas and Servier

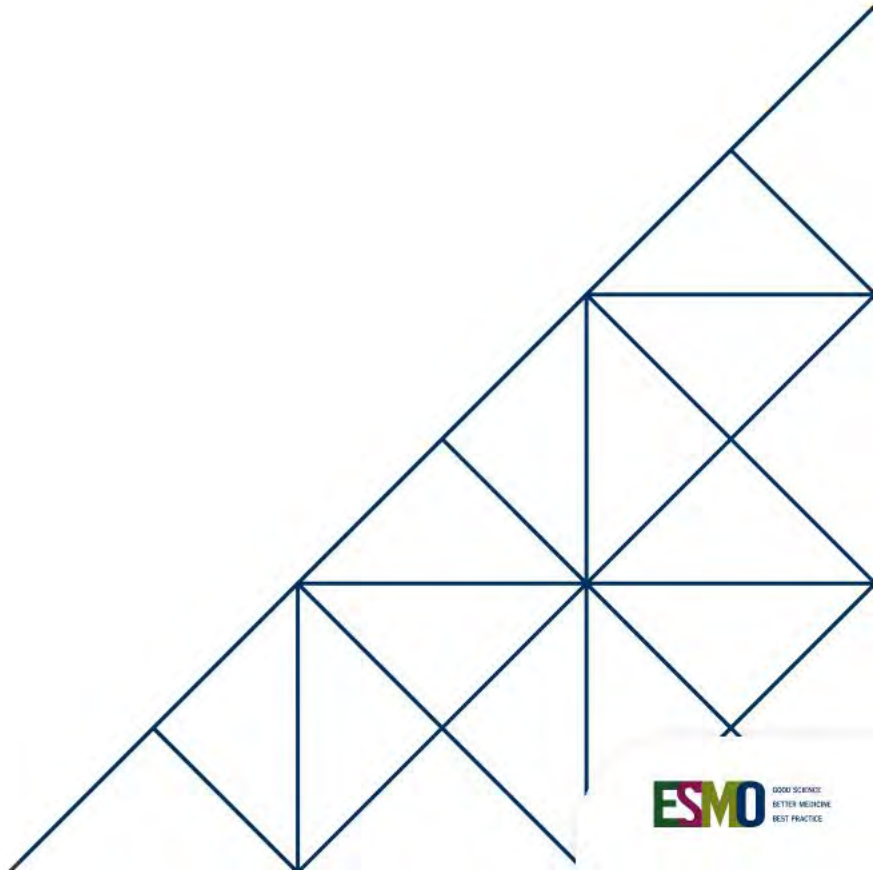
Travel grants: Lilly, Roche, Amgen; MSD

Advisory board: MSD, Astrazeneca, BMS, Beigene, Amgen



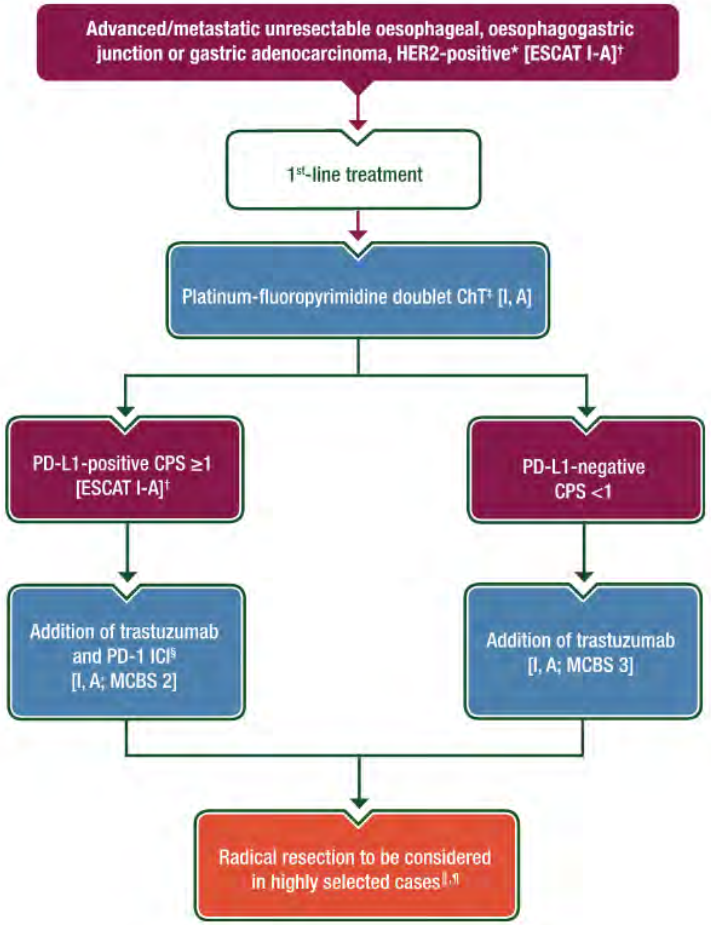
Agenda

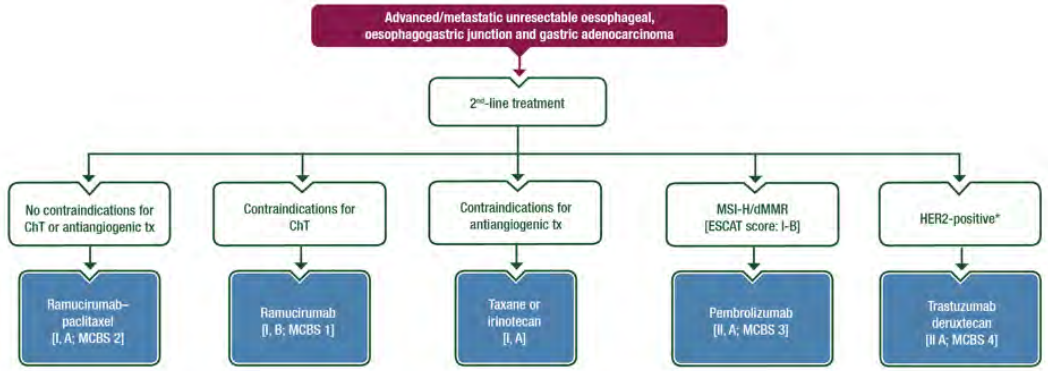
Advanced gastric cancer current practice guidelines
The patient characteristics
Baseline assessment and follow-up
Classical toxicities related with chemotherapy
Toxicities derived from the immune and targeted therapy
New drugs and combination adverse event challenges

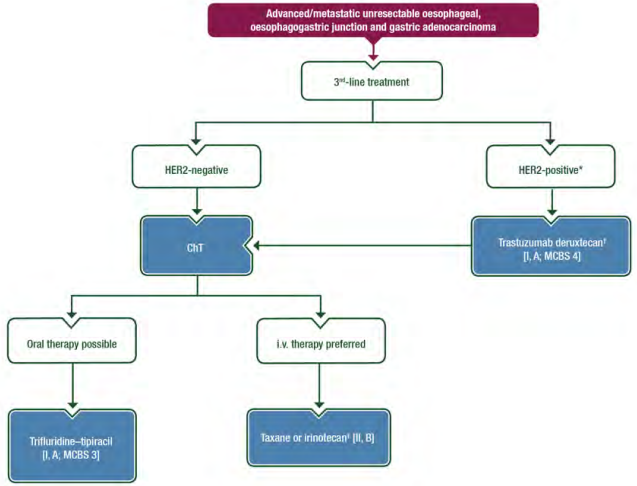


- Fleitas T.

Advanced Her2 positive gastric cancer treatment



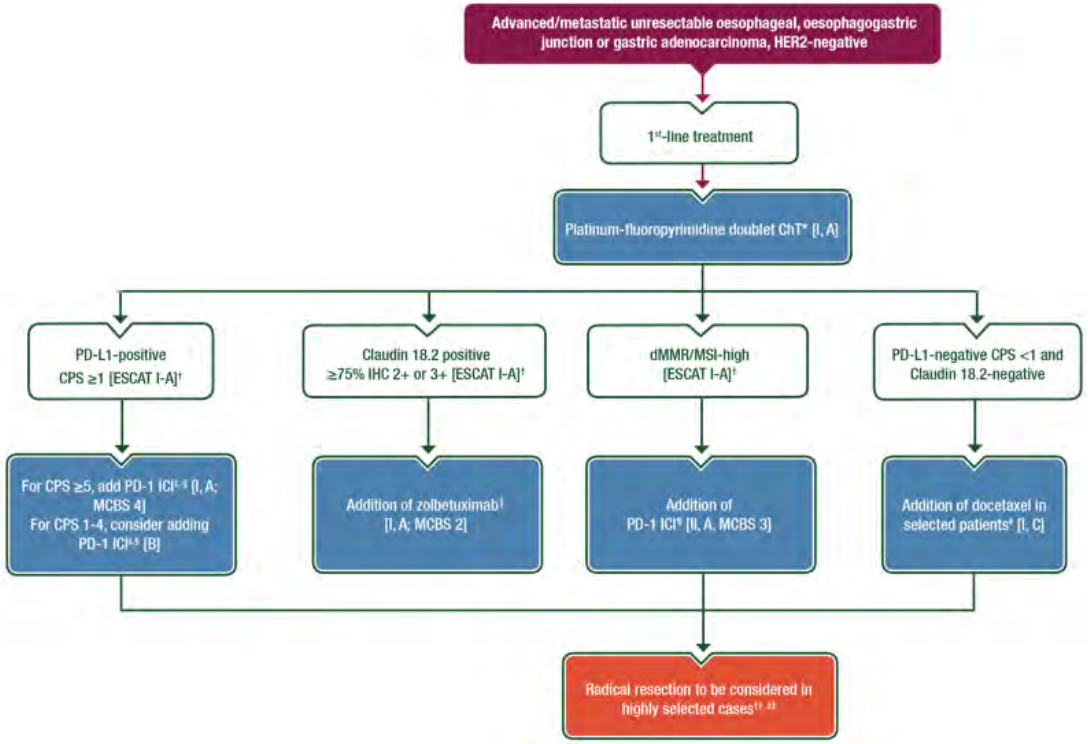


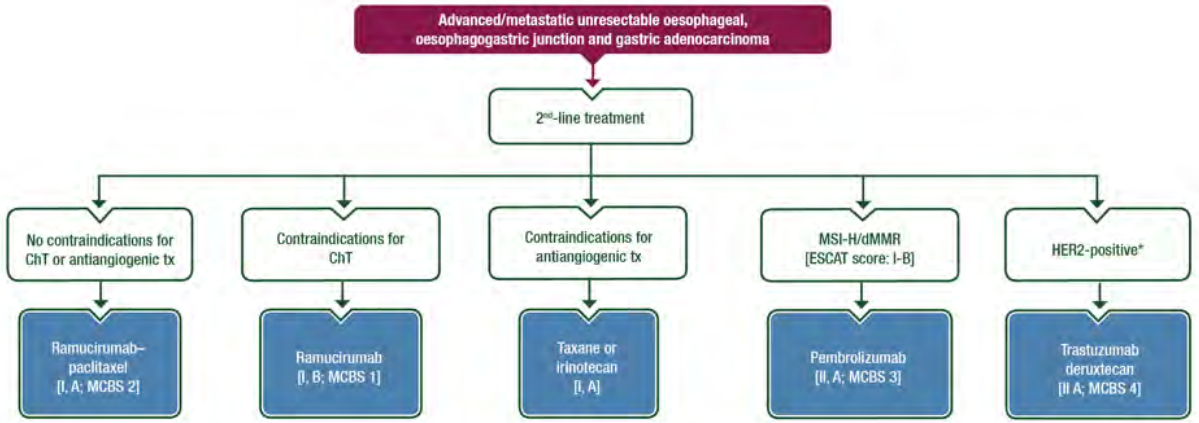


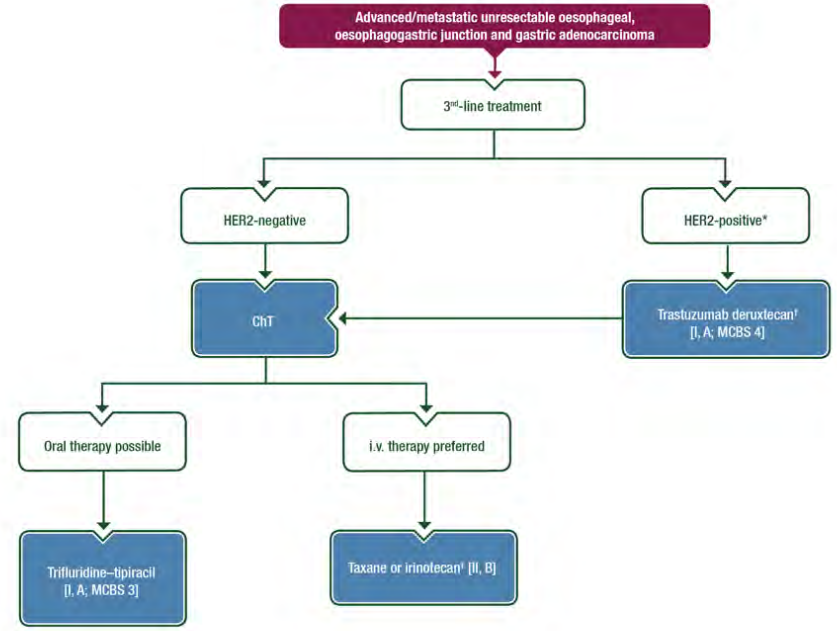
ESMO ON AIR

Lordick F. et al.Ann Oncol 2022;33(10):1005-1020. ESMO living guidelines V1.4 Sept. 2024

Advanced Her2 negative gastric cancer treatment

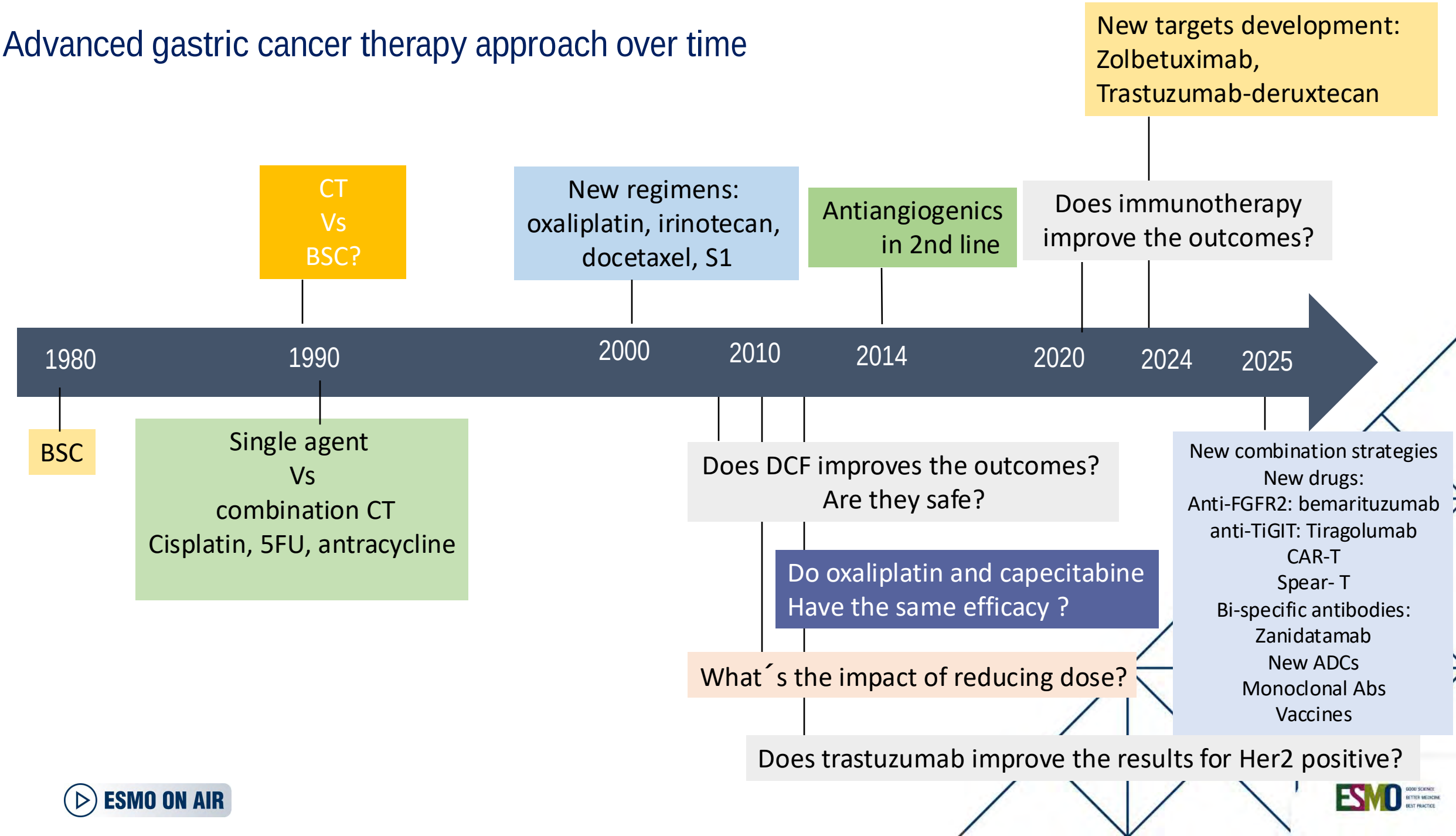






Lordick F. et al.Ann Oncol 2022;33(10):1005-1020. ESMO living guidelines V1.4 Sept. 2024

Advanced gastric cancer therapy approach over time



Patient characteristics

- The performance status is determinant for the treatment benefit

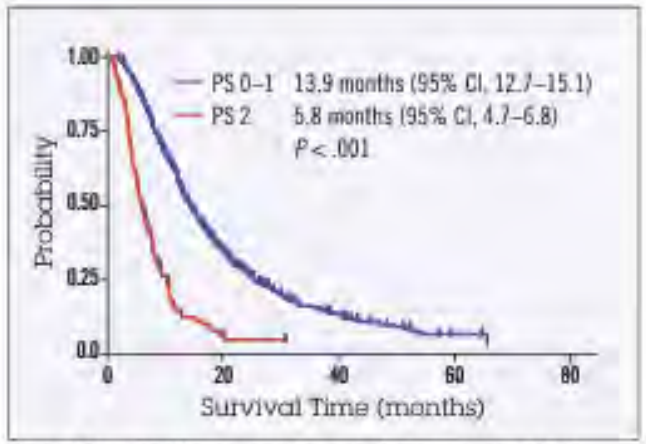


Figure 2. Kaplan-Meier survival curves of overall survival (OS). Median OS for first-line chemotherapy was significantly shorter in PS 2 patients compared to PS 0–1 patients (5.8 months vs. 13.9 months; $P < .001$).

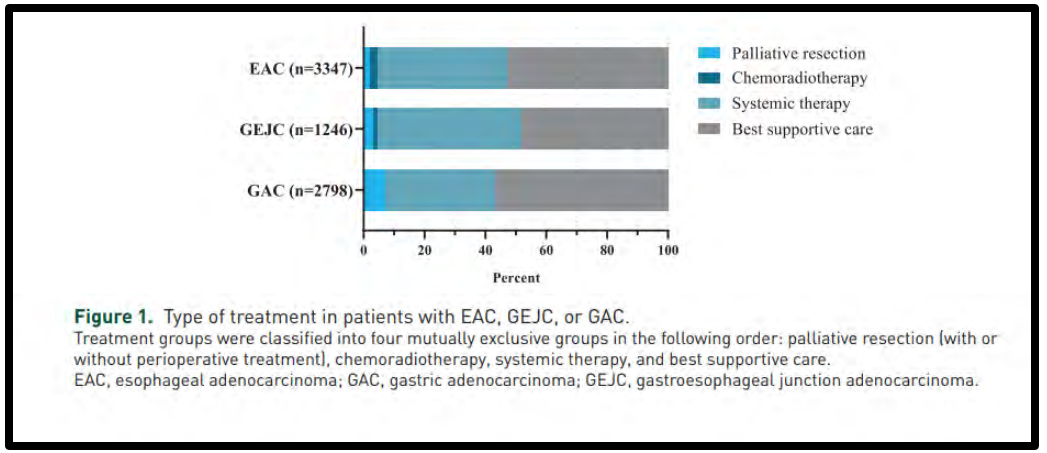


Figure 1. Type of treatment in patients with EAC, GEJC, or GAC.
Treatment groups were classified into four mutually exclusive groups in the following order: palliative resection (with or without perioperative treatment), chemoradiotherapy, systemic therapy, and best supportive care.
EAC, esophageal adenocarcinoma; GAC, gastric adenocarcinoma; GEJC, gastroesophageal junction adenocarcinoma.

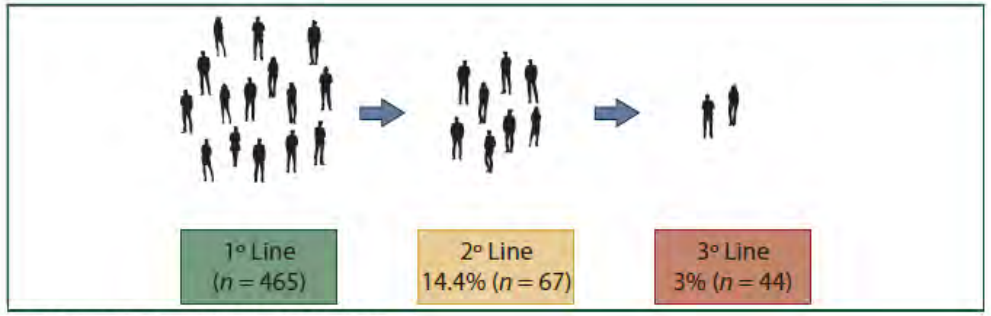


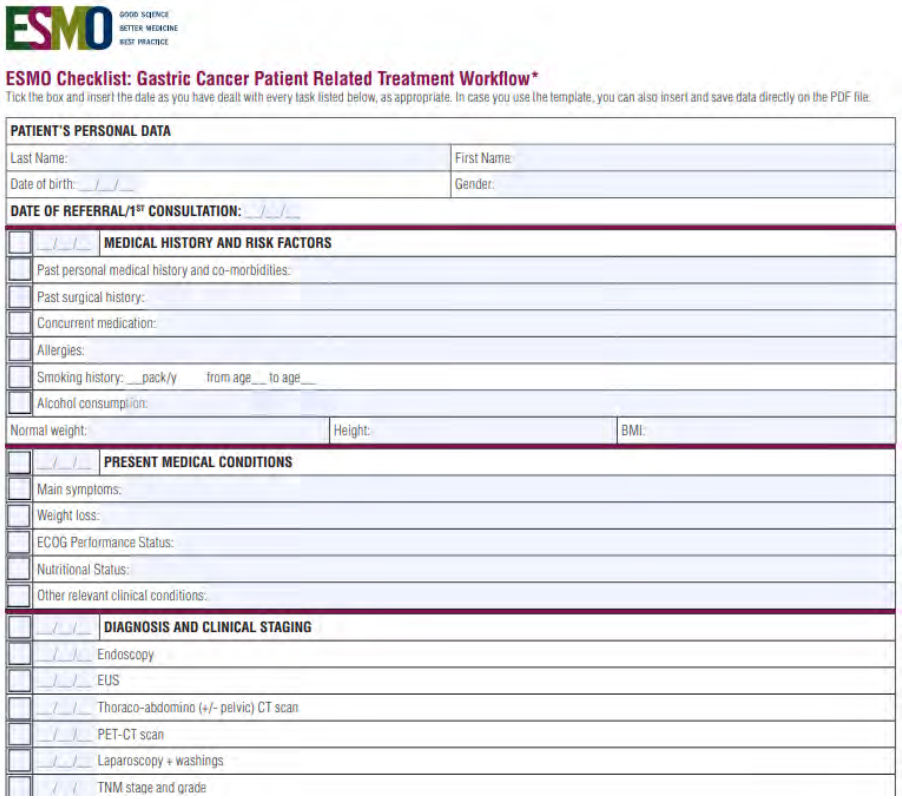
Figure 1. Percentage of patients that get to the following line.

Shitara K, et al. Gastrointest Cancer Res. 2009 Nov;3(6):220-4.

B. Freile et al. ESMO Gastrointestinal Oncology. Volume 6 - Issue C - 2024

Pape M. et al. Ther Adv Med Oncol 2023, Vol. 15: 1–13

Baseline assesment



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO Checklist: Gastric Cancer Patient Related Treatment Workflow*

Tick the box and insert the date as you have dealt with every task listed below, as appropriate. In case you use the template, you can also insert and save data directly on the PDF file.

PATIENT'S PERSONAL DATA

Last Name:	First Name:
Date of birth: __/__/__	Gender:

DATE OF REFERRAL/1ST CONSULTATION: __/__/__

MEDICAL HISTORY AND RISK FACTORS __/__/__

- Past personal medical history and co-morbidities:
- Past surgical history:
- Concurrent medication:
- Allergies:
- Smoking history: __pack/y from age__ to age__
- Alcohol consumption:

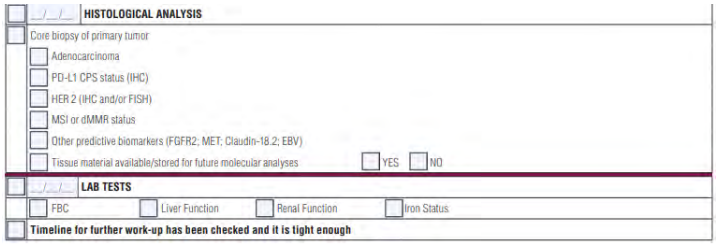
Normal weight:	Height:	BMI:

PRESENT MEDICAL CONDITIONS __/__/__

- Main symptoms:
- Weight loss:
- ECOG Performance Status:
- Nutritional Status:
- Other relevant clinical conditions:

DIAGNOSIS AND CLINICAL STAGING __/__/__

- __/__/__ Endoscopy
- __/__/__ EUS
- __/__/__ Thoraco-abdomino (+/- pelvic) CT scan
- __/__/__ PET-CT scan
- __/__/__ Laparoscopy + washings
- __/__/__ TNM stage and grade



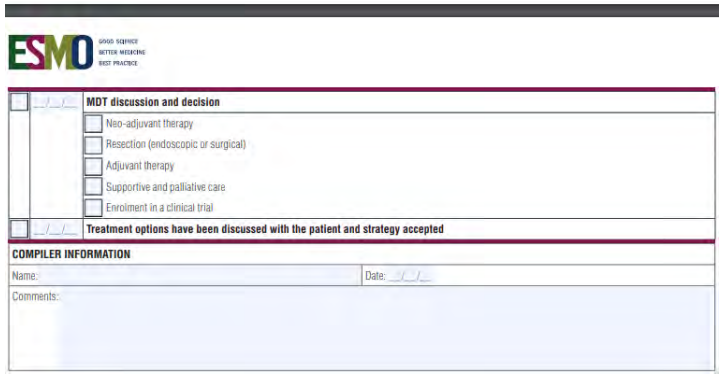
HISTOLOGICAL ANALYSIS __/__/__

- Core biopsy of primary tumor
  - Adenocarcinoma
  - PD-L1 CPS status (IHC)
  - HER 2 (IHC and/or FISH)
  - MSI or dMMR status
  - Other predictive biomarkers (FGFR2; MET; Claudin-18.2; EBV)
  - Tissue material available/stored for future molecular analyses ☐ YES ☐ NO

LAB TESTS __/__/__

- FBC ☐ Liver Function ☐ Renal Function ☐ Iron Status

Timeline for further work-up has been checked and it is tight enough



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MDT discussion and decision __/__/__

- Neo-adjuvant therapy
- Resection (endoscopic or surgical)
- Adjuvant therapy
- Supportive and palliative care
- Enrolment in a clinical trial

Treatment options have been discussed with the patient and strategy accepted __/__/__

COMPILER INFORMATION

Name:	Date: __/__/__

Comments:

ESMO ON AIR

https://oncologypro.esmo.org/oncology-in-practice/practice-tools/esmo-checklists

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Classical toxicities related with chemotherapy

The Real -2 study

Table 3. Most Common Treatment-Related Adverse Events (Safety Population).*

Adverse Event	ECF (N=234)		ECX (N=234)		EOF (N=225)		EOX (N=227)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
	percent							
Anemia†	78.4	13.1	79.5	10.5	65.8	6.5‡	64.2	8.6
Thrombocytopenia†	14.5	4.7	17.0	4.8	13.4	4.3	21.1	5.2
Neutropenia†	73.6	41.7	85.6	51.1‡	68.4	29.9§	62.9	27.6§
Febrile neutropenia†	13.2	9.3	10.5	6.7	11.5	8.5	9.8	7.8
Diarrhea	39.3	2.6	41.9	5.1	62.7	10.7§	61.7	11.9§
Stomatitis	50.9	1.3	39.3	1.7	44.4	4.4‡	38.1	2.2
Hand–foot syndrome	29.8	4.3	45.9	10.3‡	28.9	2.7	39.3	3.1
Nausea and vomiting	79.1	10.2	82.1	7.7	83.1	13.8	78.9	11.4
Peripheral neuropathy	30.0	0.4	36.3	1.7	79.6	8.4§	83.7	4.4§
Lethargy	89.7	16.6	92.7	15.5	90.2	12.9	96.1	24.9‡
Alopecia¶	81.5	44.2	82.5	47.4	75.4	27.7§	74.2	28.8§
Thromboembolism‖	16.9	NA	13.3	NA	7.7§	NA	7.5§	NA
Death within 60 days (95% CI)**	7.2 (4.7–11.1)		5.6 (3.4–9.3)		5.7 (3.4–9.5)		6.1 (3.8–10.0)	

* Patients were randomly assigned to receive one of four triplet therapies: epirubicin and cisplatin plus either fluorouracil (ECF) or capecitabine (ECX), or epirubicin and oxaliplatin plus either fluorouracil (EOF) or capecitabine (EOX). NA denotes not applicable.
† This side effect of treatment was measured in the hematologic-safety population, consisting of 236 patients in the ECF group, 229 patients in the ECX group, 231 patients in the EOF group, and 232 patients in the EOX group.
‡ P<0.01 to P<0.05 for the comparison with the ECF group.
§ P<0.001 to P<0.01 for the comparison with the ECF group.
¶ The highest grade of alopecia was grade 2, which is listed in the grade 3 or 4 column.
‖ The diagnosis of thromboembolism was made only in the per-protocol population.
** Death within 60 days after randomization was evaluated only in the intention-to-treat population.

ECF: D1= Epirubicin 50 mg/m² , Cisplatin 60 mg/m² ;
5-FU 5-fluorouracil (200 mg m(-2) day(-1))/ 21 days. Cumulated dose of Epirubicin < 900 mg/m² (max 18 cures)

ECX: D1 = Epirubicin 50 mg/m² , Cisplatin 60 mg/m² ;
D2 to 15: Capecitabine 1 g/m² x 2/d. D1 = D21. Cumulated dose of Epirubicin < 900 mg/m² (max 18 cures)

EOF: D1= Epirubicin 50 mg/m² , Oxaliplatin 130 mg/m² 5-FU 5-fluorouracil (200 mg m(-2) day(-1))/ 21 days. Cumulated dose of Epirubicin < 900 mg/m² (max 18 cures)

EOX: D1 = Epirubicin 50 mg/m² , Oxaliplatin 130 mg/m² ; D2 to 15: Capecitabine 1 g/m² x 2/d. D1 = D21. Cumulated dose of Epirubicin < 900 mg/m² (max 18 cures)

Cunningham D, et al. N Engl J Med. 2008 Jan 3;358(1):36-46.

The phase III GASTFOX study, most common Treatment-Emergent Adverse Events (TEAEs)

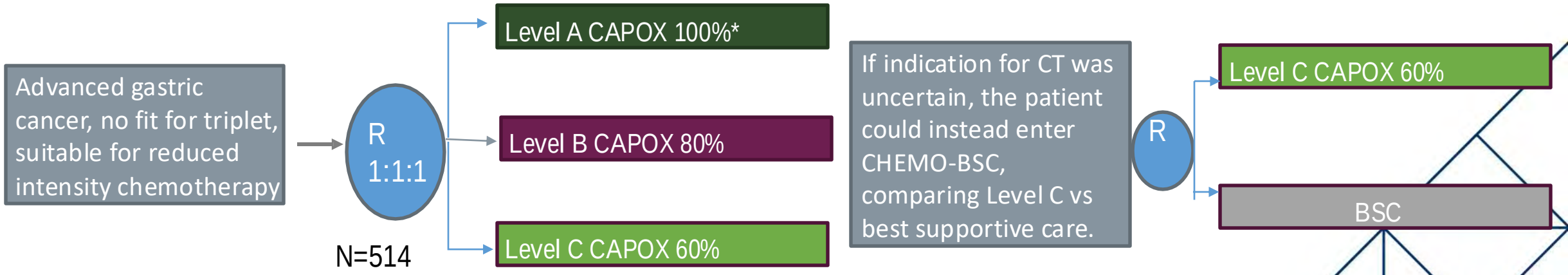
Reported in ≥20% of patients

	mFLOT/TFOX (N=249)			FOLFOX (N=249)			P value* (difference grade 3-4)
	Grade 1-2 N (%)	Grade 3 N (%)	Grade 4 N (%)	Grade 1-2 N (%)	Grade 3 N (%)	Grade 4 N (%)	
Hematologic							
Anemia	168 (67.5)	15 (6.0)	3 (1.2)	154 (61.8)	7 (2.8)	3 (1.2)	NS
Thrombocytopenia	115 (46.2)	6 (2.4)		134 (53.8)	7 (2.8)		NS
Neutropenia	44 (17.7)	45 (18.1)	20 (8.0)	68 (27.3)	33 (13.3)	11 (4.4)	0.02
Febrile neutropenia	-	7 (2.8)		-	4 (1.6)		NS
Non Hematologic							
Peripheral neuropathy	127 (51.0)	79 (31.7)		161 (64.7)	47 (18.9)	2 (0.8)	0.02
Diarrhoea	146 (58.6)	32 (12.9)	4 (1.6)	83 (33.3)	16 (6.4)		0.03
Nausea	153 (61.4)	10 (4.0)		143 (57.4)	11 (4.4)		NS
Vomiting	99 (39.8)	12 (4.8)		70 (28.1)	8 (3.2)		NS
Stomatitis	79 (31.7)	3 (1.2)	1 (0.4)	53 (21.3)	1 (0.4)		NS
Fatigue	174 (69.9)	38 (15.3)		164 (65.9)	18 (7.2)		0.005
Toxic death †	-	2 (<1)		-	1 (<1)		NS

Toxicity was evaluated on the safety set population.
† Toxic death was defined as a chemotherapy-related toxicity resulting in death.
* P value : difference in grade 3-4 toxicities between mFLOT/TFOX and FOLFOX was evaluated by Chi-Square

Special considerations: OPTIMISING CHEMOTHERAPY FOR FRAIL AND ELDERLY PATIENTS:

- Phase 3 GO2 study

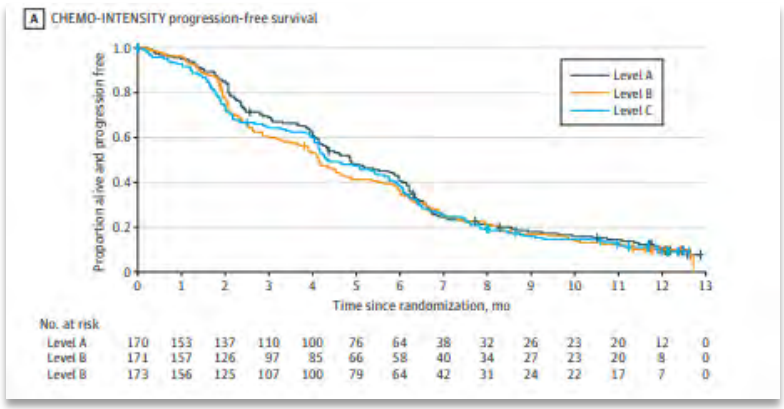


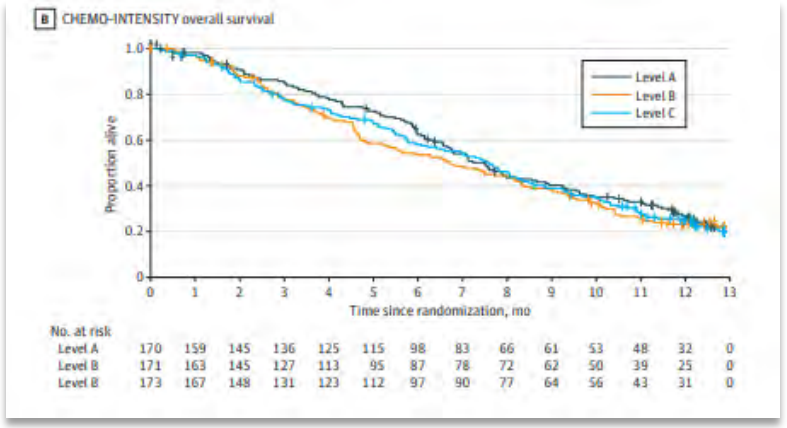
*Oxaliplatin 130 mg/m2 on day 1, capecitabine 625 mg/m2 twice daily on days 1-21, on a 21-day cycle)

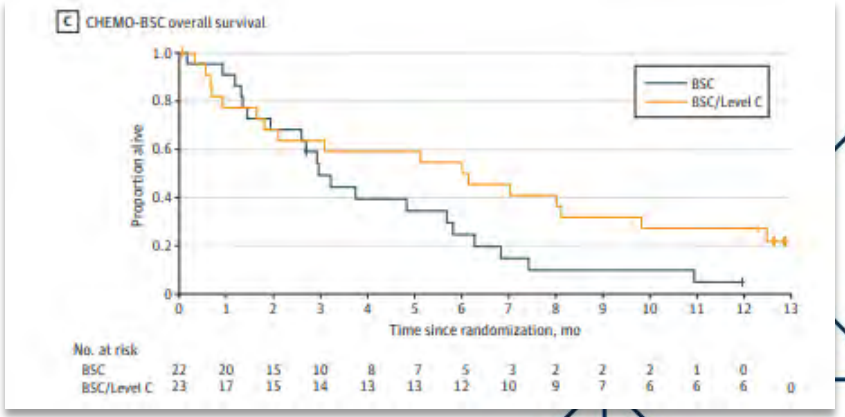
Hall PS, Swinson D, Cairns DA, et al JAMA Oncol. 2021 Jun 1;7(6):869-877.

OPTIMISING CHEMOTHERAPY FOR FRAIL AND ELDERLY PATIENTS: GO2 study

- Reducing chemotherapy intensity did not impact cancer control







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Hall PS, Swinson D, Cairns DA, et al JAMA Oncol. 2021 Jun 1;7(6):869-877.

Toxicities impact according to gender

Table 1. Continued

Baseline characteristics	Total *n* = 3274 (100%)	Men *n* = 2313 (100%)	Women *n* = 961 (100%)	*P* value[a]
5-10 ULN	90 (2.7)	65 (2.8)	25 (2.6)	
>10 ULN	71 (2.2)	55 (2.4)	16 (1.7)	
Not available	138 (4.2)	104 (4.5)	34 (3.5)	
Lactate dehydrogenase (U/l), *n* (%)				0.7586
Normal	1825 (55.7)	1291 (55.8)	534 (55.6)	
Normal to 2.5 ULN	604 (18.4)	421 (18.2)	183 (19.0)	
2.5 to 5 ULN	154 (4.7)	116 (5.0)	38 (4.0)	
5-10 ULN	59 (1.8)	39 (1.7)	20 (2.1)	
>10 ULN	18 (0.5)	12 (0.5)	6 (0.6)	
Not available	614 (18.8)	434 (18.8)	180 (18.7)	
Platelets				0.6953
Normal (100,000-450,000/µl)	2883 (88.1)	2046 (88.5)	837 (87.1)	
High (>450 000/µl)	324 (9.9)	222 (9.6)	102 (10.6)	
Low (<100 000/µl)	33 (1.0)	23 (1.0)	10 (1.0)	
Not available	34 (1.0)	22 (1.0)	12 (1.2)	
Short-course regimens				0.0452
Oxaliplatin based	1451 (44.3)	992 (42.9)	**459 (47.8)**	
Cisplatin based	642 (19.6)	468 (20.2)	174 (18.1)	
Anthracycline based	595 (18.2)	421 (18.2)	174 (18.1)	
Docetaxel based	344 (10.5)	244 (10.5)	100 (10.4)	
Irinotecan based	57 (1.7)	46 (2.0)	11 (1.1)	
Others	185 (5.7)	142 (6.1)	43 (5.4)	
Detailed regimens				0.0179
CAPOX	729 (22.3)	521 (22.5)	208 (21.6)	
FOLFOX	689 (21.0)	449 (19.4)	**240 (25.0)**	
Anthracycline-based	606 (18.5)	429 (18.5)	177 (18.4)	
XP	425 (13.0)	319 (13.4)	115 (12.0)	
Docetaxel-based	346 (11.2)	256 (11.1)	110 (11.4)	
Cisplatin–5FU	200 (6.1)	146 (6.3)	54 (5.6)	
Carboplatin–5FU	75 (2.3)	62 (2.7)	13 (1.4)	
FOLFIRI	34 (1.0)	26 (1.1)	8 (0.8)	
Others	150 (4.6)	114 (4.9)	36 (3.7)	

Significance of bold values are relevant values to consider.
5FU, fluorouracil; ECOG PS, Eastern Cooperative Oncology Group performance status; IHQ, immunohistochemistry; NLR, neutrophil-to-lymphocyte ratio; ULN, upper limit of normal; XP, capecitabine + platinum.
[a]*P* values refer to comparisons by sex and are derived from χ^2 tests for categorical variables, and Wilcoxon test for continuous variables (e.g. age, NLR).

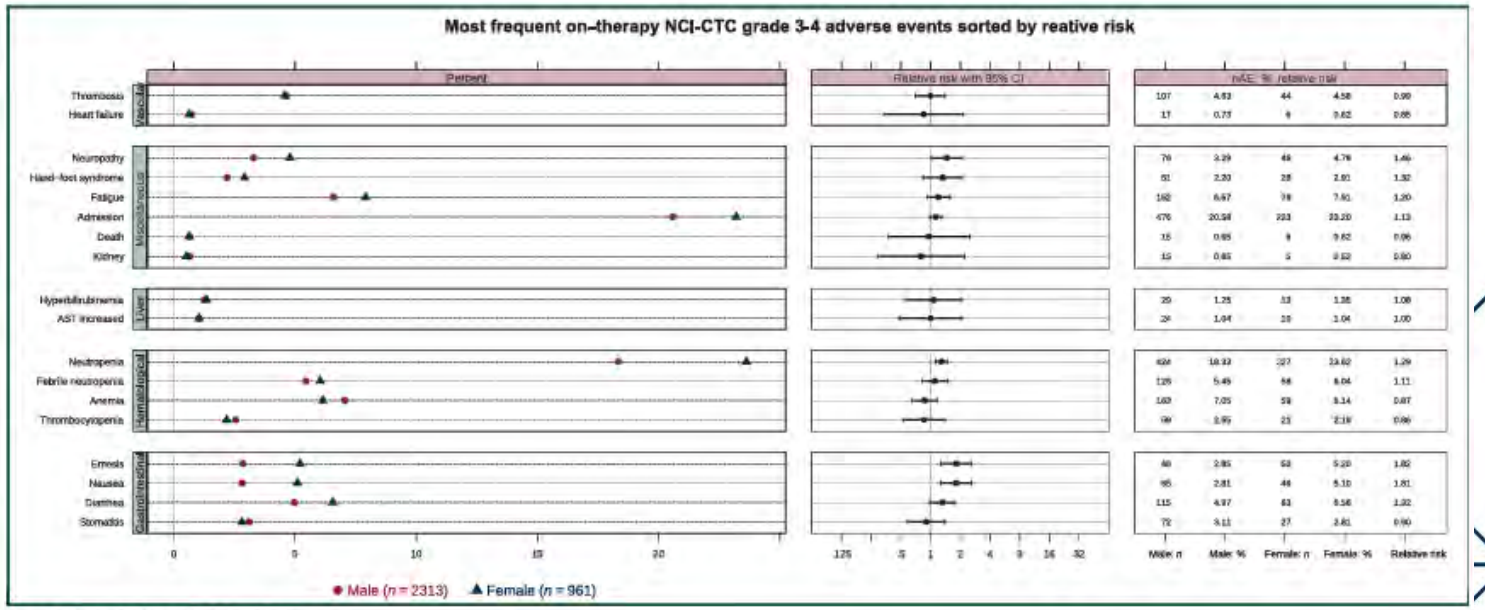


Figure 4. **Amit plot for grade 3-4 toxicity by sex.**
nAE, number of adverse events; NCI-CTC, National Cancer Institute-Common Toxicity Criteria.

Women presented more G3-4 toxicities from CT according to the AGAMENON registry, n=3274

Gallego, J. Et al. ESMO Open. 2022 Jun;7(3):100514.

Toxicities related with trastuzumab

Cisplatin + 5FU/ Capecitabine + trasztuzumab vs Cisplatine + 5-FU / Capecitabine

	Trastuzumab plus chemotherapy (n=294)		Chemotherapy alone (n=290)	
	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Any adverse event	292 (99%)	201 (68%)	284 (98%)	198 (68%)
Gastrointestinal disorders				
Nausea	197 (67%)	22 (7%)	184 (63%)	21 (7%)
Vomiting	147 (50%)	18 (6%)	134 (46%)	22 (8%)
Diarrhoea	109 (37%)	27 (9%)	80 (28%)	11 (4%)
Constipation	75 (26%)	2 (1%)	93 (32%)	5 (2%)
Stomatitis	72 (24%)	2 (1%)	43 (15%)	6 (2%)
Abdominal pain	66 (22%)	7 (2%)	56 (19%)	5 (2%)
Dysphagia	19 (6%)	7 (2%)	10 (3%)	1 (<1%)
Blood and lymphatic system disorders				
Neutropenia	157 (53%)	79 (27%)	165 (57%)	88 (30%)
Anaemia	81 (28%)	36 (12%)	61 (21%)	30 (10%)
Thrombocytopenia	47 (16%)	14 (5%)	33 (11%)	8 (3%)
Febrile neutropenia	15 (5%)	15 (5%)	8 (3%)	8 (3%)
General, metabolic, and other disorders				
Anorexia	135 (46%)	19 (6%)	133 (46%)	18 (6%)
Fatigue	102 (35%)	12 (4%)	82 (28%)	7 (2%)
Hand-foot syndrome	75 (26%)	4 (1%)	64 (22%)	5 (2%)
Weight decreased	69 (23%)	6 (2%)	40 (14%)	7 (2%)
Asthenia	55 (19%)	14 (5%)	53 (18%)	10 (3%)
Pyrexia	54 (18%)	3 (1%)	36 (12%)	0
Renal impairment	47 (16%)	2 (1%)	39 (13%)	3 (1%)
Mucosal inflammation	37 (13%)	6 (2%)	18 (6%)	2 (1%)
Nasopharyngitis	37 (13%)	0	17 (6%)	0
Chills	23 (8%)	1 (<1%)	0	0
Hypokalaemia	22 (7%)	13 (4%)	13 (4%)	7 (2%)
Dehydration	18 (6%)	7 (2%)	16 (6%)	5 (2%)
Dyspnoea	9 (3%)	1 (<1%)	16 (6%)	5 (2%)

Data show adverse events of all grades (>5%) and grade 3 or 4 adverse events (≥1%) plus adverse events of any grade with more than 5% difference between groups.

Table 4: Adverse events

Breast cancer and gastric cancer

Duration of treatment

Patients with MBC or MGC should be treated with Herceptin until progression of disease. Patients with EBC should be treated with Herceptin for 1 year or until disease recurrence, whichever occurs first; extending treatment in EBC beyond one year is not recommended (see section 5.1).

Dose reduction

No reductions in the dose of Herceptin were made during clinical trials. Patients may continue therapy during periods of reversible, chemotherapy-induced myelosuppression but they should be monitored carefully for complications of neutropenia during this time. Refer to the SmPC for paclitaxel, docetaxel or aromatase inhibitor for information on dose reduction or delays.

If left ventricular ejection fraction (LVEF) percentage drops ≥ 10 points from baseline AND to below 50 %, treatment should be suspended and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or has declined further, or if symptomatic congestive heart failure (CHF) has developed, discontinuation of Herceptin should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. All such patients should be referred for assessment by a cardiologist and followed up.

Monitoring

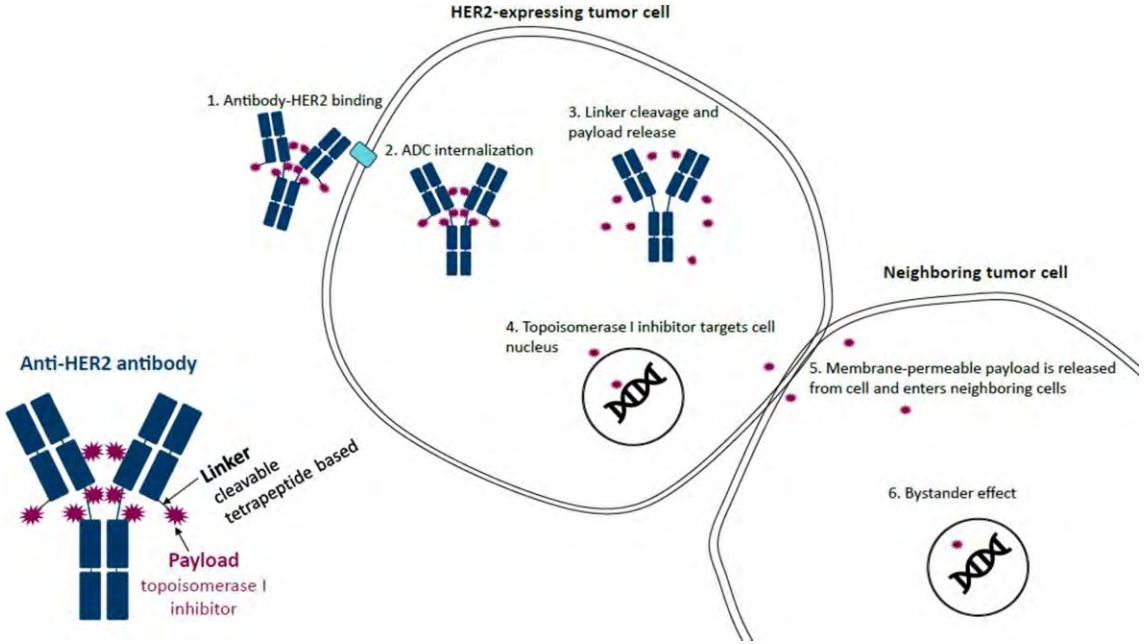
Cardiac assessments, as performed at baseline, should be repeated every 3 months during treatment and every 6 months following discontinuation of treatment until 24 months from the last administration of Herceptin.

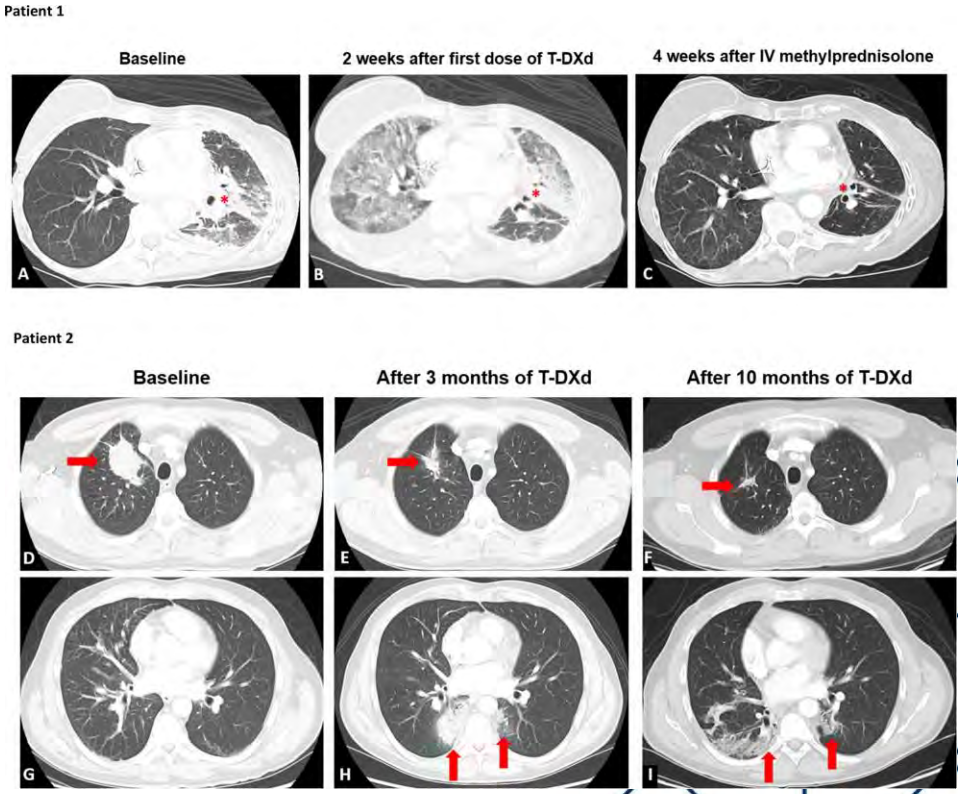
The number of patients with cardiac dysfunction (defined as a ≥10% drop in LVEF to an absolute value <50%) was low in both treatment groups (trastuzumab plus chemotherapy, 11 [5%] of 237 *vs* chemotherapy alone, two [1%] of 187).

Bang, Yung-Jue et al. The Lancet, Volume 376, Issue 9742, 687 – 697
http://www.ema.europa.eu

- Fleitas,T. ESMO ON AIR

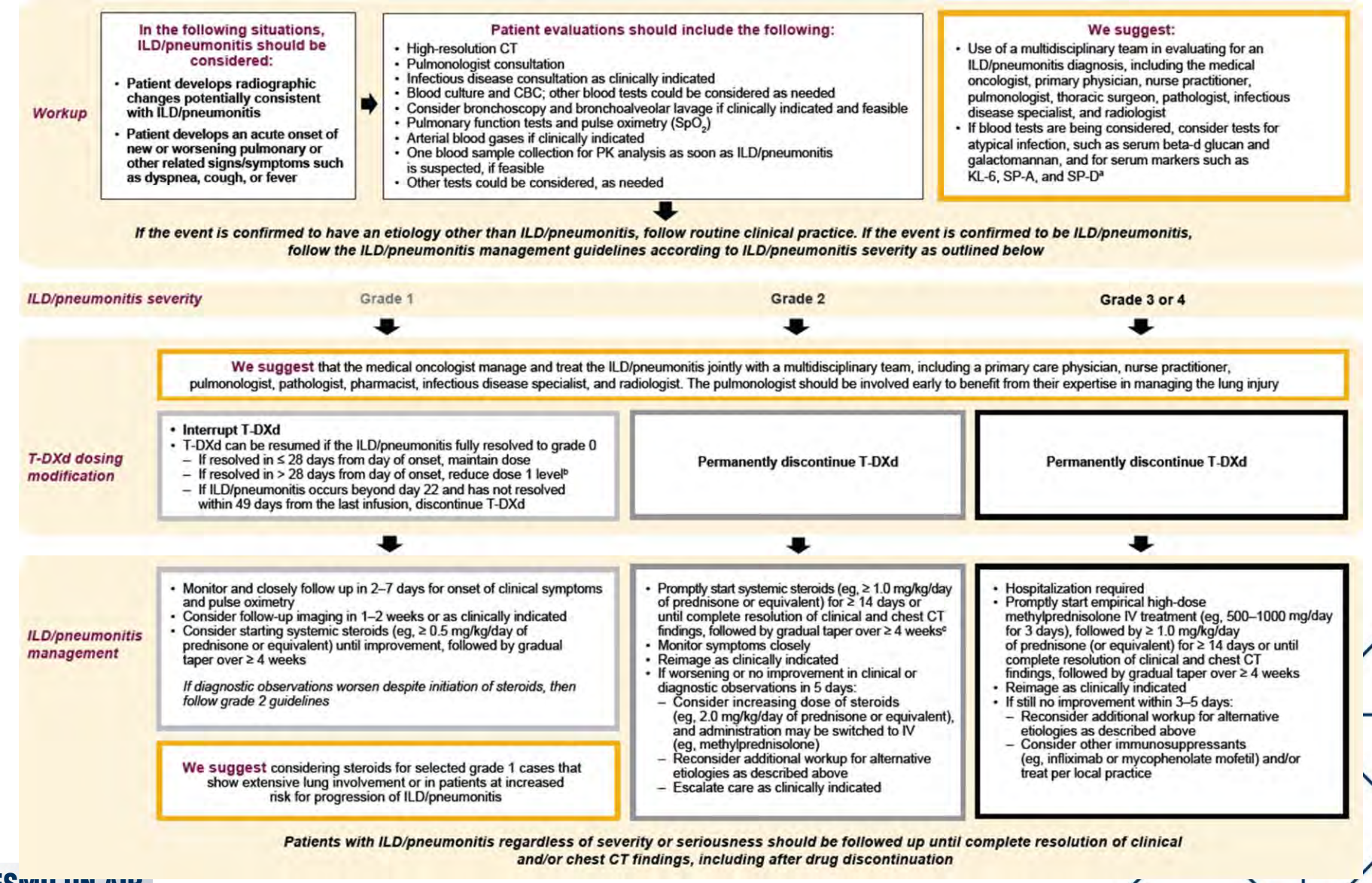
Toxicities related with trastuzumab-deruxtecan





Swain SM et al. *Cancer Treat Rev.* 2022;106:102378

Toxicities related with trastuzumab-deruxtecan



Swain SM et al. *Cancer Treat Rev.* 2022;106:102378

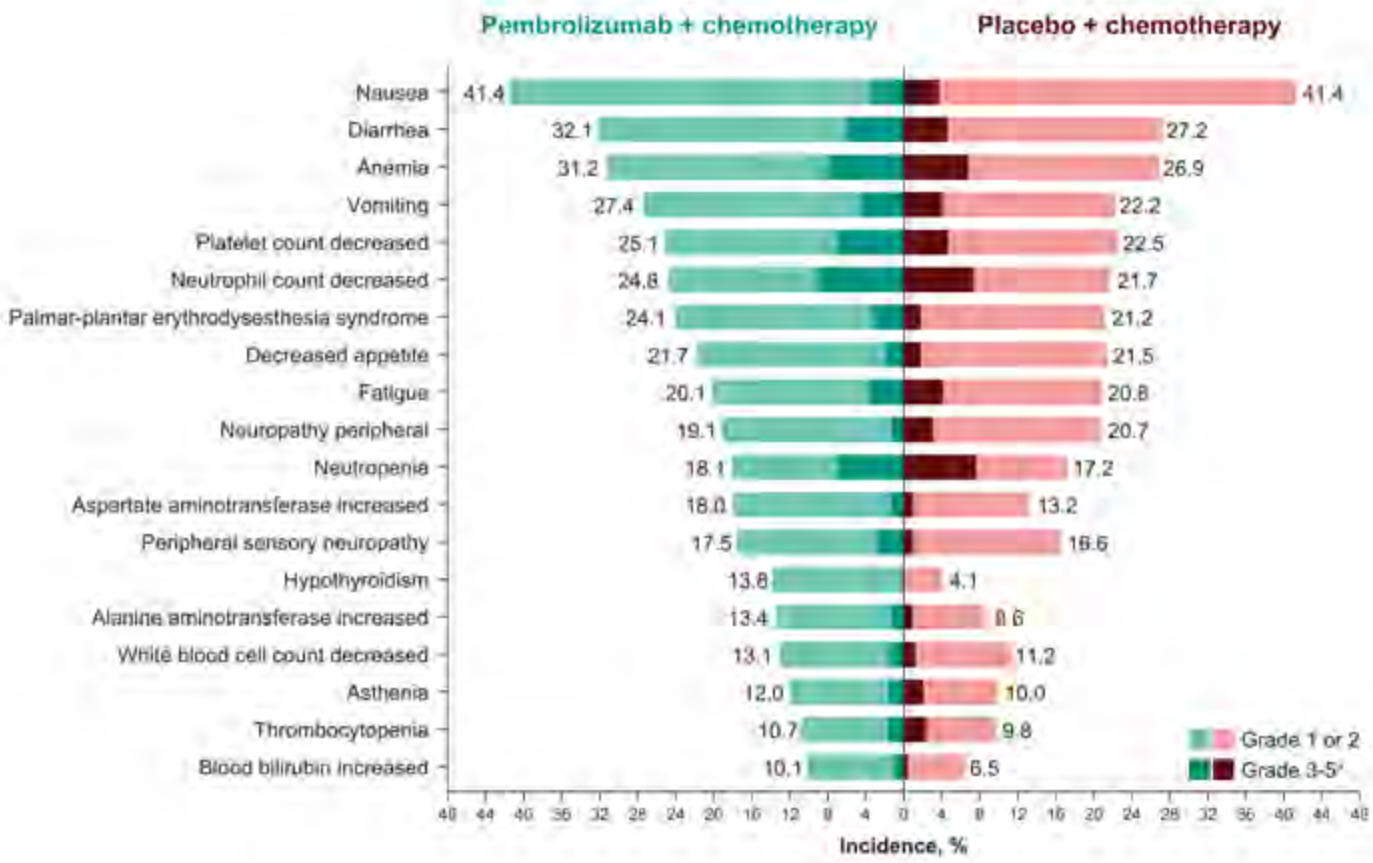
- Fleitas T.

IMMUNOTHERAPY ADVERSE EVENTS

Safety

- Treatment-related AEs occurred in 751 patients (95.7%) in the pembrolizumab plus chemotherapy group and 736 patients (93.5% in the placebo plus chemotherapy group
- Grade 3-5 treatment-related AEs occurred in 466 patients (59.4%) in the pembrolizumab plus chemotherapy group and 404 patients (51.3%) in the placebo plus chemotherapy group

Treatment-related AEs with incidence ≥10% in either treatment group



[a]In the pembrolizumab plus chemotherapy group, 8 patients died of treatment-related AEs (1 death, 1 diarrhea, 1 peripheral embolism, 1 pneumonitis, 1 pulmonary hemorrhage, 1 sepsis, 1 septic shock,1 thrombotic thrombocytopenic purpura). In the placebo plus chemotherapy group, 16 patients died of treatment-related AEs (2 acute myocardial infarction, 1 cerebral hemorrhage, 1 cerebrovascular accident, 1 diarrhea, 1 gastric perforation, 1 hepatic function abnormal, 1 neurotoxicity, 1 pneumonitis, 1 pulmonary embolism, 1 sepsis, 3 septic shock, 1 sudden death, 1 urosepsis).

Immunotherapy chronic adverse events

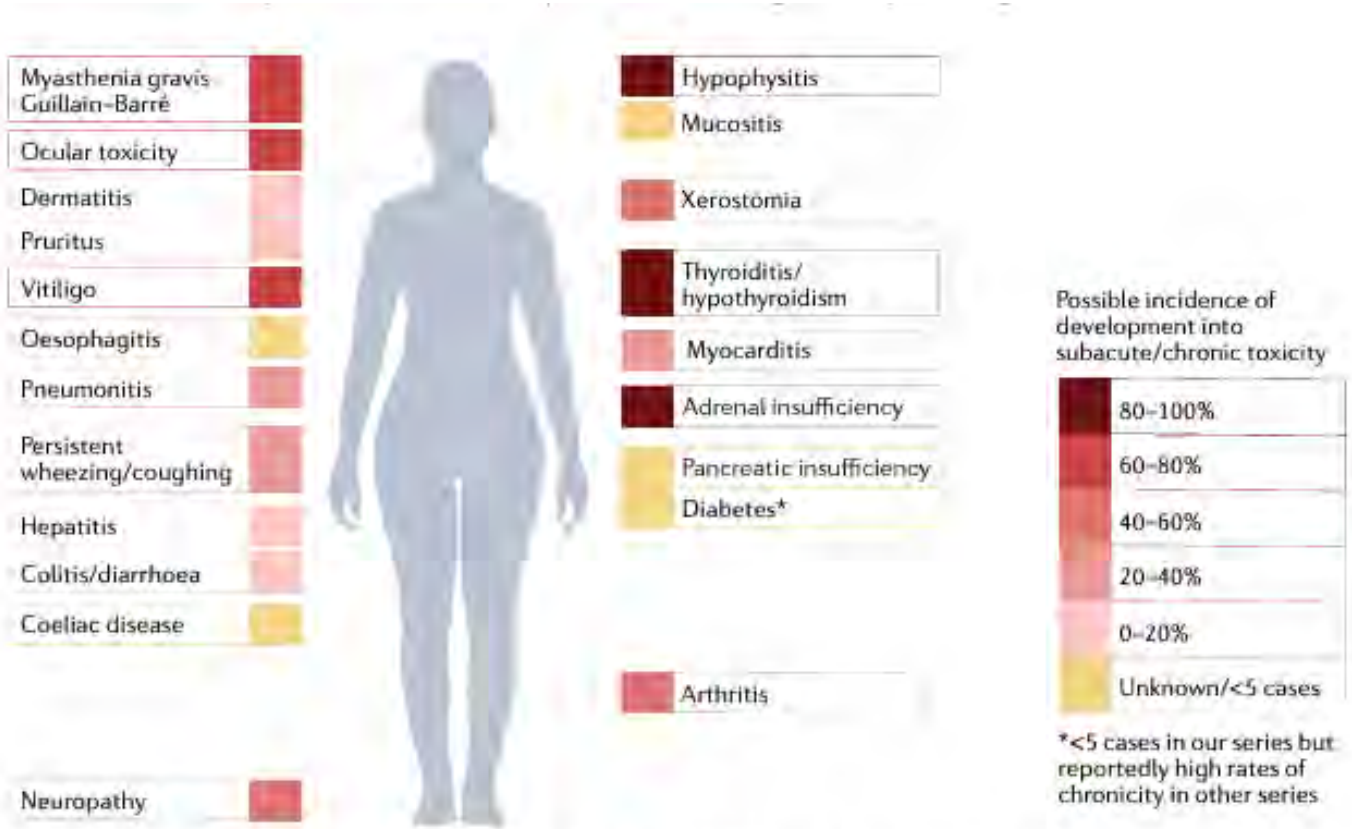


Fig. 3 | **Possible frequencies of chronic immune-checkpoint inhibitor-induced toxicities.** The exact risks of acute toxicities becoming chronic (defined as persisting for at least 12 weeks beyond treatment cessation) are currently unknown, although endocrinopathies, arthritis, xerostomia, neurotoxicities and ocular events are generally more likely to become chronic toxicities. Immune-related adverse events affecting the visceral organs seem to have a lower risk of becoming chronic. Percentages expressed are the percentages of acute toxicities that become chronic (defined as those that persist for at least 12 weeks following immune-checkpoint inhibitor discontinuation) from REF[14].

Johnson, D.B., *et al. Nat Rev Clin Oncol* **19**, 254–267 (2022).

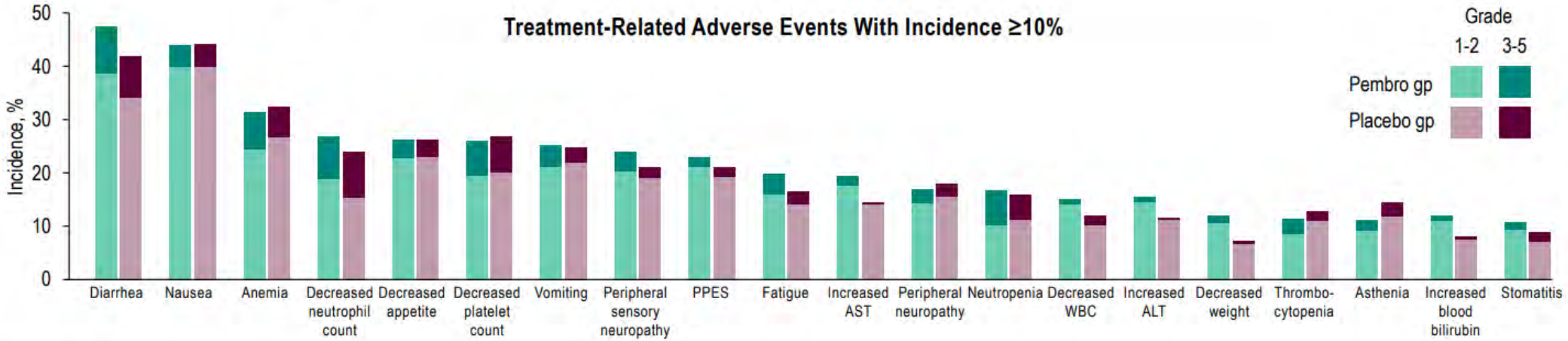
Immunotherapy + targeted therapy adverse events

KN811 FINAL RESULTS

Treatment-related Adverse Events

Summary of Adverse Events in all Treated Patients

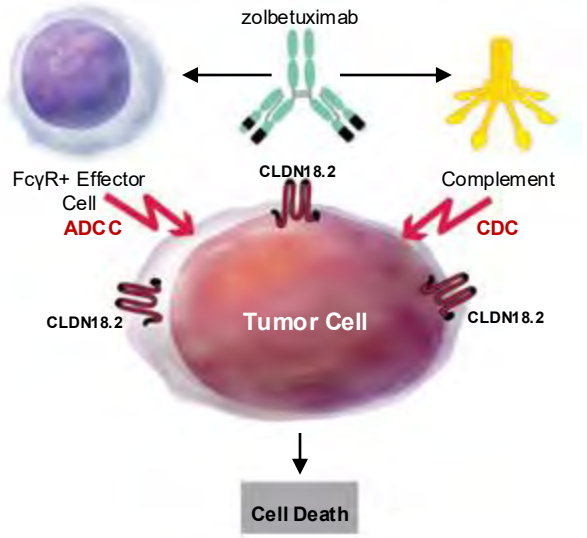
AEs, n (%)	Pembrolizumab Group N = 350	Placebo Group N = 346
Any grade AEs	348 (99)	346 (100)
Treatment-Related AEs	341 (97)	334 (97)
Serious	91 (26)	79 (23)
Grade 3-4	202 (58)	173 (50)
Grade 5	4 (1)	3 (1)
Led to discontinuation of any drug	130 (37)	117 (34)



ESMO

Data cutoff date: 20 Mar 2024. ALT, alanine aminotransferase, AST, aspartate aminotransferase, PPES, plantar-palmar erthrodysaethesia syndrome. Grade 5 treatment-related AEs of hepatitis, sepsis, cerebral infarction, and pneumonitis occurred in one patient each in the pembrolizumab group, and of pulmonary embolism, cholangitis, and myocarditis in one patient each in the placebo group.

Zolbetuximab + chemotherapy



CLDN18.2, a tight junction protein, expressed in normal and malignant gastric mucosa cells, become exposed on the surface of G/GEJ adenocarcinoma cells during malignant transformation, making it a promising target

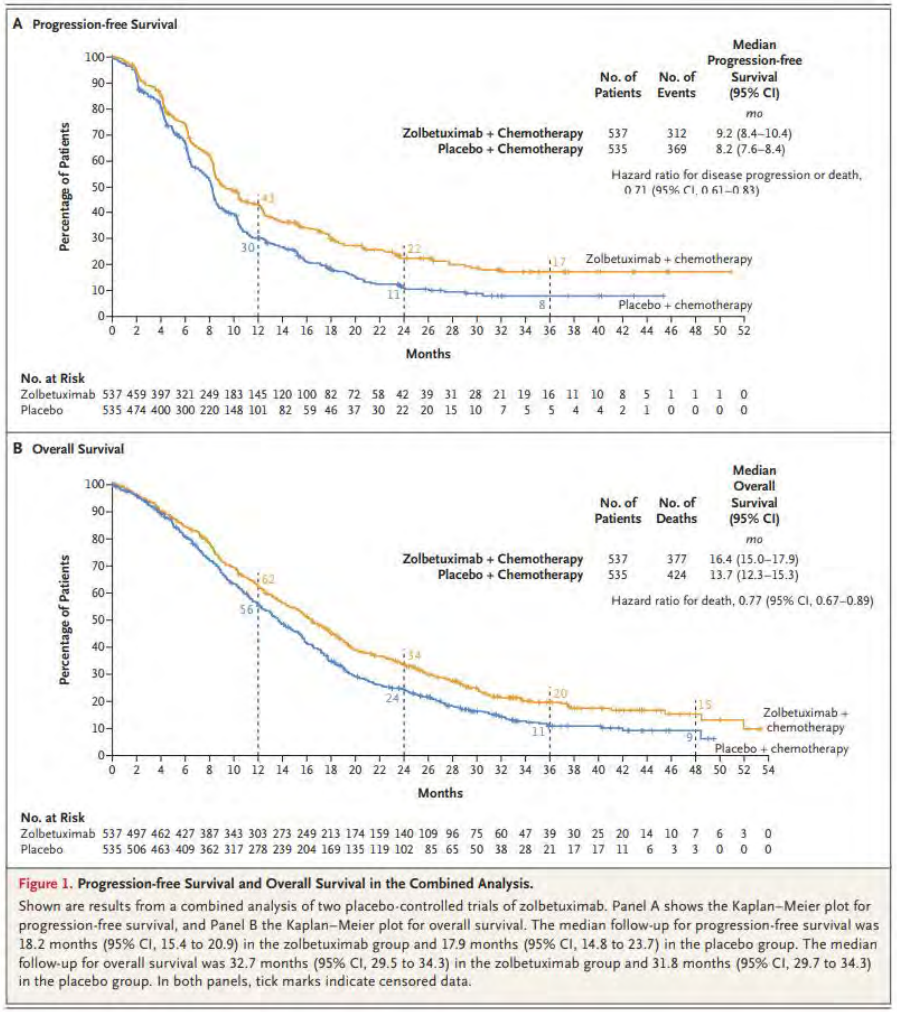


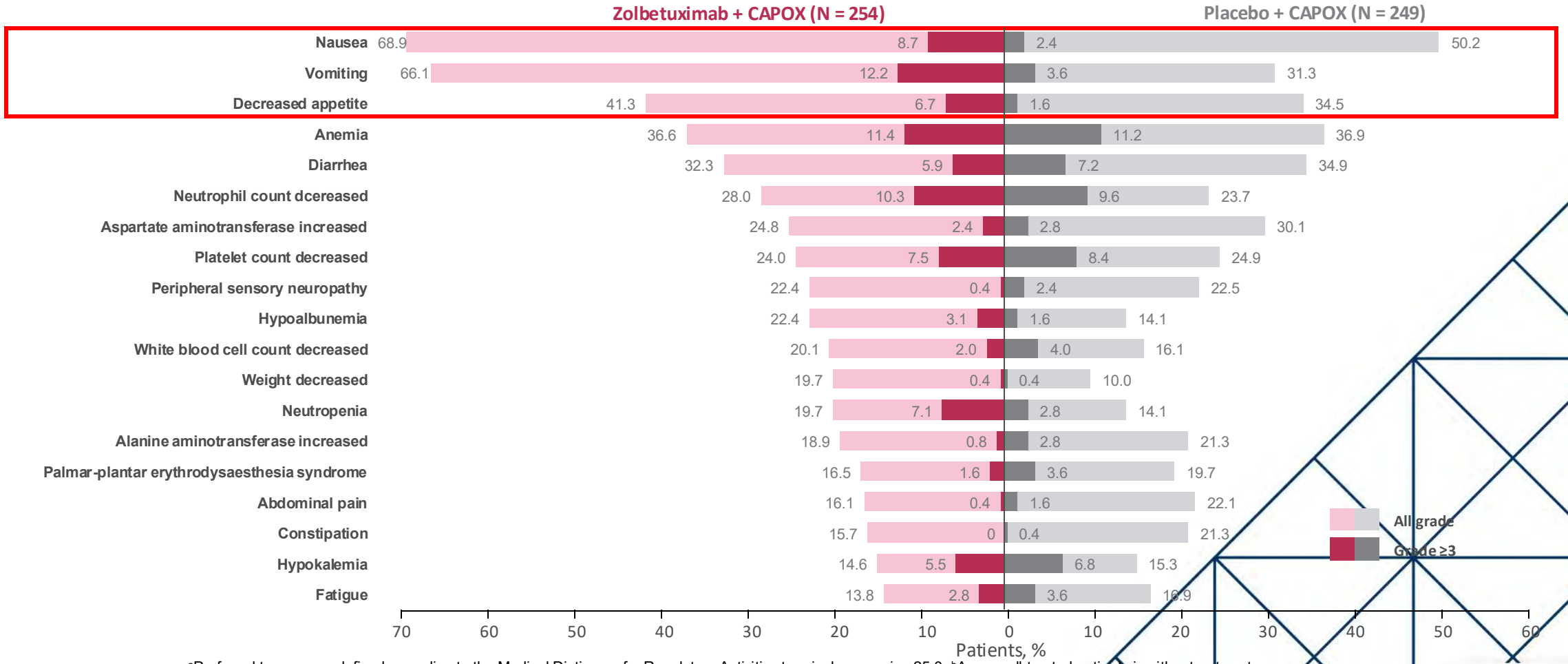
Figure 1. Progression-free Survival and Overall Survival in the Combined Analysis.
Shown are results from a combined analysis of two placebo-controlled trials of zolbetuximab. Panel A shows the Kaplan–Meier plot for progression-free survival, and Panel B the Kaplan–Meier plot for overall survival. The median follow-up for progression-free survival was 18.2 months (95% CI, 15.4 to 20.9) in the zolbetuximab group and 17.9 months (95% CI, 14.8 to 23.7) in the placebo group. The median follow-up for overall survival was 32.7 months (95% CI, 29.5 to 34.3) in the zolbetuximab group and 31.8 months (95% CI, 29.7 to 34.3) in the placebo group. In both panels, tick marks indicate censored data.

Sahin U et al. *Ann Oncol.* 2021;32:609–619;
Shitara K, et al. N Engl J Med. 2024 Sep 26;391(12):1159-1162.

Zolbetuximab adverse events in combination with chemotherapy: results from the Glow study

The most common TEAEs with zolbetuximab + CAPOX were nausea, vomiting, and decreased appetite as on-target effects

- Nausea and vomiting occurred mostly during the first zolbetuximab cycle[1]



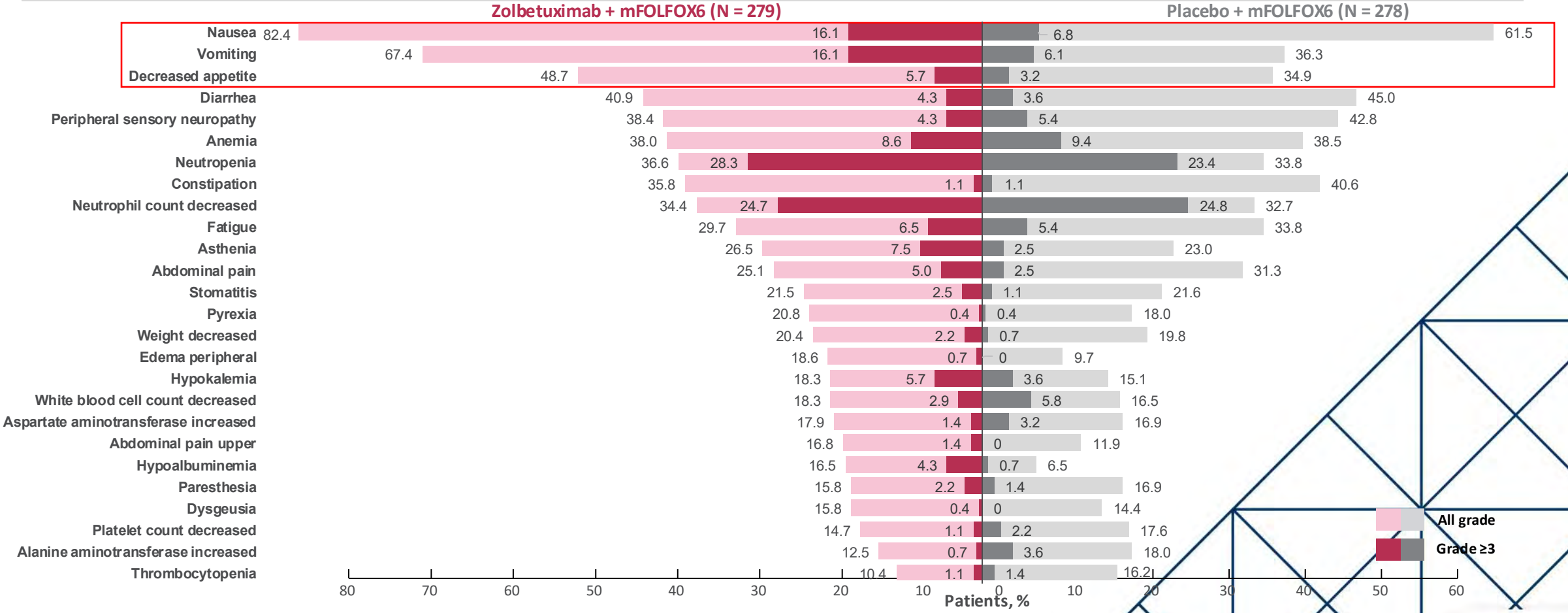
[a]Preferred terms were defined according to the Medical Dictionary for Regulatory Activities terminology version 25.0; [b]Among all treated patients in either treatment arm.

1. Shah MA et al. *Nat Med. 2023;* 29(8):2133–2141.

Zolbetuximab adverse events in combination with chemotherapy: results from the Spotlight study

- Dr

The incidence of overall TEAEs was similar between treatment arms
The most common TEAEs with zolbetuximab + mFOLFOX6 were nausea, vomiting, and decreased appetite as on-target effects
Nausea and vomiting occurred mostly during the first zolbetuximab cycle

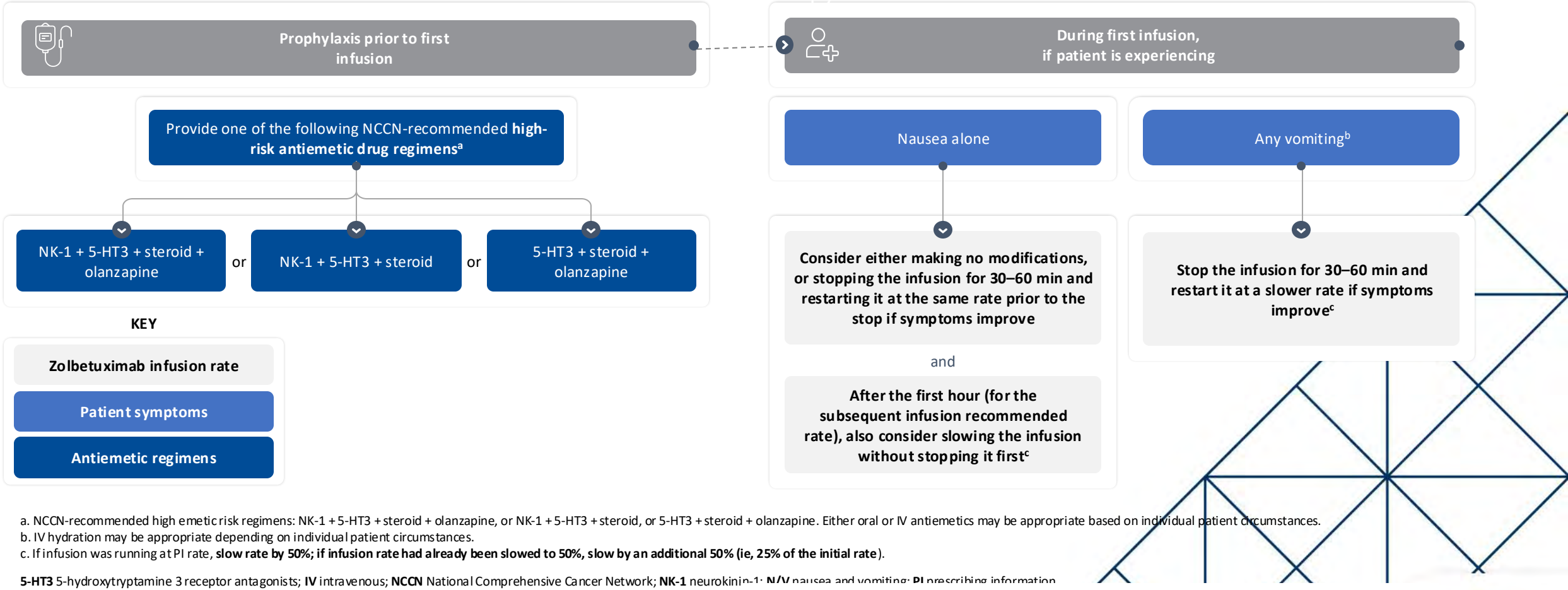


[a]Preferred terms were defined according to the Medical Dictionary for Regulatory Activities terminology version 25.0; [b]Among all treated patients in either treatment arm.

• Consensus guidance for management of nausea/vomiting in patients treated with zolbetuximab + chemotherapy: A RAND/UCLA modified Delphi panel study

- Experts from US, Europe, Japan and South Korea reviewed 382 scenarios, reaching agreement in **85%** (n = 324) of the scenarios for Round 2

Prior to and During 1st Infusion: Consensus Guidance on the Prevention and Management of N/V in Patients Treated With Zolbetuximab + Chemotherapy



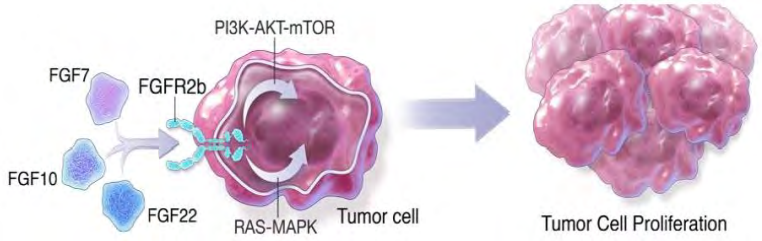
a. NCCN-recommended high emetic risk regimens: NK-1 + 5-HT3 + steroid + olanzapine, or NK-1 + 5-HT3 + steroid, or 5-HT3 + steroid + olanzapine. Either oral or IV antiemetics may be appropriate based on individual patient circumstances.
b. IV hydration may be appropriate depending on individual patient circumstances.
c. If infusion was running at PI rate, **slow rate by 50%; if infusion rate had already been slowed to 50%, slow by an additional 50% (ie, 25% of the initial rate)**.

5-HT3 5-hydroxytryptamine 3 receptor antagonists; **IV** intravenous; **NCCN** National Comprehensive Cancer Network; **NK-1** neurokinin-1; **N/V** nausea and vomiting; **PI** prescribing information

ESMO ON AIR

Klempner, S.J. et al.
Annals of Oncology, Volume 35, S202

Bemarituzumab



- FGFR2b is a member of the FGFR family (FGFR1-4) and is a splice isoform of FGFR2.
- FGFR2b overexpression: 3-61% of gastric cancer depending on tumor stage and assay.
- FGFR tyrosine kinase inhibitors have shown clinical benefit in cancers with FGFR mutations, fusions or translocations.

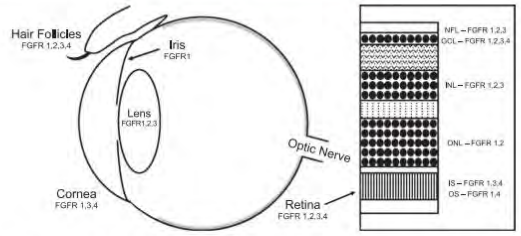


Fig. 1 – Known expression patterns of the different fibroblast growth factor receptor isoforms throughout the human eye (partially adapted from Magone et al[39]). Differential expression patterns throughout different retinal layers as reported by Kirby and Johnston 2004[41] shown on the right. NFL = nerve fiber layer; GCL = ganglion cell layer; INL = inner nuclear layer; ONL = outer nuclear layer; IS = inner segments of rods and cones; OS = outer segments of rods and cones.

Table 1 – (continued)

Drug	Study	Phase	Pts	Ocular toxicity reported (total number, percentage)
Bemarituzumab (FPA144)	Wainberg 2022[40]	II	76	Any cornea disorder (67%) Dry eye (20; 26%) Blurred vision (12; 16%) Keratitis (11; 14%) Punctate keratitis (10; 13%) Cataract (7; 9%) Limbal stem cell deficiency (6; 8%) Ulcerative keratitis (3; 4%)

CSR = central serous retinopathy; FGFR = fibroblast growth factor receptor; RPE = retinal pigment epithelium.
Ocular toxicities are listed in decreasing order of frequency for each study and as originally specified in each clinical trial to avoid misrepresentation of the describe adverse events.
‡ Charng et al reported ophthalmic details of the patients studied in Lam et al.
† Dry eye as side effect was only reported in dose expansion portion of study.

Table 2 – Summary of cases reported with prominent corneal toxicity or findings associated with FGFR inhibitor use, by publication date.

Study	Drug	Time until onset	Toxicity‡	Drug intervention	Treatment
Magone 2021[39]	Infigratinib	84 d	Grade 2 epitheliopathy OU, trichomegaly	Interruption	Topical lubrication and steroids
	Infigratinib	98 d	Grade 1 epitheliopathy OU, trichomegaly, anterior capsular changes OU	NS	Topical lubrication and steroids
	Infigratinib	117 d	Grade 3 epitheliopathy OU	Interruption	Topical lubrication and steroids
	Infigratinib	87 d	Grade 1 epitheliopathy, OU, deep demarcation line, trichomegaly OU, trichiasis OS	NS	Topical lubrication and steroids
	Infigratinib	108 d	Grade 3 epitheliopathy, recurrent erosions OD, trichomegaly	Temporary discontinuation, cyclical treatment restarted	Topical lubrication, steroids, serum tears
Bauters 2021[42]	Erdafitinib	3 m	Dry eye, corneal thinning OU	Temporary discontinuation with dose reduction	Topical lubrication
	Erdafitinib	3 m	Dry eye, corneal thinning OU, sterile ulcer OS, white cataract OU, secondary angle closure OS	Discontinuation	Topical lubrication, regenerating matrix therapy agent, serum tears, laser iridotomy, cataract surgery
	Erdafitinib	1 m	Dry eye, unilateral corneal thinning OS, white cataract OU, FGFRAR	Discontinuation	Topical lubrication, cataract surgery
Shin 2020[43]	ASP5878	55 d	Corneal dysmaturation. Diffuse opacification, epithelial staining along keratopathy demarcation	Discontinuation	NS
	Bemarituzumab	73 d	Corneal dysmaturation, superior and inferior demarcations with fluorescein staining	Discontinuation	NS
	Bemarituzumab	68 d	Corneal dysmaturation	NS	NS
Hsu 2023[44]	Erdafitinib	7 w	Severe meibomian gland dysfunction, trichiasis, corneal melt OU with bacterial superinfection	Discontinuation	Topical antibiotics, steroids, serum tears, wound healing agents

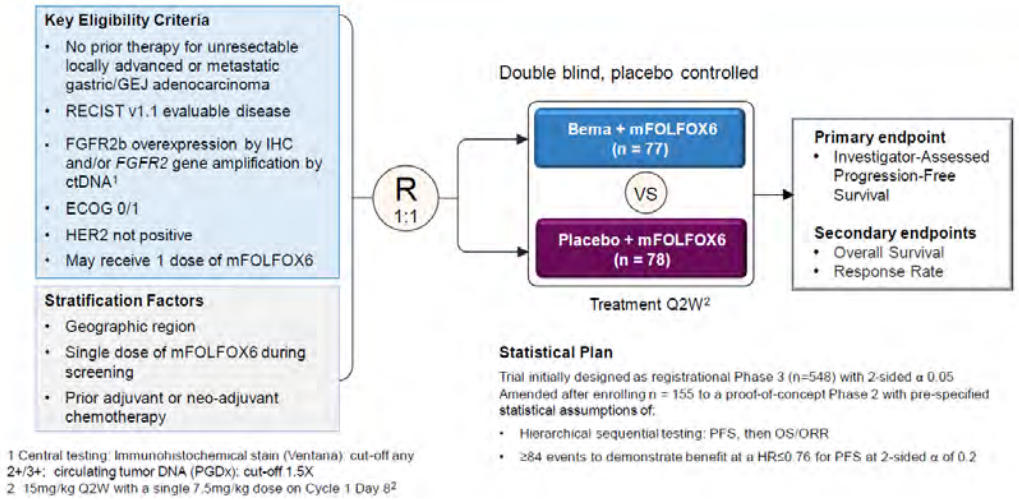
NS = not specified; d = day; w = week; m = month; OU = both eyes; OD = right eye; OS = left eye; FGFRAR = fibroblast growth factor receptor inhibitor-associated retinopathy; FGFR = fibroblast growth factor receptor.
‡ Adverse events were graded using Common Terminology Criteria for Adverse Events v5.0 when specified.

Wainberg ZA, et al. Lancet Oncol. 2022 Nov;23(11):1430-1440.
Su, Jerry et al. Survey of Ophthalmology, Volume 69, Issue 1, 34 - 41

- Fleitas T.

Bemarituzumab

FIGHT Trial Design



Summary of Selected Treatment-Emergent Adverse Events

Selected Adverse Events	Any Grade		Grade ≥ 3	
	Bema (N = 76)	Placebo (N = 77)	Bema (N = 76)	Placebo (N = 77)
Preferred Term	76 (100.0%)	76 (98.7%)	63 (82.9%)	57 (74.0%)
Nausea	36 (47.4%)	41 (53.2%)	0	3 (3.9%)
Vomiting	22 (28.9%)	24 (31.2%)	2 (2.6%)	2 (2.6%)
Diarrhoea	31 (40.8%)	24 (31.2%)	2 (2.6%)	1 (1.3%)
Stomatitis	24 (31.6%)	10 (13.0%)	7 (9.2%)	1 (1.3%)
Peripheral sensory neuropathy	15 (19.7%)	15 (19.5%)	4 (5.3%)	3 (3.9%)
Neutrophil count decreased	31 (40.8%)	33 (42.9%)	23 (30.3%)	27 (35.1%)
Platelet count decreased	14 (18.4%)	21 (27.3%)	1 (1.3%)	0
Aspartate aminotransferase increased	23 (30.3%)	15 (19.5%)	4 (5.3%)	2 (2.6%)
Alanine aminotransferase increased	22 (28.9%)	11 (14.3%)	2 (2.6%)	1 (1.3%)
Dry eye	20 (26.3%)	5 (6.5%)	2 (2.6%)	0

Trial required corneal evaluation at baseline and every 8 weeks until the end of treatment

Wainberg ZA, et al. ASCO GI 2021; Lancet Oncol. 2022 Nov;23(11):1430-1440.

- Fleitas T.

Zanidatamab

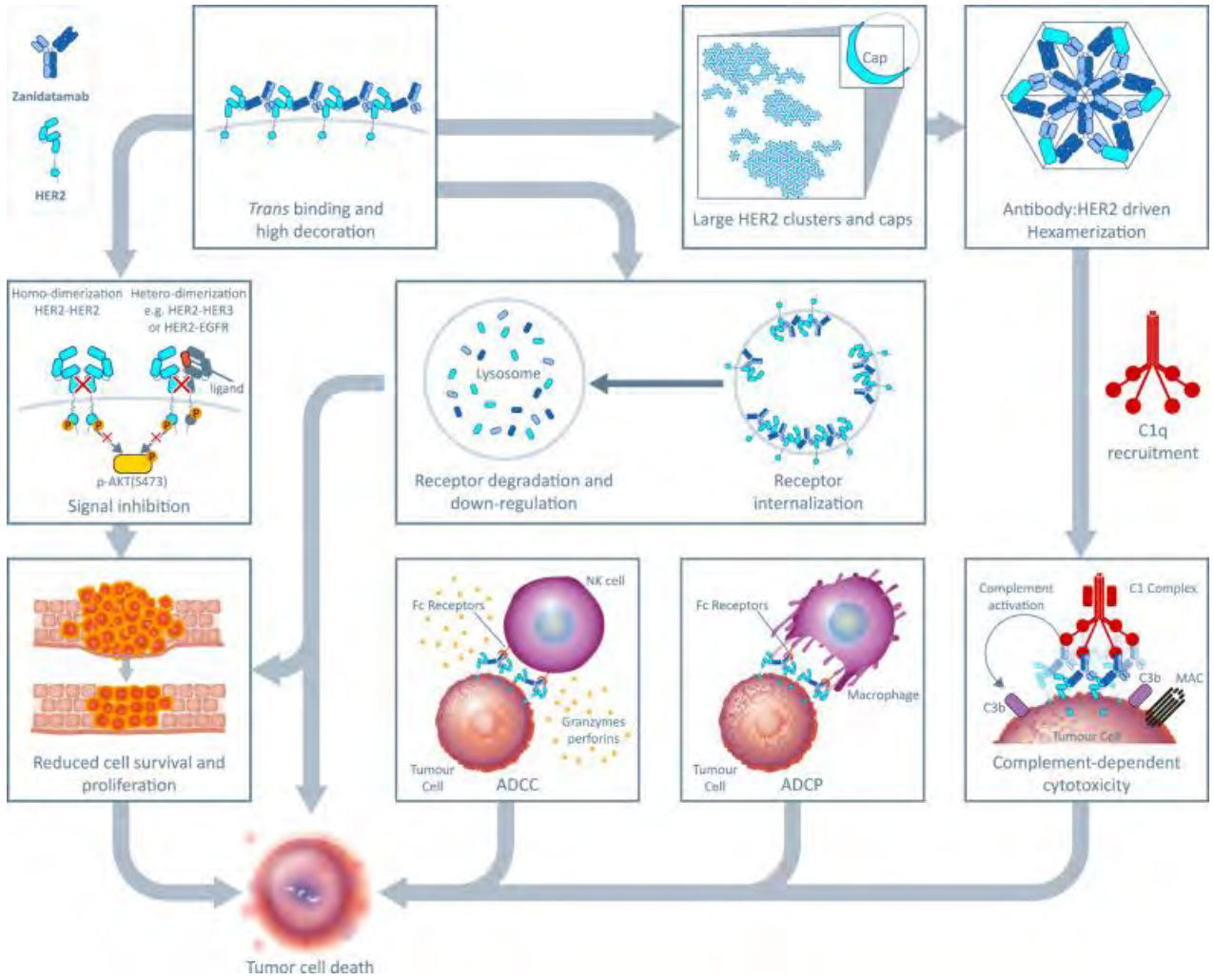


Table 3: Summary of Treatment (Zanidatamab and/or Chemotherapy)-related Adverse Events (TRAEs)

	Zanidatamab + CAPOX (n =20)		Zanidatamab + mFOLFOX6 (n = 24)		Zanidatamab + FP (n = 2)		Total (N = 46)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Any TRAE[a]	20 (100)	9 (45)	24 (100)	18 (75)	2 (100)	1 (50)	46 (100)	28 (61)
Treatment-related SAE	2 (10)	2 (10)	5 (21)	5(21)	1 (50)	1 (50)	8 (17)[b]	8(17)
TRAEs leading to zanidatamab DC	0	0	3 (13)	1 (4)	0	0	3 (7)[c]	1 (2)
TRAEs, any Grade occurring in ≥ 20% of patients or Grade ≥ 3 in ≥ 2 patients (based on the Total group)								
Diarrhea	18 (90)	6 (30)	23 (96)	9 (38)	2 (100)	1 (50)	43 (93)	16 (35)
Nausea	15 (75)	1 (5)	20 (83)	2 (8)	1 (50)	0	36 (78)	3 (7)
Peripheral neuropathy	14 (70)	0	14 (58)	0	0	0	28 (61)	0
Fatigue	6 (30)	0	14 (58)	2 (8)	0	0	20 (43)	2 (4)
Decreased appetite	7 (35)	0	12 (50)	0	1 (50)	0	20 (43)	0
Vomiting	4 (20)	1 (5)	11 (46)	3 (13)	0	0	15 (33)	4 (9)
Hypokalemia	2 (10)	0	11 (46)	7 (29)	0	0	13 (28)	7 (15)
Stomatitis	2 (10)	0	9 (38)	0	0	0	11 (24)	0
Neutrophil count decr.	3 (15)	0	7 (29)	3 (13)	0	0	10 (22)	3 (7)
Hypomagnesemia	3 (15)	0	6(25)	1 (4)	0	0	9 (20)	1 (2)
Dysgeusia	4 (20)	0	5(21)	0	0	0	9 (20)	0
Acute kidney injury	0	0	2(8)	1 (4)	1 (50)	1 (50)	3 (7)	2 (4)
WBC count decreased	0	0	7 (29)	3 (13)	0	0	7 (15)	3 (7)
Treatment-related AESIs occurring in any patient								
Infusion-related reaction	6 (30)	0	3 (13)	0	1 (50)	0	10 (22)	0
Ejection fraction decr.	0	0	2 (8)	0	0	0	2 (4)	0
Pneumonitis	0	0	0	0	0	0	0	0

Data are reported as number of patients, n (%). **a.** All AEs were recorded using the Medical Dictionary for Regulatory Activities (MedDRA) with severity graded by investigators according to the National Cancer institute Common Terminology Criteria for Adverse Events version 5.0. **b.** Treatment-related SAEs: diarrhea (3 patients), acute kidney injury (2 patients), vomiting (2 patients), hypokalemia (2 patients), hypomagnesemia (1 patient), nausea (1 patient), stomatitis (1 patient), upper GI hemorrhage (1 patient) **c.** Treatment-related adverse events that led to discontinuation of zanidatamab: diarrhea (2 patients), vomiting (1 patient).
AESI = adverse event of special interest; DC = discontinuation; SAE = serious adverse event; WBC = white blood cell.

Elimova E. ASCO GI 2023; Weisser NE, Nat Commun. 2023 Mar 13;14(1):1394.

New combination strategies

- LEAP 015: PEMBRO+ LENVATINIB

Figure 1. Study design

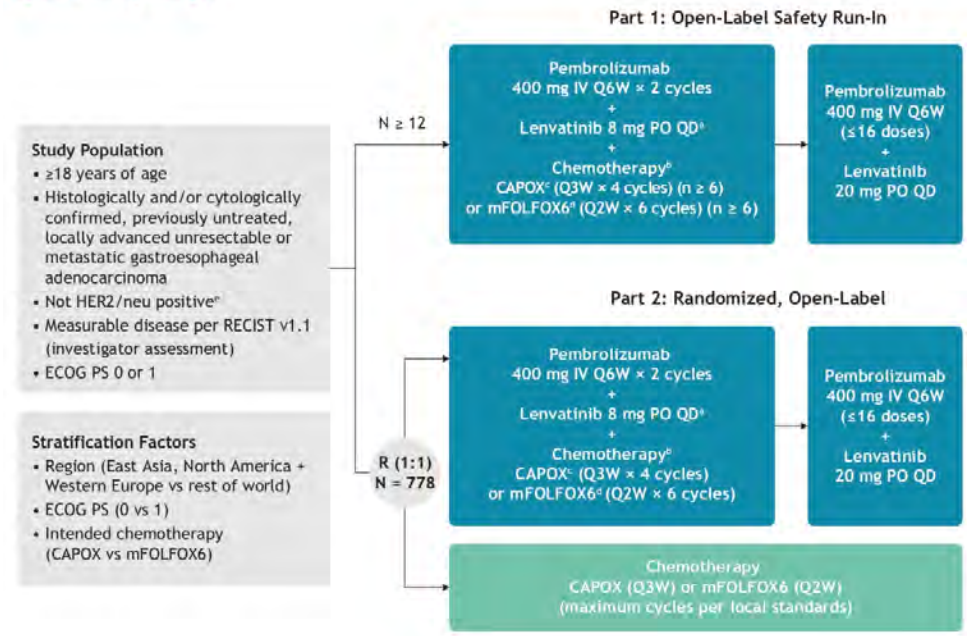
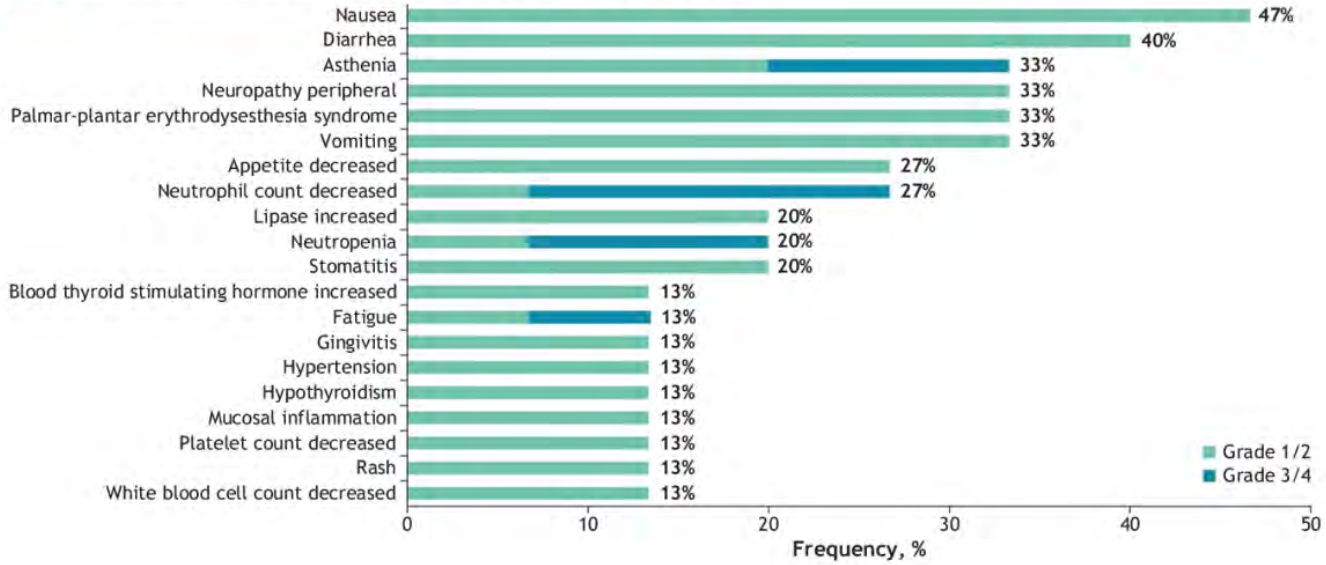


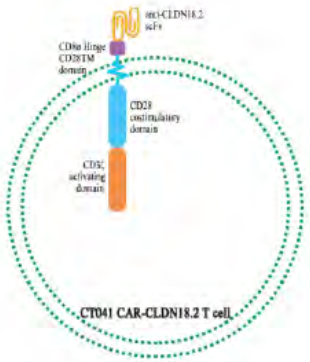
Figure 2. Treatment-related AEs with a frequency of ≥10%



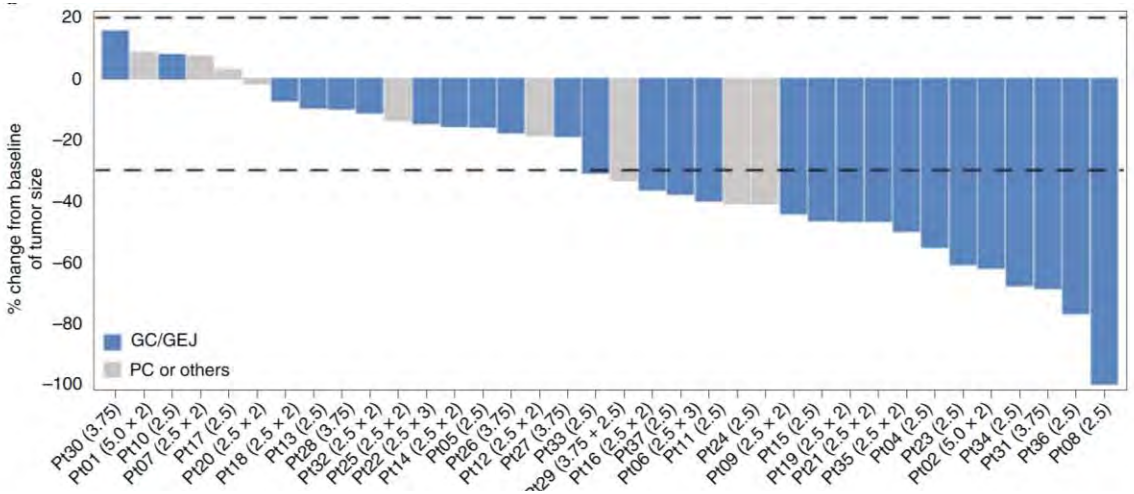
ESMO ON AIR

Weber P. et al. ASCO GI 2023

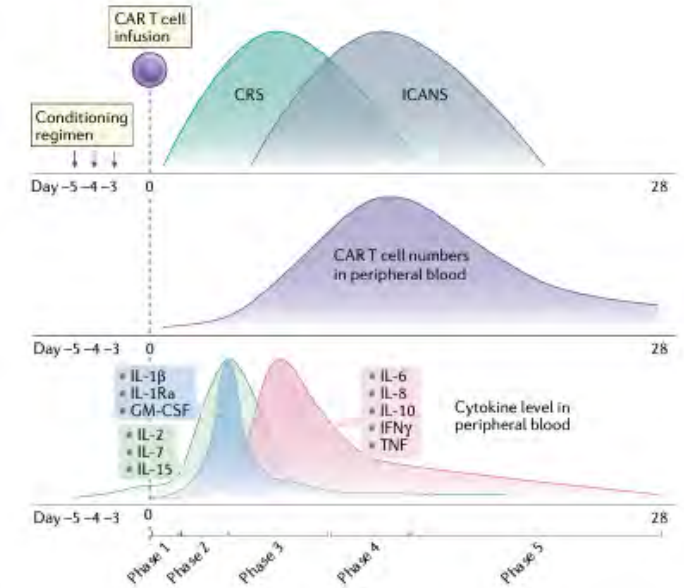
CELLULAR THERAPY for Gastric Cancer

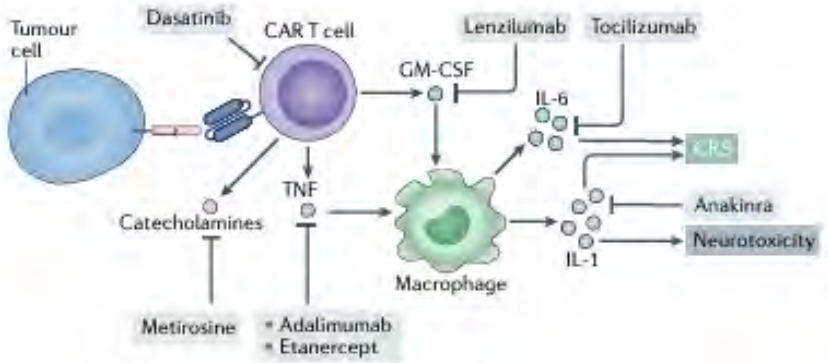


- Patient –derived (autologous) CAR T cell product
- Chimeric antigen receptor design:
  - Humanized CLDN18.2 scFV
  - CD8α hinge region, CD28 transmembrane region
  - CD28 intracellular signal domain
  - CD3ζ intracellular signal region
- IND clearance by China NMPA and US FDA
- Received orphan drug designation from FDA, EMA



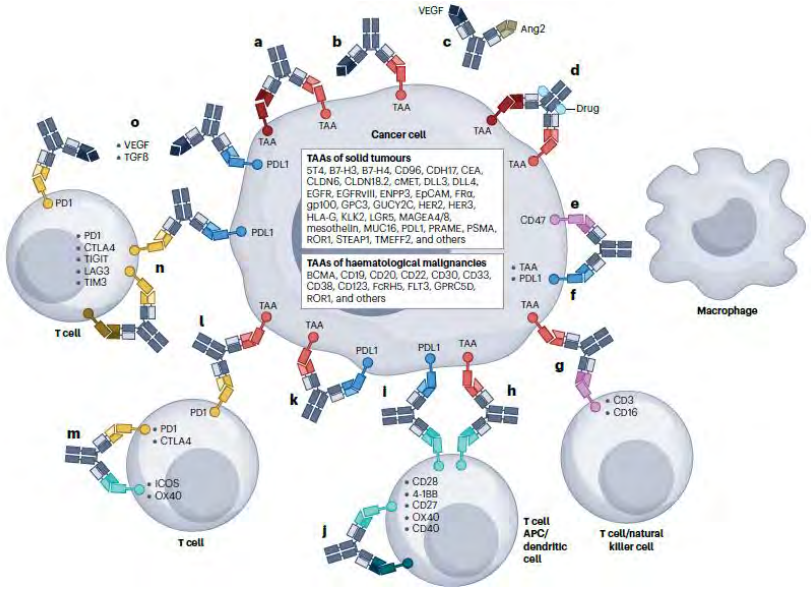
All patients experienced a grade 3 or higher hematologic toxicity. Grade 1 or 2 CRS occurred in 94.6% o. No grade 3 or higher CRS or neurotoxicities.





Qi C. et al, Nat Med 2022; Morris EC Nat Rev Immunol. 2022 Feb;22(2):85-96.

ADCs development



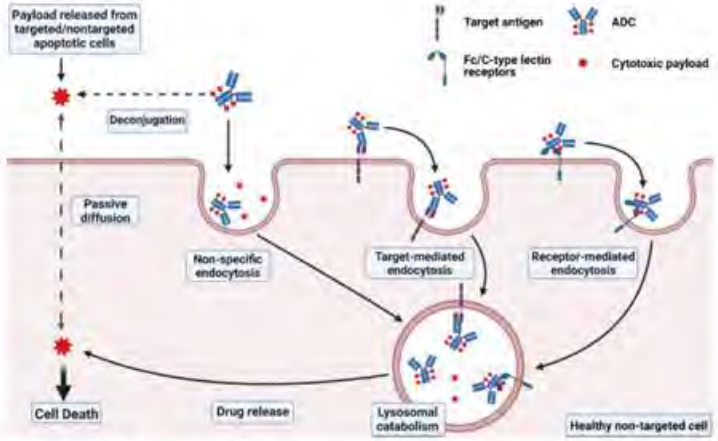


Figure 1. Mechanisms of ADC toxicity. Uptake of intact ADCs into normal cells may occur through non-specific endocytosis, or through internalization upon binding to the target antigen or to Fc/C-type lectin receptors. Payloads released from ADC deconjugation or other targeted/non-targeted apoptotic cells in the extracellular fluid may also enter normal cells via passive diffusion for membrane-permeable payloads or via non-specific endocytosis for membrane-impermeable linker-payload adducts. Created with BioRender.com.

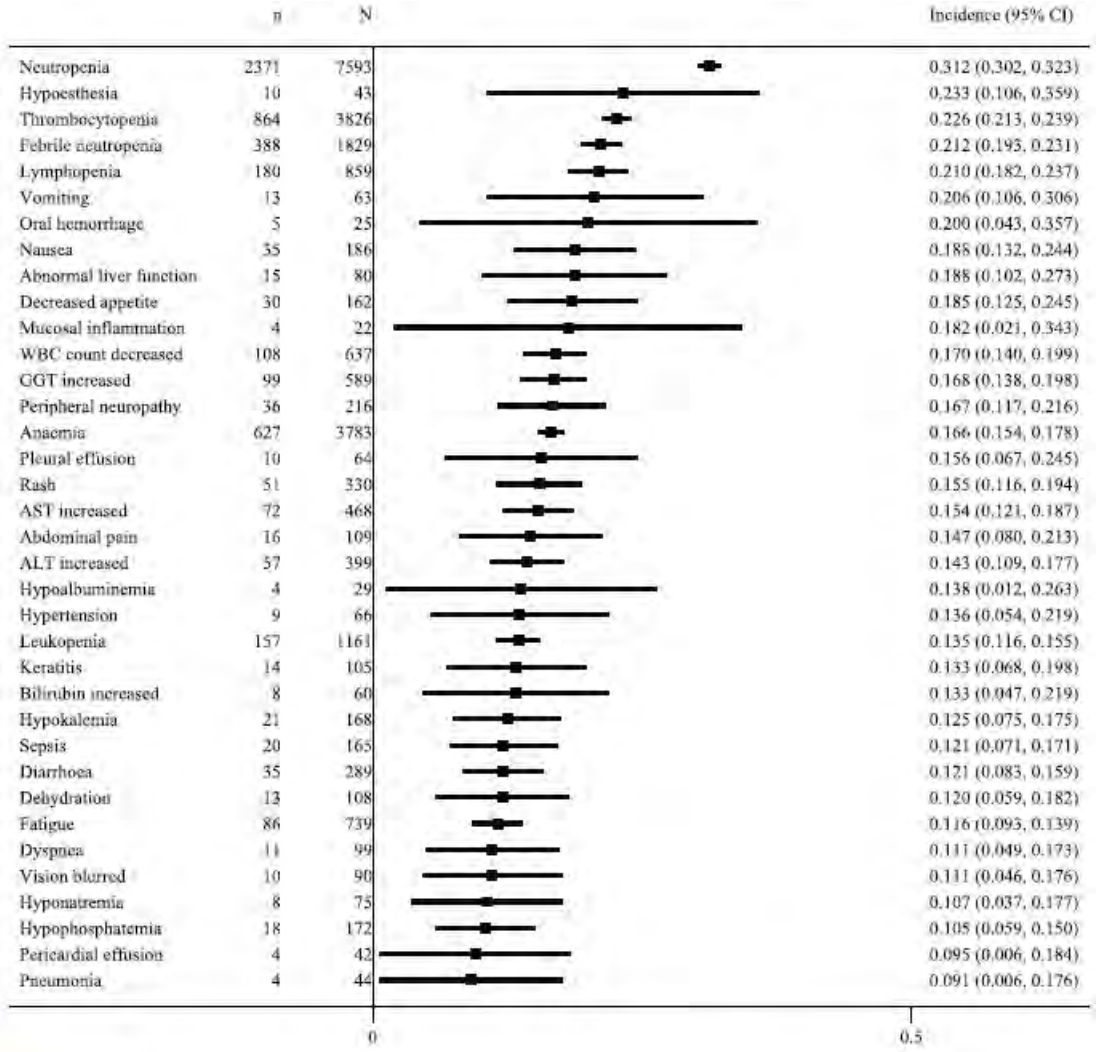


FIGURE 5 The incidence of most common grade ≥3 adverse events. ALT indicates aspartate aminotransaminase; AST, alanine aminotransferase; GGT, gamma-glutamyl transpeptidase; WBC, white blood cell.

Klein C, et al. Nat Rev Drug Discov. 2024 Apr;23(4):301-319 ; Nguyen TD, et al.Cancers (Basel). 2023 Jan 24;15(3):718; Zhu Y, Cancer. 2023 Jan 15;129(2):283-295..

Conclusions

New combination strategies including chemotherapy + targeted therapies + immunotherapy had improved the outcomes for gastric cancer patients.

The baseline assessment and support is essential for the therapeutic decision according to the patient condition, a good tolerance and QLQ during treatment.

The knowledge of the common toxicities and prevention actions to avoid or minimise them is our responsibility.

The key is to find the optimal balance between benefit and toxicity, taking into account the patient's background and the tumor characteristics