XXXIII SIMPOSIO INTERNACIONAL
INTERNATIONAL SYMPOSIUM
11 - 12 DE DICIEMBRE DE 2025
OVIEDO

Avances en la primera línea del ADC esofagogástrico estadio IV: de la evidencia a la práctica clínica

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Disclosure information

Employment: SACYL, USAL

Consultant, Advisory Role or Speaking: Merck, Amgen, Servier, Bristol-MS, MSD, Bayer, GSK, Pierre-Fabre, Astellas.

Educational, scientific activities, travel and accommodation: Merck, Amgen, Roche, Lilly, Bristol-MS, Pierre-Fabre, Servier and MSD.

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- Introducción
- Opciones de tratamiento guiadas por biomarcador
- Retos y limitaciones
- Mensajes para llevar a casa
- Reflexiones finales

Introducción

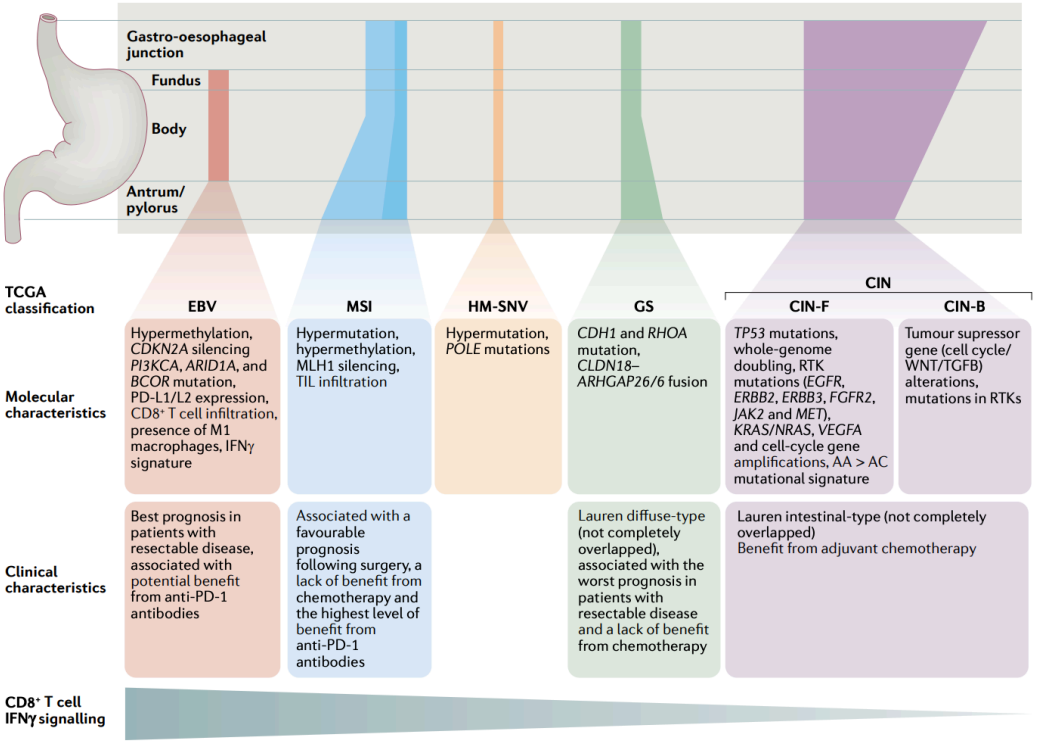
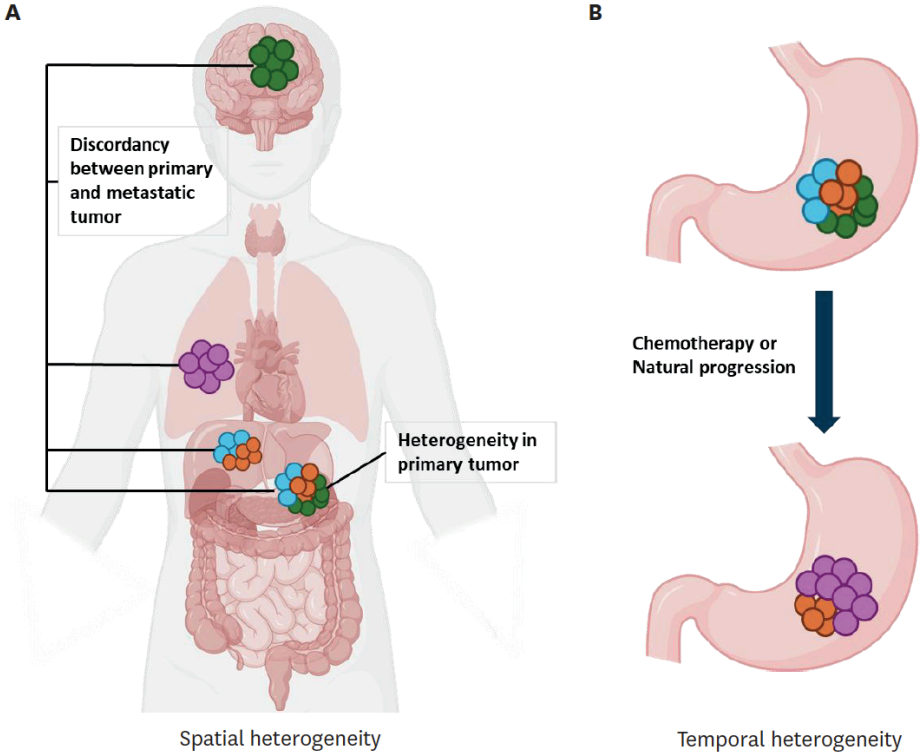


Fig. 1 | **Molecular and clinical characteristics of TCGA subtypes of G/GEJ cancer by anatomical distribution.**

Nakamura Y, et al. Nat Rev Clin Oncol, 2021

Introducción



Spatial heterogeneity

Temporal heterogeneity

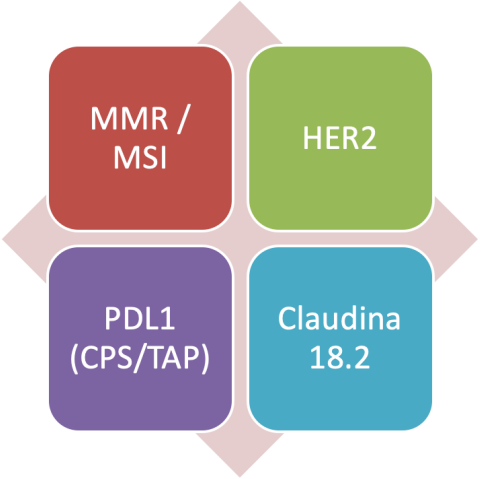
Lee HS. J Gastric Cancer. 2025 Jan;25(1):192-209

Biomarkers in gastroesophageal cancer 2025: an updated consensus statement by the Spanish Society of Medical Oncology (SEOM) and the Spanish Society of Pathology (SEAP)

Biomarkers used in GEA

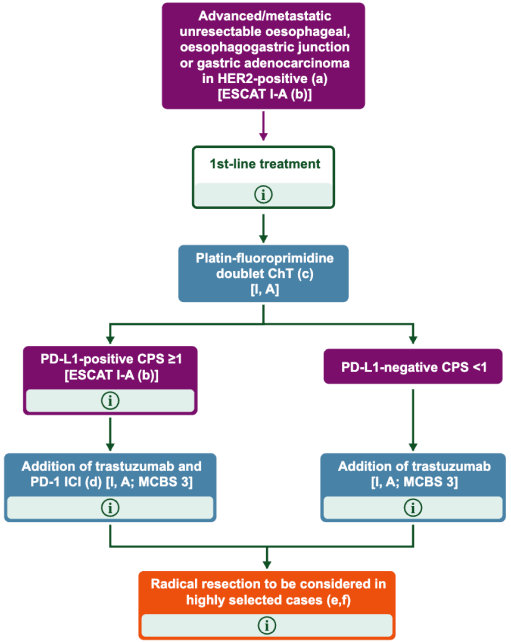
- MMR system and/or microsatellite status determination should be performed for all newly diagnosed GEA
- IHC is the preferred method for MMR testing, though PCR/NGS can also be used
- Biomarker determination for locally advanced unresectable or metastatic GEA include HER2 status, PD-L1 expression, and CLDN18.2 expression
- HER2 screening should be performed by immunohistochemistry ± HER2 in situ hybridization depending on the algorithm
- PD-L1 IHC CPS should be used, expressed as an absolute number. The terms positive/negative should be avoided. TAP is a novel score for PD-L1 assessment associated with emerging indications
- CLDN18.2 is an emerging therapeutic target evaluated by IHC

GEA, gastroesophageal adenocarcinoma; PD-L1, programmed death ligand 1; CPS, combined positive score; EMA, European Medicine Agency; dMMR/MSI, deficient mismatch repair protein/microsatellite instability; CLDN18.2, Claudin-18.2; IHC, immunohistochemistry; PCR, polymerase chain reaction; NGS, new generation sequencing



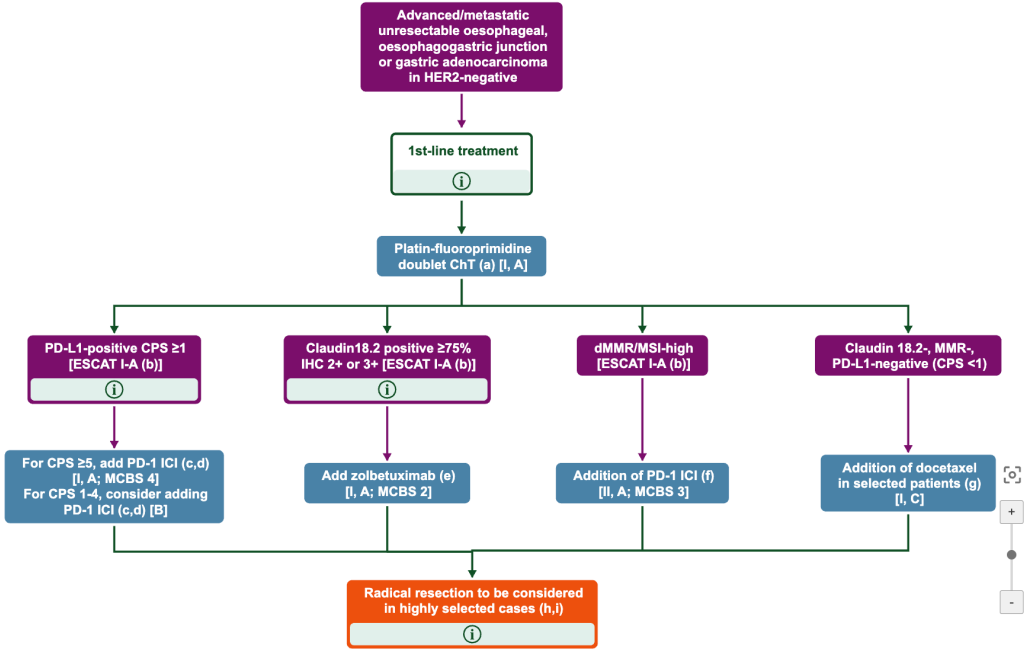
Alsina M, et al. Clin Transl Oncol, 2025

First-line for HER2-positive



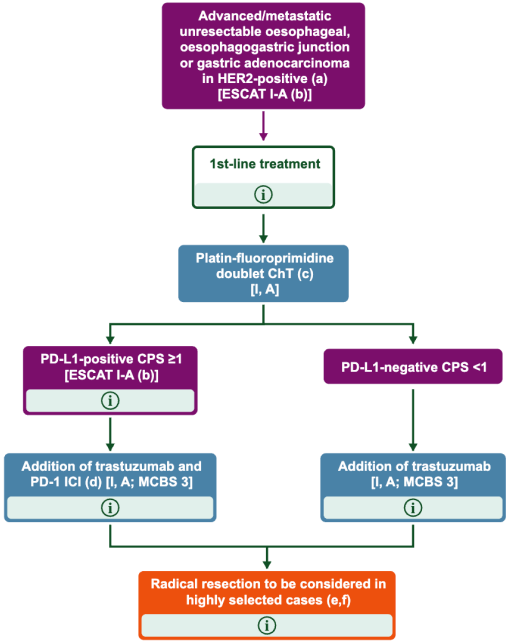
First-line for HER2-negative

v1.4 - September 2024



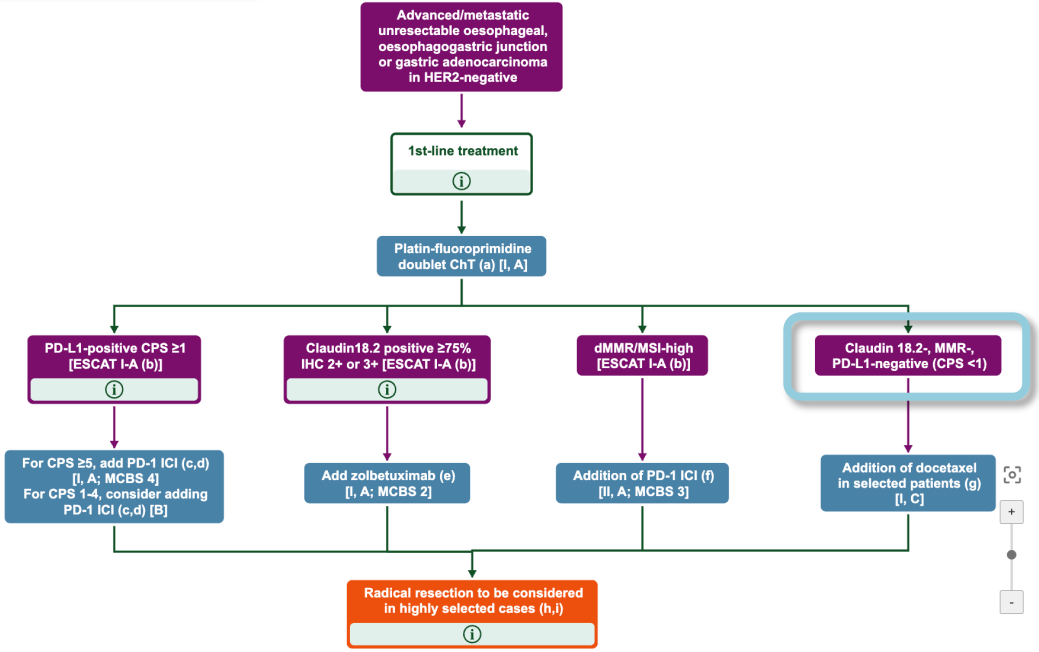
Opciones de tratamiento guiadas por biomarcador

First-line for HER2-positive



First-line for HER2-negative

v1.4 - September 2024



Opciones de tratamiento guiadas por biomarcador

First-line for HER2-negative + **Claudin 18.2-, MMR-, PD-L1-negative (CPS <1)**

Phase III Study of Docetaxel and Cisplatin Plus Fluorouracil Compared With Cisplatin and Fluorouracil As First-Line Therapy for Advanced Gastric Cancer: A Report of the V325 Study Group — 2006

TFOX versus FOLFOX in first-line treatment of patients with advanced HER2-negative gastric or gastro-oesophageal junction adenocarcinoma (PRODIGE 51-FFCD-GASTFOX): an open-label, multicentre, randomised, phase 3 trial — 2025

Van Cutsem E, et al. J Clin Oncol, 2006. Zaanan A. Lancet Oncol 2025

Opciones de tratamiento guiadas por biomarcador

First-line for HER2-negative + **Claudin 18.2-, MMR-, PD-L1-negative (CPS <1)**

GASTFOX trial

Randomized, multicenter, academic, phase III trial

Key eligibility criteria
- Previously untreated, locally advanced unresectable or metastatic G/GEJ adenocarcinoma
- HER2-negative
- ECOG PS 0-1
- Docetaxel naïve

R 1:1

- mFLOT/TFOX
- FOLFOX

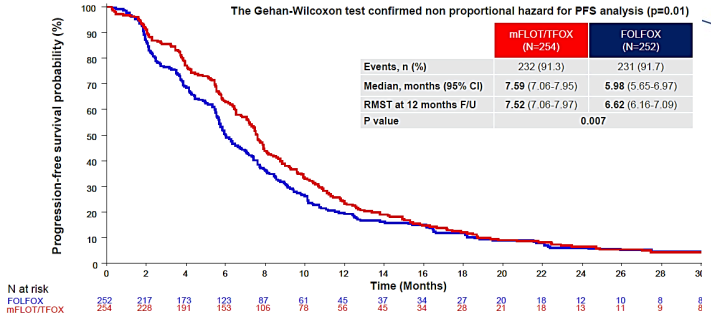
Maintenance treatment until unacceptable toxicity or disease progression

Stratification factors:

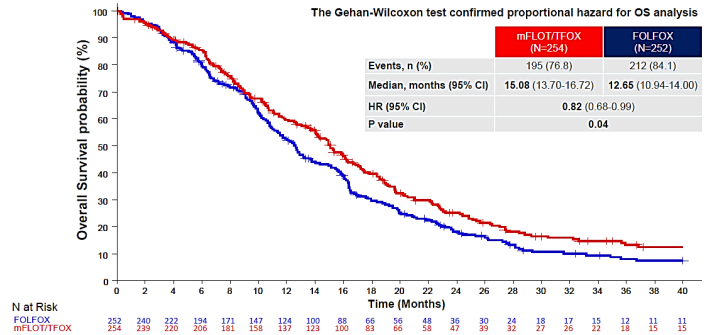
ECOG PS (0 vs 1),
prior (neo)adjuvant (yes vs no),
tumor stage (LA vs metastatic),
tumor location (G vs GEJ),
pathological subtype
(signet ring cell : yes vs no)

Recruitment period : between December 2016 and December 2022 (96 French cancer centers)
Data cutoff date for PFS and OS analysis : June 2023
Median follow up : 42.8 months

Primary endpoint: PFS



	mFLOT/TFOX (N=254)	FOLFOX (N=252)
Events, n (%)	232 (91.3)	231 (91.7)
Median, months (95% CI)	7.59 (7.06-7.95)	5.98 (5.65-6.97)
RMST at 12 months F/U	7.52 (7.06-7.97)	6.62 (6.16-7.09)
P value	0.007	



	mFLOT/TFOX (N=254)	FOLFOX (N=252)
Events, n (%)	195 (76.8)	212 (84.1)
Median, months (95% CI)	15.08 (13.70-16.72)	12.65 (10.94-14.00)
HR (95% CI)	0.82 (0.68-0.99)	
P value	0.04	

Zaanan A. Lancet Oncol 2025

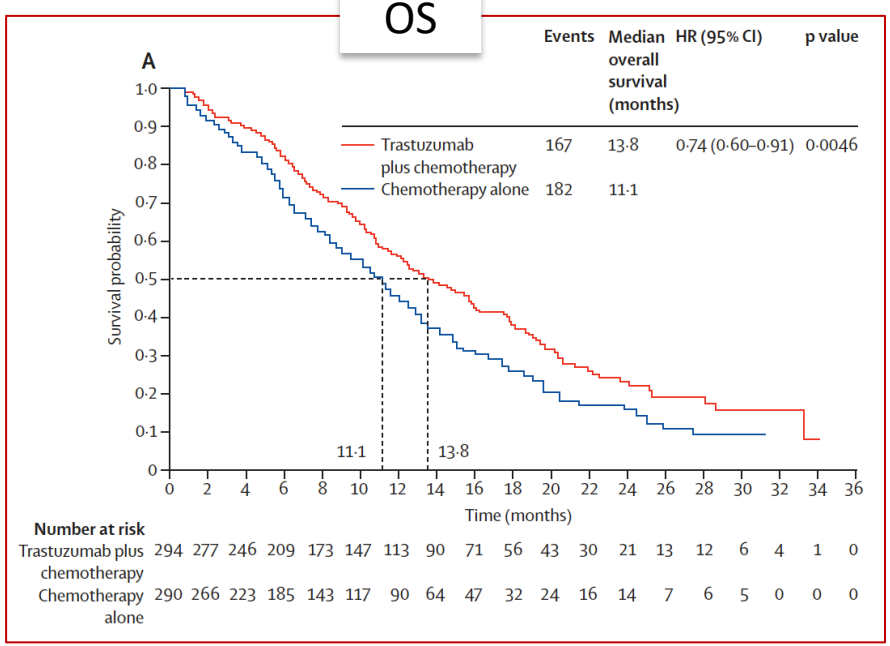
HER2+

Opciones de tratamiento guiadas por biomarcador

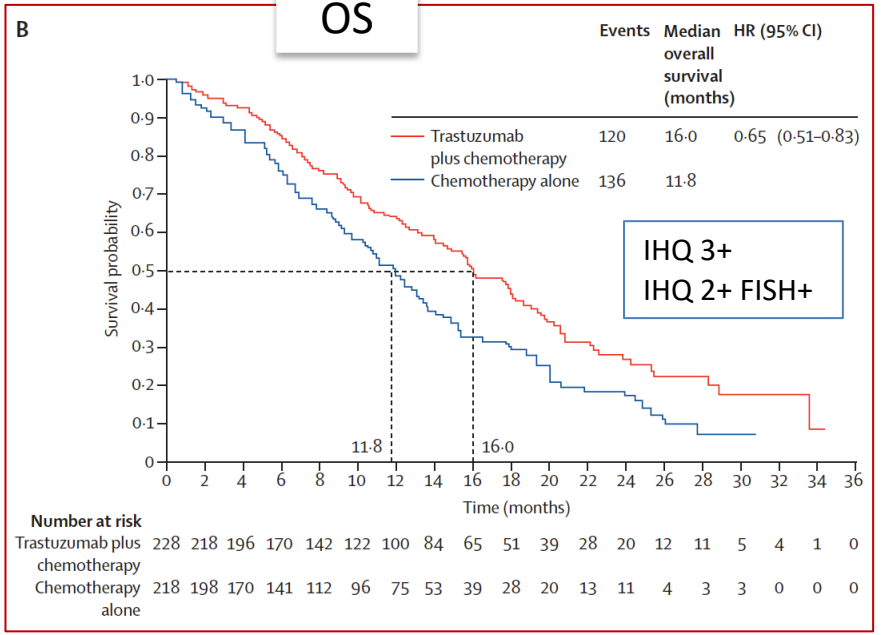
HER2+

ToGA trial

OS



OS



Patients were eligible if their tumour samples were scored as **3+ on immunohistochemistry or if they were FISH positive (HER2:CEP17 ratio ≥2).**

Bang YJ, et al. Lancet 2010.

Opciones de tratamiento guiadas por biomarcador

HER2+

Clinical Trial	First Reported Year	Drug	HER2 Definition	Phase	Line of Therapy	Intervention (Comparison)	Results
ToGA	2009	Trastuzumab	IHC 3+ and/or ISH-positive	P3	First-line	Trastuzumab + chemo (Chemotherapy)	Improvement of median OS 13.8 m vs. 11.1 m,
TyTAN	2013	Lapatinib	ISH-positive	P3	Second-line	Lapatinib + chemo (Chemotherapy)	No difference in median OS 11.0 m vs. 8.9 m, $p = 0.1044$
TRIO-013/LOGiC	2013	Lapatinib	IHC 3+ and/or ISH-positive	P2/3	First-line	Lapatinib + chemo (Chemotherapy)	No difference in median OS 12.2 m vs. 10.5 m, $p = 0.91$
GATSBY	2016	T-DM1	IHC 3+ or IHC 2+ISH-positive	P2/3	First-line	T-DM1 (Chemotherapy)	No difference in median OS 7.9 m vs. 8.6 m, $p = 0.31$
JACOB	2017	Pertuzumab	IHC 3+ or IHC 2+ISH-positive	P3	First-line	Pertuzumab + Trastuzumab + chemo (Trastuzumab + chemo)	No difference in median OS 17.5 m vs. 14.2 m, $p = 0.057$

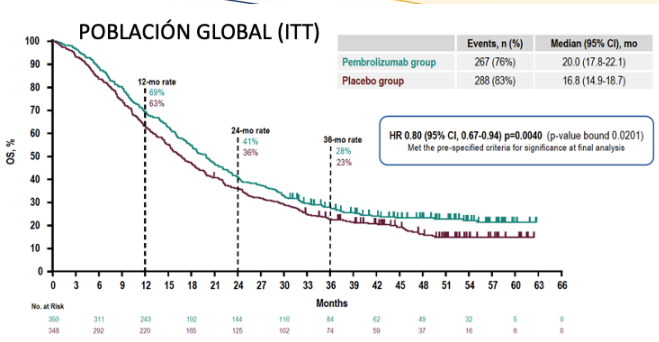
Ariga S. J Clin Med, 2023

Opciones de tratamiento guiadas por biomarcador

HER2+

Pembrolizumab plus trastuzumab and chemotherapy for HER2-positive gastric or gastro-oesophageal junction adenocarcinoma: interim analyses from the phase 3 KEYNOTE-811 randomised placebo-controlled trial

*Yelena Y Janjigian, Akihito Kawazoe, Yuxian Bai, Jianming Xu, Sara Lonardi, Jean Phillipe Metges, Patricio Yanez, Lucjan S Wyrwicz, Lin Shen, Yuriy Ostapenko, Mehmet Bilici, Hyun Cheol Chung, Kohei Shitara, Shu-Kui Qin, Eric Van Cutsem, Josep Tabernero, Kan Li, Chie-Schin Shih, Pooja Bhagia, Sun Young Rha, on behalf of the KEYNOTE-811 Investigators**



KEYNOTE-811 Study Design (NCT03615326)

Phase 3 Randomized, Placebo-Controlled

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

R 1:1 N=698

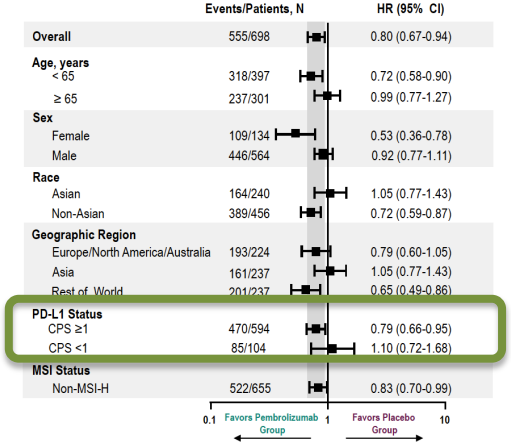
Pembrolizumab 200 mg IV Q3W + Trastuzumab and FP or CAPOX[a] for up to 35 cycles

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

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

Endpoints
- Dual primary: OS, PFS
- Secondary: ORR, DOR , safety

[a]Trastuzumab: 6 mg/kg IV Q3W following an 8 mg/kg loading dose. FP: 5-fluorouracil 800 mg/m² IV on D1-5 Q3W + cisplatin 80 mg/m² IV Q3W. CAPOX: capecitabine 1000 mg/m² BID on D1-14 Q3W + oxaliplatin 130 mg/m² IV Q3W. PFS, ORR, DOR per RECIST by BICR.



*85% PDL1 CPS ≥ 1

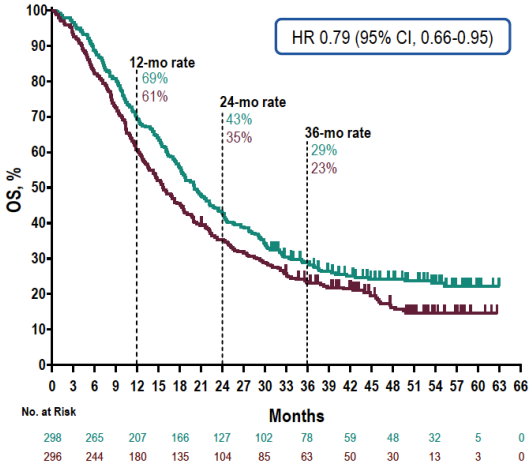
Janjigian Y, et al, ESMO 2023. Janjigian Y, et al. Lancet 2023. Lonardi S, et al, ESMO 2024.

Opciones de tratamiento guiadas por biomarcador

PDL1 CPS ≥ 1

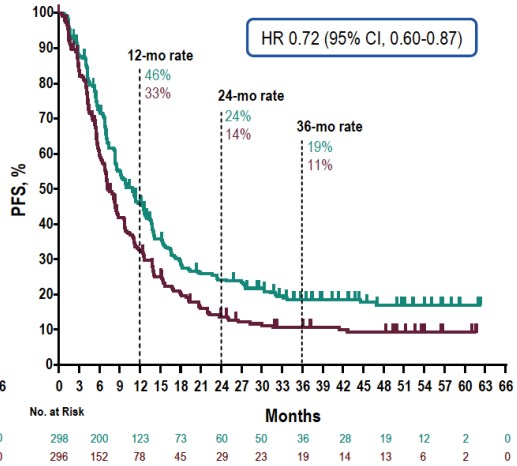
OS

	Events, n (%)	Median (95% CI), mo
Pembrolizumab group	226 (76%)	20.1 (17.9-22.9)
Placebo group	244 (82%)	15.7 (13.5-18.5)



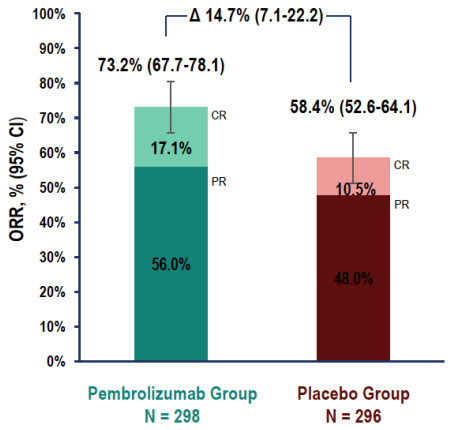
PFS

	Events, n (%)	Median (95% CI), mo
Pembrolizumab group	221 (74%)	10.9 (8.5-12.5)
Placebo group	226 (76%)	7.3 (6.8-8.4)



ORR and DOR

	Responders, n	Median DOR (range), mo
Pembrolizumab group	218	11.3 (1.1+ -to 60.8+)
Placebo group	173	9.5 (1.4+ to 60.5+)



Final Analysis: 50.2 months of follow-up

Janjigian Y, et al, ESMO 2023. Janjigian Y, et al. Lancet 2023. Lonardi S, et al, ESMO 2024.

Opciones de tratamiento guiadas por biomarcador

	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 (95% CI), mo	10.9 (8.5-12.5)	7.3 (6.8-8.4)	9.5 (8.3-12.6)	9.5 (7.9-13.0)
HR (95% CI)	0.72 (0.60-0.87)		0.99 (0.62-1.56)	
OS, median (95% CI), mo	20.1 (17.9-22.9)	15.7 (13.5-18.5)	18.2 (13.9-22.9)	20.4 (16.4-24.7)
HR (95% CI)	0.79 (0.66-0.95)		1.10 (0.72-1.68)	

Final Analysis: 50.2 months of follow-up

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

APPROVED

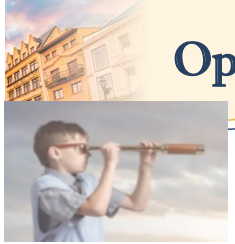
MINISTERIO DE SANIDAD

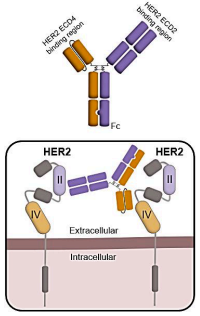
KEYTRUDA, en combinación con trastuzumab, y quimioterapia basada en fluoropirimidina y platino, está indicado para el tratamiento de primera línea del adenocarcinoma gástrico o de la unión gastroesofágica HER-2 positivo localmente avanzado irresecable o metastásico en adultos cuyos tumores expresen PD-L1 con una CPS mayor o igual a 1.	Resuelto	No incluida

Janjigian Y, et al, ESMO 2023. Janjigian Y, et al. Lancet 2023. Lonardi S, et al, ESMO 2024.

Opciones de tratamiento guiadas por biomarcador

HER2+

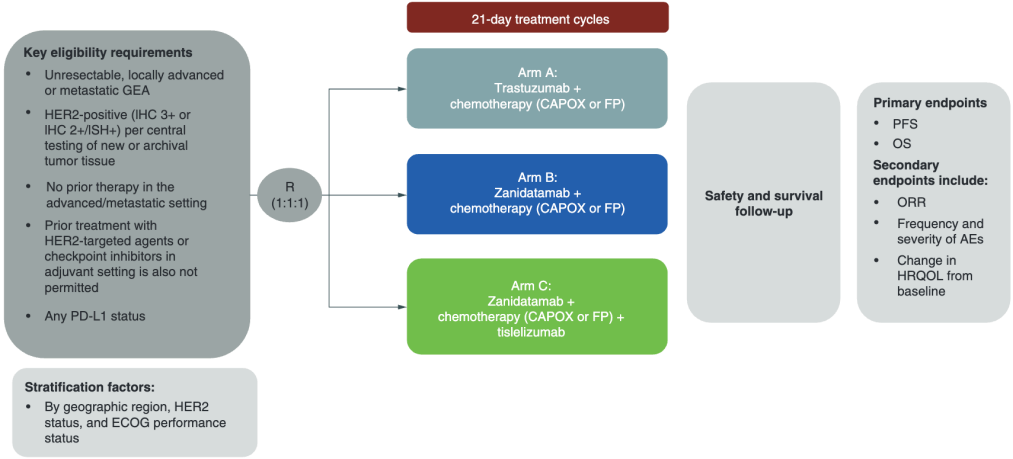




Zanidatamab plus chemotherapy as first-line treatment for patients with HER2-positive advanced gastro-oesophageal adenocarcinoma: primary results of a multicentre, single-arm, phase 2 study

ADC EG HER2+ (QT+Zanidatamab)

- ORR 76,2% (mDR: 18,7m)
- mPFS 12,5m
- mOS 36,5m



Jazz Pharmaceuticals

Positive HERIZON-GEA-01 Phase 3 Results Support Ziihera® (zanidatamab-hrii) as HER2-Targeted Agent-of-Choice and Ziihera Combination Regimens as New Standard of Care in First-Line HER2-Positive Locally Advanced or Metastatic Gastroesophageal Adenocarcinoma

November 17, 2025

Elimova E, et al. Lancet Oncol 2025. Tabernero J, et al. Future Oncol, 2022

HER2+

HER2 *low*

¿Nuevo concepto en CG?

¿Nuevas oportunidades?

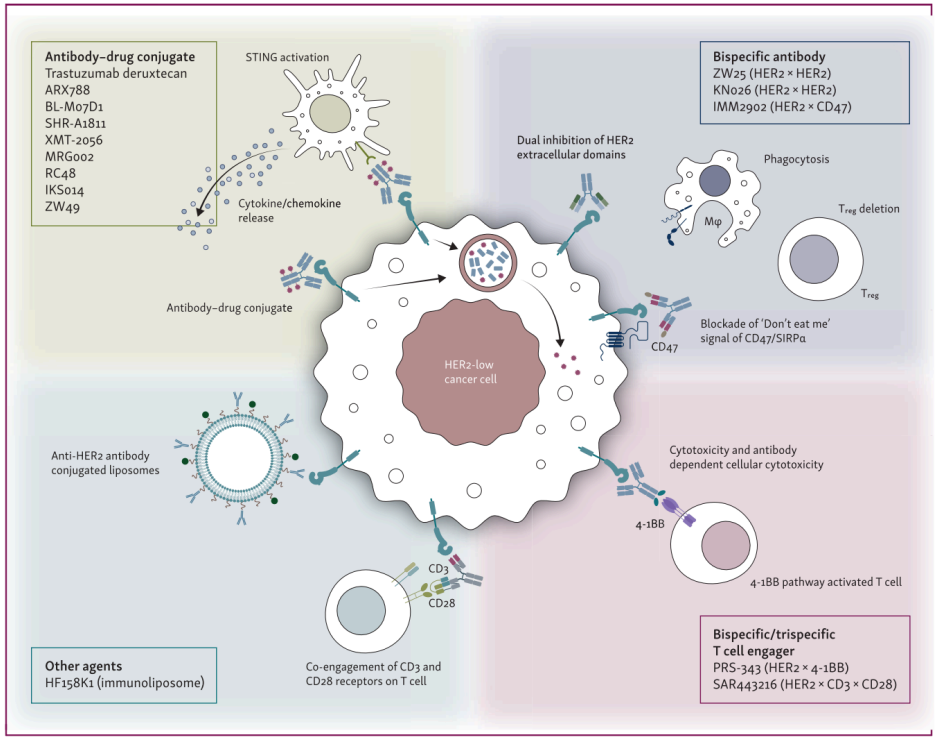


Figure 1. Mechanisms of action of therapeutic agents investigated for HER2-low gastric cancer.
HER2, human epidermal growth factor receptor 2; STING, stimulator of interferon genes.

Shimozaki K, et al. ESMO Open, 2024

PDL1

Opciones de tratamiento guiadas por biomarcador

PDL1

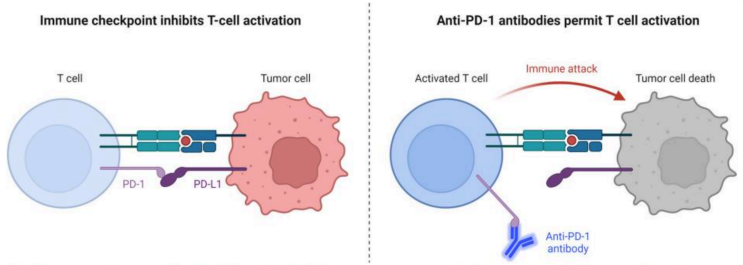
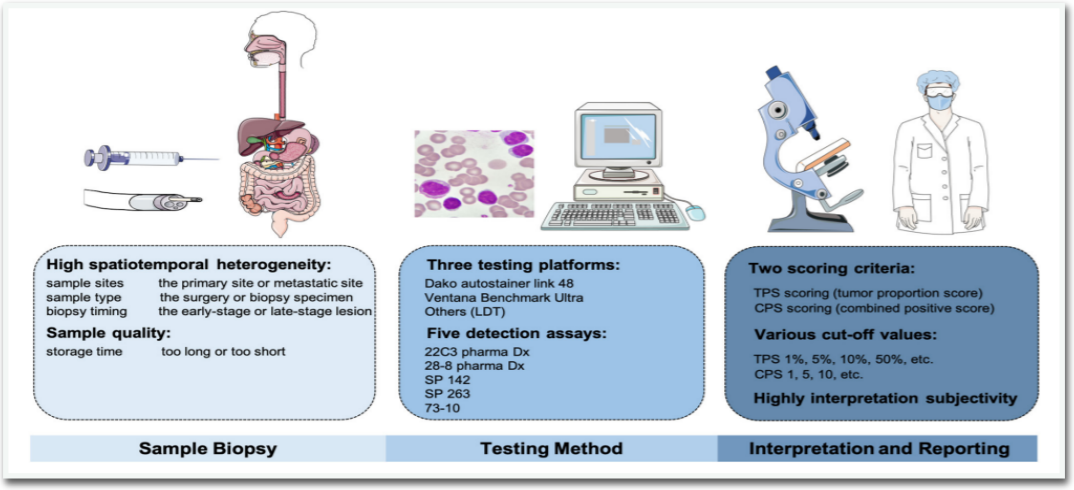


Fig. 1 Immune Checkpoint Inhibitor against Tumor Cell. Through the interaction between PD-1 expressed on the surface of T cells and PD-L1 expressed on the surface of tumor cells, the immunological checkpoint prevents T-cell activation. Through contact between PD-1 on the surface of T cells and anti-PD-1 antibodies, T cell activation and immunological attack are enabled



Marei HE, et al. Cancer Cell Int. 2023 Apr 10;23(1):64. Zeng Z et al. Front Oncol 2021;11:650481.

PDL1

Opciones de tratamiento guiadas por biomarcador

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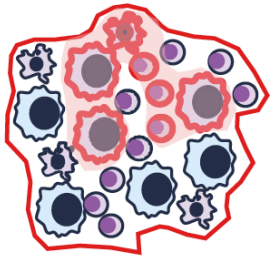
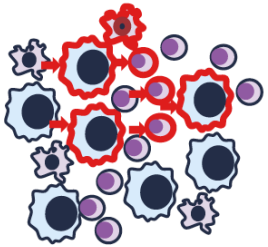
Scoring name	Formula[a]	Visual representation[b,c]	Cell types included in PD-L1 score	Score method
TAP score	$\frac{\text{Area occupied by PD-L1 stained TCs and ICs}}{\text{Tumor area}} \times 100\%$		TCs, ICs (including lymphocytes, macrophages, histiocytes, reticular dendritic cells, plasma cells, and neutrophils)	Visual estimation of tumor area that is occupied by PD-L1–expressing cells
CPS	$\frac{\text{Number of PD-L1 stained TCs and ICs}}{\text{Total number of viable TCs}} \times 100\%$		TCs, ICs (including lymphocytes and macrophages)	Counting of individual PD-L1–expressing cells and TCs

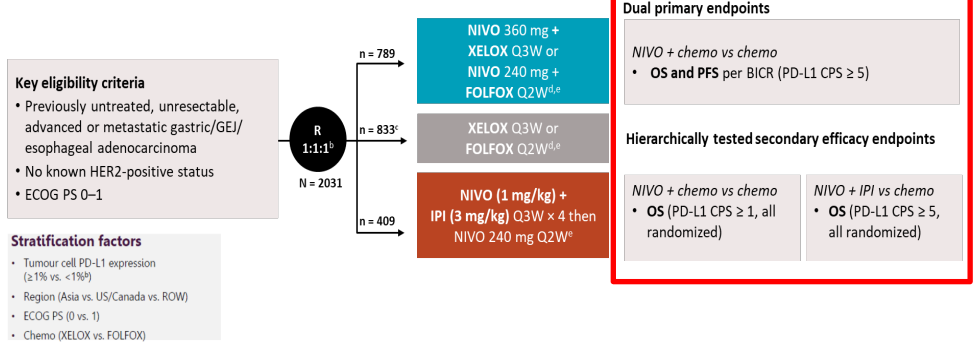
Moehler M, et al. Mod Pathol, 2025.

Opciones de tratamiento guiadas por biomarcador

PDL1

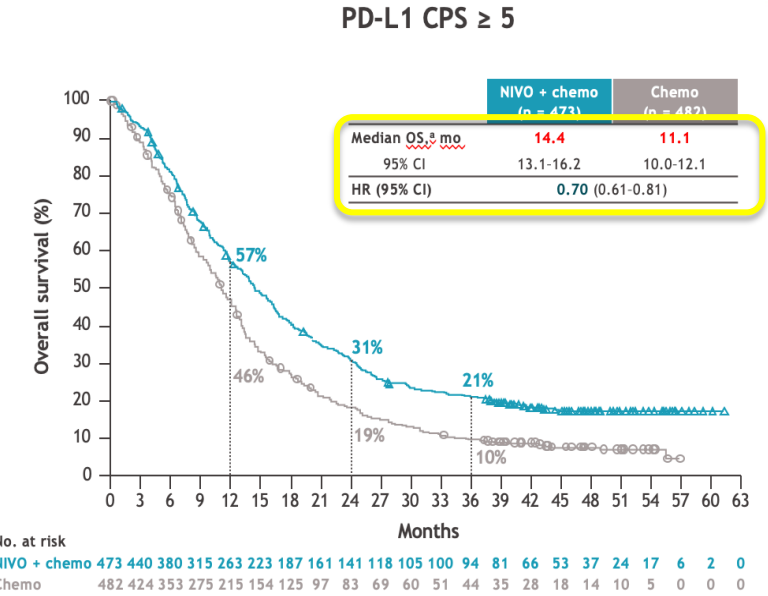
First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial

Yelena Y Janjigian*, Kohei Shitara*, Markus Moehler, Marcelo Garrido, Pamela Salman, Lin Shen, Lucjan Wyrwicz, Kensei Yamaguchi, Tomasz Skoczylas, Arinilda Campos Bragagnoli, Tianshu Liu, Michael Schenker, Patricio Yanez, Mustapha Tehfe, Ruben Kowalyszyn, Michalis V Karamouzis, Ricardo Bruges, Thomas Zander, Roberto Pazo-Cid, Erika Hitre, Kynan Feeney, James M Cleary, Valerie Poulart, Dana Cullen, Ming Lei, Hong Xiao, Kaoru Kondo, Mingshun Li, Jaffer A Ajani



100% ADC (GC 70%; UGE 17%; Esófago 13%)

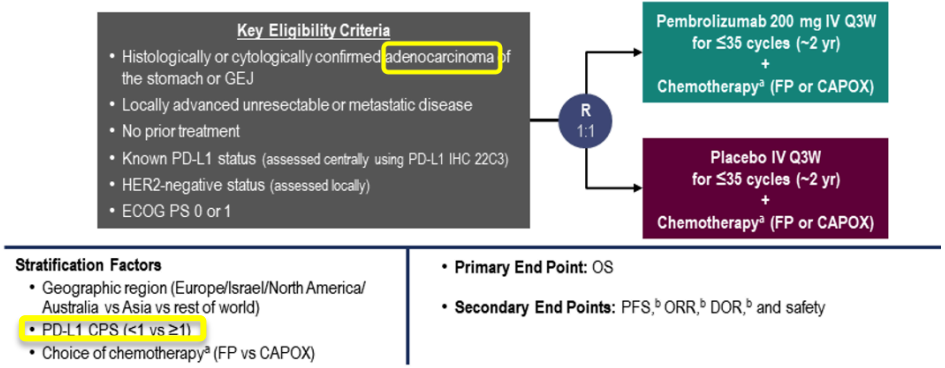
PDL1 CPS ≥ 5: 60%



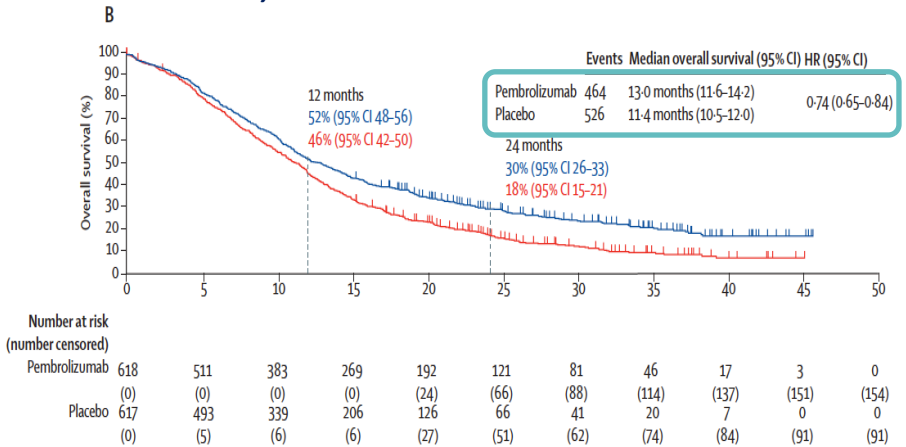
Janjigian YY, et al. *Lancet* 2021;398:27-40. Moehler M. ESMO2020, LBA6

Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): a multicentre, randomised, double-blind, phase 3 trial

*Sun Young Rha, Do-Youn Oh, Patricio Yañez, Yuxian Bai, Min-Hee Ryu, Jeeyun Lee, Fernando Rivera, Gustavo Vasconcelos Alves, Marcelo Garrido, Kai-Keen Shiu, Manuel González Fernández, Jin Li, Maeve A Lowery, Timuçin Çil, Felipe Melo Cruz, Shukui Qin, Suxia Luo, Hongming Pan, Zev A Wainberg, Lina Yin, Sonal Bordia, Pooja Bhagia, Lucjan S Wyrwicz, on behalf of the KEYNOTE-859 investigators**



OS, PDL1 CPS ≥ 1



100% ADC (GC 79%; UGE 21%)

PDL1 CPS ≥ 1: 78%

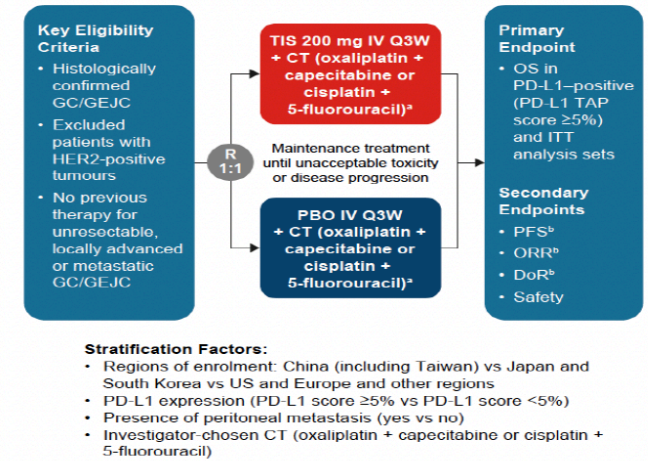
Rha SY, et al. Lancet Oncol 2023;24:1181-95.

PDL1

Tislelizumab plus chemotherapy versus placebo plus chemotherapy as first line treatment for advanced gastric or gastro-oesophageal junction adenocarcinoma: RATIONALE-305 randomised, double blind, phase 3 trial

Miao-Zhen Qiu,[1] Do-Youn Oh,[2] Ken Kato,[3] Tobias Arkenau,[4] Josep Tabernero,[5]

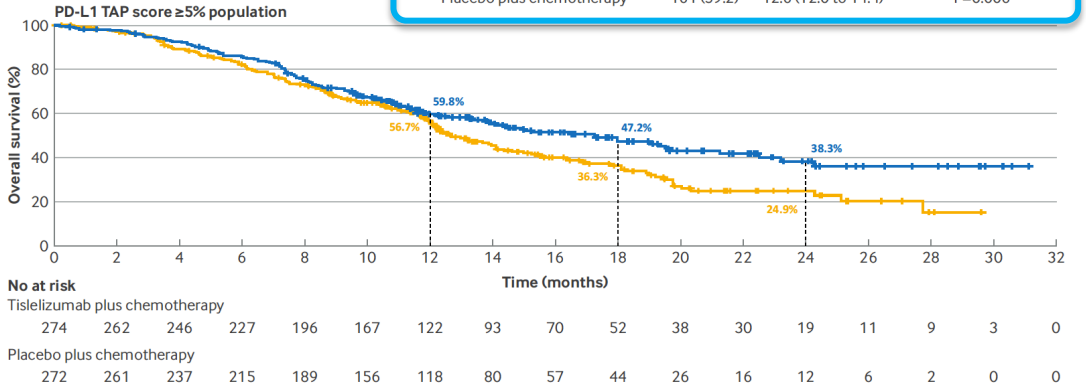
RATIONALE 305 Diseño



Stratification Factors:
- Regions of enrolment: China (including Taiwan) vs Japan and South Korea vs US and Europe and other regions
- PD-L1 expression (PD-L1 score ≥5% vs PD-L1 score <5%)
- Presence of peritoneal metastasis (yes vs no)
- Investigator-chosen CT (oxaliplatin + capecitabine or cisplatin + 5-fluorouracil)

OS, PDL1 TAP ≥ 5%

	No of events (%)	Median overall survival (95% CI) (months)	Stratified hazard ratio (95% CI) Log-rank test P value
Tislelizumab plus chemotherapy	130 (47.4)	17.2 (13.9 to 21.3)	0.74 (0.59 to 0.94)
Placebo plus chemotherapy	161 (59.2)	12.6 (12.0 to 14.4)	P=0.006



100% ADC. (GC 80%; UGE 20%)

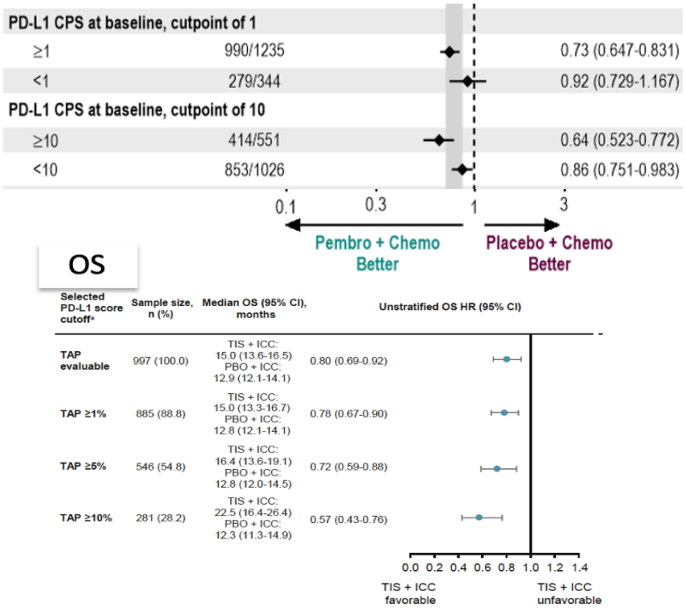
PDL1 TAP ≥ 5%: 55%

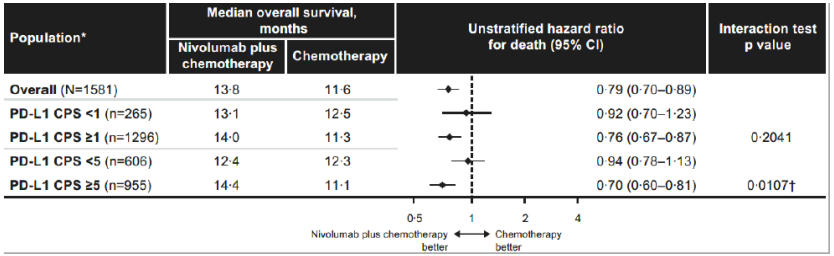
Qui MZ, et al. BMJ 2024. Correa MC, et al. ESMO 2024 #1437P

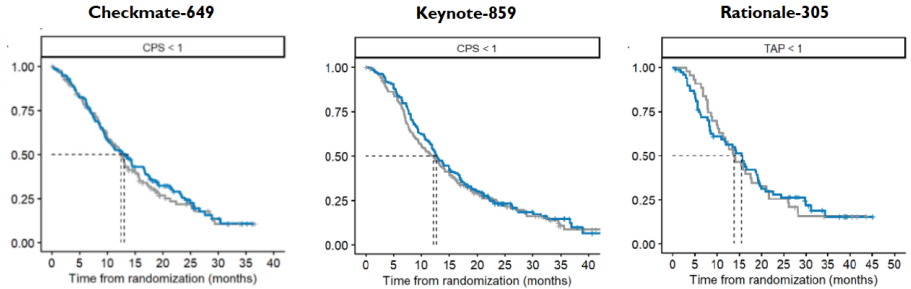
Opciones de tratamiento guiadas por biomarcador

Ausencia de beneficio sin expresión de PDL1

Mayor magnitud de beneficio a mayor expresión de PDL1







Janjigian YY, et al. *Lancet* 2021. Rha SY, et al. Lancet Oncol 2023. Moehler M, et al. Mod Pathol, 2025. September, 2024 FDA Meeting of the ODAC

Opciones de tratamiento guiadas por biomarcador

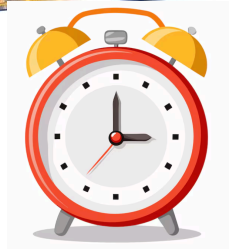
PDL1

MINISTERIO DE SANIDAD

KEYTRUDA, en combinación con quimioterapia basada en fluoropirimidina y platino, está indicado para el tratamiento de primera línea del adenocarcinoma gástrico o de la unión gastroesofágica HER-2 negativo localmente avanzado irresecable o metastásico en adultos cuyos tumores expresen PD-L1 con una CPS mayor o igual a 1	Resuelto	Sí, con restricción a la indicación autorizada: Se restringe a pacientes cuyos tumores expresen PD-L1 con una CPS>=10
OPDIVO en combinación con quimioterapia de combinación basada en fluoropirimidina y platino está indicado para el tratamiento de primera línea de pacientes adultos con adenocarcinoma gástrico, de la unión gastroesofágica o de esófago avanzado o metastásico HER2 negativo cuyos tumores expresan PD-L1 con una puntuación positiva combinada (CPS, por sus siglas en inglés) >= 5.	Resuelto	Sí, financiada indicación autorizada
Tevimbra, en combinación con quimioterapia basada en platino y fluoropirimidina, está indicado para el tratamiento de primera línea del adenocarcinoma gástrico o de la unión gastroesofágica (UGE) HER-2 negativo localmente avanzado irresecable o metastásico en pacientes adultos cuyos tumores expresen PD-L1 con una puntuación de positividad del área tumoral (TAP, por sus siglas en inglés) ≥5 % (ver sección 5.1).	Resuelto	Sí, financiada indicación autorizada

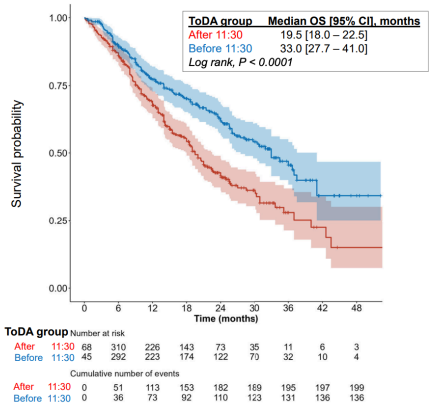
BIFIMED:https://www.sanidad.gob.es/profesionales/medicamentos.do

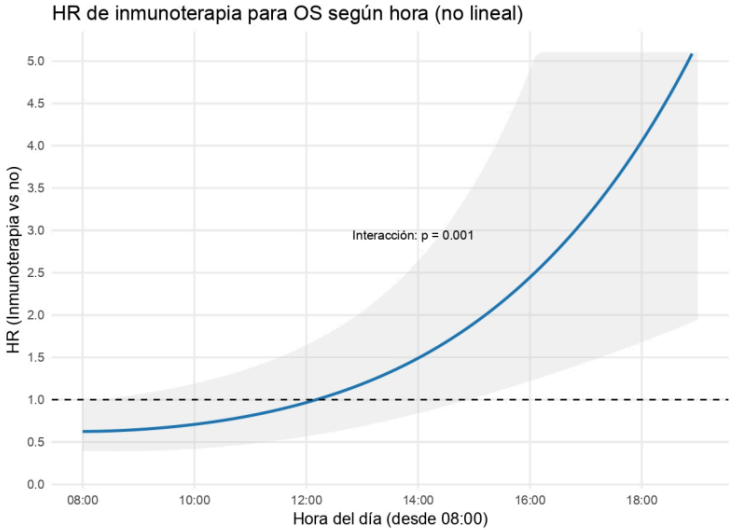
Opciones de tratamiento guiadas por biomarcador



Análisis continuo del PD-L1 CPS para selección precisa de quimioinmunoterapia en pacientes con cáncer gastroesofágico avanzado: datos del registro AGAMENON/SEOM

Overall survival according to time-of-day of combined immuno-chemotherapy for advanced non-small cell lung cancer: a bicentric bicontinental study





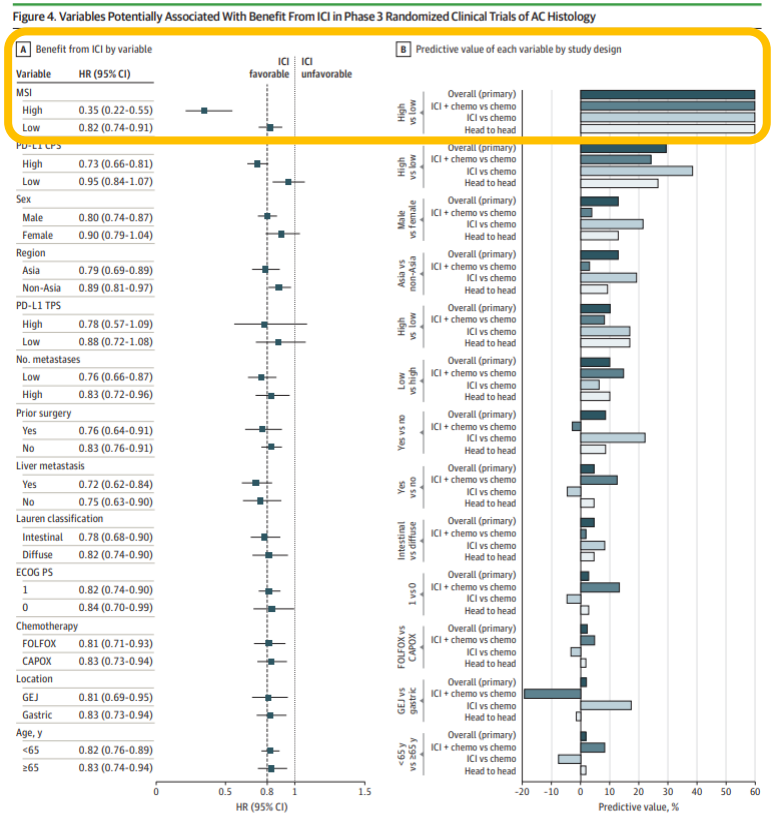
Huang Z et al. EBioMedicine, 2025. Marin G, et al. SEOM2025

MMR
MSI

Opciones de tratamiento guiadas por biomarcador

MMR
MSI

5% GC Stage IV
20% GC Stage I-III



dMMR/MSI-H es el predictor de respuesta a inmunoterapia más potente

Harry H. Yoon et al. JAMA Oncol 2022.

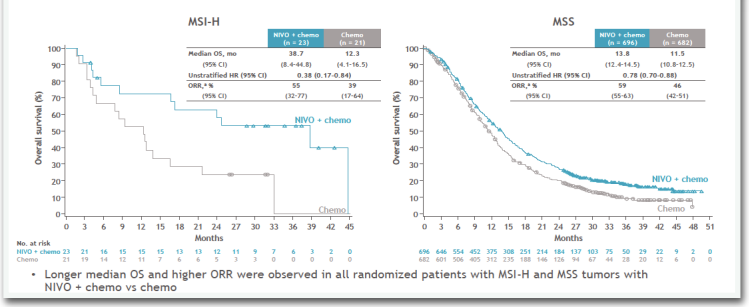
Opciones de tratamiento guiadas por biomarcador

MMR
MSI

XXXIII SIMPOSIO INTERNACIONAL INTERNATIONAL SYMPOSIUM
11 - 12 DE DICIEMBRE DE 2025

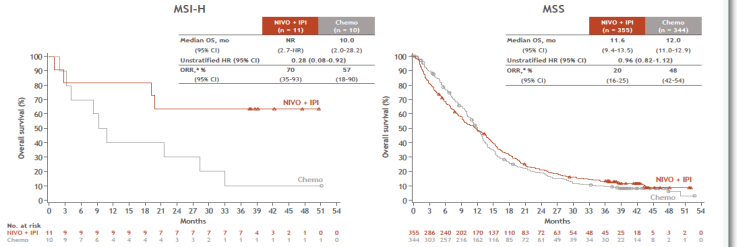
Nivolumab plus chemotherapy or ipilimumab vs chemotherapy as first-line treatment for advanced gastric cancer/gastroesophageal junction cancer/ esophageal adenocarcinoma: CheckMate 649 study

Efficacy by MSI status: NIVO + chemo vs chemo



- Longer median OS and higher ORR were observed in all randomized patients with MSI-H and MSS tumors with NIVO + chemo vs chemo

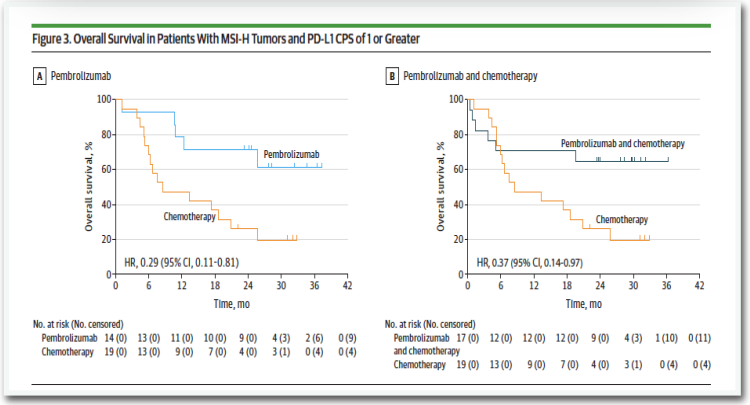
Efficacy by MSI status: NIVO + IPI vs chemo



- Longer median OS and higher ORR observed in all randomized patients with MSI-H tumors with NIVO + IPI vs chemo, although sample size was small

JAMA Oncology | Original Investigation

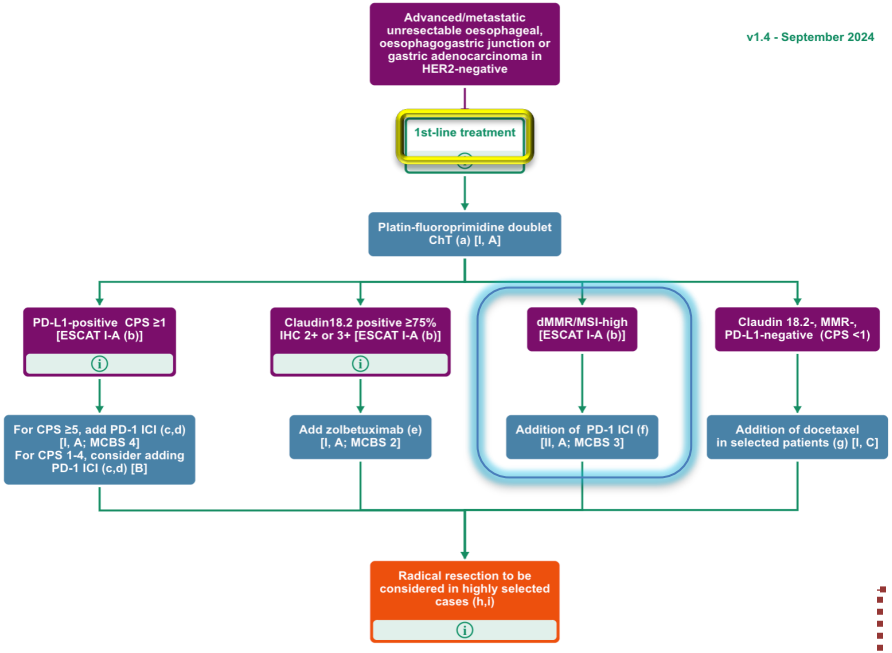
Efficacy and Safety of Pembrolizumab or Pembrolizumab Plus Chemotherapy vs Chemotherapy Alone for Patients With First-line, Advanced Gastric Cancer
The KEYNOTE-062 Phase 3 Randomized Clinical Trial



Shitara JAMA Oncol 2020, Janjigian ESMO 2021, Meta-analysis Pietrantonio ESMO Open 2021

Opciones de tratamiento guiadas por biomarcador

MMR
MSI



ORIGINAL ARTICLE

Pembrolizumab in microsatellite instability high or mismatch repair deficient cancers: updated analysis from the phase II KEYNOTE-158 study

M. Maio[1*], P. A. Ascierto[2], L. Manzyuk[3], D. Motola-Kuba[4], N. Penel[5], P. A. Cassier[6], G. M. Bariani[7], A. De Jesus Acosta[8], T. Doi[9], F. Longo[10], W. H. Miller, Jr[11,12], D.-Y. Oh[13,14,15], M. Gottfried[16], L. Xu[17], F. Jin[17], K. Norwood[17] & A. Marabelle[18]

EMA APPROVED

MINISTERIO DE SANIDAD

KEYTRUDA en monoterapia está indicado para el tratamiento de los siguientes tumores con MSI-H o dMMR en adultos con cáncer gástrico, de intestino delgado o biliar, irresecable o metastásico que ha progresado durante o después de al menos un tratamiento previo	Resuelto	Sí, financiada indicación autorizada

¿En 1L dMMR/MSI-H PDL1 negativo?

ESMO Gastric Cancer Living Guidelines. Maio, M., et al.Annals of Oncology, 2022. FT Europea Pembrolizumab

Claudina
18.2

Opciones de tratamiento guiadas por biomarcador

Claudina 18.2

Proteína de membrana: **componente estructural** importante de las proteínas de unión estrecha.
Función de valla: regula la permeabilidad del tejido, el transporte paracelular y la transducción de señales.

Expresada sólo en mucosa gástrica.
Se mantiene y se expone durante la trasformación maligna. Por tanto, se expresa en **cáncer gástrico y UGE** (ectópicamente expresada en otros tumores – páncreas, CNMP, ovario…)

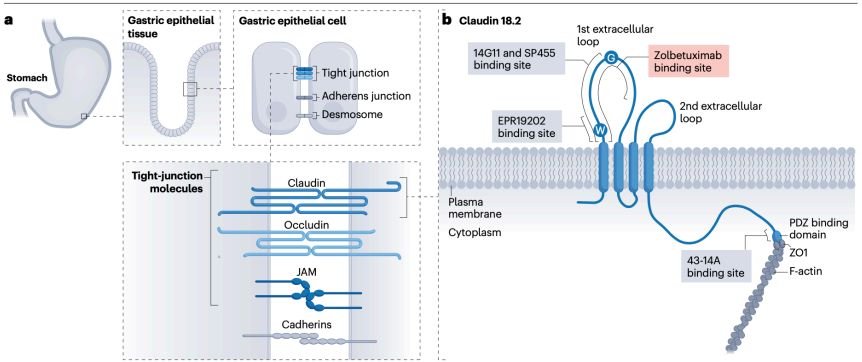
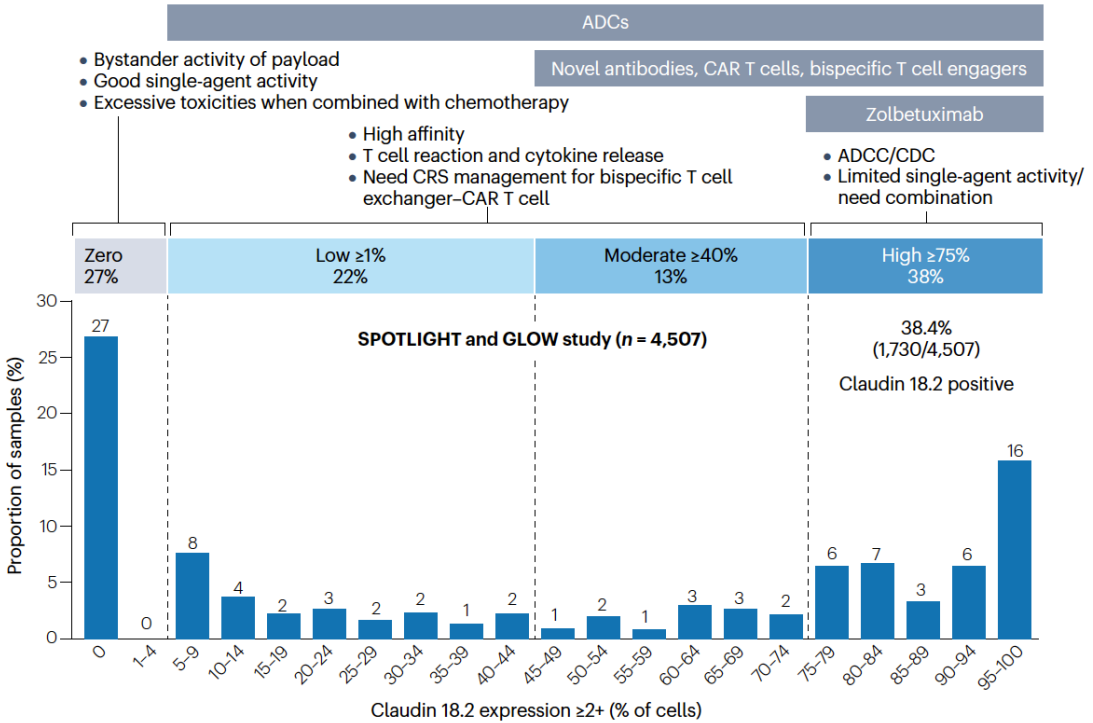


Fig. 1 | Claudin 18.2 structure, function and expression patterns. a, Claudin 18.2 is highly selectively expressed in the nonmalignant gastric mucosa, in which it is located at the most apical side of the paracellular space where it constitutes the tight-junction complex. **b**, Claudin 18.2 is a transmembrane protein with two extracellular loops that bind to claudin 18.2 molecules expressed on the surfaces of neighbouring cells, where they form a selectively permeable barrier that enables tissue-specific permeability and thus supports the polarity of gastric epithelial cells. This figure illustrates the binding sites for the therapeutic monoclonal antibody zolbetuximab plus the various diagnostic antibodies used to determine claudin 18.2 expression. ZO1, zonula occludens 1.

Nakayama I, et al. Nat Rev 2023.

Claudina 18.2

Opciones de tratamiento guiadas por biomarcador



Expresión Claudina 18.2:

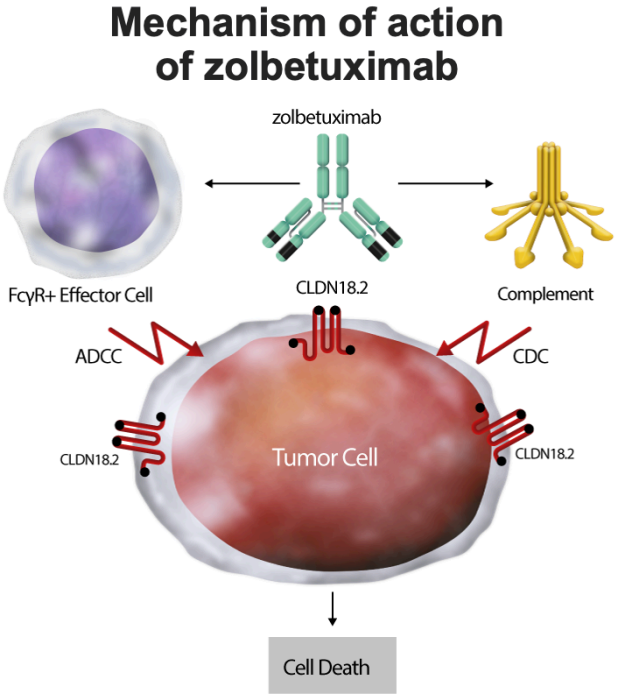
- High: tinción moderada o intensa (2+/3+) en ≥75% de las células.

Nakayama I, et al. Nat Rev 2023.

Zolbetuximab: (*first in class*)

Ac IgG1 quimérico

Citotoxicidad celular dependiente de anticuerpo (ADCC) y citotoxicidad dependiente de complemento (CDC).



Adapted from Singh P et al. *J Hematol Oncol.* 2017; 10(1):105.

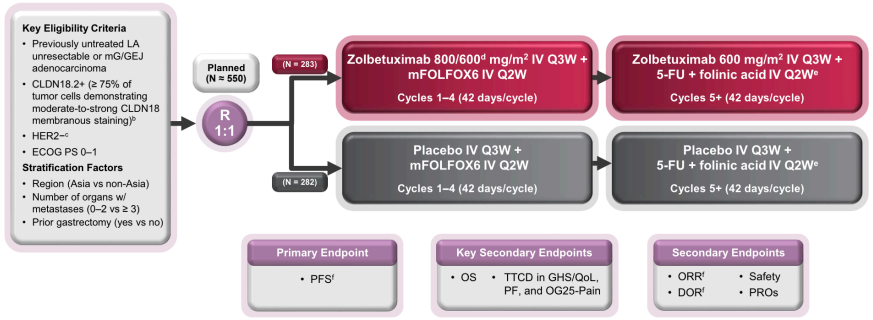
Zolbetuximab: (*first in class*)

Ac IgG1 quimérico

Citotoxicidad celular dependiente de anticuerpo (ADCC) y citotoxicidad dependiente de complemento (CDC).

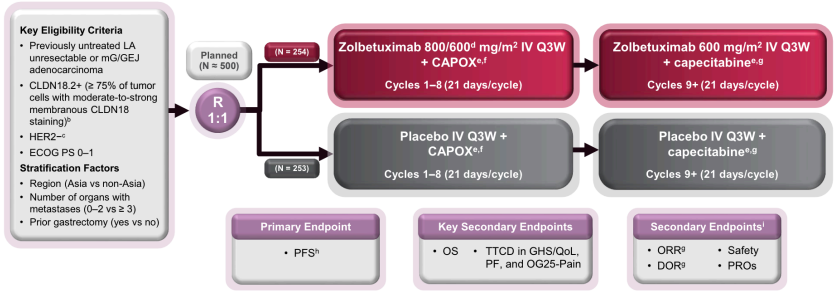
Study Design: SPOTLIGHT

Global[a], Randomized, Double-blinded, Placebo-controlled, Phase 3 Trial



Study Design: GLOW

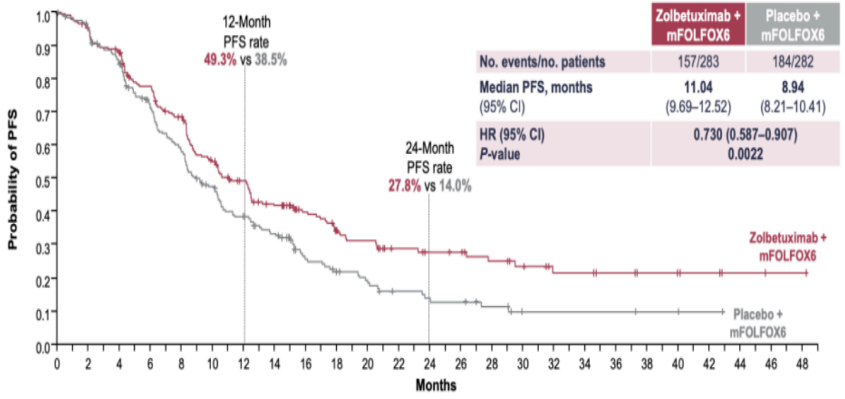
Global[a], Randomized, Double-blinded, Placebo-controlled, Phase 3 Trial



Ajani JA, et al. ESMO 2023 (#LBA82). Lordick F, et al. ESMO 2023 (#LBA81)

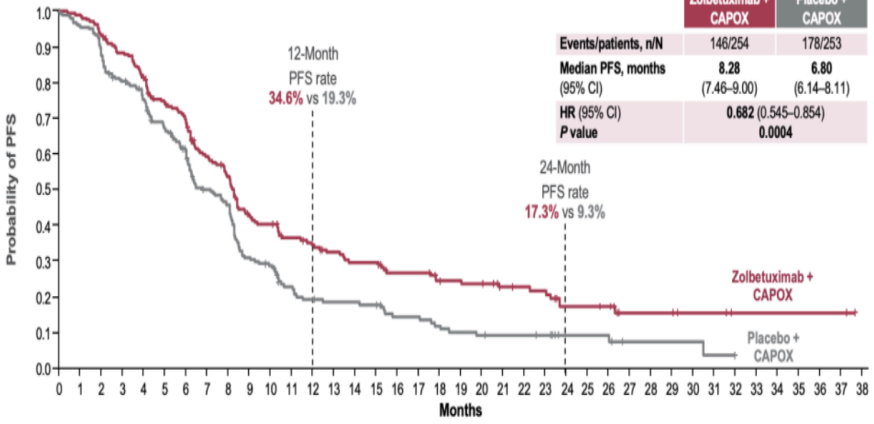
Primary Endpoint: PFS

SPOTLIGHT
Zolbetuximab+FOLFOX



	Zolbetuximab + mFOLFOX6	Placebo + mFOLFOX6
No. events/no. patients	157/283	184/282
Median PFS, months (95% CI)	11.04 (9.69–12.52)	8.94 (8.21–10.41)
HR (95% CI) *P*-value	0.730 (0.587–0.907) 0.0022	

GLOW
Zolbetuximab+CapeOX

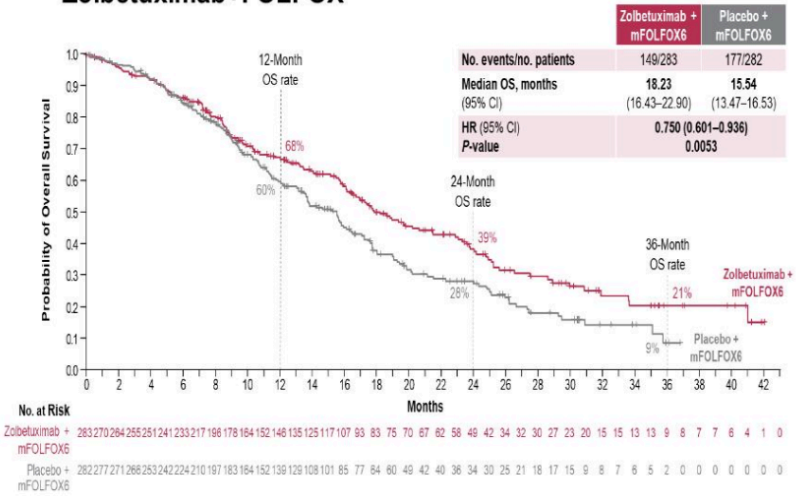


	Zolbetuximab + CAPOX	Placebo + CAPOX
Events/patients, n/N	146/254	178/253
Median PFS, months (95% CI)	8.28 (7.46–9.00)	6.80 (6.14–8.11)
HR (95% CI) *P* value	0.682 (0.545–0.854) 0.0004	

Ajani JA, et al. ESMO 2023 (#LBA82). Lordick F, et al. ESMO 2023 (#LBA81) Shitara K, et al. Lancet 2023; Shah M, et al. Nature Med 2023.

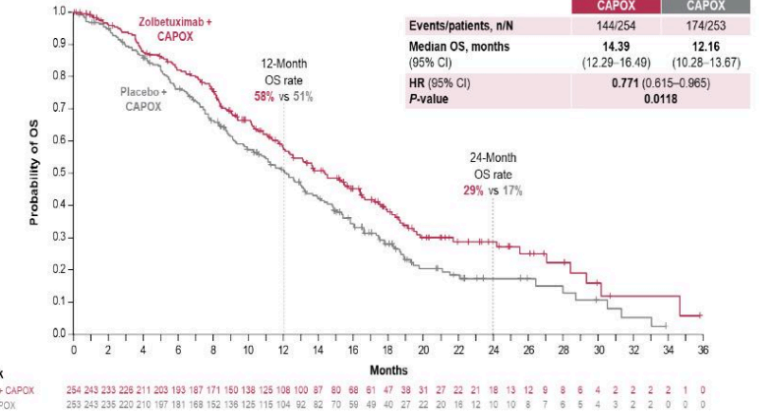
Overall Survival

SPOTLIGHT
Zolbetuximab+FOLFOX



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

GLOW
Zolbetuximab+CapeOX

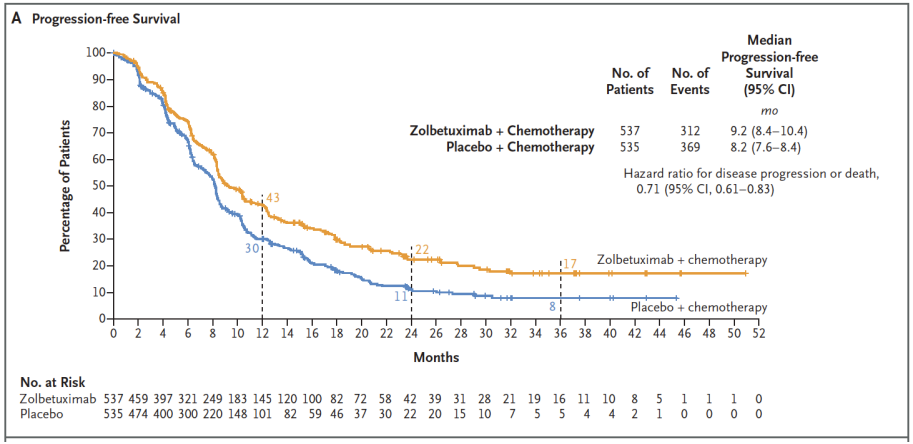


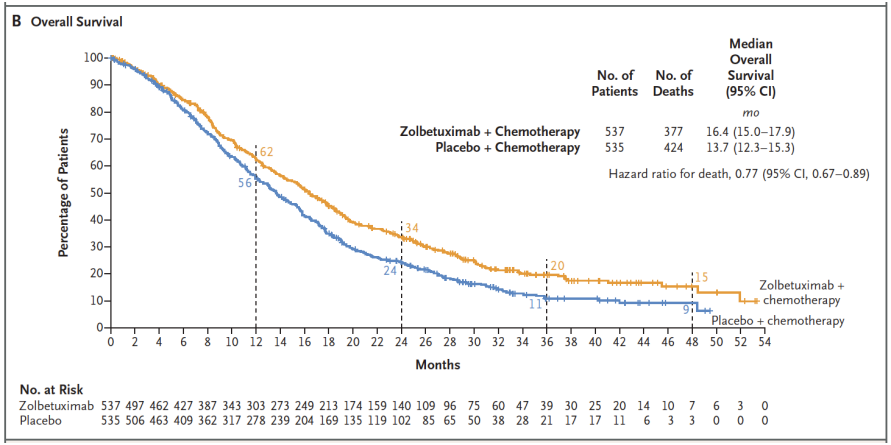
	Zolbetuximab + CAPOX	Placebo + CAPOX
Events/patients, n/N	144/254	174/253
Median OS, months (95% CI)	14.39 (12.29–16.49)	12.16 (10.28–13.67)
HR (95% CI)	0.771 (0.615–0.965)	
P-value	0.0118	

Main toxicity: nausea and vomiting at 1st infusion

Ajani JA, et al. ESMO 2023 (#LBA82). Lordick F, et al. ESMO 2023 (#LBA81) Shitara K, et al. Lancet 2023; Shah M, et al. Nature Med 2023.

Zolbetuximab in Gastric or Gastroesophageal Junction Adenocarcinoma





EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

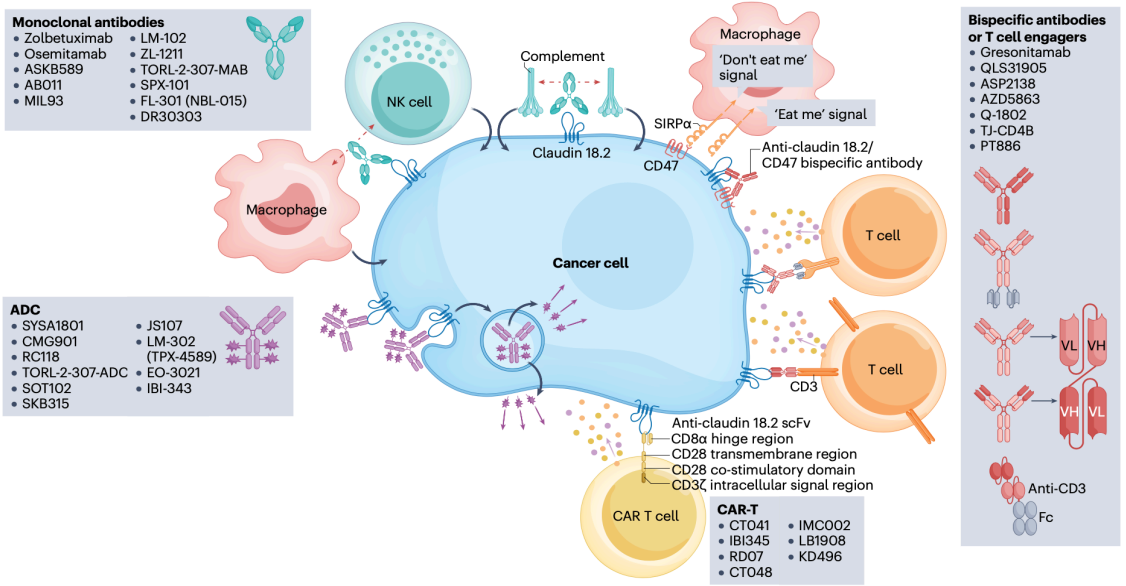
APPROVED

MINISTERIO DE SANIDAD

Vyloy, en combinación con quimioterapia basada en platino y fluoropirimidina, está indicado para el tratamiento de primera línea de pacientes adultos con adenocarcinoma gástrico o de la unión gastroesofágica (UGE) HER2 negativo localmente avanzado irresecable o metastásico cuyos tumores son positivos para Claudina (CLDN) 18.2 (ver sección 4.2).	En estudio

Shitara K, et al. N Engl J Med 2024

Developmental Claudin 18.2-targeted therapies



Claudin 18.2-targeting antibody–drug conjugate CMG901 in patients with advanced gastric or gastro-oesophageal junction cancer (KYM901): a multicentre, open-label, single-arm, phase 1 trial

Claudin-18 isoform 2-specific CAR T-cell therapy (satri-cel) versus treatment of physician's choice for previously treated advanced gastric or gastro-oesophageal junction cancer (CT041-ST-01): a randomised, open-label, phase 2 trial

Nakayama I, et al. Nat Rev 2023. Ruan DY, et al. Lancet Oncol 2025. Qi C, et al. Lancet 2025.

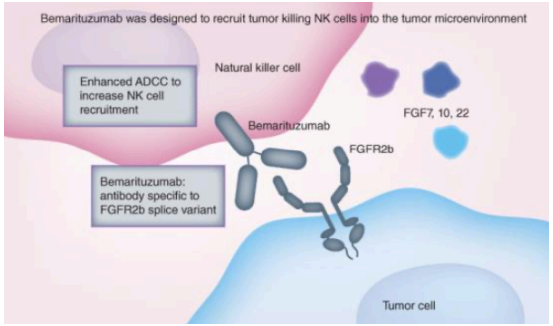
Opciones de tratamiento guiadas por biomarcador

Otros

Otros

FGFR2b

20-30% GC
Mal pronóstico



Bemarituzumab in patients with FGFR2b-selected gastric or gastro-oesophageal junction adenocarcinoma (FIGHT): a randomised, double-blind, placebo-controlled, phase 2 study

Zev A Wainberg, Peter C Enzinger, Yoon-Koo Kang, Shukui Qin, Kensei Yamaguchi, In-Ho Kim, Anwaar Saeed, Sang Cheul Oh, Jin Li,

⇨ FORTITUDE-102 (NCT05052801)

PHASE 3: *Bemarituzumab + Chemotherapy + Nivolumab Vs Chemotherapy + Nivolumab for FGFR2b Overexpressed untreated advanced GC/GOJC.*

⇨ FORTITUDE-101 (NCT05111626)

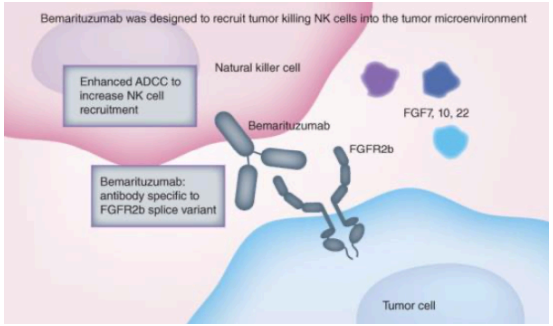
PHASE 3: *Bemarituzumab + Chemotherapy Vs Chemotherapy for FGFR2b Overexpressed untreated advanced GC/GOJC.*

Wainberg ZA, et al. Lancet Oncol 2022

Otros

FGFR2b

20-30% GC
Mal pronóstico



Bemarituzumab in patients with FGFR2b-selected gastric or gastro-oesophageal junction adenocarcinoma (FIGHT): a randomised, double-blind, placebo-controlled, phase 2 study

Zev A Wainberg, Peter C Enzinger, Yoon-Koo Kang, Shukui Qin, Kensei Yamaguchi, In-Ho Kim, Anwaar Saeed, Sang Cheul Oh, Jin Li,

⇨ FORTITUDE-102 (NCT05052801)

PHASE 3: *Bemarituzumab + Chemotherapy + Nivolumab Vs Chemotherapy + Nivolumab for FGFR2b Overexpressed untreated advanced GC/GOJC.*

⇨ FORTITUDE-101 (NCT05111626)

PHASE 3: *Bemarituzumab + Chemotherapy Vs Chemotherapy for FGFR2b Overexpressed untreated advanced GC/GOJC.*

➢ A global phase 3, randomized, double blind trial

Key Eligibility Criteria

- No prior therapy for locally unresectable or metastatic gastric or GEJ adenocarcinoma
  - One cycle of mFOLFOX6 permitted
- FGFR2b overexpression (2+/3+) at any % of tumor cells (TC) by central IHC, later amended to ≥ 10% 2+/3+ TC staining*
- Not known to be HER2-positive

Stratification: Geography (US/EU vs Japan/South Korea vs ROW), **ECOG** (0 vs 1), **PD-L1 status** (CPS ≥ 5 vs < 5 or indeterminate)†

R 1:1

Bemarituzumab + mFOLFOX6‡
FGFR2b ≥ 10% (N = 159)
Safety Analysis (N = 275)

Placebo + mFOLFOX6‡
FGFR2b ≥ 10% (N = 165)
Safety Analysis (N = 267)

Treatment on bemarituzumab
(15 mg/kg Q2W + 7.5 mg/kg on cycle 1 day 8)

Primary Endpoint
- OS in FGFR2b ≥ 10% 2+/3+ TC

Key Secondary Endpoints
- PFS in FGFR2b ≥ 10% 2+/3+ TC
- ORR in FGFR2b ≥ 10% 2+/3+ TC
- Safety in all randomized patients

Wainberg ZA, et al. Lancet Oncol 2022. Rha SY, et al. ESMO 2025.

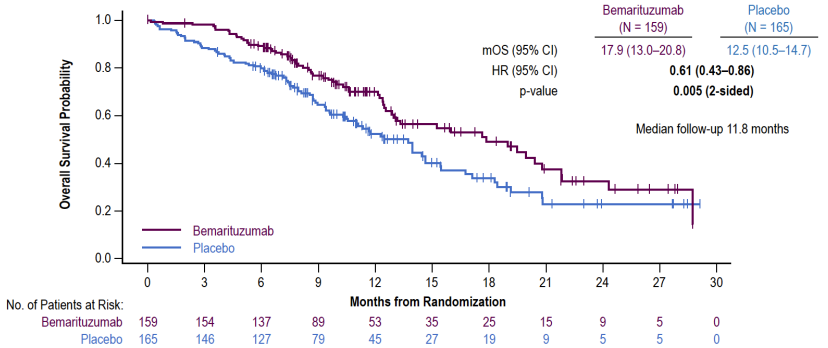
Otros

FGFR2b

BERLIN 2025 ESMO congress

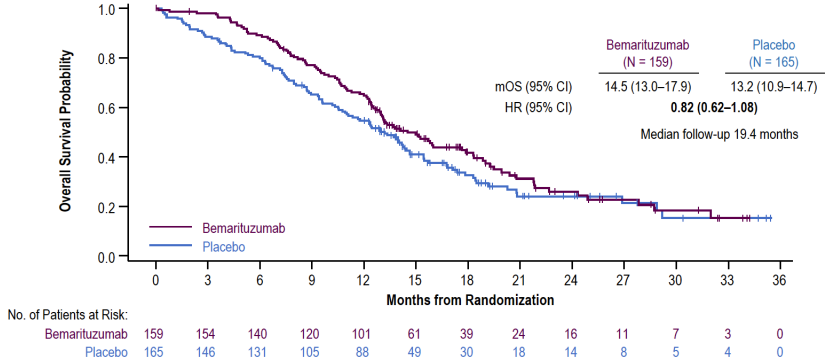
Bemarituzumab (BEMA) plus chemotherapy for advanced or metastatic FGFR2b-overexpressing gastric or gastroesophageal junction cancer (G/GEJC): FORTITUDE-101 phase 3 study results

Patients with FGFR2b overexpression in ≥ 10% of tumor cells



The OS primary objective was met at the prespecified interim analysis favoring bemarituzumab

Patients with FGFR2b overexpression in ≥ 10% of tumor cells



Attenuation of the treatment effect was observed at a descriptive analysis after longer follow-up

Rha SY, et al. ESMO 2025.

Retos y Limitaciones

Retos y Limitaciones

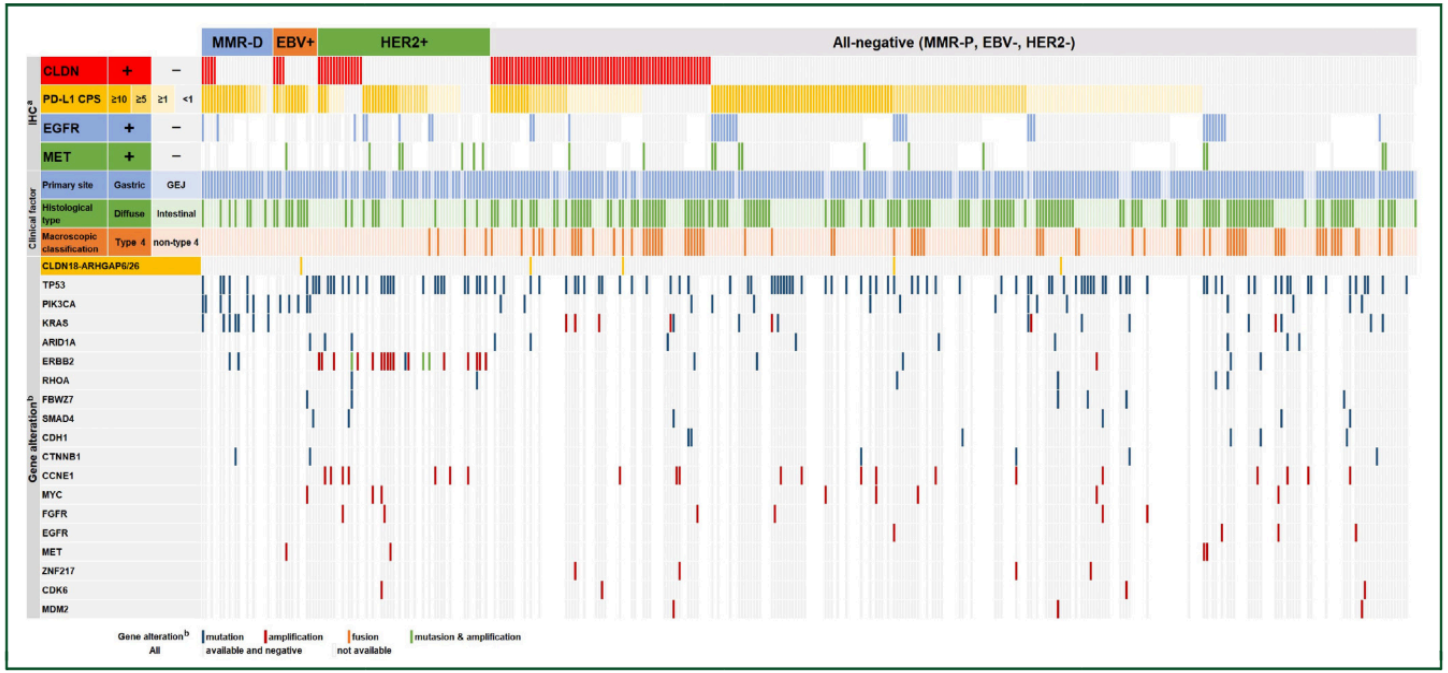
1- Retos en el diagnóstico y captura de la heterogeneidad tumoral

- Muestra (adecuada, cantidad, localización, discordancias…)
- Re-biopsia (heterogeneidad temporal, mecanismos resistencia…)
- Nuevas tecnologías (BL, NGS…)

2- Co-expresión de biomarcadores

3- Regulatorios (acceso a la terapia innovadora)

Superposición, Co-expresión de BK



Kubota Y, et al. ESMO Open 2023

Superposición, Co-expresión de BK

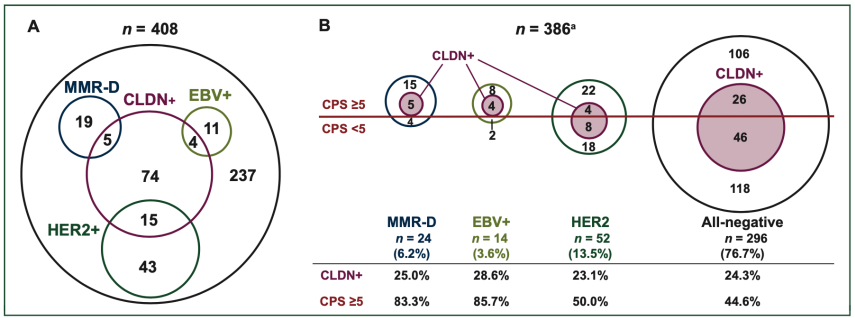
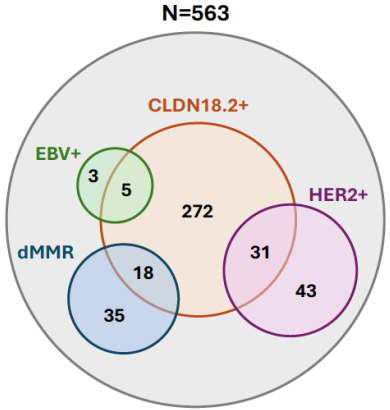
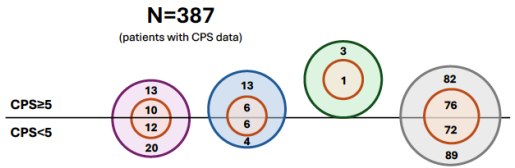


Figure 2. Relationship between CLDN and other biomarkers (A) and PD-L1 CPS (B). All-negative: negative for neither MMR-D, EBV nor HER2.
CLDN, claudin; CPS, combined positive score; EBV, Epstein–Barr virus; HER2, human epidermal growth factor receptor 2; MMR-D, mismatch repair deficient; MMR-P, mismatch repair proficient.
[a]Patients with available CPS results.





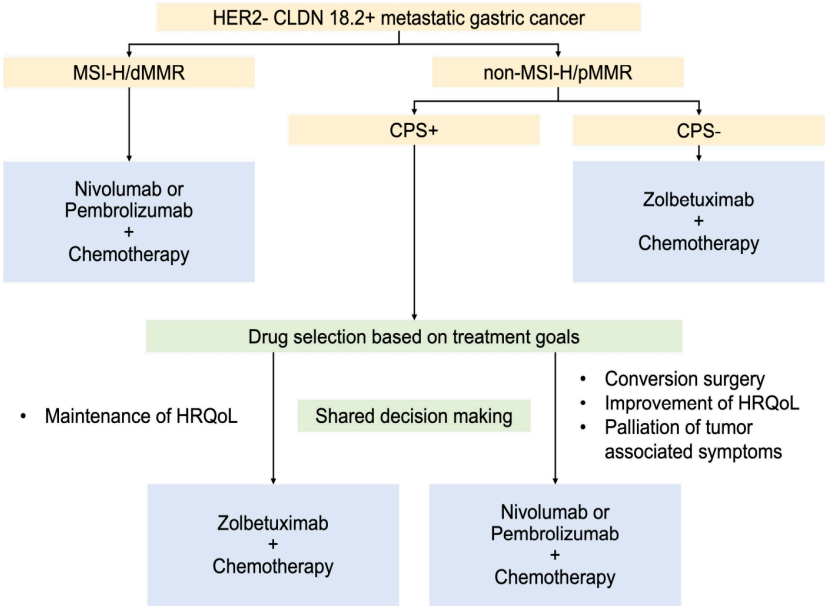
	HER2+ n=55 (14.2%)	dMMR n=29 (7.8%)	EBV+ n=4	All-negative n=301
CLDN18.2+	22 (40%)	12 (41.4%)	1 (25%)	148 (49.2%)
CPS ≥1	45 (81.8%)	25 (86.2%)	4 (100%)	204 (67.8%)
CPS ≥5	25 (45.5%)	19 (65.5%)	4 (100%)	130 (43.2%)
CPS ≥10	11 (20%)	14 (48.3%)	3 (75%)	87 (28.9%)

CLDN18-2 y PD-L1 (CPS) cut-offs

Se observó el **estado CLDN18.2-high** en:
26/276 (45,7%) con CPS ≥1,
83/176(47,2%) con CPS ≥5
52/113 (46,0%) con CPS ≥10

Kubota Y, et al. ESMO Open 2023. Terán E, et al. SEOM 2025

Superposición, Co-expresión de BK



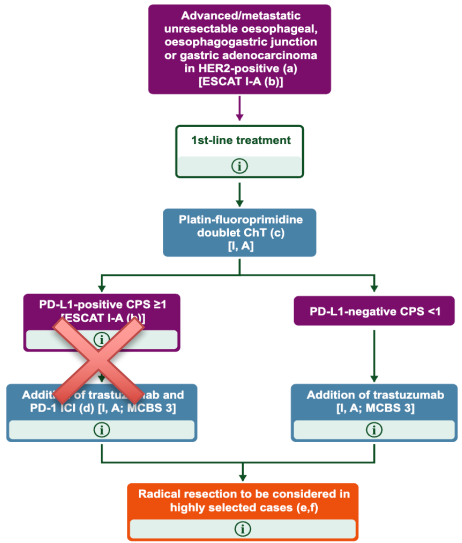
MMR	HER2	CLDN18	PD-L1 (CPS)	Recommended regimen	% of patients
dMMR				Immunotherapy ± Chemo	5%
pMMR	Positive		≥ 1	Chemo + Trastuzumab ± Pembrolizumab	13%
	Negative	Positive	< 5	Chemo + Zolbetuximab	22%
			5 - 9	Chemo + Zolbetuximab, or Chemo + Nivolumab/Pembrolizumab/Tislelizumab	8%
			≥ 10		3%
		Negative	< 1	Chemotherapy alone	5%
			1 - 9	Chemotherapy +/- Nivolumab/Pembrolizumab/Tislelizumab	23%
			≥ 10	Chemotherapy + Nivolumab/Pembrolizumab/Tislelizumab	20%

Mijiyama Y, Cancers, 2025. Alsina M, et al. Clin Transl Oncol, 2025

3- Regulación

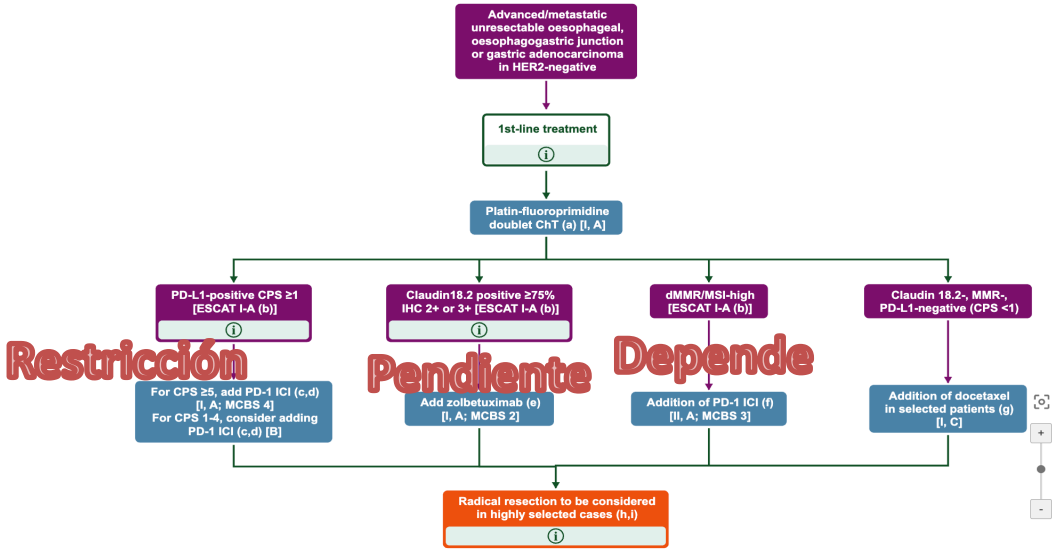
GOBIERNO DE ESPAÑA · MINISTERIO DE SANIDAD · agencia española de medicamentos y productos sanitarios

First-line for HER2-positive



First-line for HER2-negative

v1.4 - September 2024



ESMO Gastric Cancer Living Guidelines, v1.4 – September 2024

Mensajes para llevar a casa

- ✓ **Biomarcadores** obligatorios 1L (validados con aplicabilidad clínica):
  MMR/MSI, HER2, PDL1, Claudina 18.2

- ✓ QT basada en FP y platino continúa siendo el pilar del tto ADC EG avanzado
  - ✓ Añadir Docetaxel: opción en ADC EG sin BK, pacientes seleccionados

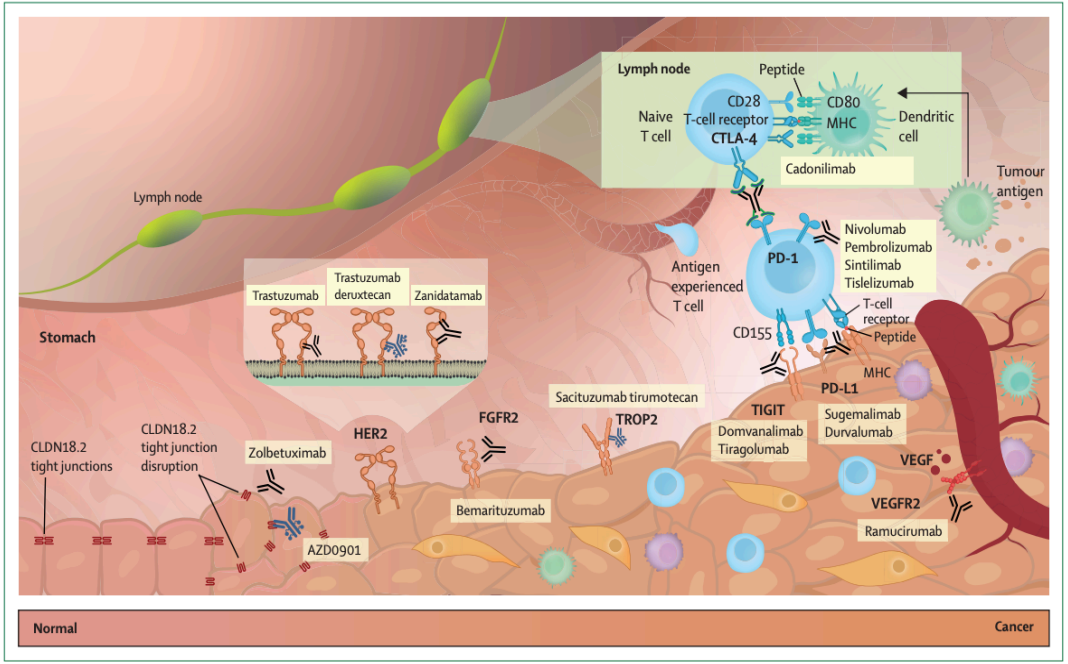
- ✓ QT + antiPD1: 1L ADC EG avanzado PDL1+. (CPS **≥ 10,** Pembro[1]; CPS **≥ 5,** Nivo; TAP **≥ 5%**, Tisle)

- ✓ QT + Trastuzumab + Pembrolizumab[2]: 1L ADC EG avanzado HER2+/PDL1+

- ✓ QT+ Zolbetuximab[3]: 1L ADC EG avanzado Claudina 18.2 +

[1]Financiado España (CPS ≥1: aprobación EMA). [2]No financiado en España. [3]Pendiente financiación España.

Reflexiones finales



Raghav S, et al. Lancet 2025.

Nuevas estrategias para BK conocidos, nuevos BK como potenciales dianas

Garantizar la equidad y accesibilidad (al diagnóstico y a la terapia)

XXXIII SIMPOSIO INTERNACIONAL
INTERNATIONAL SYMPOSIUM
11 - 12 DE DICIEMBRE DE 2025
OVIEDO

Muchas gracias

Dra. Rosario Vidal Tocino

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Profesora Asociada – Universidad de Salamanca

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