XX JORNADA DE ACTUALIZACIÓN

ASCO GI 2026

24 de febrero de 2026

¿Qué hay de nuevo en los tumores esófago-gástricos?

Cinta Hierro Carbó, MD MSc PhD

Clinical Lead Early phase Clinical Trial Unit (ECTU B-ARGO)

Consultant Medical Oncologist Gastrointestinal Tumors Group

Medical Oncology Department, Catalan Institute of Oncology (ICO)-Badalona

Badalona-Applied Research Group in Oncology (B-ARGO)/CARE-IGTP

Universitat Autònoma de Barcelona (UAB)_Can Ruti campus

DISCLOSURES

Cinta Hierro

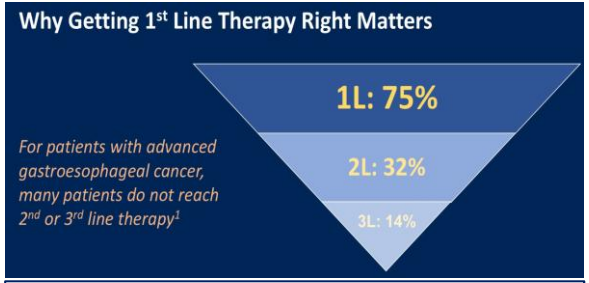
- **Financial interests (speaker, consultancy):** Lilly, MSD, BMS, AstraZeneca, GLG, Jazz Pharmaceuticals, BeOne, Astellas
- **Research funding (via Institution):** Merck
- **Non-Financial interests (principal investigator):** BMS, MSD, ALX Oncology, JAZZ Pharmaceuticals, AstraZeneca, Relay Therapeutics, Abbvie, Medicenna
- **Other (travel fees):** BMS, MSD, Roche, Amgen, AstraZeneca, Jazz Pharmaceuticals, BeOne

OUTLINE

Oral abstract sessions

1. Is immunotherapy needed for CLDN18.2+ gastric cancers? Phase II ILUSTRO trial (*LBA284*)

2. Zanidatamab as the new kid on the block for first line HER2+ gastric cancers: HERIZON-GEA-01 phase III trial (*LBA285*)



Lin D. ASCO GI Meeting 2026

1. IS IMMUNOTHERAPY NEEDED FOR CLDN18.2+ GASTRIC CANCERS?

1.1. ZOLBETUXIMAB AS FIRST-IN-CLASS CLDN18-2 mAb

Claudin 18.2 is highly selectively expressed in the tight-junctions (TJ) of non-malignant **gastric mucosa**, and only with malignant transformation, gastric epithelial cells lose their cellular polarity, resulting in **disruption of claudin 18.2 expression**

Zolbetuximab is a IgG1 mAb selectively targeting CLDN18.2 which **activates antibody-dependent cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC)**

Results from GLOW and SPOTLIGHT ph3 trials confirmed **improvement in mPFS in first palliative line for HER2- CLDN18.2+** advanced/recurrent GOJ/GC patients

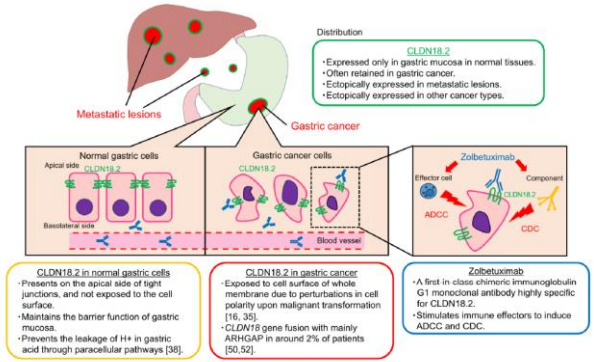
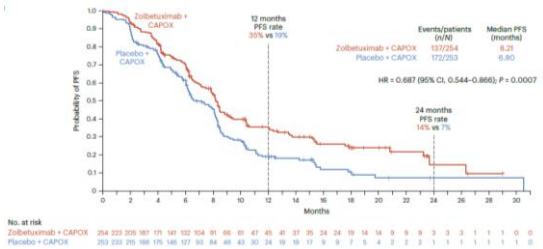
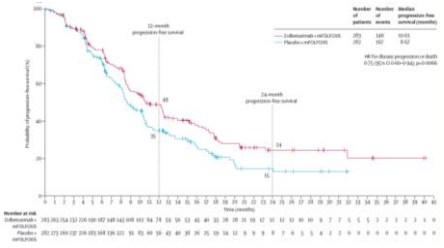


Figure 2. Main characteristics of claudin18.2 and zolbetuximab.
ADCC, activate antibody-dependent cytotoxicity; CDC, complement-dependent cytotoxicity; CLDN18.2, claudin18.2.

A central cut-off minimum level of CLDN18.2 expression ≥2+ on 75% of tumor cells (≈40-48% mGC/GOJ patients)[3-5]



[1]GLOW ph3 trial (CAPOX +- zolbetuximab)
mPFS 8.2 vs 6.8 m (HR 0.687; 95% CI 0.544-0.866; p=0.0007)



[2]SPOTLIGHT ph3 trial (FOLFOX6 +- zolbetuximab)
mPFS 10.61 vs 8,67 m (HR 0.75; 95% CI 0.60-0.94; p=0.0066)

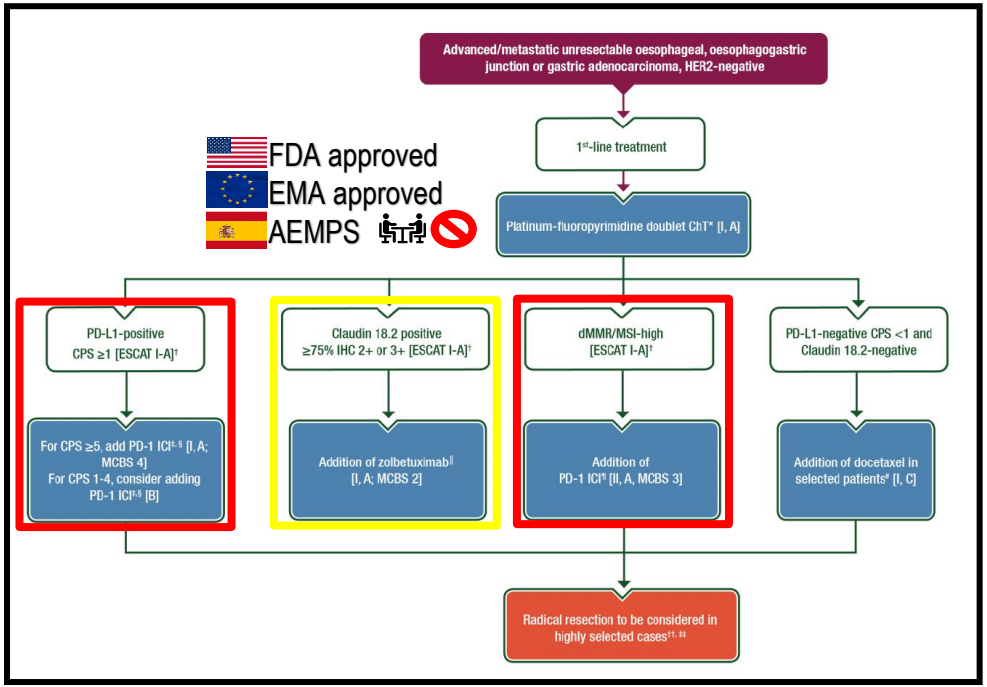
[1]Shah MA.NatMed.2023;29(8):2133-41; [2]Shitara K.Lancet.2023;401(10389):1655-68; [3]Sahin U.AnnOncol.2021 May;32(5):609-619; [4]Kubota.ESMOOpen.2023 Feb;8(1):100762; [5]Terán E.ESMOOpen.2026 Vol 11, issue 2, 106053

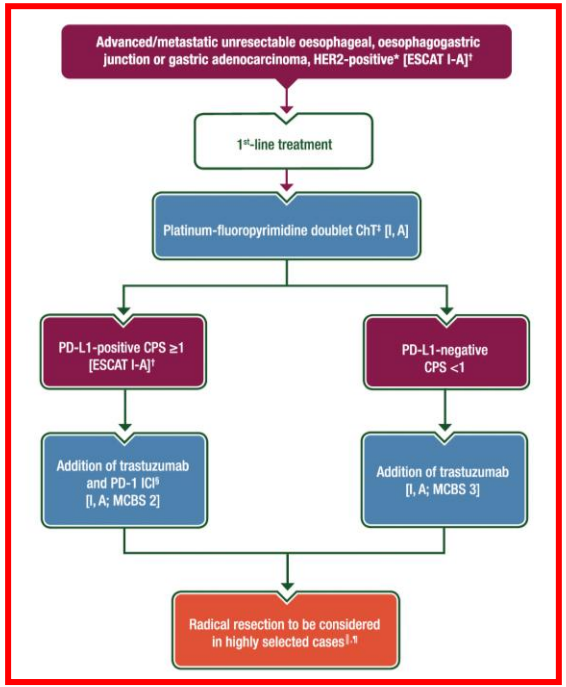
1.2. GASTRIC CANCER GUIDELINES

Zolbetuximab was first approved in Japan in March 2024

a) Is there room for CLDN18.2-targeted agents in the HER2+ subset ?

b) What is the best option in CLDN18.2+ but CPS PD-L1 >5% or dMMR/MSI-H ?



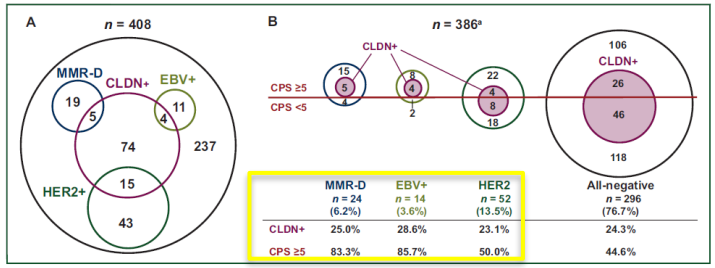


ESMO Gastric Cancer Living Guidelines, v1.4 September 2024. Available at: https://www.esmo.org/living-guidelines/esmo-gastric-cancer-living-guideline Accessed May 2025

1.3. OVERLAPPING BIOMARKERS IN CLDN18.2+ GASTRIC CANCERS

In a single-centre Japanese[1] cohort of 408 mGC/GOJ, **CDLN18.2+ across the four TCGA molecular subtypes** and **mOS not significantly different between CLDN18.2+ and negative groups**

In an European[2] multicenter study with 563 mGC/GOJ, **47.2% patients were CLDN18.2+ and CPS ≥5% → 167 pts treated with IO**



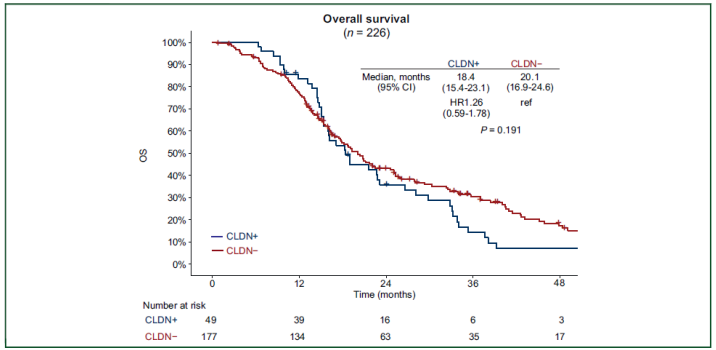


Figure 4. Kaplan–Meier plots of overall survival (OS) in patients who received standard first-line chemotherapy (platinum + fluoropyrimidine, *n* = 226).
HR, hazard ratio; ref, reference.

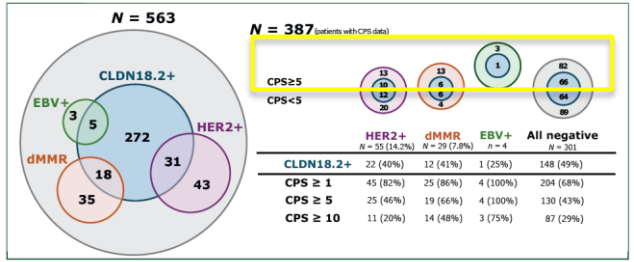
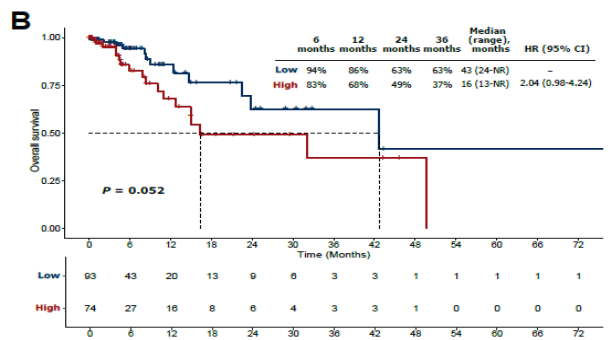


Figure 2. Biomarker overlap in gastroesophageal adenocarcinoma (GEA) stratified by PD-L1 CPS.



CLDN18.2-high expressors treated with 1L Cht+IO showed a tendency toward shorter mOS (16.0 versus 43.0 months; HR 2.04, 95% CI 0.98-4.24; *P* = 0.052) compared with those with low CLDN18-2 expression

[1]Kubota.ESMOOpen.2023 Feb;8(1):100762; [2]Terán E.ESMOOpen.2026 Vol 11, issue 2, 106053

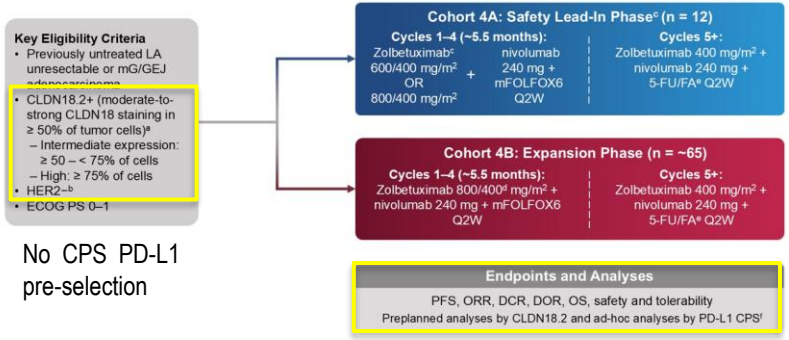
1.4. THE FIRST LINE DILEMMA: ChT+zolbetuximab or ChT+IO in 1L CLDN18.2+/CPS PDL1≥5%?

CLDN18.2-high tumors harbor distinct clinicopathological and molecular characteristics and data suggest poorer outcomes with IO-based strategies:

- SEQUENTIAL THERAPY: anti-CLDN18.2 therapy over IO, regardless of the PD-L1 threshold?
- COMBINATION THERAPY: anti-CLDN18.2 therapy plus IO, guided by PD-L1 cut-off?

Phase 2 ILUSTRO trial of 1L zolbetuximab plus mFOLFOX6 and nivolumab in patients with CLDN18.2+ locally advanced (LA) unresectable or metastatic gastric or gastroesophageal junction (mG/GEJ) adenocarcinoma

ILUSTRO Cohort 4 Study Design



No CPS PD-L1 pre-selection

Patient Demographics and Baseline Characteristics

Parameter[a]		Cohort 4A + 4B (N = 77)
Age, years	Median (range)	61.0 (37.0–86.0)
Sex, *n* (%)	Male	48 (62.3)
	Female	29 (37.7)
Race, *n* (%)	Asian	53 (79.1)
	White	14 (20.9)
Previous treatment, *n* (%)	Surgery alone	3 (4.3)
	Surgery followed by chemotherapy	3 (4.3)
	Chemotherapy followed by surgery	1 (1.4)
Primary site, *n* (%)	Stomach	64 (86.5)
	Gastroesophageal junction	10 (13.5)

Parameter[a]		Cohort 4A + 4B (N = 77)
Number of metastatic sites, *n* (%)	0–2	54 (70.1)
	≥ 3	23 (29.9)
Lauren classification, *n* (%)	Diffuse	53 (70.7)
	Intestinal	10 (13.3)
	Mixed	3 (4.0)
	Other	9 (12.0)
ECOG PS, *n* (%)	0	51 (66.2)
	1	26 (33.8)
Measurable disease, *n* (%)	Yes	63 (81.8)
	No	14 (18.2)
CLDN18.2 expression, *n* (%)	High[b]	65 (85.5)
	Intermediate[c]	11 (14.5)
PD-L1 status, *n* (%)	CPS ≥ 1	49 (65.3)
	CPS < 1	26 (34.7)

Shitara. K. ASCO GI Meeting 2026_JClinOncol Jan 2026, vol 44, 2 suppl

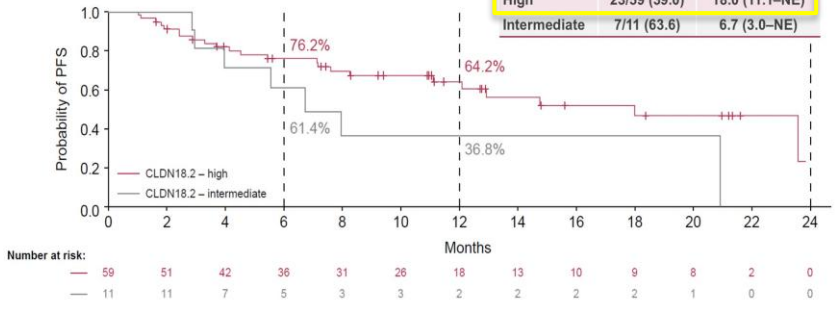
Impressive efficacy for first palliative line in HER2- patients with triplet Cht + zolbetuximab + nivolumab reaching mPFS 18 months

Of note, **subgroup with CLDN18.2 high/CPS PD-L1 ≥1% greatest benefit** mPFS ≈ 2 years

PFS Stratified by CLDN18.2 Expression in Cohort 4B

Median PFS was 18.0 months in the CLDN18.2-high population

CLDN18.2	Events/n (%)	Median PFS, months (95% CI)
High	23/59 (39.0)	18.0 (11.1–NE)
Intermediate	7/11 (63.6)	6.7 (3.0–NE)



Data are shown for the safety analysis set. One patient had no evaluable CLDN18.2 status. PFS was assessed by investigators per RECIST v1.1. Median (95% CI) follow-up times in Cohort 4B were 11.5 (9.4–15.6) months and 11.3 (3.9–NE) months for the high CLDN18.2 expression and intermediate CLDN18.2 expression subgroups, respectively.

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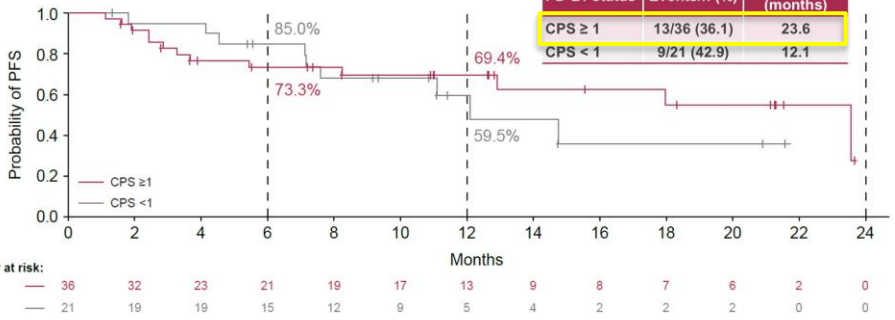
PFS by PD-L1 CPS in the CLDN18.2-High Population in Cohort 4B

Median PFS was 23.6 months in patients with PD-L1 CPS ≥ 1

PD-L1 status	Events/n (%)	Median PFS (months)
CPS ≥ 1	13/36 (36.1)	23.6
CPS < 1	9/21 (42.9)	12.1



Data are shown for the safety analysis set. PFS was assessed by investigators per RECIST v1.1. Median (95% CI) follow-up times in Cohort 4B were 23.6 (12.9–NE) months and 12.1 (7.2–NE) months for CPS ≥ 1 and CPS < 1, respectively.

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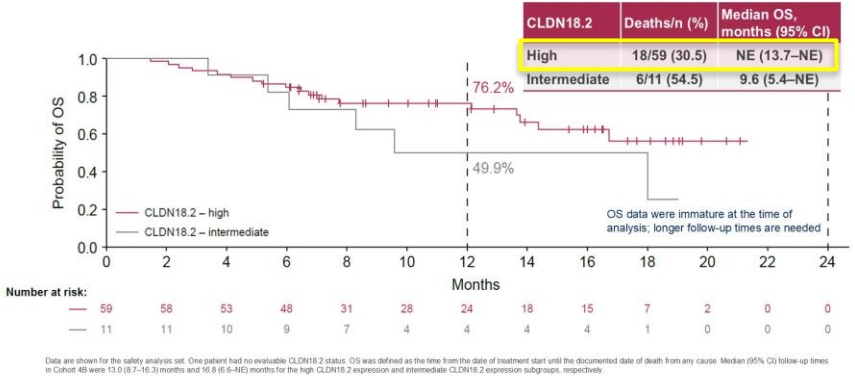
Greater survival (mOS NE) also in CLDN18.2 high expressors **and also response outcomes (ORR 68%)**

OS Stratified by CLDN18.2 Expression in Cohort 4B

OS was immature at data cutoff but favorable in the CLDN18.2-high population

CLDN18.2	Deaths/n (%)	Median OS, months (95% CI)
High	18/59 (30.5)	NE (13.7–NE)
Intermediate	6/11 (54.5)	9.6 (5.4–NE)



Data are shown for the safety analysis set. One patient had no evaluable CLDN18.2 status. OS was defined as the time from the date of treatment start until the documented date of death from any cause. Median (95% CI) follow-up times in Cohort 4B were 13.0 (8.7–16.3) months and 16.8 (6.6–NE) months for the high CLDN18.2 expression and intermediate CLDN18.2 expression subgroups, respectively.

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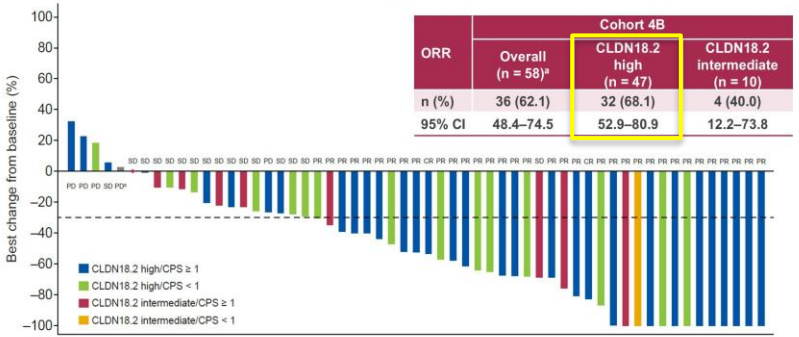
Tumor Responses in Patients in Cohort 4B

ORR was 68.1% in patients in the CLDN18.2-high group

ORR	Cohort 4B		
	Overall (n = 58)[a]	CLDN18.2 high (n = 47)	CLDN18.2 intermediate (n = 10)
n (%)	36 (62.1)	32 (68.1)	4 (40.0)
95% CI	48.4–74.5	52.9–80.9	12.2–73.8



Data are shown for the full analysis set. ORR data include patients with measurable disease. Waterfall plot (n = 57) includes all patients with baseline and postbaseline measurements, and does not include patients classified as non-CR/non-PD. [a]One patient had no evaluable CLDN18.2 status. [b]This patient had no evaluable CPS status.

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Nausea as on-target effect class-related AE (up to 80% any grade), **but no ≥ G3 → learning curve of N/V guidelines**

No new or unexpected AEs with the addition of nivolumab

TEAEs Occurring in ≥ 20% of All Treated Patients in Cohort 4A + 4B

Most common adverse event was nausea; all events were low grade

Event, n (%)	Cohort 4A + 4B (N = 77)	
Any grade Related to any study drug	76 (98.7) 76 (98.7)	
Grade ≥ 3	51 (66.2)	
Serious Related to any study drug	29 (37.7) 18 (23.4)	
TEAEs in ≥ 20% of patients by preferred terms, *n* (%)	**Any grade**	**Grade ≥ 3**
Nausea	62 (80.5)	0
Decreased appetite	56 (72.7)	6 (7.8)
Neutrophil count decreased	35 (45.5)	25 (32.5)
Peripheral sensory neuropathy	35 (45.5)	2 (2.6)
Vomiting	29 (37.7)	3 (3.9)
Diarrhea	28 (36.4)	1 (1.3)
Pyrexia	24 (31.2)	0
Anemia	19 (24.7)	2 (2.6)
Constipation	17 (22.1)	0

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Table 3. Prophylaxis before first zolbetuximab infusion
Provide any of the NCCN-recommended treatment options for high-emetic-risk regimens[a]
NK-1 antagonist + 5-HT3 antagonist + dexamethasone + olanzapine[b]
NK-1 antagonist + 5-HT3 antagonist + dexamethasone
5-HT3 antagonist + dexamethasone + olanzapine

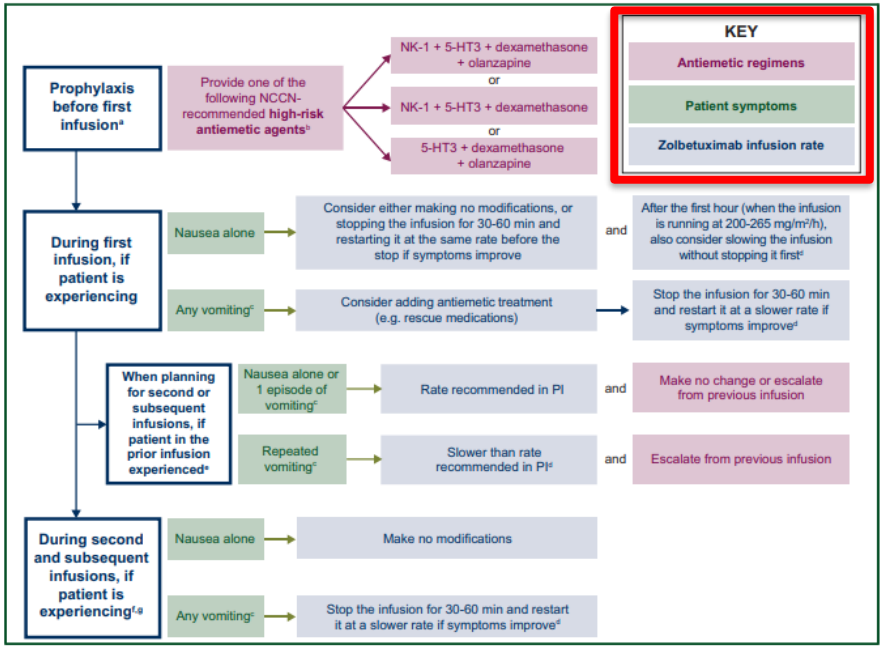


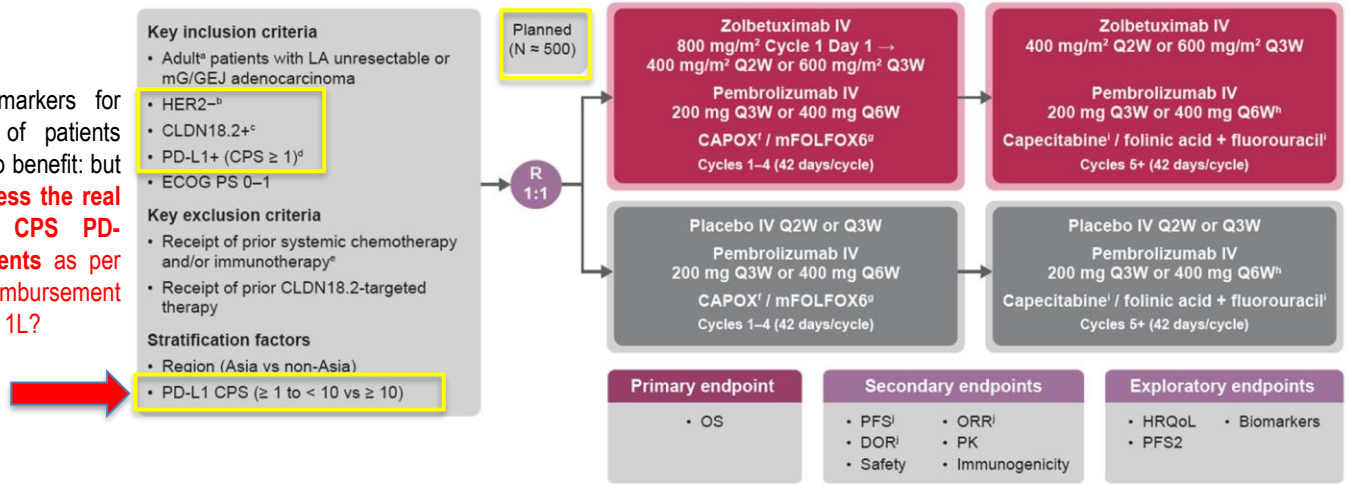
Figure 2. Consensus guidance and essential strategies on the prevention and management of nausea and vomiting in patients treated with zolbetuximab plus chemotherapy.

Shitara. K. ASCO GI Meeting 2026_JClinOncol Jan 2026, vol 44, 2 suppl; Klempner S.et al.*ESMOgastrointestinal*. 2025, vol 7, 100131

1.5. WHAT DOES THE HER2- CLDN18.2+ CPS PDL1≥1% FUTURE LOOK LIKE?

Defined biomarkers for the subset of patients more likely to benefit: but **How to assess the real benefit in CPS PD-L1≥5% patients** as per Spanish' reimbursement of ChT+IO in 1L?

Phase 3 LUCERNA (NCT06901531) Study Design



[a]≥ 18 years of age; [b]HER2 IHC score of 0+/1+, or HER2 IHC score of 2+ if ISH−, per local or central testing; [c]≥ 75% of tumor cells demonstrating moderate-to-strong membranous CLND18 staining using the VENTANA CLDN18 (43-14A) RxDx Assay per central testing; [d]Using the Agilent PD-L1 IHC 22C3 pharmDx assay per central testing; [e]1 prior dose of CAPOX or mFOLFOX6, with or without pembrolizumab, is allowed; [f]Oral capecitabine 1000 mg/m² twice daily on Days 1–14 and 22–35, and IV oxaliplatin 130 mg/m² Q3W; [g]Folinic acid 400 mg/m², fluorouracil 400 mg/m² bolus followed by 2400 mg/m², and oxaliplatin 85 mg/m², IV Q2W; [h]Up to 24 months; [i]Per investigator discretion; [j]Per RECIST version 1.1 by investigator assessment.

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No third arm with control GLOW/SPOTLIGHT's arm (CAPOX/FOLFOX+zolbetuximab) : **is the triplet combination really needed?**

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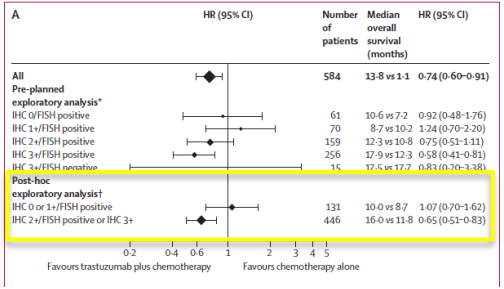
2. ZANIDATAMAB AS THE NEW KID ON THE BLOCK FOR FIRST LINE HER2+ GASTRIC CANCERS

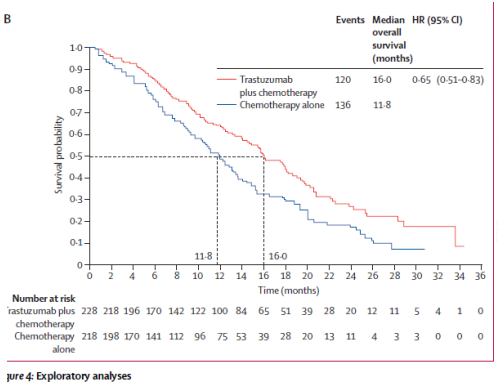
2.1. HER2 AS PROGNOSTIC AND PREDICTIVE BIOMARKER IN GASTRIC CANCER

ERBB2 is a member from the EGFR family proteins, known to be **a poor prognostic factor associated with more aggressive biology and higher recurrence rates**[1]. HER2 overexpression or amplification occurs in **~20%** GEA[2]

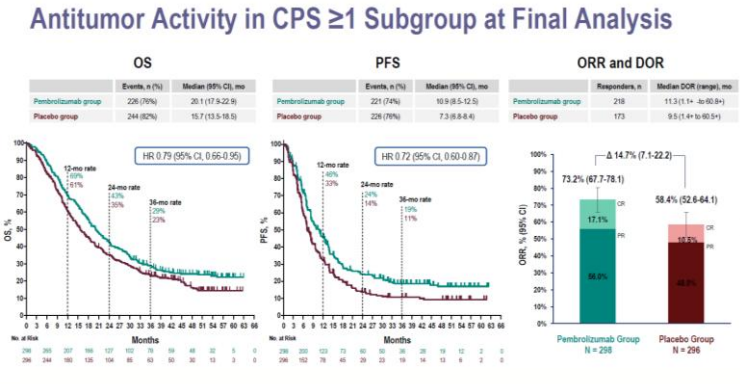
Results from TOGA and KEYNOTE-811 ph3 trials confirmed **improvement in mOS in first palliative line for HER2+ and then CPS PD-L1≥1%** advanced/recurrent GOJ/GC patients

Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial





ure 4: Exploratory analyses

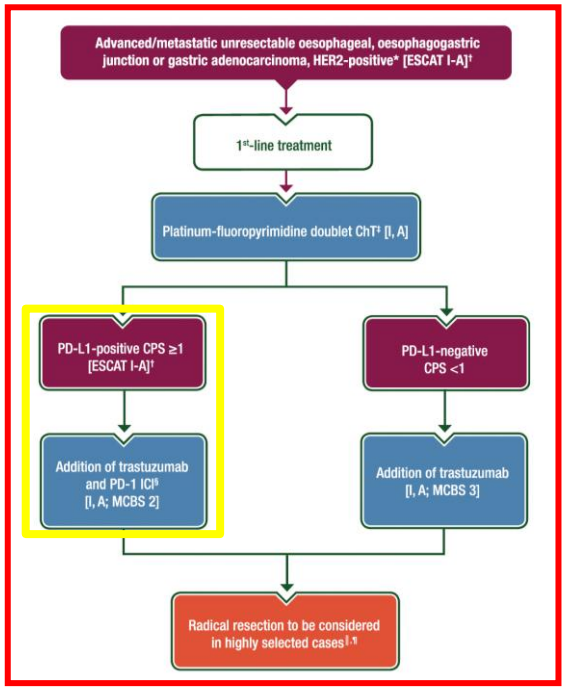


[3]TOGA ph3 trial (CDDP/5FU +- zolbetuximab)
mOS 16 vs 11.8 m (HR 0.65; 95% CI 0.51-0.83)
post-hoc exploratory analysis in patients IHC 2+/FISHamp or IHC 3+

[4]KEYNOTE-811 ph3 trial (CDDP/5FU or CAPOX + trastuzumab +- pembrolizumab)
mOS 20.1 vs 15.7 m (HR 0.79; 95% CI 0.66-0.95)
Subgroup final analysis in patients CPS PD-L1 ≥ 1%

[1]Abrahao-Machado LF. WorldJGastroenterol. 2016;22(19):4619–4625; [2]Shah Oh D-Y. NatRevClinOncol. 2020;17(1):33–48; [3]Bang Y-J. Lancet. 2010;376:687–697; [4]Janjigian YY. Lancet. 2023;402:2197–2208

2.2. GASTRIC CANCER GUIDELINES



FDA approved
EMA approved
AEMPS

What have we learnt from HER2+ GEA tumors?[2] Rationale for combinations aiming to boost the immune system

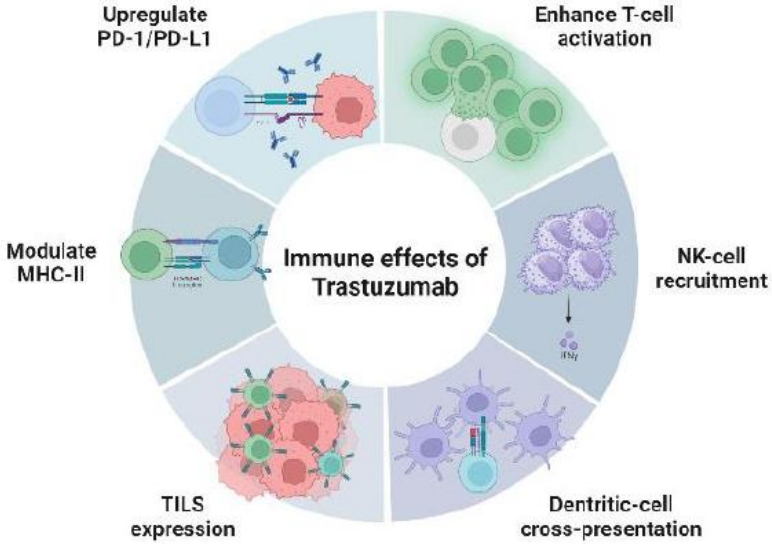


Figure 1. Immune effects of trastuzumab observed in preclinical studies.

[1] ESMO Gastric Cancer Living Guidelines, v1.4 September 2024. Available at: https://www.esmo.org/living-guidelines/esmo-gastric-cancer-living-guideline Accessed May 2025; [2] Pous A. IntJMolSci. 2023 Jul 13;24(14):11403

2.3. NEW DRUGS IN THE HORIZON: ZANIDATAMAB

2025 ASCO ANNUAL MEETING

Long-term outcomes and overall survival for zanidatamab + chemotherapy in HER2-positive advanced or metastatic gastroesophageal adenocarcinoma: 4-year follow-up of a phase 2 trial

Elena Elimova,[1] Jaffer Ajani,[2] Howard Burris,[3] Crystal S. Denlinger,[4] Syma Iqbal,[5] Yoon-Koo Kang,[6] Jwa Hoon Kim,[7] Keun-Wook Lee,[8] Bruce Lin,[9] Rutika Mehta,[10] Do-Youn Oh,[11] Sun Young Rha,[12] Chengzhi Xie,[13] Diana Shpektor,[13] Philip M. Garfin,[13] Geoffrey Ku[14]

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

Single arm trial: Zanidatamab + clinician's choice of chemotherapy
Zanidatamab[a,b] IV Q3W + CAPOX[c]
Zanidatamab[a,b] IV Q3W + FP[d]
Zanidatamab[b,e] IV Q2W + mFOLFOX6[f]
After the first 25 patients were enrolled and treated, antidiarrheal prophylaxis[g] was added for all subsequent patients

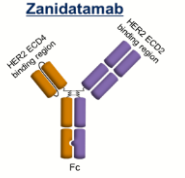
CT/MRI scans Q6W per RECIST v1.1[1]

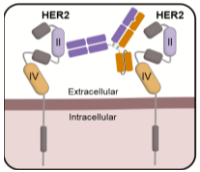
Plasma ctDNA samples at baseline and on treatment using NGS testing (Guardant360)

Primary endpoint
- Investigator-assessed confirmed ORR

Select secondary endpoints
- DOR
- PFS
- OS
- Rate and severity of AEs

Exploratory endpoint
- Potential biomarkers for prognostic prediction



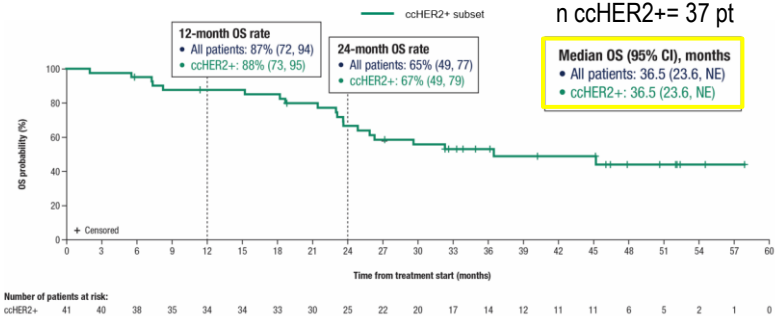


Dual (ECD2 & 4) HER2-targeted bsAb with multiple MoAs[1]:

- Facilitation of HER2 internalization and subsequent degradation
- Reduction of HER2 on the cell surface
- Inhibition of HER2 downstream signaling pathways
- Activation of immune-mediated effects (CDC, ADCC and phagocytosis)

Overall Survival

n=46 pt
n ccHER2+= 37 pt



Safety Outcomes

TRAEs (any component)[a], n (%)	All Patients (N = 46) Any grade	Grade 3 or 4
Any	46 (100)	30 (65)
Serious	8 (17)	8 (17)
Most Common[b]		
Diarrhea	43 (93)	18 (39)
Nausea	37 (80)	3 (7)
Peripheral sensory neuropathy	30 (65)	0
Fatigue	24 (52)	2 (4)
Decreased appetite	21 (46)	0
Vomiting	16 (35)	4 (9)
Hypokalemia	14 (30)	10 (22)
Stomatitis	13 (28)	0
Anemia	12 (26)	1 (2)
Dysgeusia	11 (24)	0
Decreased neutrophil count	10 (22)	2 (4)
Hypomagnesaemia	10 (22)	1 (2)
PPE syndrome	10 (22)	1 (2)
IRRs	10 (22)	0

[a]TRAEs could be related to zanidatamab and/or chemotherapy. [b]Any-grade TRAEs occurred in ≥20% of all patients.
AESI, adverse event of special interest; IRR, infusion-related reactions; PPE, palmar-plantar erythrodysesthesia; TRAE, treatment-related adverse event.

- There were no treatment-related deaths
- **AESIs:**
  - IRRs (10 [22%])
  - Non-infectious pulmonary toxicities (1 [2%])
  - No left ventricular dysfunction or grade ≥2 heart failure

After the first 25 patients were enrolled, protocol was amended to omit 5-FU bolus (mFOLFOX6) and to introduce mandatory antidiarrheal prophylaxis (all patients)
- Loperamide 4 mg twice daily starting on the first treatment day of cycle 1 and continuing for at least 7 days

After introduction of mandatory antidiarrheal prophylaxis, patients had:
- Lower incidence of any-cause grade 3 diarrhea (56% before vs 24% after)
- No discontinuations due to diarrhea (2 patients before vs 0 patients after)

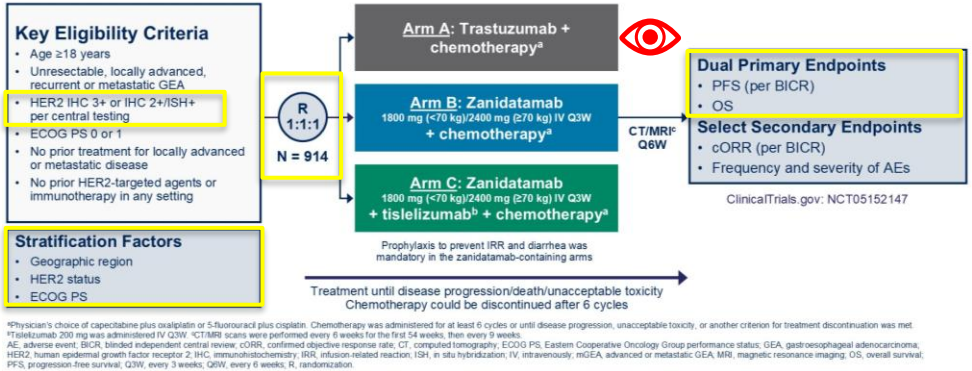
Elimova E. ASCO Meeting 2025 JClinOncol Jun 2025, vol 43, 16 suppl;4013

2.4. HERIZON-GEA-01 TRIAL: PRACTICE-CHANGING IN FIRST-LINE FOR HER2+ mGOJ/GC?

Zanidatamab + chemotherapy ± tislelizumab for first-line HER2-positive locally advanced, unresectable, or metastatic gastroesophageal adenocarcinoma: Primary analysis from HERIZON-GEA-01

HERIZON-GEA-01 Study Design

Global phase 3 trial of zanidatamab + chemotherapy ± tislelizumab vs trastuzumab + chemotherapy in previously untreated patients with HER2+ mGEA



[a]Physician's choice of capecitabine plus oxaliplatin or 5-fluorouracil plus cisplatin. Chemotherapy was administered for at least 6 cycles or until disease progression, unacceptable toxicity, or another criterion for treatment discontinuation was met. [b]Tislelizumab 200 mg was administered IV Q3W. [c]CT/MRI scans were performed every 6 weeks for the first 54 weeks, then every 9 weeks.
AE, adverse event; BICR, blinded independent central review; cORR, confirmed objective response rate; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; GEA, gastroesophageal adenocarcinoma; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IRR, infusion-related reaction; ISH, in situ hybridization; IV, intravenously; mGEA, advanced or metastatic GEA; MRI, magnetic resonance imaging; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; Q6W, every 6 weeks; R, randomization.

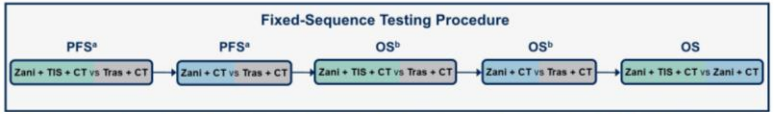
Neither CPS PD-L1 pre-selection nor stratification & control arm TOGA

Timing design before KEYNOTE-811 global regulatory approvals

Statistical Design

Results presented with median FU of 2 years

- **Dual primary endpoints (PFS and OS): Analyzed in the intent-to-treat population using log-rank tests with a 2-sided α = 0.05**
  - **Primary PFS analysis**: After target event count was reached and patients had ≥7 months of follow-up
  - **First interim OS analysis**: Performed at the time of data cutoff for the primary PFS analysis



[a]For the primary analysis of PFS, the 2-sided alpha was 0.05. [b]For the first interim analysis of OS, the 2-sided alpha was 0.020.
CT, chemotherapy; OS, overall survival; PFS, progression-free survival; TIS, tislelizumab; Tras, trastuzumab; Zani, zanidatamab.

Baseline Demographics and Disease Characteristics

Demographics and clinical characteristics were balanced across all 3 treatment arms

	Zanidatamab + tislelizumab + CT (n = 302)	Zanidatamab + CT (n = 304)	Trastuzumab + CT (n = 308)
Age, median (range), years	63.0 (22–81)	62.5 (25–87)	64.0 (21–84)
Male sex	244 (80.8)	244 (80.3)	238 (77.3)
Geographic region			
Asia	159 (52.6)	163 (53.6)	165 (53.6)
EU/North America	95 (31.5)	91 (29.9)	93 (30.2)
Rest of the world	48 (15.9)	50 (16.4)	50 (16.2)
ECOG PS[a]			
0	121 (40.1)	134 (44.1)	120 (39.0)
1	180 (59.6)	170 (55.9)	188 (61.0)
Disease status			
Metastatic	284 (94.0)	295 (97.0)	299 (97.1)
Unresectable locally advanced	18 (6.0)	9 (3.0)	9 (2.9)

	Zanidatamab + tislelizumab + CT (n = 302)	Zanidatamab + CT (n = 304)	Trastuzumab + CT (n = 308)
Anatomical subtype			
Gastric	208 (68.9)	204 (67.1)	226 (73.4)
GEJ	74 (24.5)	61 (20.1)	60 (19.5)
Esophageal	20 (6.6)	39 (12.8)	22 (7.1)
HER2 IHC 3+	251 (83.1)	251 (82.6)	255 (82.8)
PD-L1 status[b]			
TAP score <1%	90 (29.8)	108 (35.5)	98 (31.8)
TAP score ≥1%	187 (61.9)	178 (58.6)	188 (61.0)
Choice of chemotherapy backbone			
CAPOX	273 (90.4)	276 (90.8)	282 (91.6)
FP	29 (9.6)	28 (9.2)	26 (8.4)

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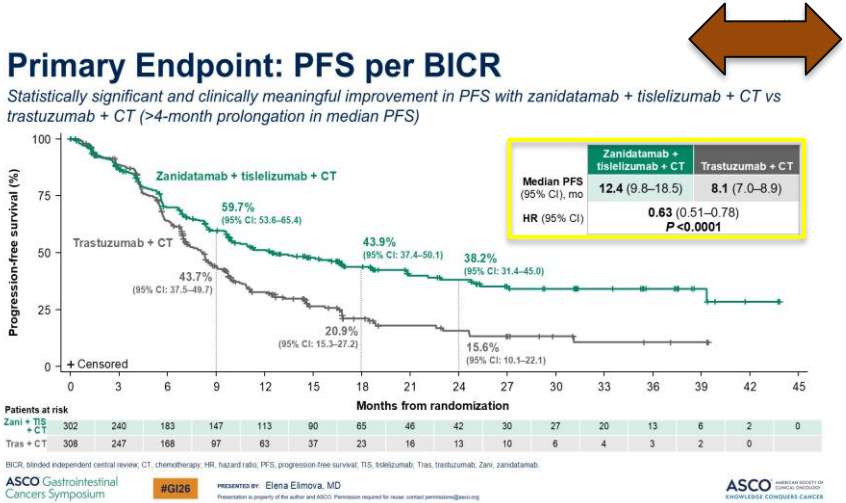
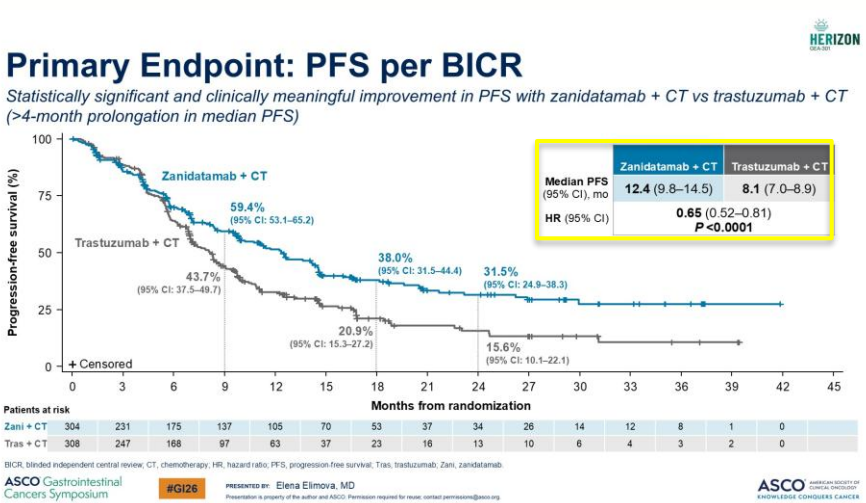
Increased efficacy for first palliative line in HER2+ patients with both triplet ChT + zanidatamab + tislelizumab and also with doublet ChT + zanidatamab, reaching mPFS of 12.4 months with both regimens





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PFS benefit is seen across most pre-specified subgroups, **including TAP PD-L1 <1%** (study not stratified by PD-L1 expression!)

Of note, HER2 IHC2+/ISH+ show less benefit…small *n* of patients

HERIZON GEA-301

PFS in Key Prespecified Subgroups

Improvements in PFS were generally consistent across major prespecified subgroups

Subgroup	Category	Events/patients: Zanidatamab + tislelizumab + CT	Zanidatamab + CT	Trastuzumab + CT	Zani + TIS + CT vs Tras + CT: PFS HR[a] (95% CI)	Zani + CT vs Tras + CT: PFS HR[a] (95% CI)
All patients		**154/302**	**160/304**	**196/308**	**0.63 (0.51–0.78)**	**0.65 (0.52–0.81)**
Age, years	<65	79/163	94/174	105/162	0.55 (0.41–0.74)	0.63 (0.47–0.83)
	≥65	75/139	66/130	91/146	0.71 (0.52–0.96)	0.72 (0.53–1.00)
Geographic region	Asia	78/159	81/163	106/165	0.56 (0.42–0.75)	0.64 (0.48–0.86)
	EU/NA	47/95	49/91	55/93	0.65 (0.44–0.97)	0.73 (0.49–1.08)
	ROW	29/48	30/50	35/50	0.74 (0.45–1.23)	0.63 (0.39–1.04)
ECOG PS	0	51/121	63/134	74/120	0.51 (0.35–0.73)	0.63 (0.45–0.89)
	1	103/180	97/170	122/188	0.69 (0.53–0.90)	0.70 (0.53–0.91)
Anatomical subtype	Gastric	105/208	112/204	140/226	0.61 (0.47–0.79)	0.74 (0.57–0.95)
	GEJ	43/74	29/61	44/60	0.70 (0.46–1.08)	0.52 (0.32–0.83)
	Esophageal	6/20	19/39	12/22	0.32 (0.12–0.85)	0.60 (0.29–1.25)
HER2 status	IHC 3+	121/251	125/251	167/255	0.54 (0.43–0.69)	0.55 (0.43–0.69)
	IHC 2+/ISH+	33/51	35/51	29/52	1.08 (0.65–1.78)	1.73 (1.06–2.83)
PD-L1 status	TAP <1%	47/90	61/108	71/98	0.47 (0.32–0.69)	0.62 (0.44–0.87)
	TAP ≥1%	91/187	94/178	114/188	0.65 (0.49–0.86)	0.74 (0.56–0.98)

[a]The widths of the confidence intervals were not adjusted for multiplicity and cannot be used to infer treatment effects.
CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; EU, European Union; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IHC, immunohistochemistry; ISH, in situ hybridization; NA, North America; PD-L1, programmed death-ligand 1; PFS, progression-free survival; ROW, rest of world; TAP, tumor area positivity; TIS, tislelizumab; Tras, trastuzumab; Zani, zanidatamab.

ASCO Gastrointestinal Cancers Symposium #GI26

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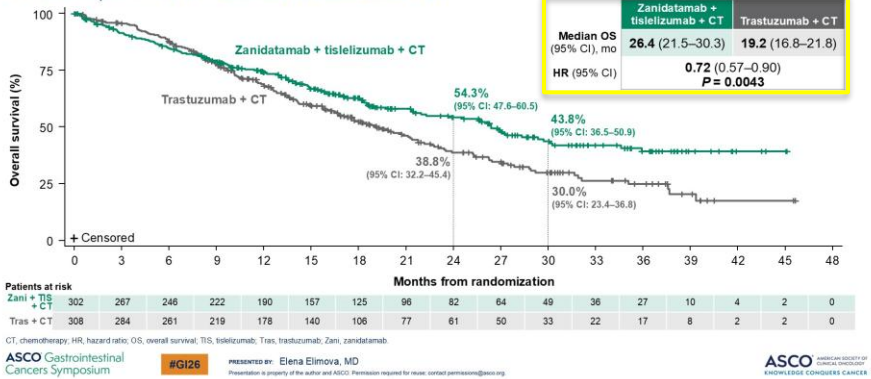
Statistically significant 28% reduction in the risk of death with triplet ChT + zanidatamab + tislelizumab arm, exceeding 26.4 months

Strong trend toward statistical significance for OS favouring doublet ChT + zanidatamab arm also, reaching 24.4 months

Primary Endpoint: Overall Survival

Zanidatamab + tislelizumab + CT demonstrated a statistically significant and clinically meaningful OS benefit with a >7-month improvement in median OS vs trastuzumab + CT



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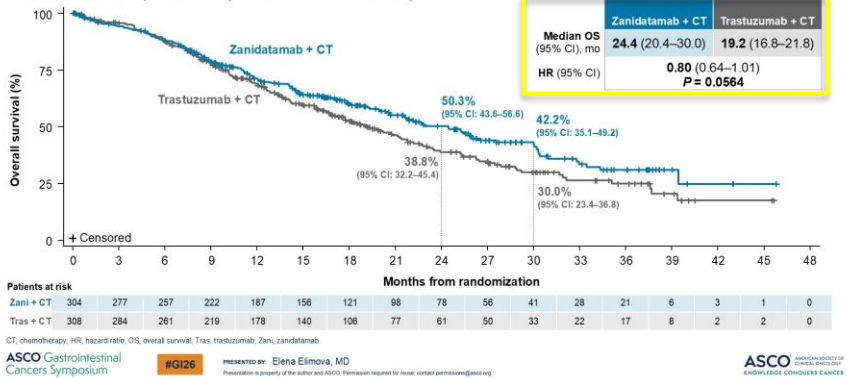
Primary Endpoint: Overall Survival

At this interim analysis, there was a strong trend toward significance for OS favoring zanidatamab + CT vs trastuzumab + CT (5-month improvement in median OS)



Historical benchmark: ChT + trastuzumab in TOGA mOS **16 months** vs KEYNOTE-811 mOS **15.7 months** in CPS PD-L1 ≥ 1%

Control arm in HERIZON-GEA-01 with ChT + trastuzumab did much better ≈ 19.2 months (almost paralleling the results achieved in KEYNOTE-811 trial for HER2+/CPS PD-L1 ≥ 1% patients treated ChT + trastuzumab + pembrolizumab of mOS 20.1 months)

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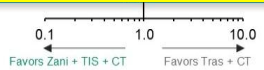
PFS benefit is seen across most pre-specified subgroups, **including TAP PD-L1 <1%** (study not stratified by PD-L1 expression!)

HERIZON GEA-301

OS in Key Prespecified Subgroups

Improvements in OS occurred across major prespecified subgroups, including regions and PD-L1 TAP scores

Subgroup	Category	Events/patients: Zanidatamab + tislelizumab + CT	Events/patients: Trastuzumab + CT	Zani + TIS + CT vs Tras + CT: OS HR[a] (95% CI)
All patients		134/302	170/308	0.72 (0.57–0.90)
Age, years	<65	68/163	99/162	0.60 (0.44–0.82)
	≥65	66/139	71/146	0.91 (0.65–1.28)
Geographic region	Asia	63/159	89/165	0.64 (0.46–0.88)
	EU/NA	46/95	52/93	0.84 (0.57–1.25)
	ROW	25/48	29/50	0.80 (0.47–1.36)
ECOG PS	0	41/121	52/120	0.72 (0.48–1.09)
	1	92/180	118/188	0.72 (0.55–0.95)
Anatomical subtype	Gastric	87/208	127/226	0.63 (0.48–0.83)
	GEJ	42/74	33/60	1.14 (0.72–1.80)
	Esophageal	5/20	10/22	0.51 (0.17–1.52)
HER2 status	IHC 3+	106/251	138/255	0.70 (0.55, 0.91)
	IHC 2+/ISH+	28/51	31/52	0.83 (0.50, 1.39)
PD-L1 status	TAP <1%	38/90	65/98	0.49 (0.33–0.74)
	TAP ≥1%	79/187	92/188	0.82 (0.60–1.10)



[a]The widths of the confidence intervals were not adjusted for multiplicity and cannot be used to infer treatment effects.
CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; EU, European Union; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IHC, immunohistochemistry; ISH, in situ hybridization; NA, North America; OS, overall survival; PD-L1, programmed death-ligand 1; ROW, rest of world; TAP, tumor area positivity; TIS, tislelizumab; Tras, trastuzumab; Zani, zanidatamab.

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HERIZON GEA-301

Safety Summary

The safety profile was generally manageable, and no unexpected safety signals were identified

	Zanidatamab + tislelizumab + CT (n = 294)[a]	Zanidatamab + CT (n = 305)[a]	Trastuzumab + CT (n = 302)
Duration of treatment, median (IQR), weeks	43.1 (56.7)	31.0 (53.8)	30.0 (32.2)
Any-grade TEAE, n (%)	293 (99.7)	301 (98.7)	297 (98.3)
TRAE, n (%)	289 (98.3)	296 (97.0)	291 (96.4)
Grade ≥3	211 (71.8)	180 (59.0)	180 (59.6)
Serious TEAEs, n (%)	172 (58.5)	150 (49.2)	128 (42.4)
Treatment-related	121 (41.2)	86 (28.2)	61 (20.2)
TEAEs leading to death, n (%)	28 (9.5)	25 (8.2)	22 (7.3)
Treatment-related	7 (2.4)	1 (0.3)	4 (1.3)
Discontinuation due to TRAEs, n (%)			
Any component	125 (42.5)	105 (34.4)	88 (29.1)
Zanidatamab or trastuzumab	35 (11.9)	26 (8.5)	7 (2.3)
Tislelizumab	42 (14.3)	—	—
AESIs[b], n (%)	102 (34.7)	93 (30.5)	56 (18.5)
IRRs	74 (25.2)	77 (25.2)	40 (13.2)
Noninfectious pulmonary toxicities	20 (6.8)	4 (1.3)	3 (1.0)
Left ventricular dysfunction	26 (8.8)	19 (6.2)	13 (4.3)
Immune-mediated AEs[b], n (%)	111 (37.8)	38 (12.5)	31 (10.3)

[a]Five patients who were assigned to the zanidatamab-tislelizumab-chemotherapy arm did not receive tislelizumab. Data from these patients are summarized in the zanidatamab-chemotherapy arm. [b]AESIs for zanidatamab were IRRs, noninfectious pulmonary toxicities, and left ventricular dysfunction; AESIs for tislelizumab were IRRs and immune-mediated AEs. AESIs for zanidatamab and tislelizumab were reported in all treatment groups, even if the study agent was not administered in that group.
AE, adverse event; AESI, AE of special interest; CT, chemotherapy; IQR, interquartile range; IRR, infusion-related reaction; TEAE, treatment-emergent AE; TRAE, treatment-related AE.

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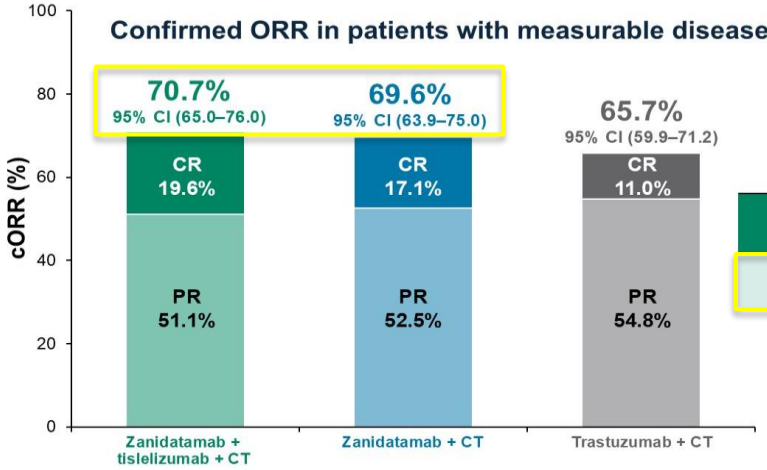
IS IT WORTH IT THEN THE TOXICITY?

The addition of anti-PD-1 blockade translates into deeper (ORR 70.7%) and prolonged (DOR 20.7 months) responses with triplet combination, widening subsequent radical options for this subset of patients with more disease-controlled symptoms and delayed clinical deterioration

HERIZON GEA-301

Key Secondary Endpoint: Antitumor Activity

Responses were deeper and more durable in the zanidatamab-containing arms vs the trastuzumab + CT arm



Median DOR (95% CI), mo

Zanidatamab + tislelizumab + CT (n = 195)	Zanidatamab + CT (n = 186)	Trastuzumab + CT (n = 198)
20.7 (12.6–37.7)	**14.3** (11.5–21.9)	**8.3** (6.7–9.8)

cORR was defined as the proportion of patients achieving a best overall response of CR or PR, as determined by BICR using RECIST v1.1, with the response confirmed at a subsequent visit ≥28 days after the initial assessment. DOR was assessed among patients with measurable disease at baseline who achieved a confirmed objective response by BICR per RECIST v1.1. The widths of the confidence intervals were not adjusted for multiplicity and cannot be used to infer treatment effects.
BICR, blinded independent central review; cORR, confirmed ORR; CR, complete response; CT, chemotherapy; DOR, duration of response; ORR, objective response rate; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

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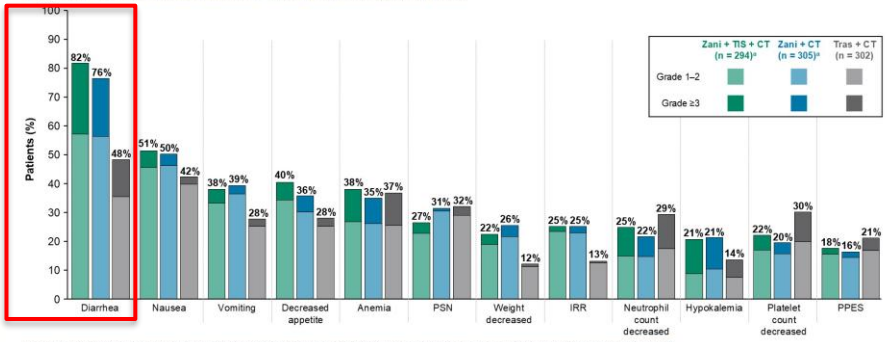
Common TRAEs (≥20% of Patients in Any Arm)

Diarrhea was the most common TRAE in all treatment arms



*Five patients who were assigned to the zanidatamab-tislelizumab-chemotherapy arm did not receive tislelizumab. Data from these patients are summarized in the zanidatamab-chemotherapy arm.
CT, chemotherapy; IRR, infusion-related reaction; PPES, palmar-plantar erythrodysesthesia syndrome; PSN, peripheral sensory neuropathy; TIS, tislelizumab; TRAE, treatment-related adverse event; Tras, trastuzumab; Zani, zanidatamab.

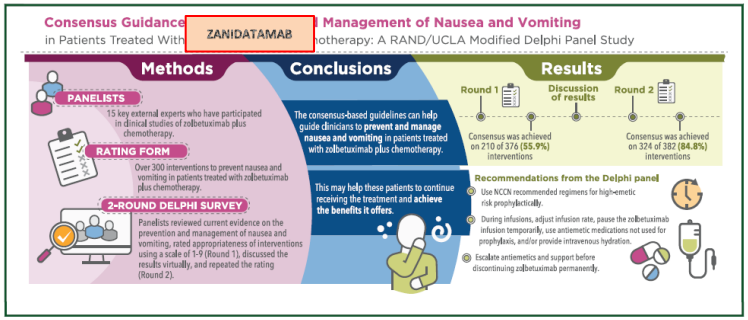
Treatment-Emergent Diarrhea

Treatment-emergent diarrhea generally occurred early in treatment and resolved within 3 weeks, and few patients discontinued zanidatamab due to diarrhea

	Zanidatamab + tislelizumab + CT (n = 294)ª	Zanidatamab + CT (n = 305)ª	Trastuzumab + CT (n = 302)
Treatment-related diarrhea, n (%)			
Any grade	240 (81.6)	233 (76.4)	146 (48.3)
Grade ≥3	72 (24.5)	61 (20.0)	39 (12.9)
Treatment-related diarrhea leading to discontinuation, n (%)			
Any component	22 (7.5)	15 (4.9)	5 (1.7)
Zanidatamab or trastuzumab	12 (4.1)	4 (1.3)	0
Tislelizumab	6 (2.0)	—	—
Time to first onset of diarrhea, median (IQR), days			
Any grade	7.0 (14.5)	6.0 (12.0)	10.0 (30.0)
Grade ≥3	16.0 (43.0)	11.0 (23.0)	37.0 (56.0)
Duration of first diarrhea event, median (95% CI), days			
Any grade	14.0 (11.0–18.0)	17.0 (13.0–20.0)	10.0 (7.0–15.0)
Grade ≥3	8.0 (7.0–9.0)	9.0 (6.0–11.0)	9.0 (6.0–12.0)

Mandatory diarrhea prophylaxis for patients in the zanidatamab-containing arms
Loperamide (4 mg BID) for the first 7 days of cycle 1 only

*Five patients who were assigned to the zanidatamab-tislelizumab-chemotherapy arm did not receive tislelizumab. Data from these patients are summarized in the zanidatamab-chemotherapy arm.
BID, twice daily; CT, chemotherapy; IQR, interquartile range.



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
ESMO GASTROINTESTINAL ONCOLOGY

ORIGINAL ARTICLE

Consensus guidance for prevention and management of nausea and vomiting in patients treated with ZANIDATAMAB chemotherapy: a RAND/UCLA modified Delphi panel study

S. J. Klempner[1,*], R. A. Pazo-Cid[2], S. Lonardi[3], L. Swanson[4], M. J. Arango[5], P. Enzinger[6], A. H. Ko[7], G. M. Vaccaro[8], K. Yamaguchi[9], A. Saeed[10], K.-W. Lee[11], K. Shitara[12], D. Ilson[13], J. A. Ajani[14], R. Fuldeore[15], S. Braun[15], M. S. Broder[16] & M. A. Shah[17]

Elimova E. ASCO GI Meeting 2026; Klempner S.et al.*ESMOgastrointestinal*. 2025, vol 7, 100131

MESSAGES TO TAKE HOME

- The ILUSTRO trial addresses timely question of administering frontline combined CLDN18.2 plus IO combination = **greatest opportunity for impact in survival (mPFS up to 23.6 months in CLDN18.2 high/CPS PD-L1 ≥ 1% patients)**
- Safety and tolerability consistent with prior studies of zolbetuximab, **though improvement in N/V management**
- Small (n=77 pt) single arm data → needs confirmation in global study = **chance for evaluating whether survival benefit increases with PD-L1 expression** (CPS PDL1 ≥5%? LUCERNA's ≥10%)

- The HERIZON-GEA-01 trial is the first large global trial to beat previous oucomes in 1L HER2+ mGOJ/GC patients **demonstrating its dual primary endpoints mPFS > 1 year (12.4m with both zani arms),** and a clinically meaningful **mOS benefit for triplet >2 years (26.4m)**
- PFS and OS **benefits observed in patients independently of TAP scores**, although the study was not stratified by PD-L1 expression
- Comparator arm considered **not standard in countries with KEYNOTE-811 implemented** **Zanidatamab-related diarrhoea might need consensus management** to facilitate the learning curve of oncologists, specialy when overlapping with tislelizumab-related irAE

THANK YOU FOR YOUR ATTENTION

chierro@iconcologia.net

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