19as Jornadas HITOS ONCOLÓGICOS: LO MEJOR DE 2024
MADRID 20 - 21 NOVIEMBRE 2024

Cáncer gástrico: Inmunoterapia y otros avances en la enfermedad metastásica

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Disclosure information

Employment: SACYL, USAL

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

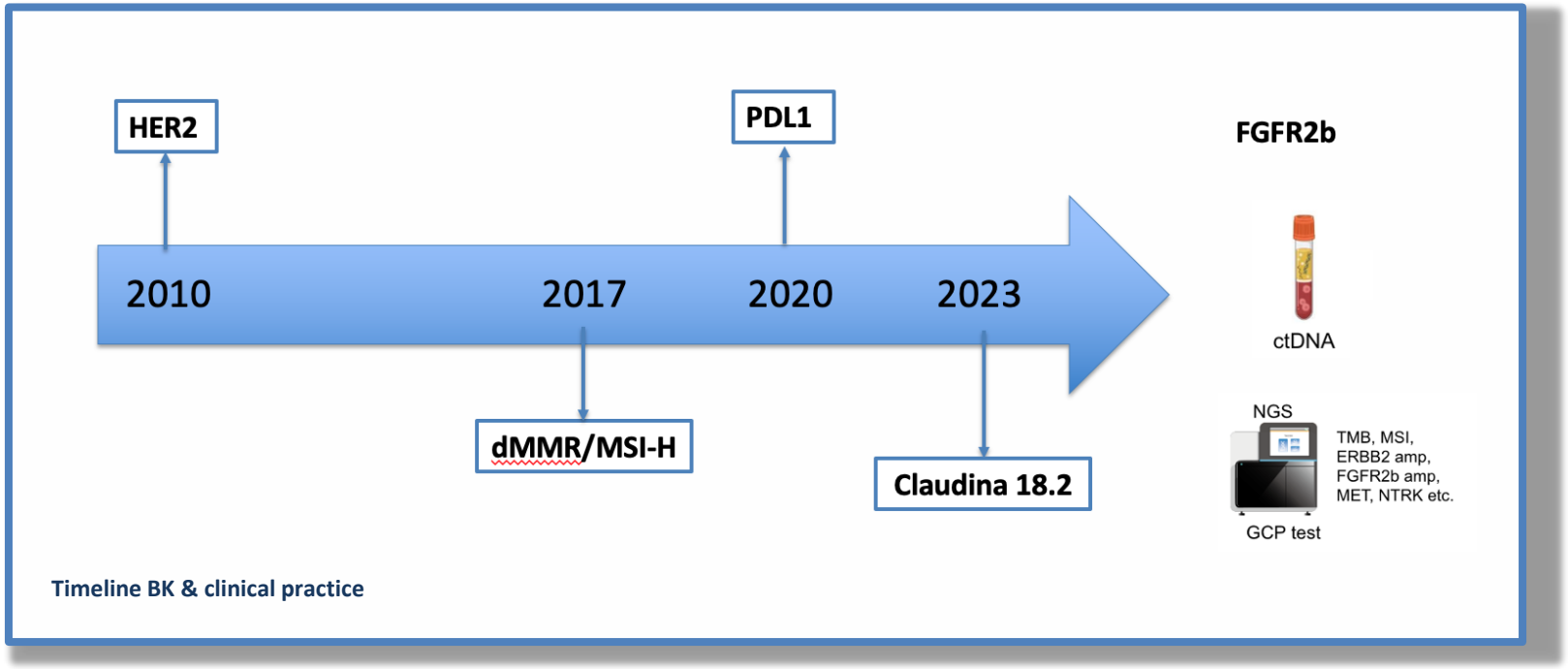
Educational, scientific activities, travel and accommodation: Merck, Amgen, Roche, Lilly, Sanofi, Bristol-MS, Pierre-Fabre, Servier and MSD.

BIOMAR

INMUNC

La inmunoterapia y la medicina de precisión son una realidad en los tumores esofagogástricos avanzados

BIOMARCADORES



Bang YJ, et al. Lancet 2010 . Le DT, et al. Science 2017. Sun JM, et al. Lancet 2021. Janjigian YY, et al. *Lancet* 2021. Rha SY, et al. Lancet Oncol 2023. Shitara K, et al. Lancet 2023; Shah M, et al. Nature Med 2023. Wainberg ZA, et al. Lancet Oncol 2022. Sato Y, et al. J Clin Med 2023

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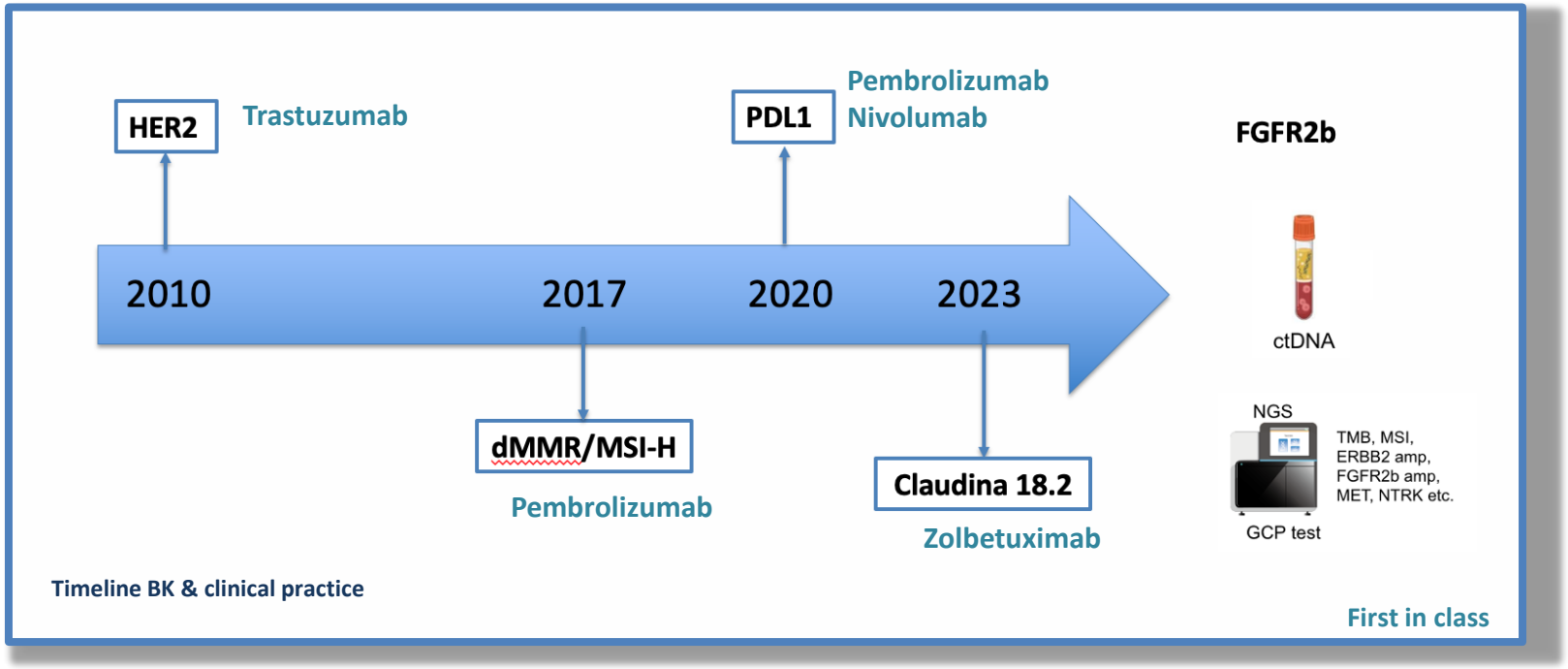
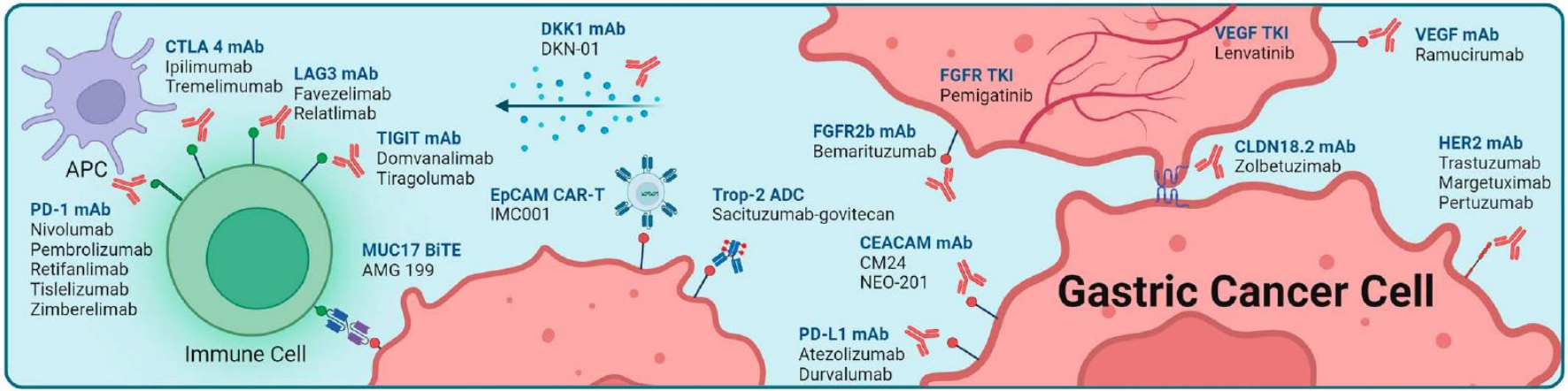
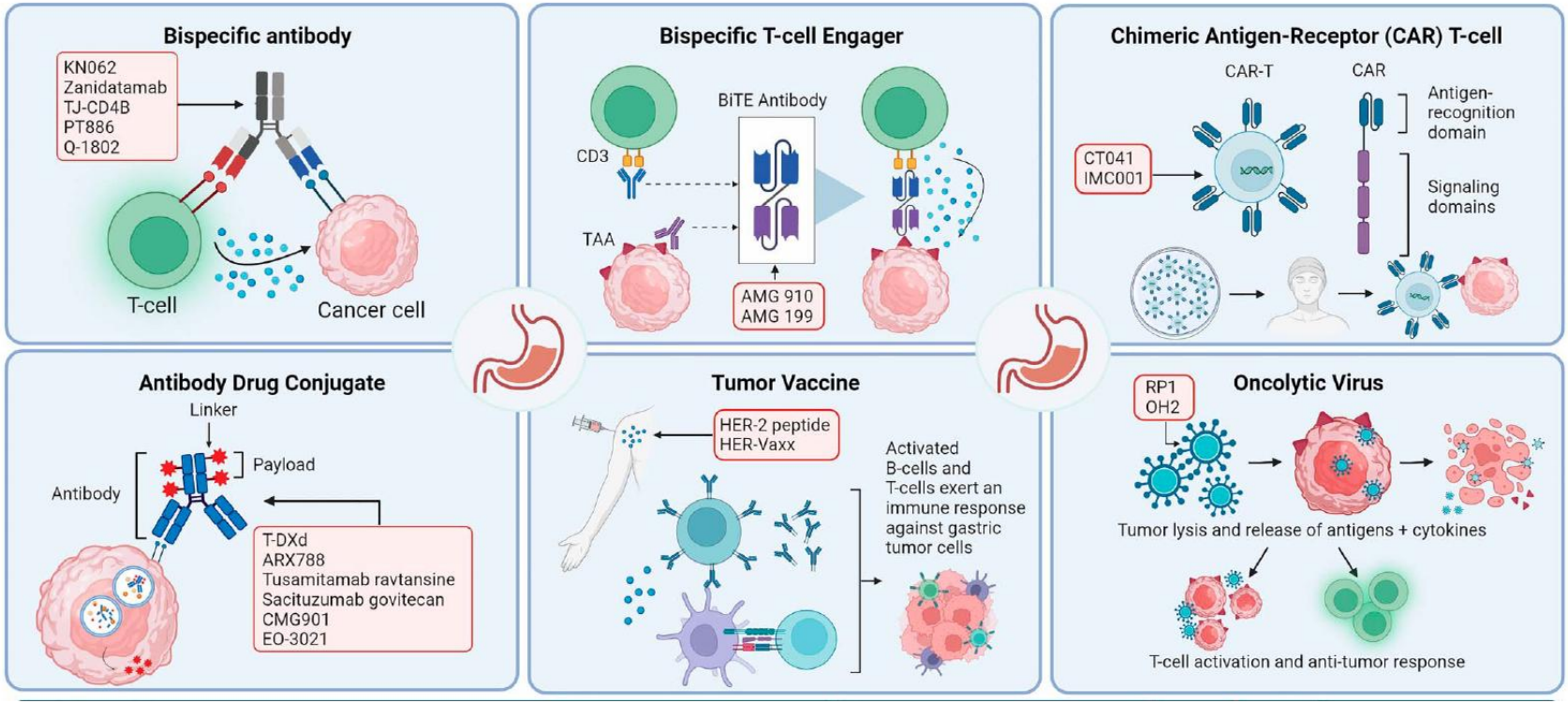


Bang YJ, et al. Lancet 2010 . Le DT, et al. Science 2017. Sun JM, et al. Lancet 2021. Janjigian YY, et al. *Lancet* 2021. Rha SY, et al. Lancet Oncol 2023. Shitara K, et al. Lancet 2023; Shah M, et al. Nature Med 2023. Wainberg ZA, et al. Lancet Oncol 2022. Sato Y, et al. J Clin Med 2023



Updated targets and therapies in gastroesophageal cancer

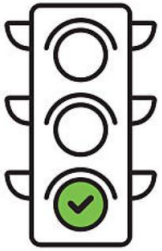
Balmaceda NB, et al. ASCO Edu Book 2024



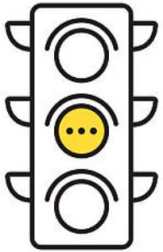
Technologic advances in gastroesophageal cancer

Balmaceda NB, et al. ASCO Edu Book 2024

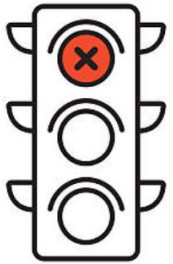
Biomarcadores Establecidos:
- HER2
- PDL1
- dMMR/MSI-H



Biomarcadores Emergentes:
- Claudina 18.2
- VEB

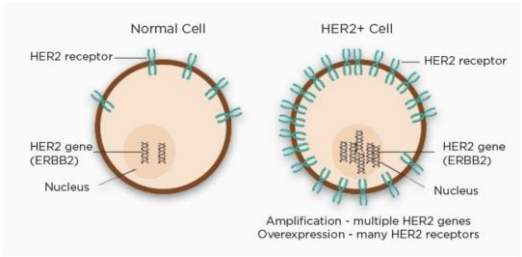


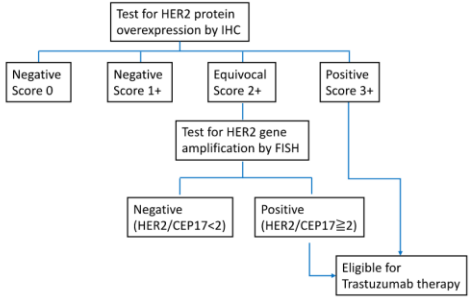
Biomarcadores a futuro:
- FGFR2b
- NGS
- ctDNA



HER2+

15-20% GC



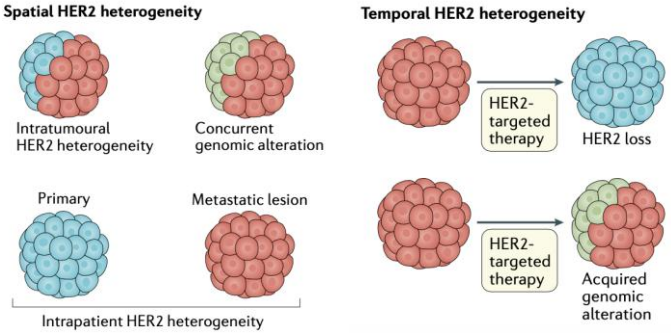


Score	Surgical specimen	Biopsy
0	No membranous staining or staining of < 10% of the tumor cells	No membranous staining or staining only in rare cells (less than 5 cohesive cells)
1+	Staining is weak or detected in only one part of the membrane in ≥ 10% of the cells	Staining is weak or detected in only one part of the membrane of at least 5 cohesive cells
2+	Moderate/weak complete or basolateral membranous staining in ≥ 10% of the cells	Moderate/weak complete or basolateral membranous staining of at least 5 cohesive cells
3+	Strong complete or basolateral membranous staining in ≥ 10% of the neoplastic cells	Strong complete or basolateral membranous staining of at least 5 cohesive cells

Sobre-expresión Her2 depende de:
- Localización (+ proximal)
- Subtipo histológico (+ intestinal)
- Grado de diferenciación (+ G1-G2)

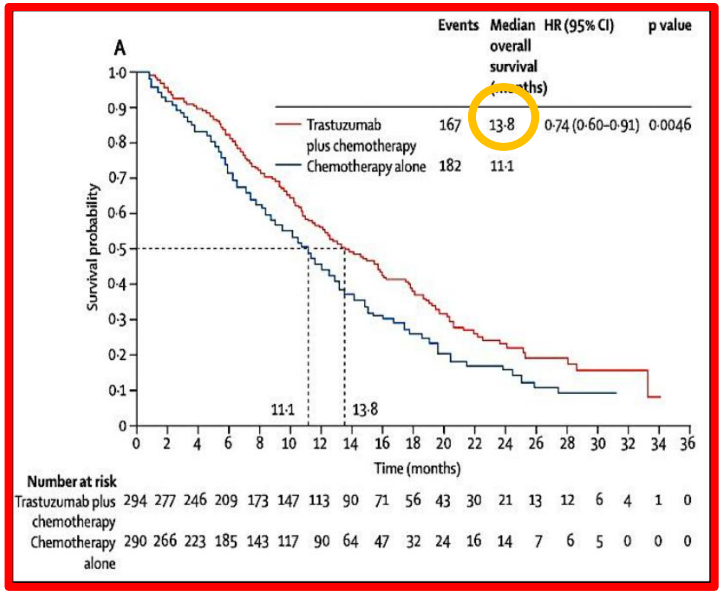
Heterogeneidad intratumoral, espacial y temporal.

Factor pronóstico controvertido



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

HER2+



Study	Line	N	Treatment Arms	OS (m)	Hazard Ratio	
TOGA[1]	1st	584	Cape-P/FP Cape-P/FP-trastuzumab	11.1 13.8	HR = 0.74 p < 0.01	✓
LOGIC[2]			XELOX	10.5	HR = 0.91	✗
JACOB[3]						✗
TyTAN[4]						✗
GATSBY[5]						✗
WJOG7112G[6] (Ph II)			Trastuzumab	9.95	HR= 1.230 p = 0.199	✗

Heterogeneidad intratumoral

Activación aberrante de vía PIK3CA (downstream)

Amplificación simultanea de EGFR, MET y CCNE1

Perdida de positividad bajo presión de tratamiento con Trastuzumab (30%)

1.Bang YJ, et al. Lancet 2010. 2. Hecht JR, et al. J Clin Oncol 2015. 3. Tabernero J, et al. Lancet Oncol 2018. 4. Satoh T, et al. J clin Oncol 2014. 5. Thuss-Patience P, et al. Lancet Oncol 2017. 6. Makiyama A, et al. J Clin Oncol 2020.

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.

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

HER2+

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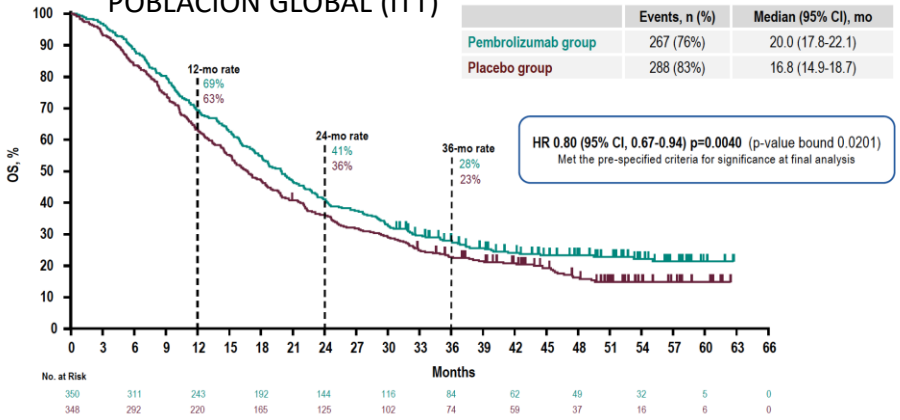
Final Analysis: 50.2 months of follow-up

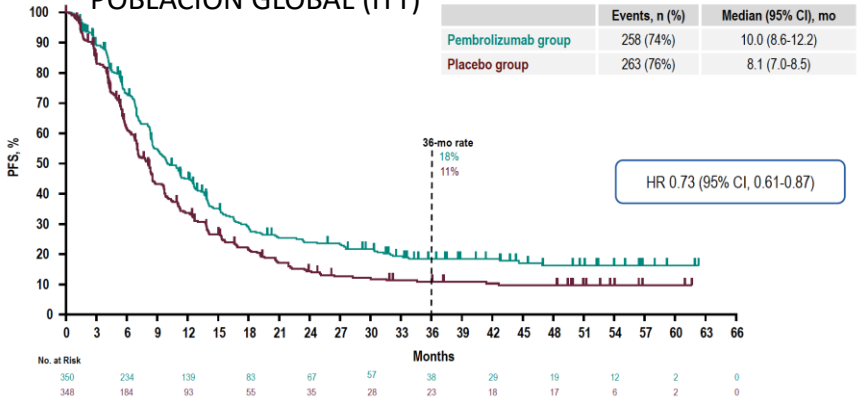
POBLACIÓN GLOBAL (ITT)



	Events, n (%)	Median (95% CI), mo
Pembrolizumab group	267 (76%)	20.0 (17.8-22.1)
Placebo group	288 (83%)	16.8 (14.9-18.7)

HR 0.80 (95% CI, 0.67-0.94) p=0.0040 (p-value bound 0.0201)
Met the pre-specified criteria for significance at final analysis

POBLACIÓN GLOBAL (ITT)



	Events, n (%)	Median (95% CI), mo
Pembrolizumab group	258 (74%)	10.0 (8.6-12.2)
Placebo group	263 (76%)	8.1 (7.0-8.5)

HR 0.73 (95% CI, 0.61-0.87)

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

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

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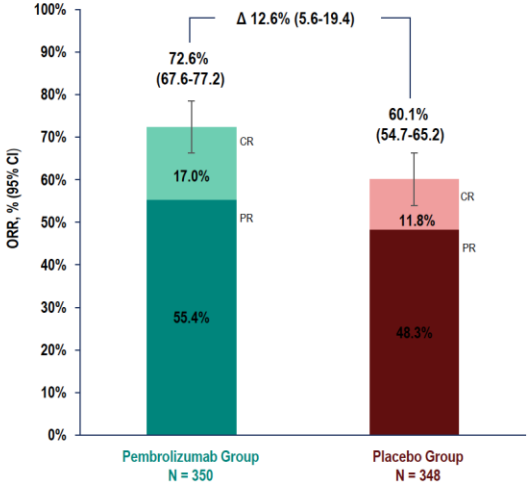
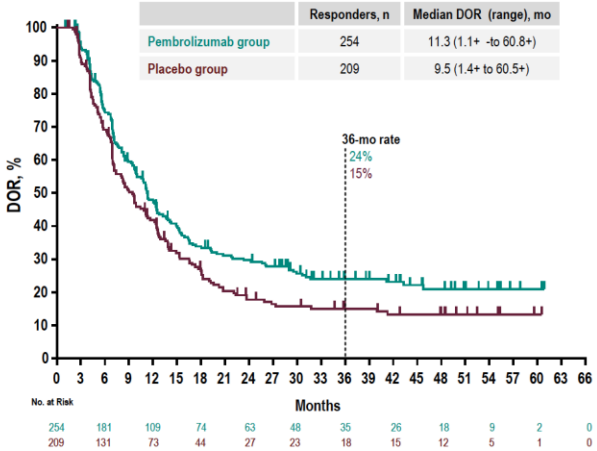
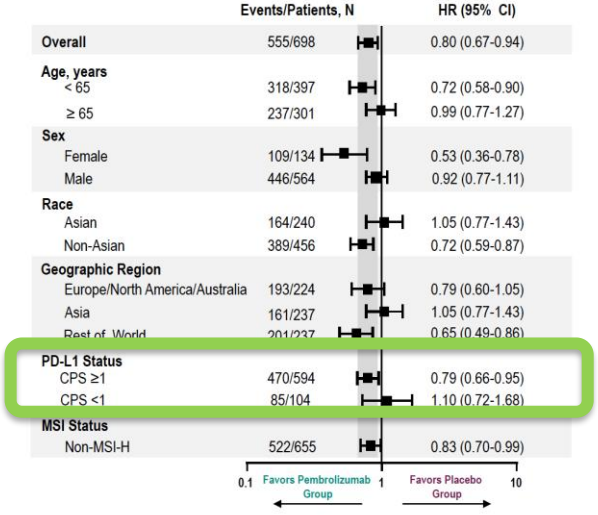
POBLACIÓN GLOBAL (ITT)





Overall Survival in Key Subgroups at Final Analysis (ITT)



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

HER2+

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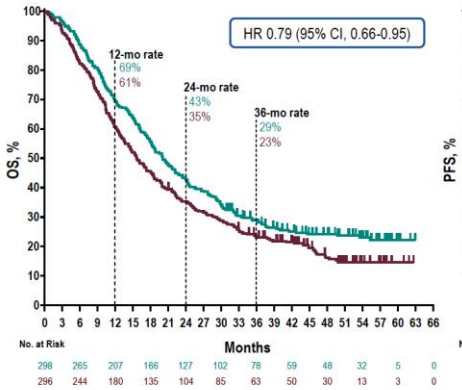
Final Analysis: 50.2 months of follow-up

POBLACIÓN **PDL1 CPS ≥ 1**

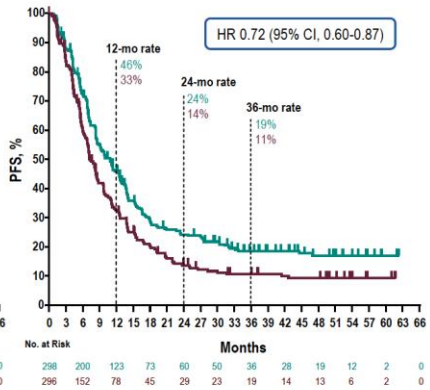
OS

	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)



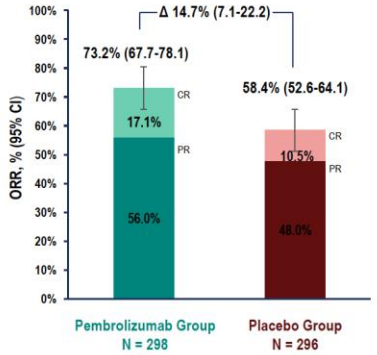
PFS

	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+)



Sinergia con PDL1

*85% PDL1 CPS ≥ 1

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

HER2+

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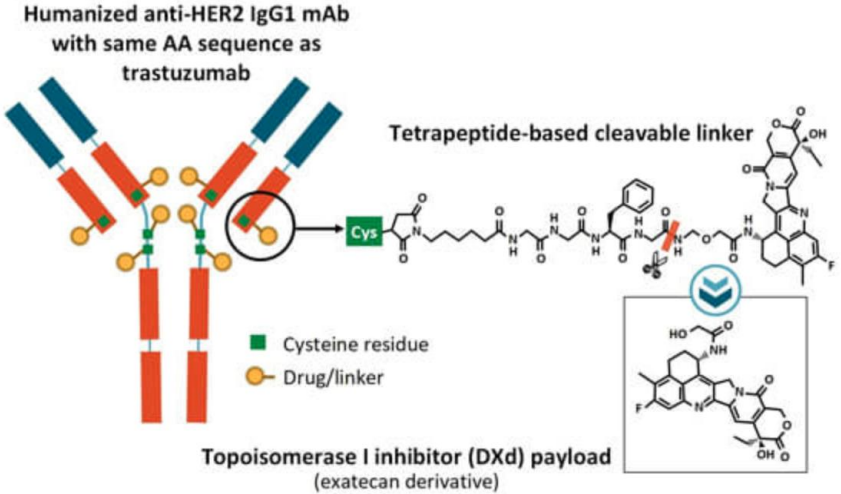
Final Analysis: 50.2 months of follow-up

EMA APPROVED

	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)	

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

HER2+



HER2+

ORIGINAL ARTICLE

Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer

K. Shitara, Y.-J. Bang, S. Iwasa, N. Sugimoto, M.-H. Ryu, D. Sakai, H.-C. Chung,

Study objective

- To evaluate the efficacy and safety of trastuzumab deruxtecan (T-Dxd) in patients with HER2-positive advanced gastric or GEJ adenocarcinoma

Key patient inclusion criteria

- Advanced gastric or GEJ adenocarcinoma
- HER2-positive (IHC3+ or IHC2+/ISH+)
- ≥2 prior regimens including a fluoropyrimidine and a platinum agent
- Progression on trastuzumab-containing regimen

(n=743)

R 2:1

- T-Dxd 6.4 mg/kg q3w (n=125)
- Irinotecan or paclitaxel (physician's choice) (n=62)

PRIMARY ENDPOINT

- ORR (ICR)

SECONDARY ENDPOINTS

- OS, PFS, safety

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Trastuzumab Deruxtecan (N=125)	Physician's Choice of Chemotherapy (N=62)
No. of previous systemic therapies for advanced or metastatic disease — no. (%)		
2	66 (53)	38 (61)
3	34 (27)	18 (29)
≥4	25 (20)	6 (10)
Previous treatment — no. (%)		
Therapy containing trastuzumab	125 (100)	62 (100)
Therapy containing taxane	105 (84)	55 (89)
Therapy containing ramucirumab	94 (75)	41 (66)
Irinotecan or other topoisomerase I inhibitor	8 (6)	5 (8)
Immune checkpoint inhibitor	44 (35)	17 (27)

Variable	Trastuzumab Deruxtecan (N=119)	Physician's Choice of Chemotherapy (N=56)
Objective response†		
No. of patients	61	8
Percent of patients (95% CI)	51 (42–61)	14 (6–26)
Best response — no. (%)		
Complete response	11 (9)	0
Partial response	50 (42)	8 (14)
Stable disease	42 (35)	27 (48)
Progressive disease	14 (12)	17 (30)
Could not be evaluated	2 (2)	4 (7)

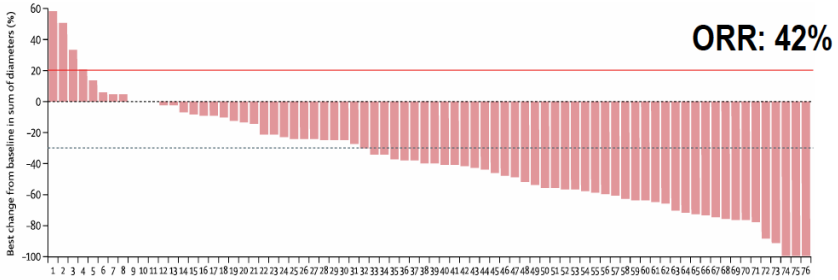
OS: 12.5m Vs 8.4m (HR 0.59)
PFS: 5.6m Vs 3.5m (HR 0.47)

Shitara K, et al. NEJM, 2020. Yamaguchi K, et al. Ann Oncol 2020;31(suppl):abstr O-11 (ESMO-GI 2020)

HER2+

Trastuzumab deruxtecan in patients in the USA and Europe with HER2-positive advanced gastric or gastroesophageal junction cancer with disease progression on or after a trastuzumab-containing regimen (DESTINY-Gastric02): primary and updated analyses from a single-arm, phase 2 study

Eric Van Cutsem, Maria di Bartolomeo, Elizabeth Smyth, Ian Chau, Haeseong Park, Salvatore Siena, Sara Lonardi, Zev A Wainberg, Jaffer Ajani, Joseph Chao, Yelena Janjigian, Amy Qin, Jasmeet Singh, Ferdous Barlaskar, Yoshinori Kawaguchi, Geoffrey Ku



ORR: 42%

mPFS: 5.6 mos; mOS: 12.1 mos

DESTINY-Gastric02

Objective: To determine the efficacy and safety of T-DXd monotherapy in Western patients with HER2 positive (IHC 3+, IHC 2+/ISH+), unresectable or metastatic gastric or GEJ cancer who progressed on or after a trastuzumab-containing dose

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

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

Primary endpoint
- Confirmed ORR by ICR

Secondary endpoints[b]
- PFS by ICR
- OS
- DOR
- Safety

tcomes

- Primary
27.3-49.

(95% CI,

EMA APPROVED

Trastuzumab-deruxtecan en monoterapia está indicado para el tratamiento de pacientes adultos con adenocarcinoma gástrico o de la unión gastroesofágica **HER2-positivo** avanzado que han recibido una pauta previa con trastuzumab.

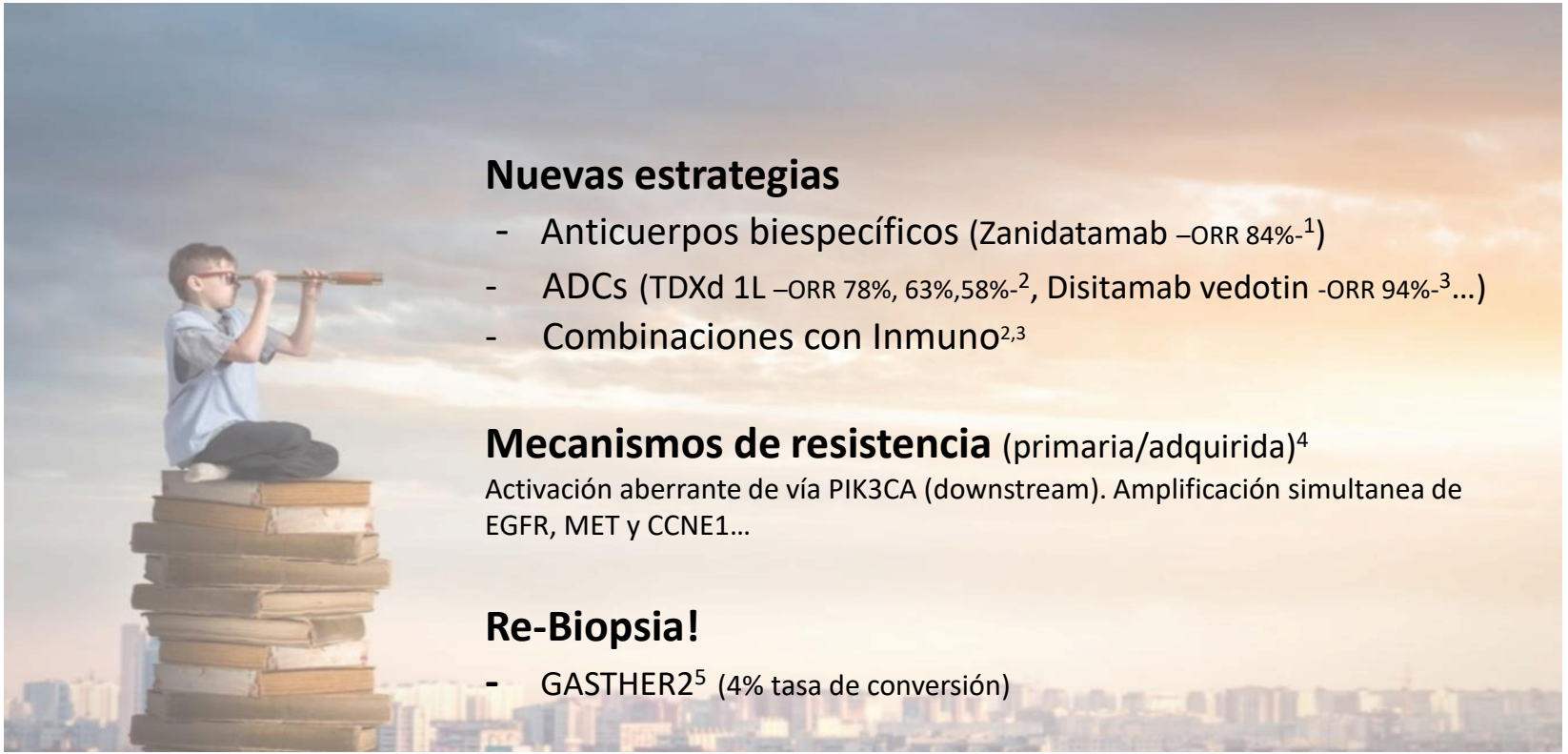
⇨ DESTINY-Gastric04 (NCT04704934)

PHASE 3: *HER2 positive metastatic/unresectable gastric/GEJ cancer (vs ramucirumab and paclitaxel) 2L.*

** Central HER2 confirmation by fresh biopsy after PD on trastuzumab is required*

Van Cutsem E, et al ESMO 2021. Van Cutsem E, et al. Lancet Oncol 2023. Ku G, et al. ESMO 2022.

HER2+



Nuevas estrategias

- Anticuerpos biespecíficos (Zanidatamab –ORR 84%-[1])
- ADCs (TDXd 1L –ORR 78%, 63%,58%-[2], Disitamab vedotin -ORR 94%-[3]…)
- Combinaciones con Inmuno[2,3]

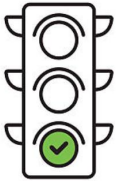
Mecanismos de resistencia (primaria/adquirida)[4]

Activación aberrante de vía PIK3CA (downstream). Amplificación simultanea de EGFR, MET y CCNE1…

Re-Biopsia!

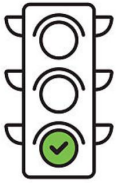
- GASTHER2[5] (4% tasa de conversión)

1. Elimova E, et al. ESMO 2024. 2. Janjigian Y, et al. ESMO 2024. 3. Li S, et al. ASCO 2024. 4. Janjigian Y, et al. Cancer Discover 2018. 5. Hyung J, et al Cancer Res Treat 2024.



PDL1

PDL1 CPS ≥ 1: 80%
PDL1 CPS ≥ 5: 60%



PDL1

PDL1 CPS ≥ 1: 80%
PDL1 CPS ≥ 5: 60%

¡ Determinación Complicada !

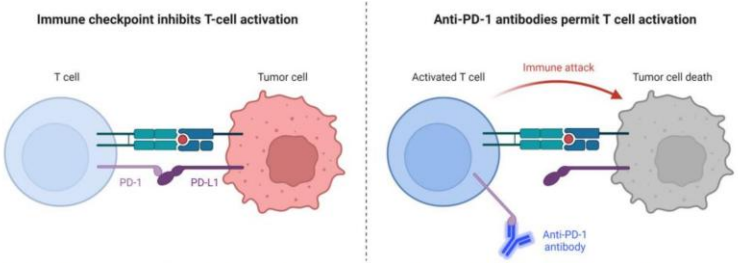
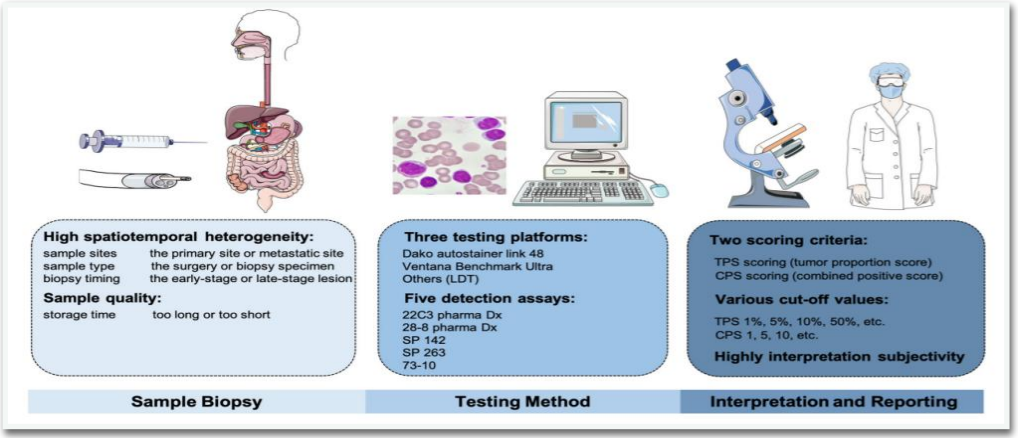
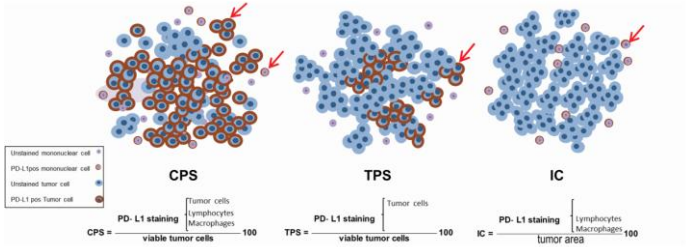


Fig. 1 Immune Checkpoint Inhibitor against Tumor Cell. Through the interaction between PD-1 expressed on the surface of T cells and PD-L1 expressed on the surface of tumor cells, the immunological checkpoint prevents T-cell activation. Through contact between PD-1 on the surface of T cells and anti-PD-1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



INMUNOTERAPIA



Marei HE, et al. Cancer Cell Int. 2023 Apr 10;23(1):64. Janjigian Y. ESMO 2023.

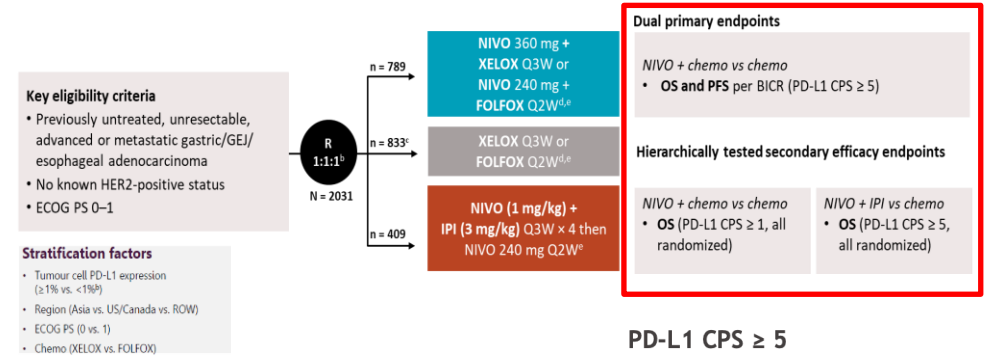
Zeng Z et al. Front Oncol 2021;11:650481. Sajjadi E. Ecancer. 2020.

Inmunoterapia y otros avances CG avanzado

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%; Esofago 13%)

- PDL1 CPS ≥ 5: 60%

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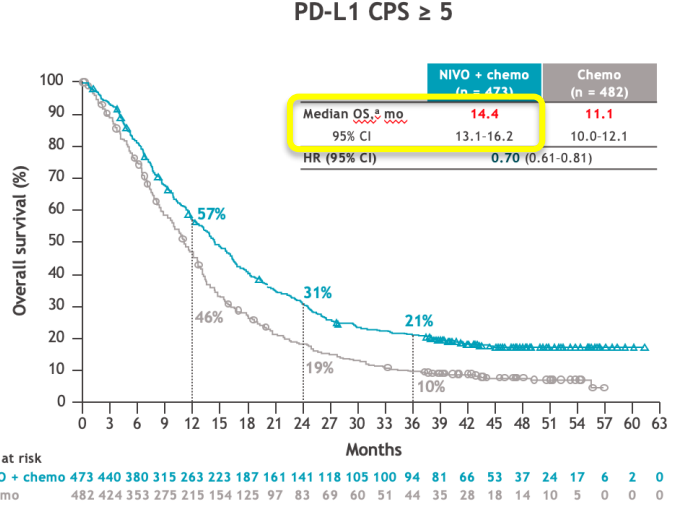
agencia española de medicamentos y productos sanitarios



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

PDL1

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*

Key Eligibility Criteria

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

R 1:1

Pembrolizumab 200 mg IV Q3W for ≤35 cycles (~2 yr) + Chemotherapy[a] (FP or CAPOX)

Placebo IV Q3W for ≤35 cycles (~2 yr) + Chemotherapy[a] (FP or CAPOX)

Stratification Factors

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

- **Primary End Point:** OS
- **Secondary End Points:** PFS,[b] ORR,[b] DOR,[b] and safety

- 100% ADC

(GC 79%; UGE 21%)

- PDL1 CPS ≥ 1: 78%

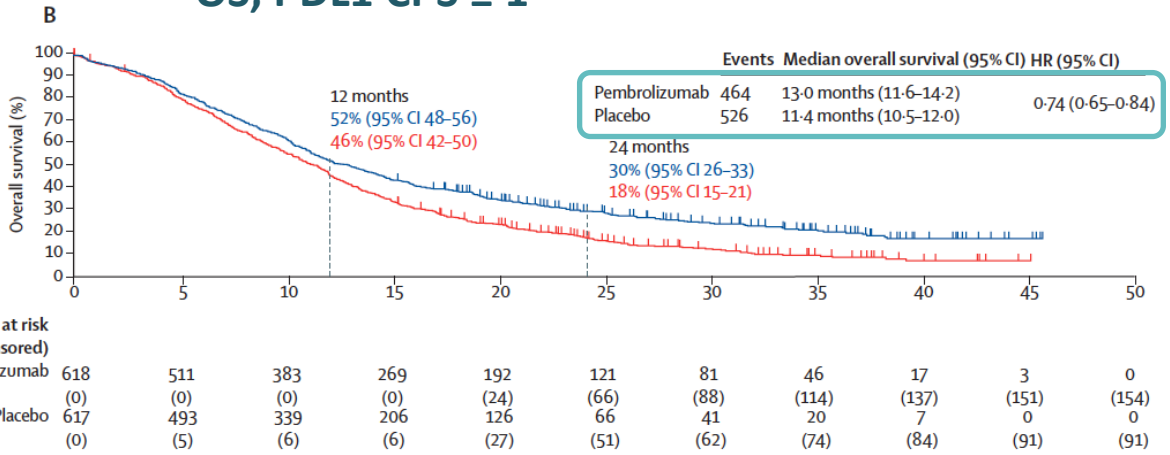
Rha SY, et al. Lancet Oncol 2023;24:1181-95.

PDL1

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



EMA APPROVED

Diciembre 2023

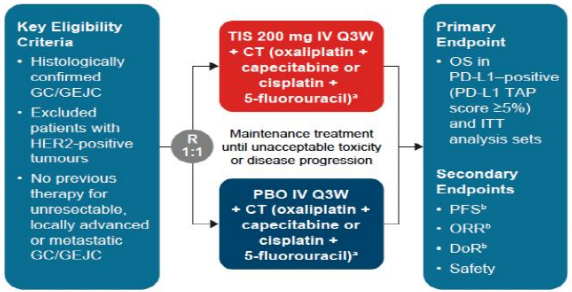
Rha SY, et al. Lancet Oncol 2023;24:1181-95.

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

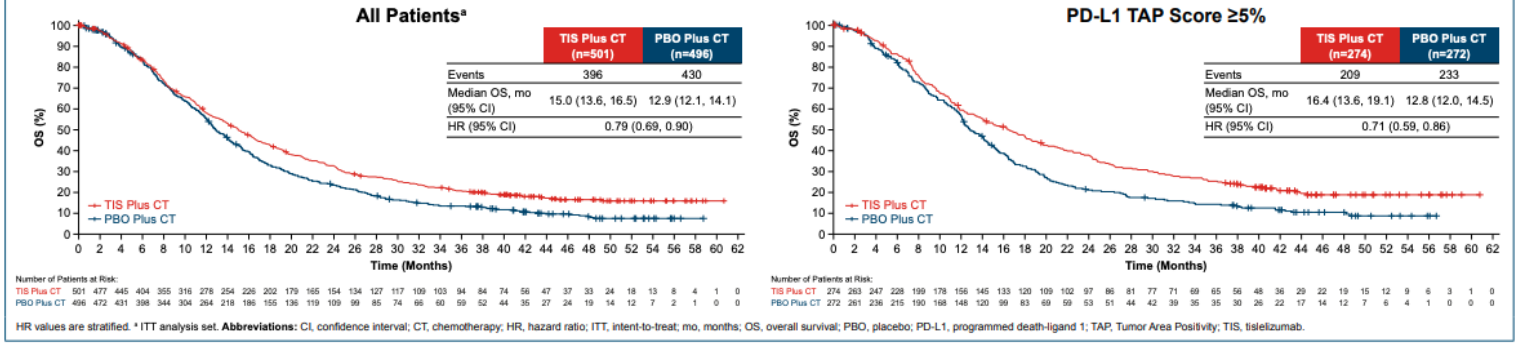
Miao-Zhen Qiu,[1] Do-Youn Oh,[2] Ken Kato,[3] Tobias Arkenau,[4] Josep Tabernero,[5]

RATIONALE 305 Diseño



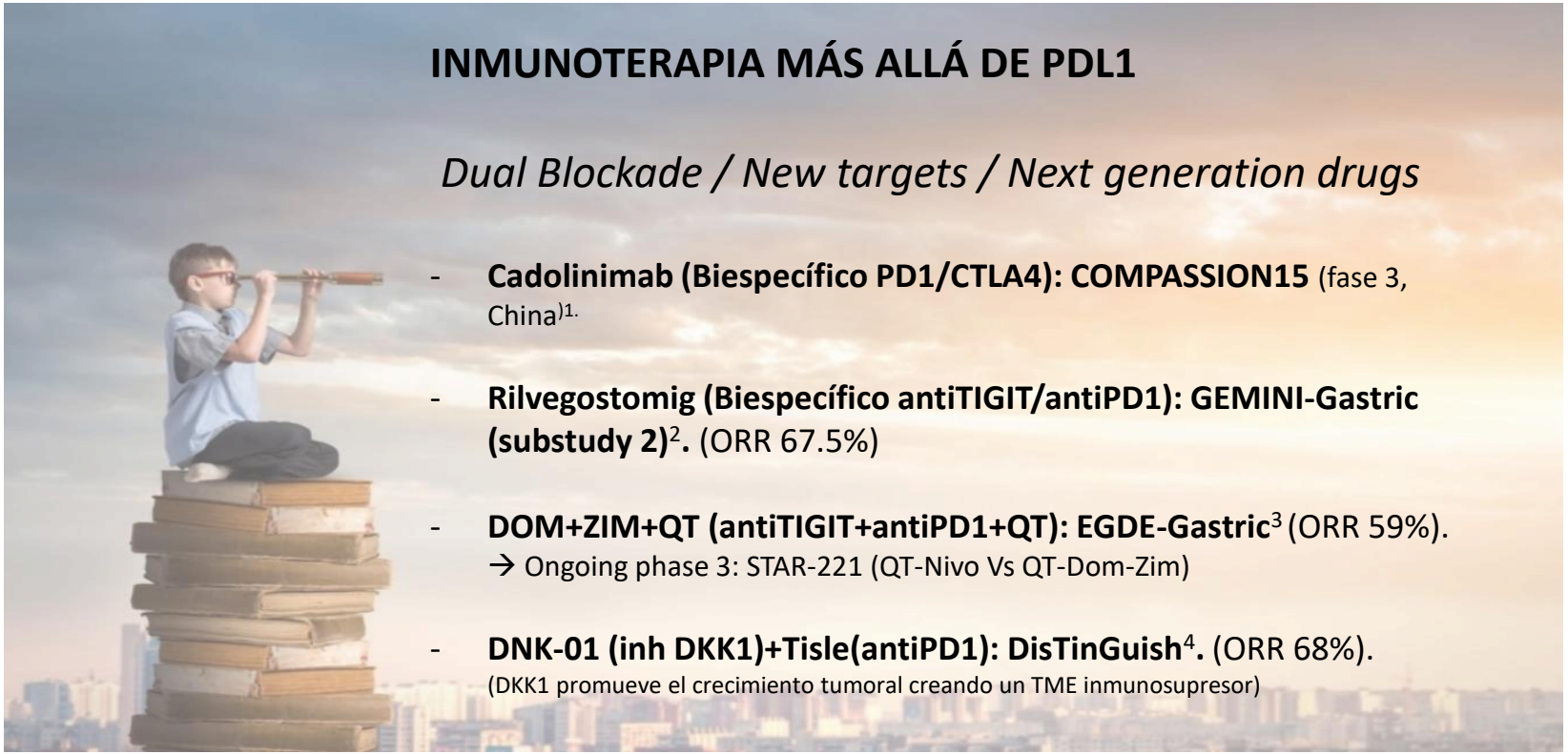
Stratification Factors:
- Regions of enrolment: China (including Taiwan) vs Japan and South Korea vs US and Europe and other regions
- PD-L1 expression (PD-L1 score ≥5% vs PD-L1 score <5%)
- Presence of peritoneal metastasis (yes vs no)
- Investigator-chosen CT (oxaliplatin + capecitabine or cisplatin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

Figure 2. Kaplan-Meier Curves of OS at 3-year Follow-up



HR values are stratified. [a] ITT analysis set. **Abbreviations:** CI, confidence interval; CT, chemotherapy; HR, hazard ratio; ITT, intent-to-treat; mo, months; OS, overall survival; PBO, placebo; PD-L1, programmed death-ligand 1; TAP, Tumor Area Positivity; TIS, tislelizumab.

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



INMUNOTERAPIA MÁS ALLÁ DE PDL1

Dual Blockade / New targets / Next generation drugs

- **Cadolinimab (Biespecífico PD1/CTLA4): COMPASSION15** (fase 3, China)[1].
- **Rilvegostomig (Biespecífico antiTIGIT/antiPD1): GEMINI-Gastric (substudy 2)[2].** (ORR 67.5%)
- **DOM+ZIM+QT (antiTIGIT+antiPD1+QT): EGDE-Gastric**[3] (ORR 59%).
  → Ongoing phase 3: STAR-221 (QT-Nivo Vs QT-Dom-Zim)
- **DNK-01 (inh DKK1)+Tisle(antiPD1): DisTinGuish**[4]**.** (ORR 68%).
  (DKK1 promueve el crecimiento tumoral creando un TME inmunosupresor)

1- Ji J, et al. AACR 2024. 2- Rivera et al. ESMO2024. 3- Janjigian Y et al. ASCO 2024. 4- Klempner et al. ASCO 2023.

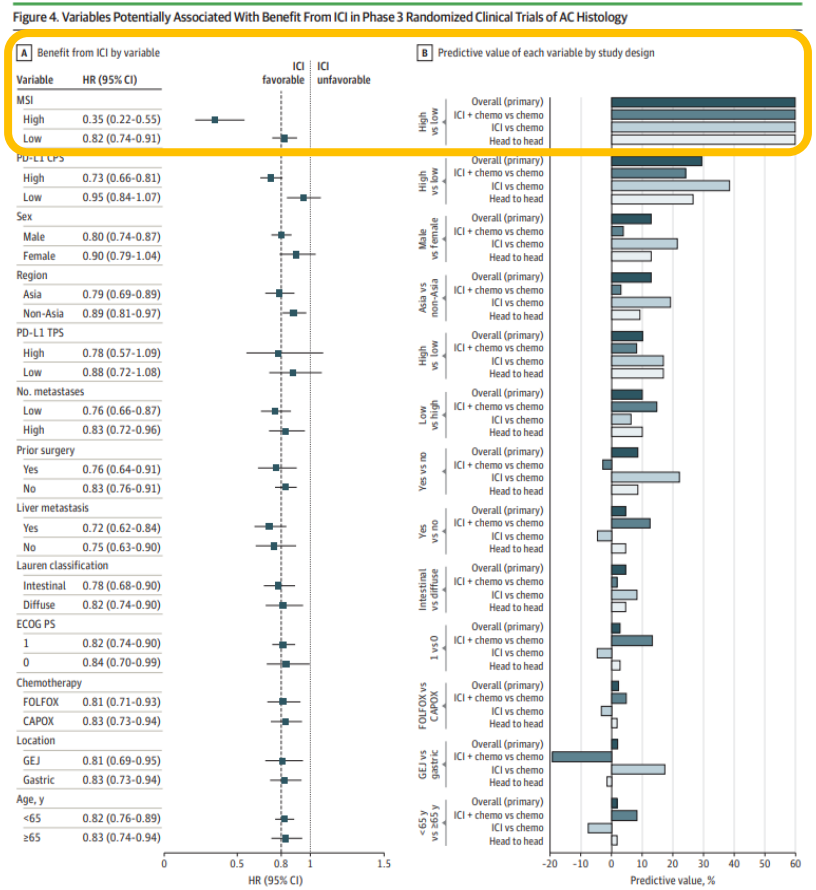
dMMR/MSI-H

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

JAMA Oncology | Original Investigation

Association of PD-L1 Expression and Other Variables With Benefit From Immune Checkpoint Inhibition in Advanced Gastroesophageal Cancer
Systematic Review and Meta-analysis of 17 Phase 3 Randomized Clinical Trials

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



Harry H. Yoon et al. JAMA Oncol 2022;8(10):1456-1465

dMMR/MSI-H

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

Table 3. Summary of efficacy outcomes by tumor types with the highest number of enrolled patients

	Endometrial $n = 68$	Gastric $n = 42$	Small intestine $n = 25$	Ovarian $n = 24$	Cholangiocarcinoma/ biliary tract $n = 22$	Pancreatic $n = 22$
ORR, % (95% CI)	48.5 (36.2-61.0)	31.0 (17.6-47.1)	48.0 (27.8-68.7)	33.3 (15.6-55.3)	40.9 (20.7-63.6)	18.2 (5.2-40.3)
Best objective response, *n* (%)						
CR	10 (14.7)	4 (9.5)	4 (16.0)	3 (12.5)	3 (13.6)	1 (4.5)
PR	23 (33.8)	9 (21.4)	8 (32.0)	5 (20.8)	6 (27.3)	3 (13.6)
SD	13 (19.1)	7 (16.7)	7 (28.0)	2 (8.3)	3 (13.6)	3 (13.6)
PD	19 (27.9)	15 (35.7)	5 (20.0)	12 (50.0)	8 (36.4)	8 (36.4)
Not evaluable	1 (1.5)	1 (2.4)	—	—	—	—
No assessment	2 (2.9)	6 (14.3)	1 (4.0)	2 (8.3)	2 (9.1)	7 (31.8)
DOR, median (range), months	NR (2.9 to 47.1+)	NR (6.3 to 51.1+)	NR (2.1+ to 41.8+)	NR (4.2 to 43.5+)	30.6 (6.2 to 40.5+)	NR (8.1 to 24.3+)
Median PFS, months (95% CI)	13.1 (4.9-34.4)	3.2 (2.1-12.9)	23.4 (4.3-NR)	2.2 (2.0-6.2)	4.2 (2.1-24.9)	2.1 (1.9-3.4)
PFS rate ≥3 years[a], %	33.9	28.5	49.1	29.2	12.7	NR
Median OS, months (95% CI)	NR (32.4-NR)	11.0 (5.8-31.5)	NR (16.2-NR)	33.6 (11.0-NR)	19.4 (6.5-NR)	3.7 (2.1-9.8)
OS rate ≥3 years[a], %	62.1	34.5	58.7	42.6	30.3	22.7

'+' indicates no progressive disease by the time of last disease assessment.

CI, confidence interval; CR, complete response; DOR, duration of response; NR, not reached; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

[a]As per Kaplan–Meier method for censored data.

Maio, M., et al.Annals of Oncology, 2022. FT Europea Pembrolizumab

dMMR/MSI-H

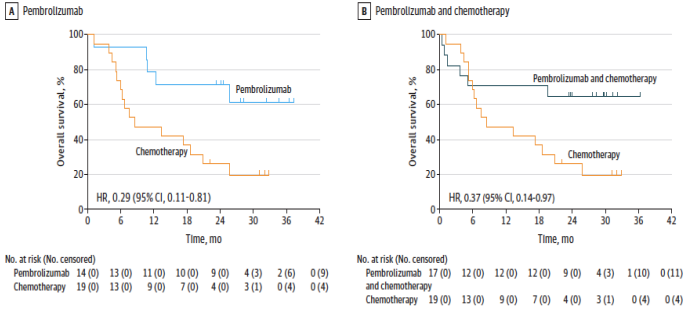
Nivolumab plus chemotherapy or ipilimumab vs chemotherapy as first-line treatment for advanced gastric cancer/gastroesophageal junction cancer/ esophageal adenocarcinoma: CheckMate 649 study

JAMA Oncology | Original Investigation

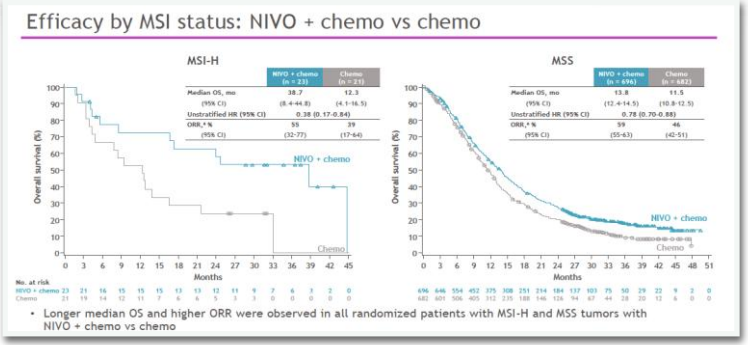
Efficacy and Safety of Pembrolizumab or Pembrolizumab Plus Chemotherapy vs Chemotherapy Alone for Patients With First-line, Advanced Gastric Cancer

The KEYNOTE-062 Phase 3 Randomized Clinical Trial

Figure 3. Overall Survival in Patients With MSI-H Tumors and PD-L1 CPS of 1 or Greater

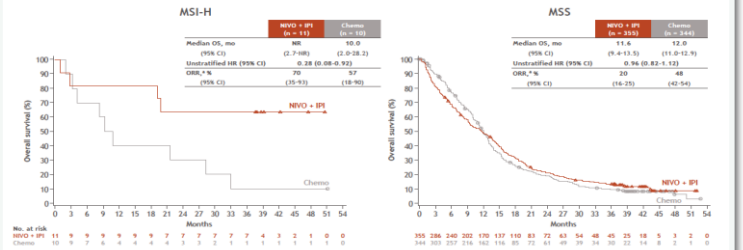


Efficacy by MSI status: NIVO + chemo vs chemo



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

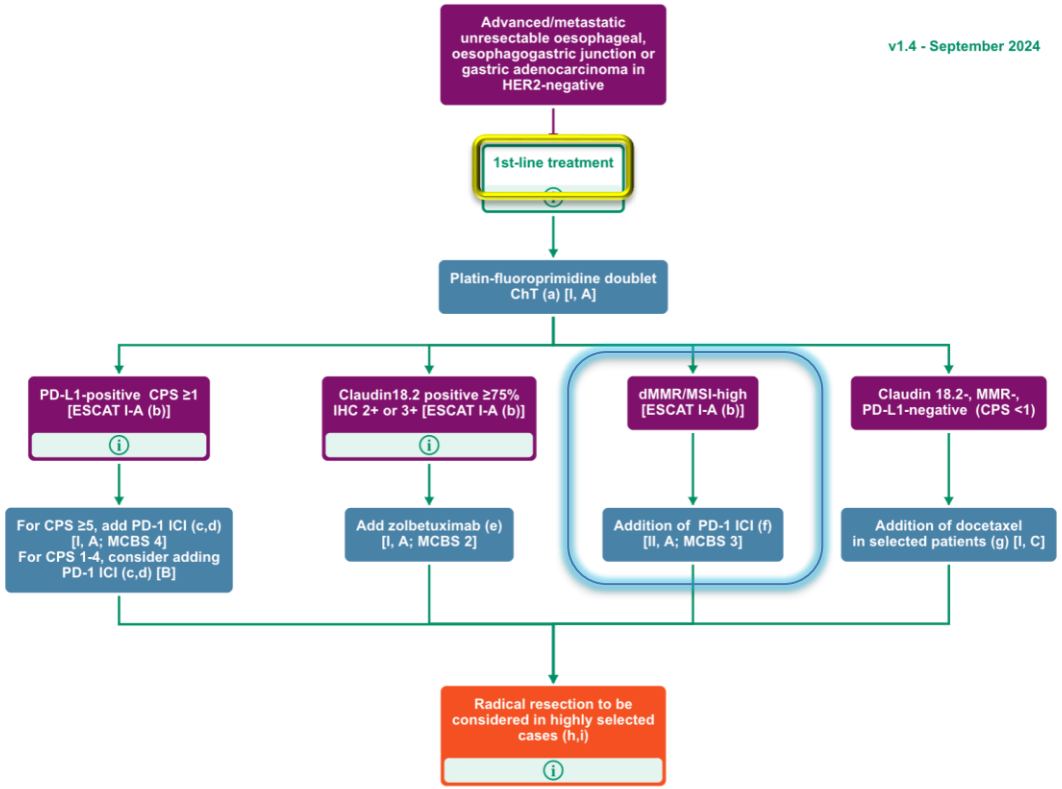
Efficacy by MSI status: NIVO + IPI vs chemo



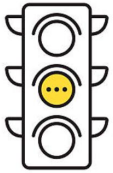
- Longer median OS and higher ORR observed in all randomized patients with MSI-H tumors with NIVO + IPI vs chemo, although sample size was small

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

dMMR/MSI-H



ESMO Gastric Cancer Living Guidelines. (v1.4 – September 2024)



Claudina 18.2

High: 35%

Claudina 18.2

High: 35%

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…)

Expresión Claudina 18.2:
- High: tinción moderada o fuerte (2+/3+) en ≥75% de las células.

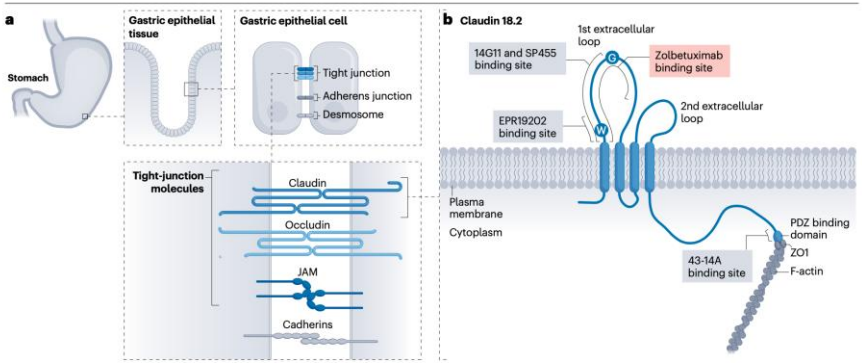


Fig. 1 | Claudin 18.2 structure, function and expression patterns. a, Claudin 18.2 is highly selectively expressed in the nonmalignant gastric mucosa, in which it is located at the most apical side of the paracellular space where it constitutes the tight-junction complex. **b**, Claudin 18.2 is a transmembrane 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.

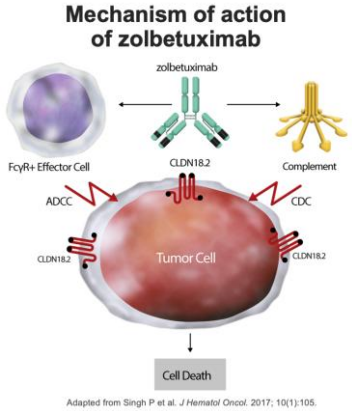
Nakayama I, et al. Nat Rev 2023.

Claudina 18.2

Zolbetuximab: (*first in class*)

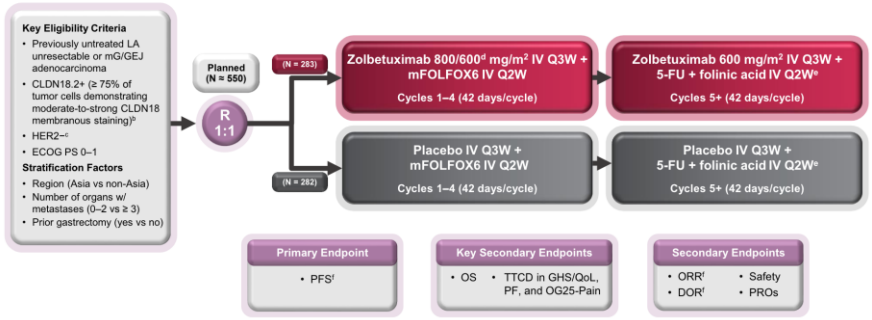
Ac IgG1 quimérico

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



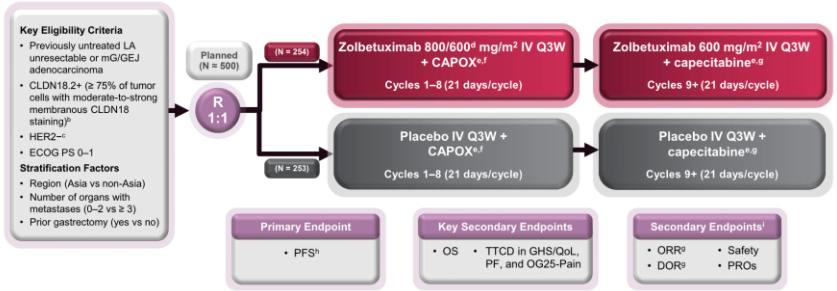
Study Design: SPOTLIGHT

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



Study Design: GLOW

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

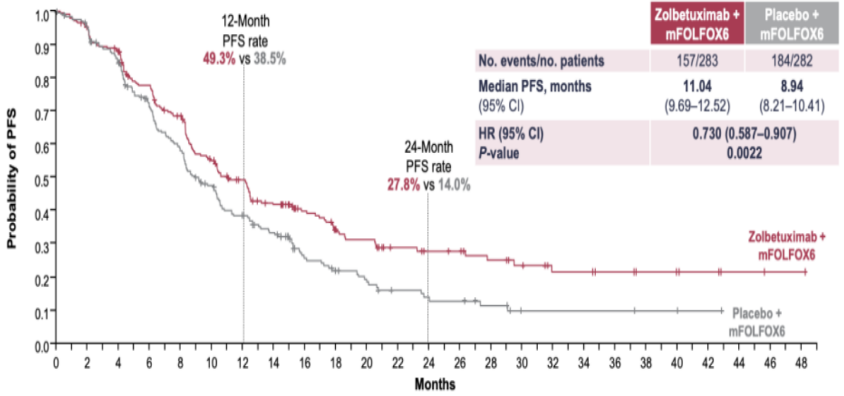


Más población asiática

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

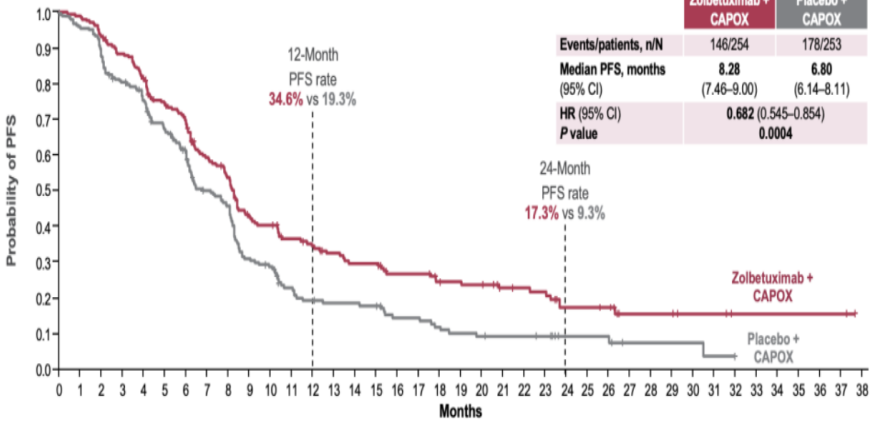
Claudina 18.2

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

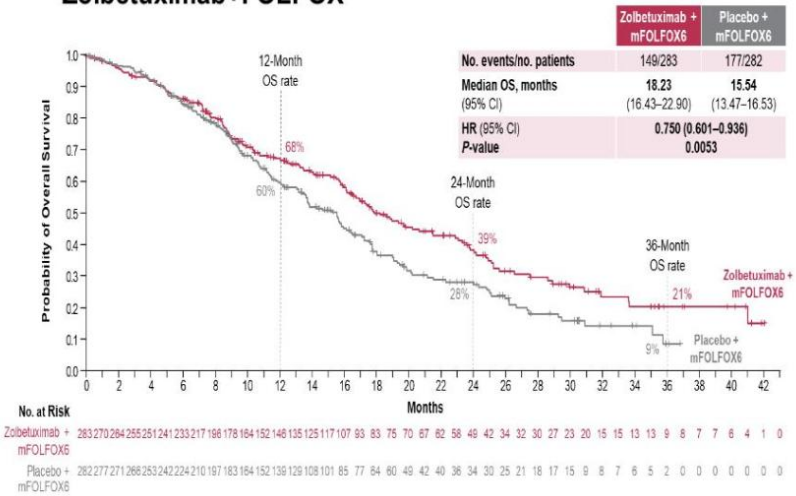


	Zolbetuximab + CAPOX	Placebo + CAPOX
Events/patients, n/N	146/254	178/253
Median PFS, months (95% CI)	8.28 (7.46–9.00)	6.80 (6.14–8.11)
HR (95% CI) *P* value	0.682 (0.545–0.854) 0.0004	

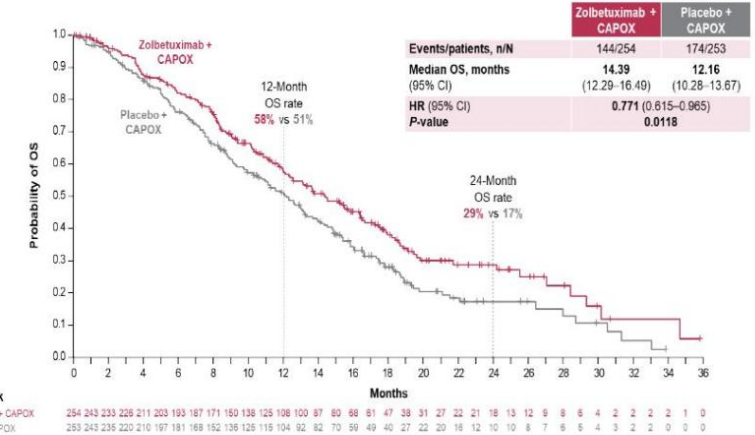
Ajani JA, et al. ESMO 2023 (#LBA82). Lordick F, et al. ESMO 2023 (#LBA81) Shitara K, et al. Lancet 2023; Shah M, et al. Nature Med 2023.

Claudina 18.2

SPOTLIGHT
Zolbetuximab+FOLFOX



GLOW
Zolbetuximab+CapeOX



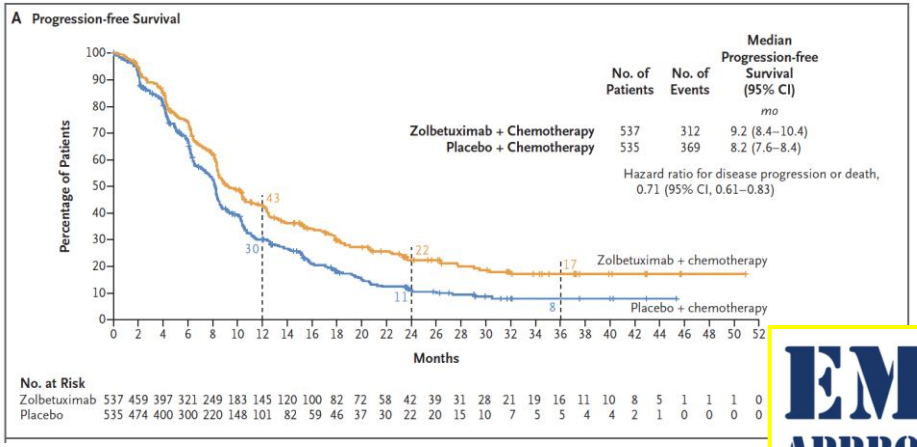
Main toxicity: nausea and vomiting at 1st infusion

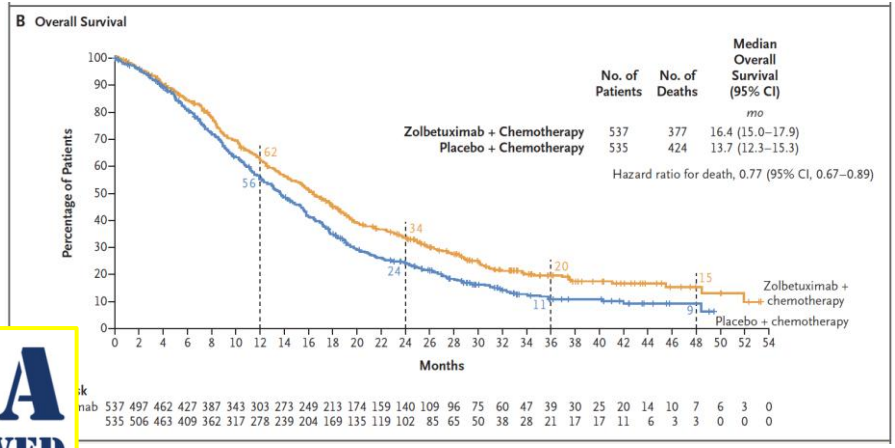
Ajani JA, et al. ESMO 2023 (#LBA82). Lordick F, et al. ESMO 2023 (#LBA81) Shitara K, et al. Lancet 2023; Shah M, et al. Nature Med 2023.

Claudina 18.2

CORRESPONDENCE

Zolbetuximab in Gastric or Gastroesophageal Junction Adenocarcinoma





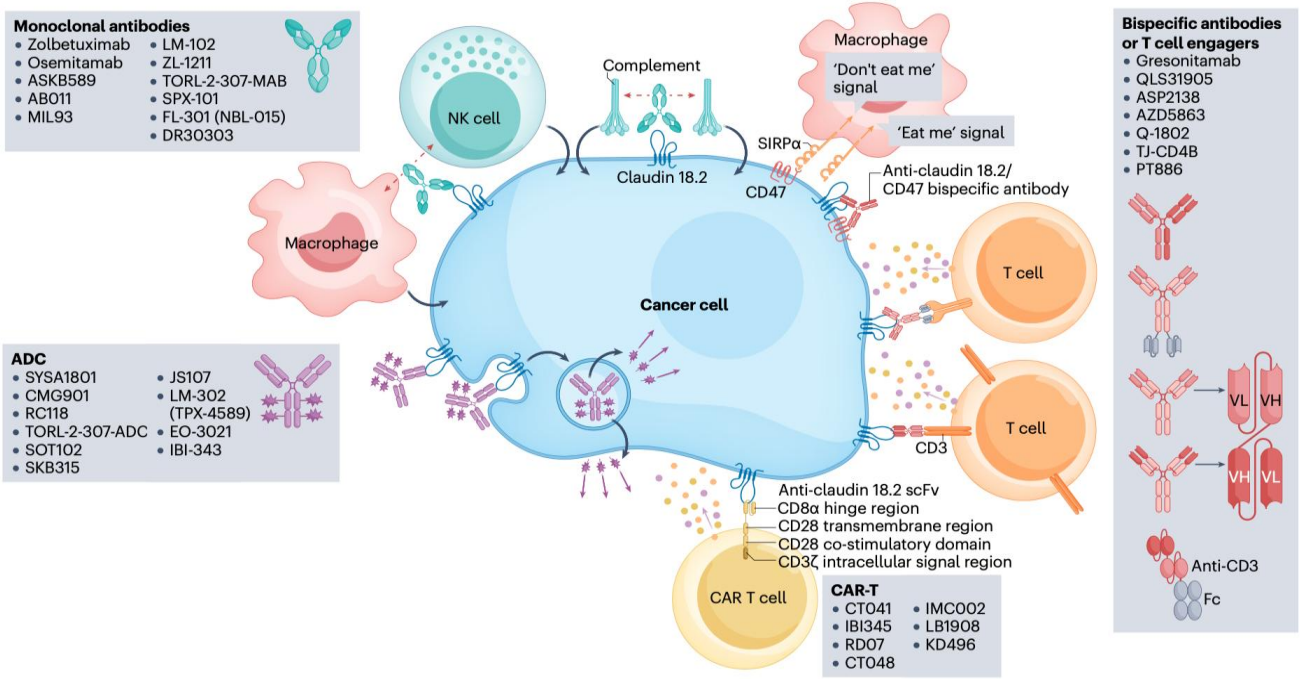
EMA APPROVED

Septiembre 2024

Shitara K, et al. N Engl J Med 2024

Claudina 18.2

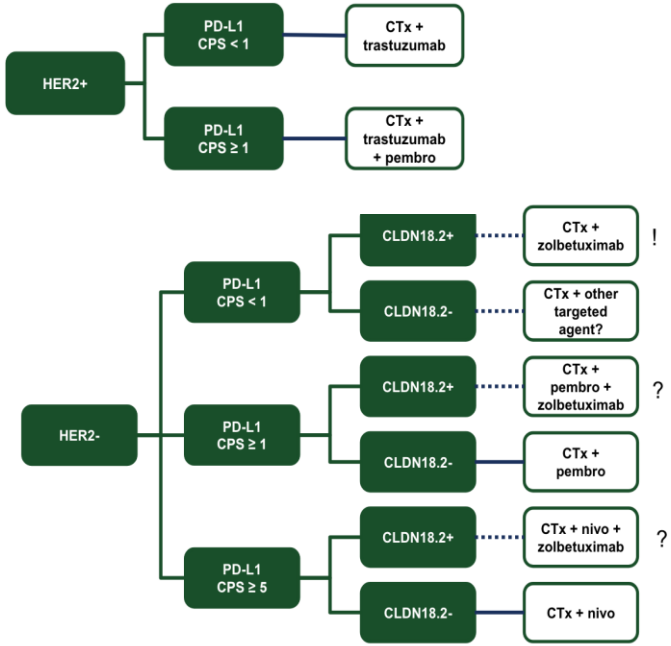
Developmental Claudin 18.2-targeted therapies



Nakayama I, et al. Nat Rev 2023.

Potential therapy algorithm according to biomarker status

1L therapy in advanced unresectable/metastatic mG/GEJ ADC



Superposición, Co-expresión de BK

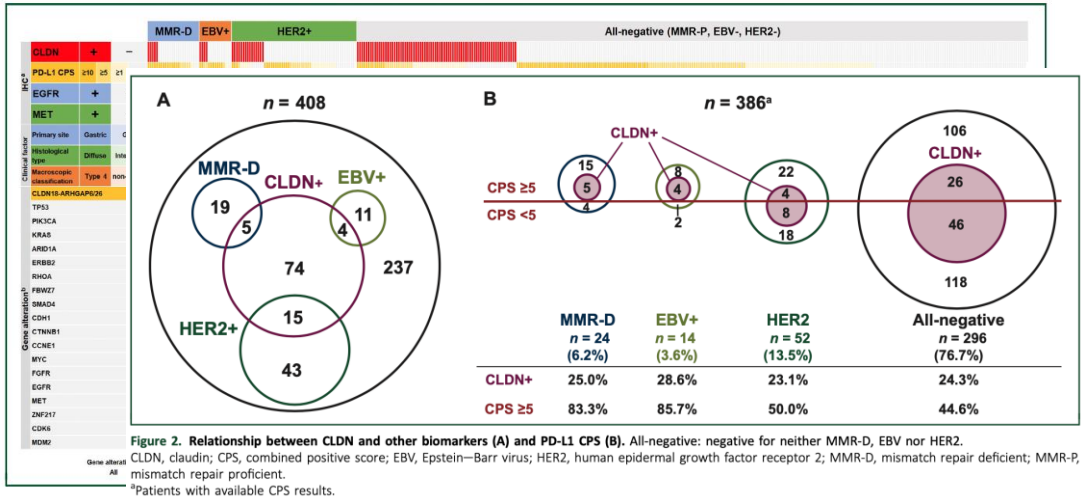
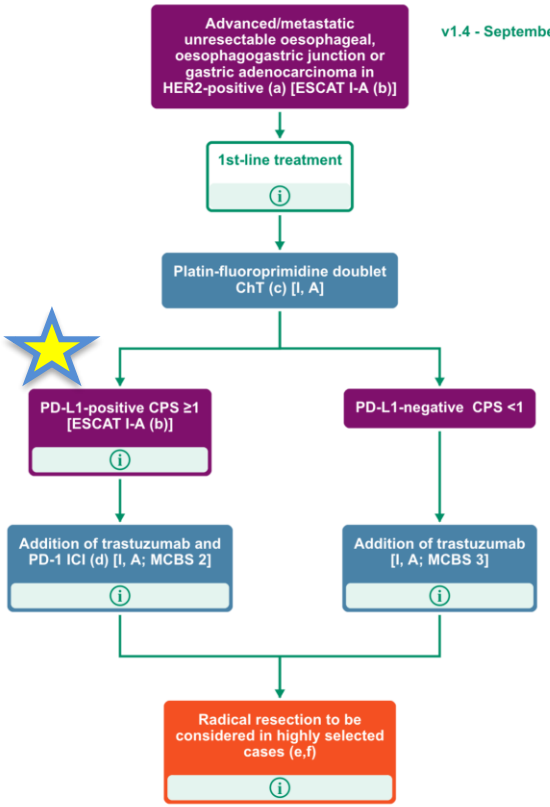


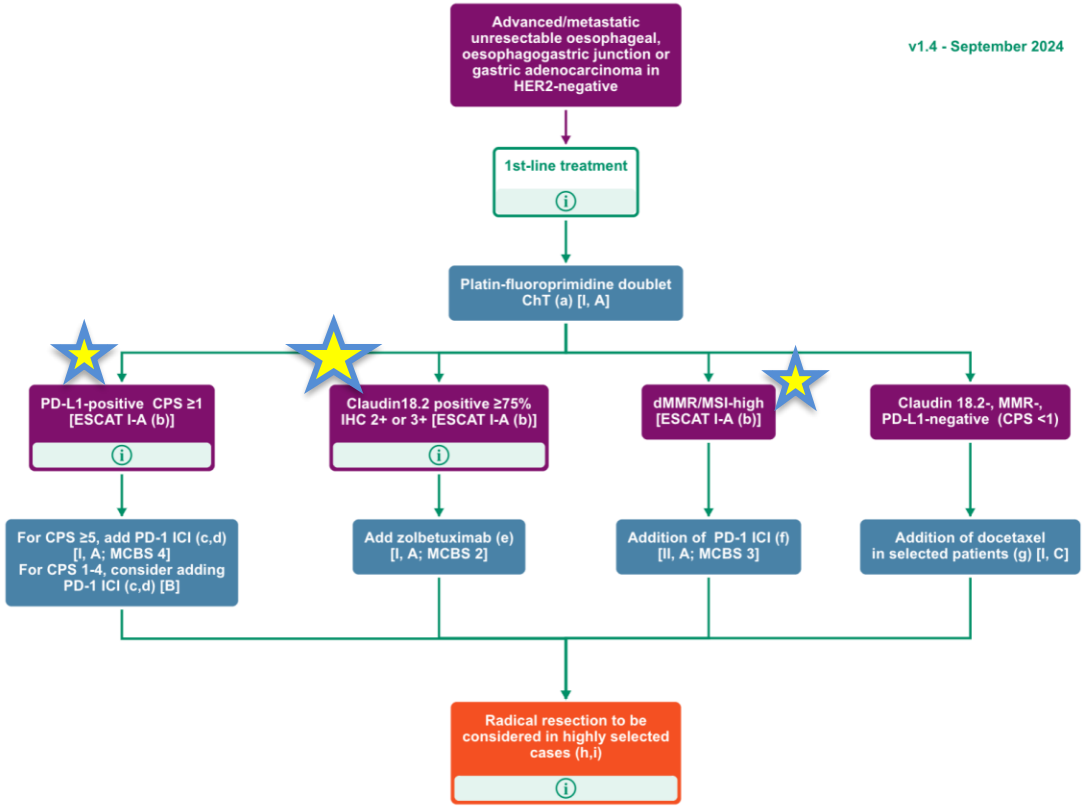
Figure 2. Relationship between CLDN and other biomarkers (A) and PD-L1 CPS (B). All-negative: negative for neither MMR-D, EBV nor HER2. CLDN, claudin; CPS, combined positive score; EBV, Epstein—Barr virus; HER2, human epidermal growth factor receptor 2; MMR-D, mismatch repair deficient; MMR-P, mismatch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

Kubota Y, et al. ESMO Open 2023

Lorenzana S, ESMO 2023

ESMO Gastric Cancer Living Guideline





Mensajes para llevar a casa

- ✓ **Biomarcadores** obligatorios: MMR/MSI, HER2, PDL1, Claudina 18.2
  1. Recomendable: VEB
  2. A futuro: FGFR2b, otros
- ✓ QT basada en FP y platino continúa siendo el pilar de tto CG avanzado.
- ✓ QT + antiPD1: aprobado 1L CG avanzado PDL1+. (CPS ≥ **1**, Pembro; CPS ≥ **5**, Nivo)
- ✓ QT + Trastuzumab + Pembrolizumab: aprobado 1L CG avanzado HER2+/PDL1+
- ✓ QT+ Zolbetuximab: aprobado 1L CG avanzado Claudina 18.2 +

Reflexiones

1. La **Inmunoterapia** y l nan parte de la práctica clínica en cáncer gástri

2. Garantizar la equidad y a la terapia)

3. Nuevas estrategias par no potenciales dianas

Muchas gracias

- **Dra. Rosario Vidal Tocino**
- Servicio Oncología Médica
- Hospital Universitario de Salamanca –IBSAL
- Profesora Asociada – Universidad de Salamanca

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