VHIO Vall d'Hebron Instituto de Oncología

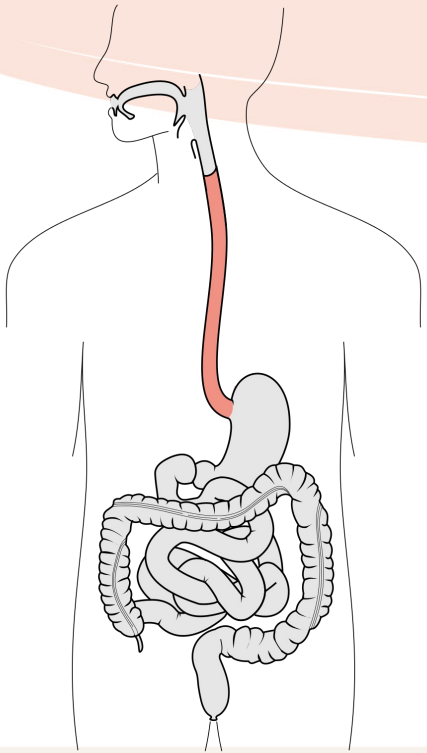
Vall d'Hebron Barcelona Campus Hospitalari

# XVII SIMPOSIUM BASES BIOLÓGICAS DEL CÁNCER E INNOVACIÓN TERAPÉUTICA

MÁS DE 20 AÑOS A LA VANGUARDIA DE LA FORMACIÓN EN LA BIOLOGÍA Y TRATAMIENTO DEL CÁNCER

SALAMANCA, 22 Y 23 DE MAYO DE 2025

# Therapeutic algorithm in advanced esophagogastric adenocarcinoma



**Eduardo Terán Brage, MD PhD**

*Medical Oncologist and Clinical Researcher*

*Upper Gastrointestinal Cancer Unit*

*Vall d`Hebron University Hospital // Vall d`Hebron Institute of Oncology (VHIO)*

*ACTEG-Young coordinator (ACTEG-SCBO)*

# Disclosure Information

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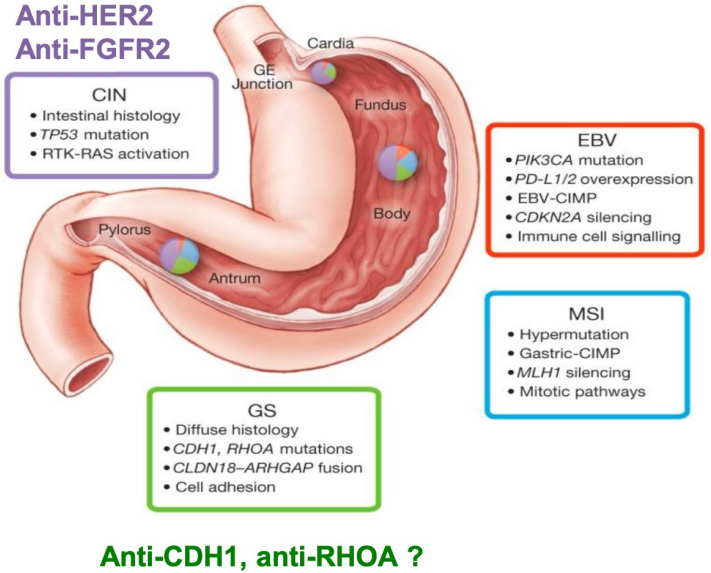
- **Consultant or Advisory Role:** none.
- **Stock Ownership:** none.

# Agenda

1. Overview
2. ESMO Gastric Cancer Guidelines
3. HER2
4. PDL1
5. MSI-H/dMMR
6. CLDN-18.2
7. New biomarkers on the horizon
8. Take-home messages

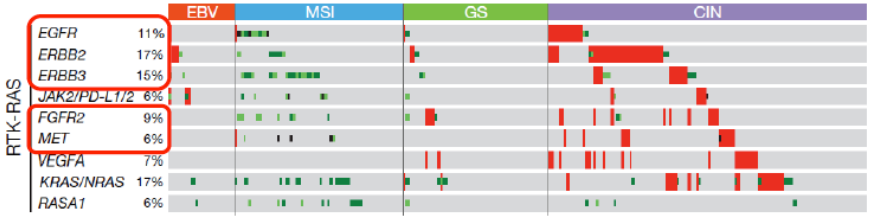
# Overview



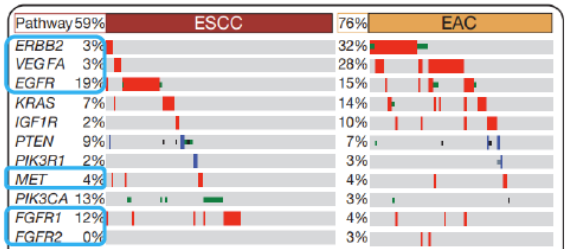

**Anti-CDH1, anti-RHOA ?**

**TCGA subtypes**

**TCGA: gastric adenocarcinoma**




**TCGA: esophageal cancer**




- Predominant RTK alterations:
  - G/GEJ AC: HER2, EGFR, FGFR2, MET
  - ESCC: EGFR, FGFR1, MET, HER2

Treatment strategies based more on the **biology** over the anatomy

Cancer Genome Atlas Research Network, Nature. 2014.

# Overview

## Predictive biomarkers in oesophagogastric adenocarcinoma

**Ph III**
**HER2-amp (IHC and ISH)**
**PD-L1 (CPS)**
**CLAUDIN-18.2**

**Ph II/III**
**subgroups**
**dMMR/MSI-H**
**EBV**
TMB

**Promising Ph I/II**
**FGFR2B-amp**
*MET*-amp
*EGFR*-amp
*ALK*-fus
*PIK3CA*-mut
*TROP2*-amp
*VEGF*-amp
HER2low

# ESMO Gastric Cancer Guidelines

ESMO LIVING GUIDELINES

## 1L TREATMENT: PLATINUM+FLUOROPIRIMIDINE +/- Targeted therapy

**Which targeted therapy?**

**1. HER2**

**2. PD-L1** *(CPS)*

- (+) **Trastuzumab + ICI**
  *Pembrolizumab (CPS≥1)*
  *KEYNOTE 811 trial 2023*
- (-) **Trastuzumab**
  *ToGA trial 2010*

**2.1. PD-L1** *(CPS)*

- (+) **ICI**
  *Nivolumab (CPS ≥5)*
  *Pembrolizumab (CPS≥1)*
  *CheckMate 649 trial 2021*
  *KEYNOTE 859 trial 2023*

**2.2. CLDN 18.2**

- (+) **Zolbetuximab**
  *GLOW trial (+CAPOX) 2023*
  *SPOTLIGHT trial (+FOLFOX) 2023*

**2.3. dMMR/MSI-H**

- (+) **ICI**
  *Subgroup analyses from CheckMate 649, KEYNOTE-062 and KEYNOTE-859*
  *benefit if PD-1 1L dMMR/MSI-high GC*

**All 2.1, 2.2, 2.3**

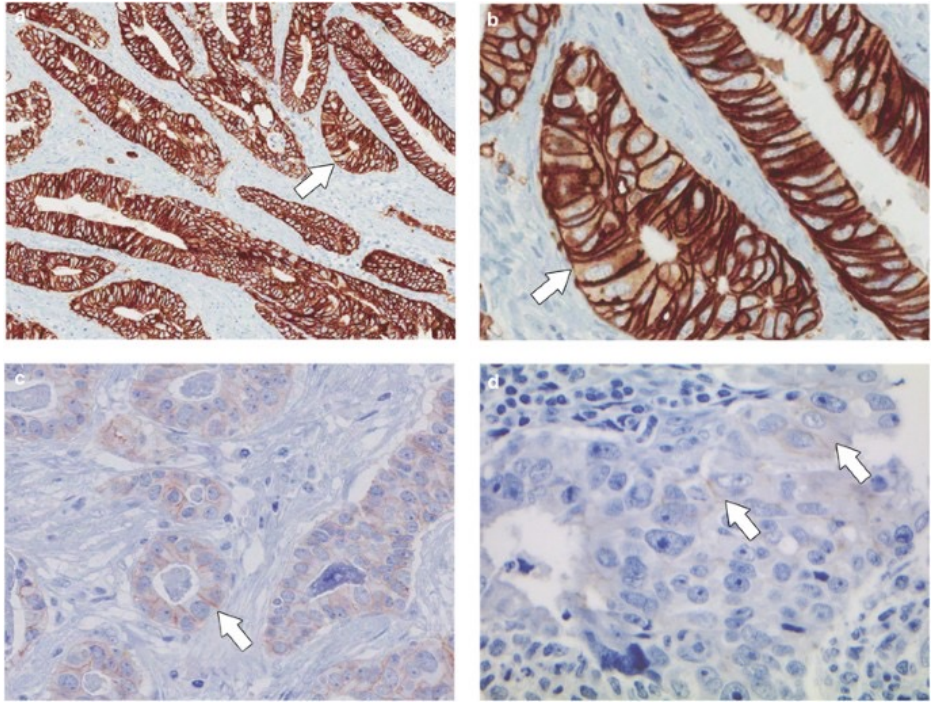
- (-) **Consider addition docetaxel (selected patients)**
  **TFLOX/mFLOT**
  *GASTFOX-PRODIGE 51 trial 2023*

# Sometimes is not that straightforward…

# First stop 📍

## HER2

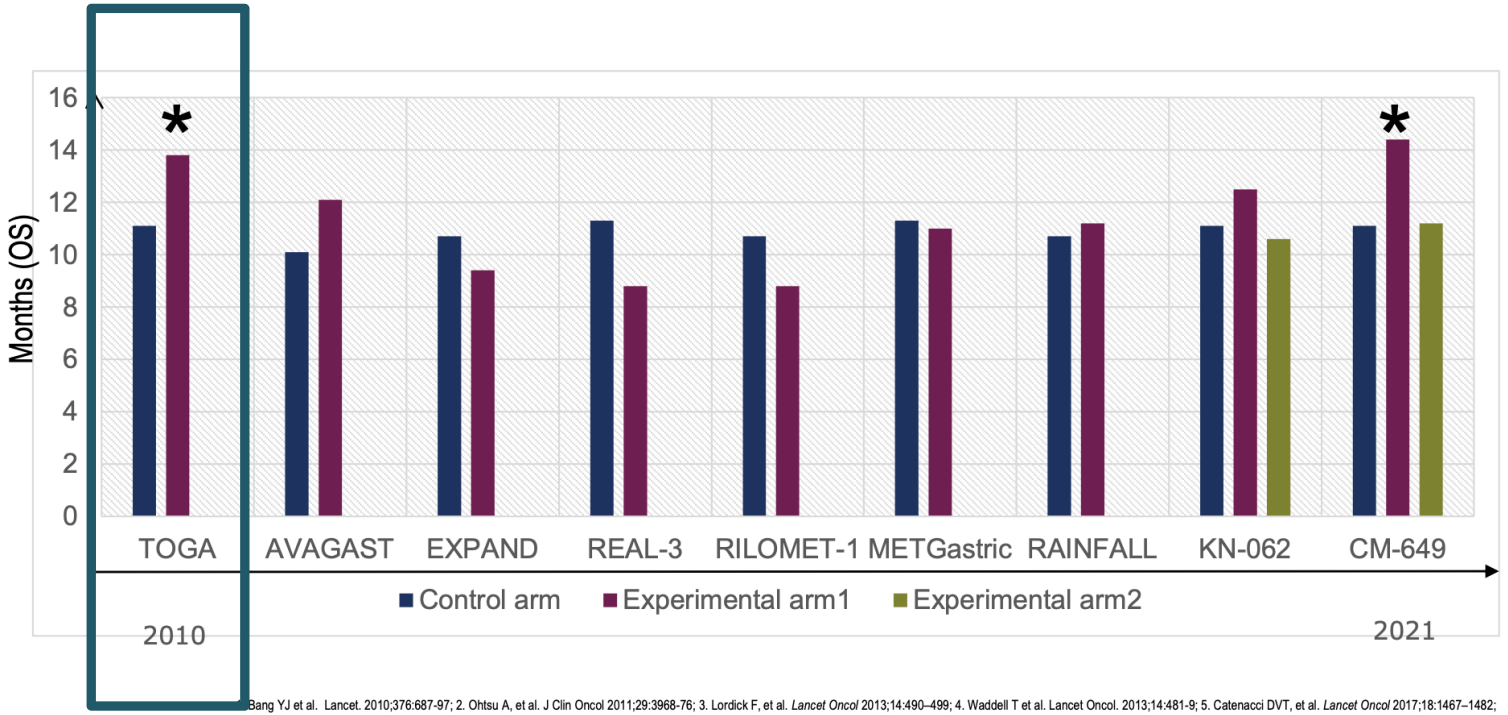
15–20%



Rüschoff J, et al. Mod Pathol. 2012 May;25(5):637-50. doi: 10.1038/modpathol.2011.198.

# HER2 pathway

## HER2 blockade for HER2 amplified advanced GEA was defined as standard of care in 2010




Bang YJ et al. Lancet. 2010;376:687-97; 2. Ohtsu A, et al. J Clin Oncol 2011;29:3968-76; 3. Lordick F, et al. *Lancet Oncol* 2013;14:490–499; 4. Waddell T et al. Lancet Oncol. 2013;14:481-9; 5. Catenacci DVT, et al. *Lancet Oncol* 2017;18:1467–1482; 6. Shah MA, et al. *JAMA Oncol* 2017;3:620–627; 7. Fuchs CS, et al. *Lancet Oncol* 2019;20:420–435; 8. Tabernero J et al. JAMA Oncol. 2020;6:1571-1580; 9. Janjigian YY, et al. *Lancet* 2021;398:27-40

# HER2 pathway

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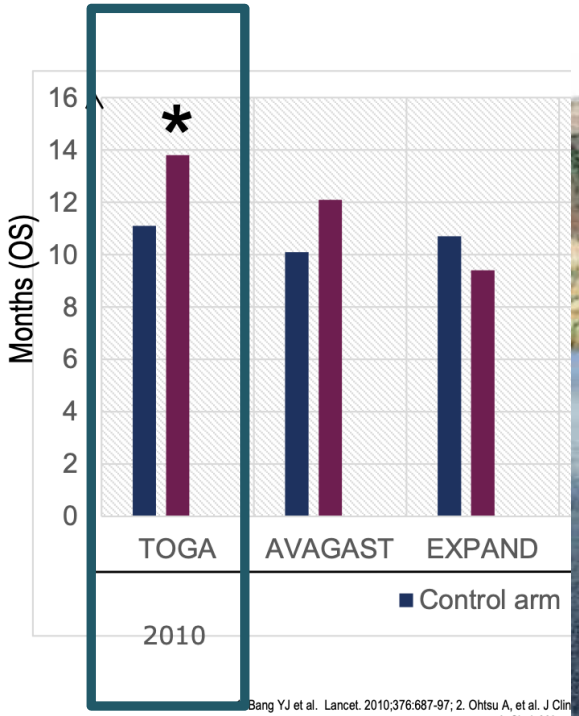



Bang YJ et al. Lancet. 2010;376:687-97; 2. Ohtsu A, et al. J Clin
6. Shah MA, et

# HER2 pathway: Understanding of HER2+ GEA

## History of HER2-targeted Gastric Cancer Studies

| 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, $p = 0.0046$ |
| 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, $p = 0.057$ |

**NEGATIVE Phase 3 trials with antiHER2 therapy in GEA**

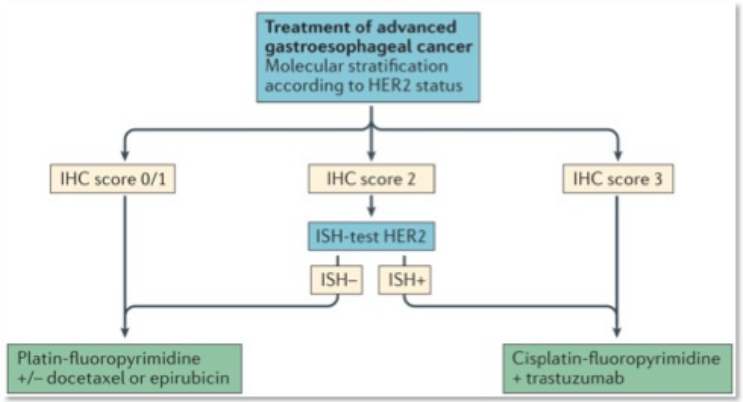


Ariga S et al. J Clin. Med. 2023, 12,3391

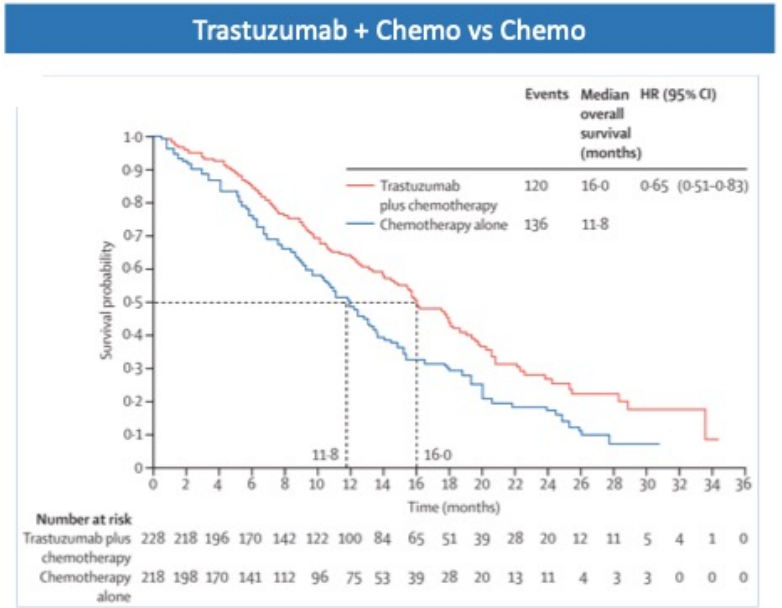
# HER2 pathway

**HER2 blockade for HER2 amplified advanced GEA was defined as standard of care in 2010**

## HER2 test algorithm for treatment selection

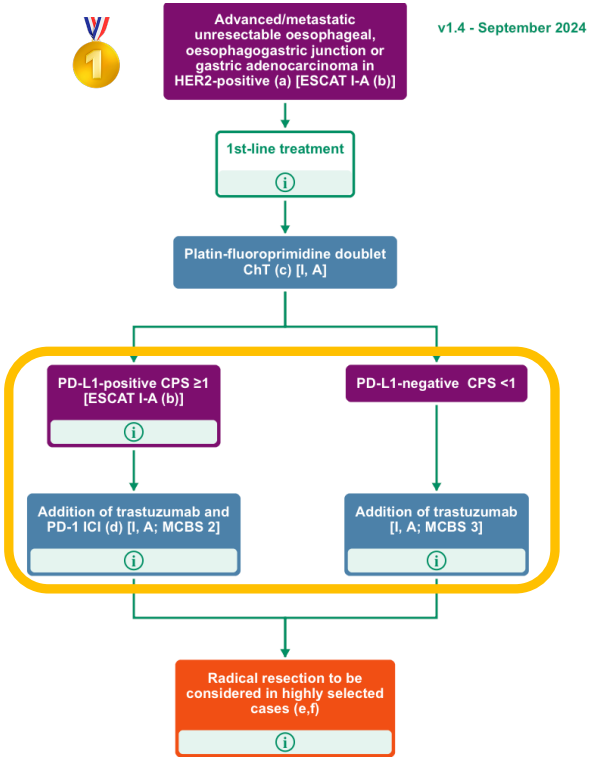


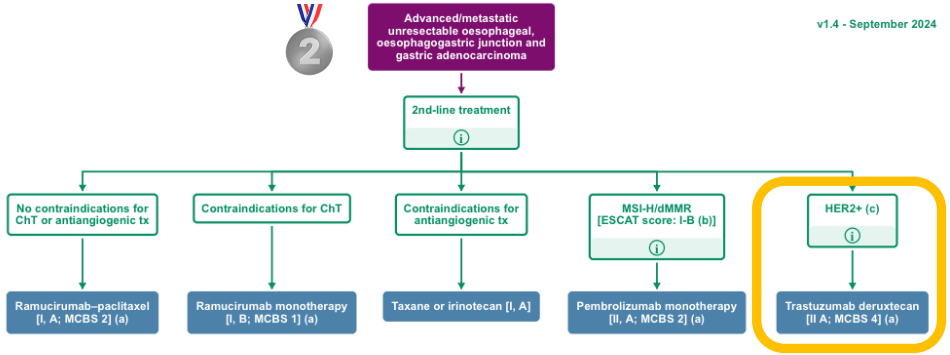

## TOGA – HER2 IHC 3+ or IHC2+ and FISH+

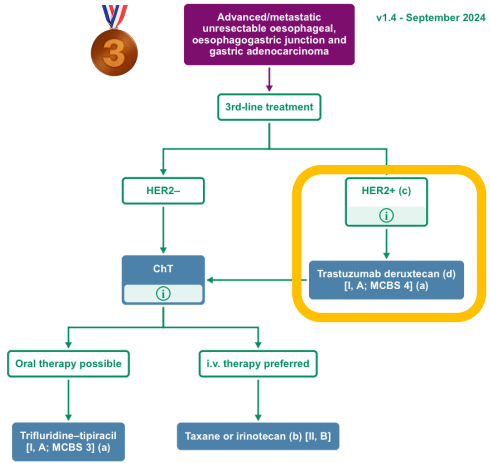



Bang YJ, et al. Lancet 2010;376:687–697
Lordick F, Janjigian YY. Nat Rev Clin Oncol. 2016 Jun;13(6):348-60

# HER2 pathway: How we treat HER2-positive advanced GEA?



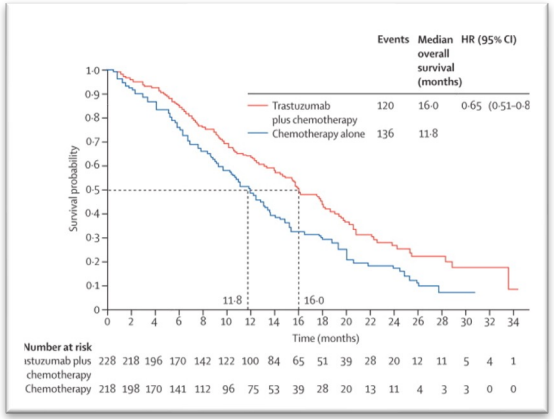



# HER2 pathway: How we treat HER2-positive advanced GEA?

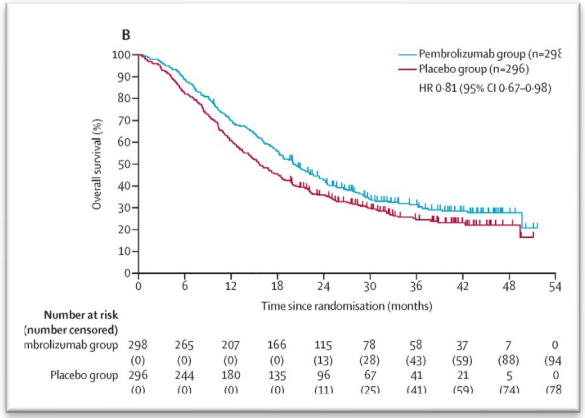
## I line

### ToGA 2010




**CT-Trastuzumab**

### KEYNOTE 811 2023, 2024



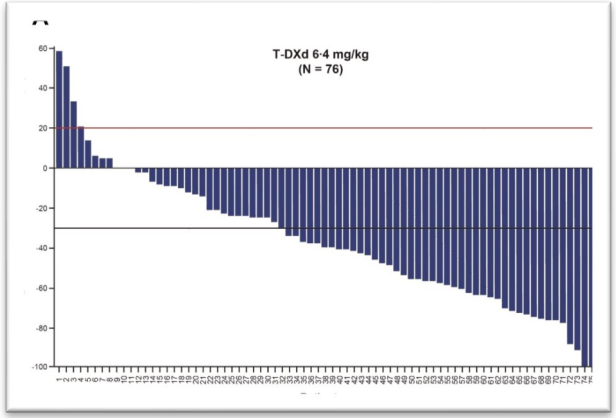

**CT-TTZ- Pembrolizumab**

Gastric or gastro-oesophageal junction (GEJ) adenocarcinoma

KEYTRUDA, in combination with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1.

## 2/3 line

### Destiny-Gastric 01 2020 / 02 2023




**T-Dxd**

Gastric cancer

Enhertu as monotherapy is indicated for the treatment of adult patients with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen.

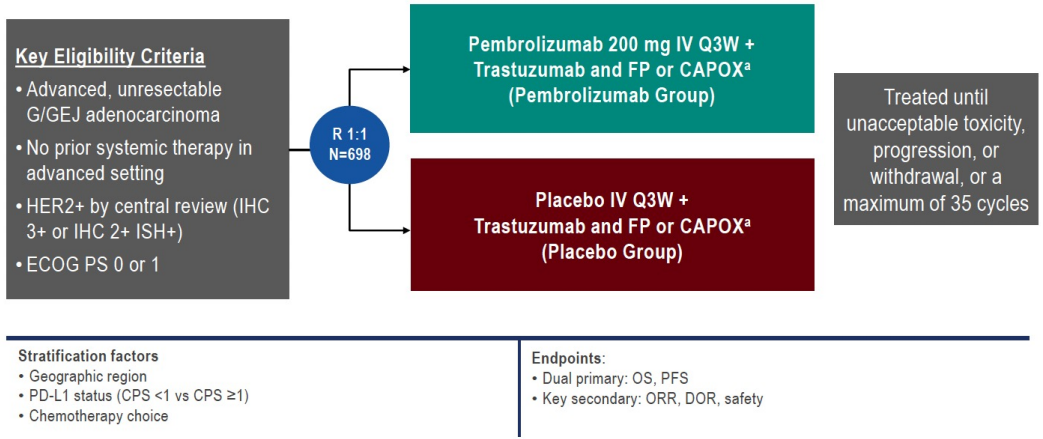
# HER2 pathway: How we treat HER2-positive advanced GEA?

## I line KEYNOTE-811: Study Design

### Overall Survival From Final Analysis of the Phase 3 KEYNOTE-811 Study Evaluating Pembrolizumab Plus Trastuzumab and Chemotherapy in Unresectable or Metastatic HER2+ Gastric/GEJ Adenocarcinoma

Yelena Y. Janjigian,[1] Akihito Kawazoe,[2] Yuxian Bai,[3] Jianming Xu,[4] Sara Lonardi,[5*] Jean Phillipe Metges,[6] Patricio Yanez,[7] Lucjan S. Wyrwicz,[8] Lin Shen,[9] Yuriy Ostapenko,[10] Mehmet Bilici,[11] Hyun Cheol Chung,[12] Kohei Shitara,[2] Mauricio Mahave,[13] Eric Van Cutsem,[14] Josep Tabernero,[15] Linzhi Xu,[16] Kanu P. Sharan,[16] Pooja Bhagia,[16] Sun Young Rha[12]

Phase 3 Randomized, Placebo-Controlled Study of First-Line Pembrolizumab Plus Chemotherapy and Trastuzumab Versus Placebo in HER2+ G/GEJ Cancer (NCT03615326)



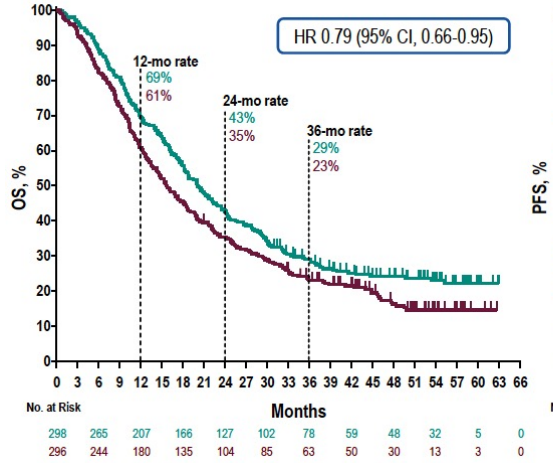

Janjigian YY, et al. Lancet. 2023 Dec 9;402(10418):2197-2208.

# HER2 pathway: How we treat HER2-positive advanced GEA?

## KEYNOTE-811: Antitumor Activity in CPS ≥1 Subgroup at Final Analysis

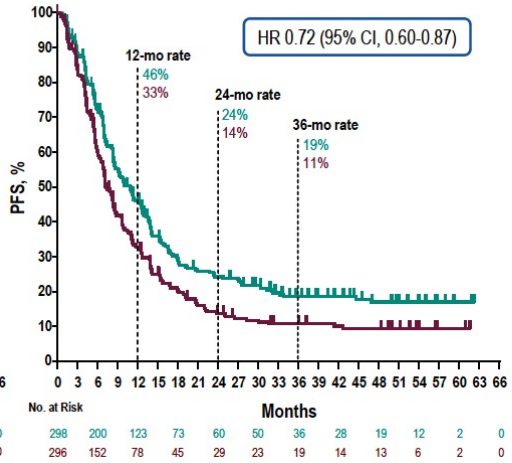
### OS

| | 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) |



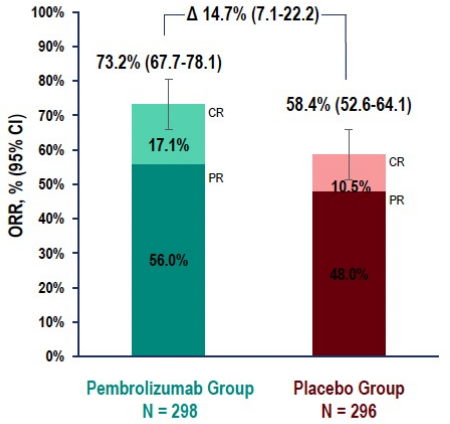

### PFS

| | 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+) |




Janjigian YY, et al. Lancet. 2023 Dec 9;402(10418):2197-2208.

# HER2 pathway: How we treat HER2-positive advanced GEA?

## KEYNOTE-811: Antitumor Activity in CPS <1 Subgroup at Final Analysis

| | PD-L1 CPS <1 | |
|---|---|---|
| | Pembrolizumab Group N = 52 | Placebo Group N = 52 |
| **PFS**, median (95% CI), mo | 9.5 (8.3-12.6) | 9.5 (7.9-13.0) |
| HR (95% CI) | 0.99 (0.62-1.56) | |
| **OS**, median (95% CI), mo | 18.2 (13.9-22.9) | 20.4 (16.4-24.7) |
| HR (95% CI) | 1.10 (0.72-1.68) | |

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Gastric or gastro-oesophageal junction (GEJ) adenocarcinoma

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Janjigian YY, et al. Lancet. 2023 Dec 9;402(10418):2197-2208.

# HER2 pathway: How we treat HER2-positive advanced GEA?

## How to approach progression after first line HER2 blockade?

# HER2 pathway: How we treat HER2-positive advanced GEA?

## Trastuzumab-Deruxtecan vs Chemotherapy for relapsed HER2 amplified advanced GEA

**3 or + lines** **DESTINY-Gastric01**

- Multicenter, open-label, randomized phase II study

*Stratified by region (Japan vs Korea), ECOG PS (0 vs 1), HER2 status (IHC 3+ vs IHC 2+/ISH+)*

Adult patients with HER2+* locally advanced or metastatic gastric or GEJ cancer that progressed on ≥ 2 prior regimens† (N = 188)

*Randomized 2:1*

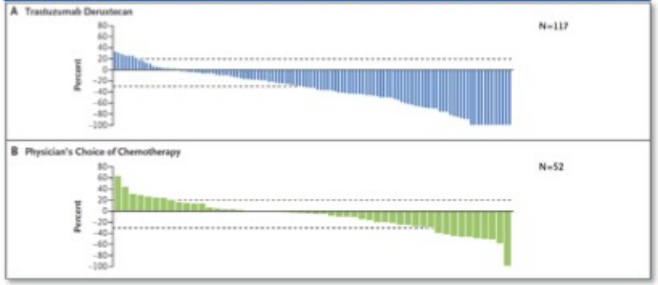
- **T-DXd** 6.4 mg/kg, 3-week cycles (n = 126)
- **Physician's choice:** **Irinotecan** 150 mg/m² every 2 weeks or **Paclitaxel** 80 mg/m² Days 1, 8, 15 every 4 weeks (n = 62)

*Until PD, unacceptable AEs, or pt withdrawal*

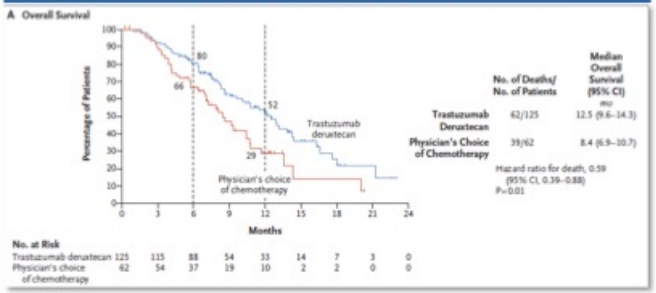
*HER2+ based on IHC 3+ or IHC 2+/ISH+ according to ASCO/CAP guidelines.
†Prior regimens included fluoropyrimidine, a platinum agent, and trastuzumab or approved biosimilar.

- Primary endpoint: ORR by ICR (RECIST v1.1)
- Secondary endpoints: OS (key), DoR, PFS, DCR, confirmed ORR, safety

**Objective confirmed overall response rate 43% vs 12%**




**Overall survival (median) 12.5 vs 8.4 months**

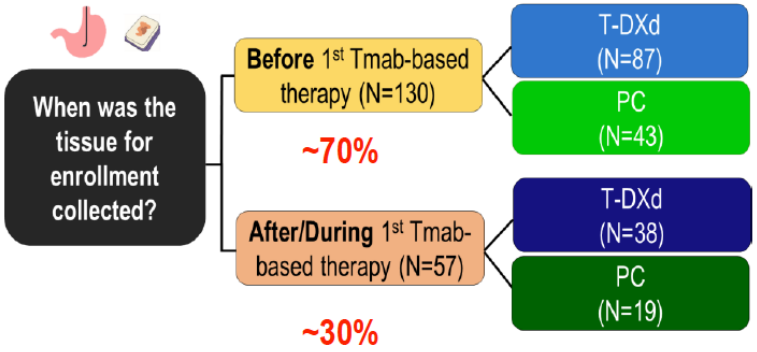



Shitara K, et al. N Eng J Med 2020;382:2419-2430.

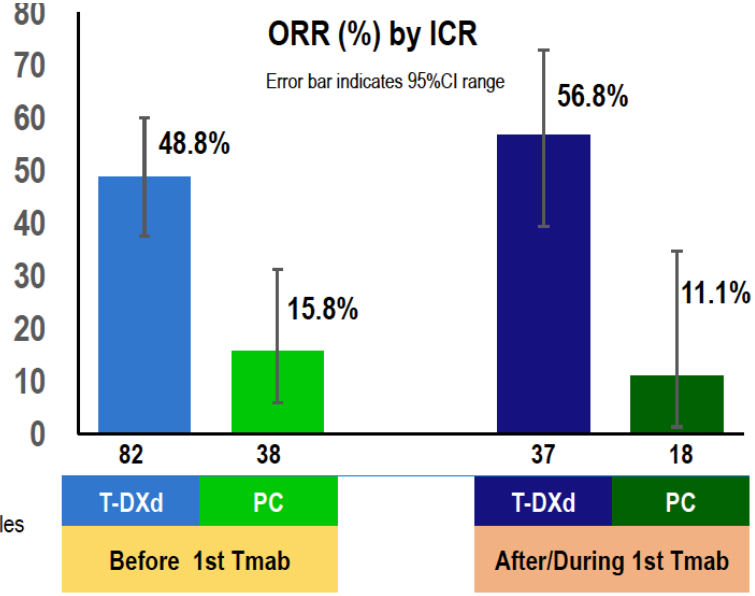
# HER2 pathway: How we treat HER2-positive advanced GEA?

## Trastuzumab-Deruxtecan vs Chemotherapy for relapsed HER2 amplified advanced GEA

**3 or + lines** **DESTINY-Gastric01**




*: patients were enrolled based on HER2 testing using archival and fresh tumor samples




*: includes data for the response evaluable set: all randomized patients who received ≥1 dose of study drug and had measurable tumors based on independent central review at baseline.

Shitara K, et al. ESMO-GI 2021. Shitara K, et al. N Eng J Med 2020;382:2419-2430.

# HER2 pathway: How we treat HER2-positive advanced GEA?

## 2/3 line DESTINY-Gastric02: Study Design

PARIS 2022 ESMO congress

**Updated Analysis of DESTINY-Gastric02: a Phase 2 Single-Arm Trial of Trastuzumab Deruxtecan (T-DXd) in Western Patients with HER2-Positive Unresectable/Metastatic Gastric/Gastroesophageal Junction (GEJ) Cancer Who Progressed on or After Trastuzumab-Containing Regimen**

An open-label, multicenter phase 2 study in Western patients with HER2+ gastric or GEJ cancer who had progressed on a trastuzumab-containing regimen (NCT04014075)

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

→ T-DXd 6.4 mg/kg Q3W N = 79[a] →

**Primary endpoint**
- Confirmed ORR by ICR

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

- Primary results of DESTINY-Gastric02 (data cutoff, April 9, 2021; median follow up 5.9 months) demonstrated a cORR of **38.0%** (95% CI, 27.3-49.6), and safety consistent with the established T-DXd safety profile[1]
- Here, we report OS and updated efficacy and safety results, with 7 additional months of follow-up (data cutoff, November 8, 2021)

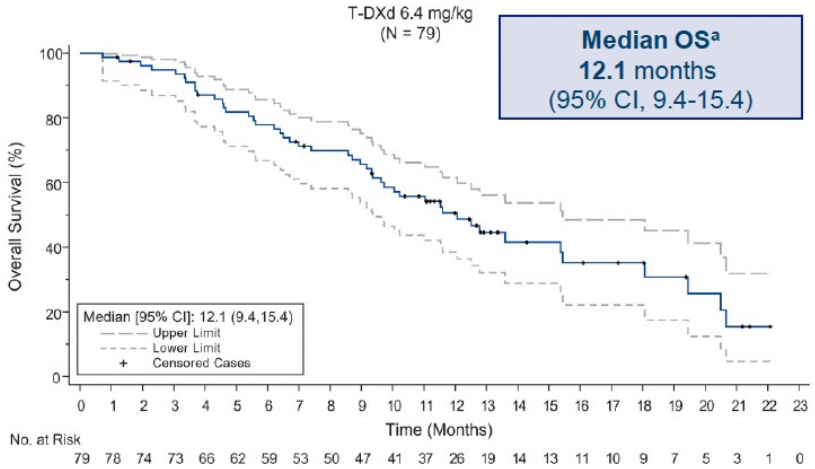


Geoffrey Ku, et al. ESMOParis2022.

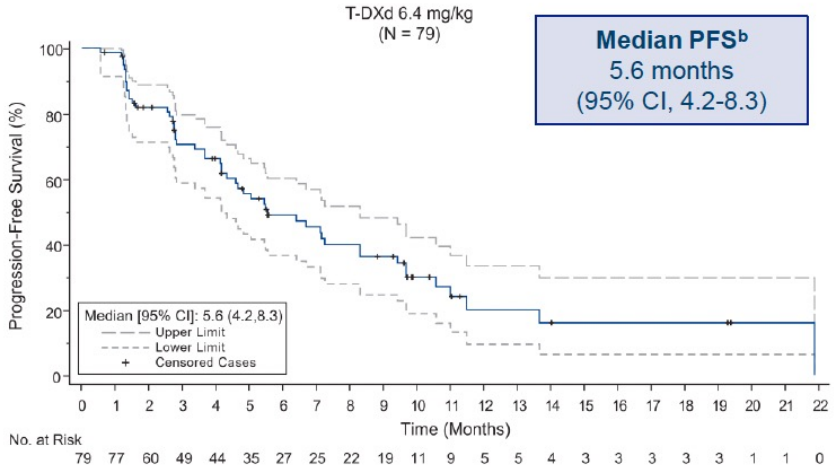
# HER2 pathway: How we treat HER2-positive advanced GEA?

## DESTINY-Gastric02: Overall Survival and Progression-Free Survival

### Kaplan-Meier Plot of OS




### Kaplan-Meier Plot of PFS by ICR

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Gastric cancer

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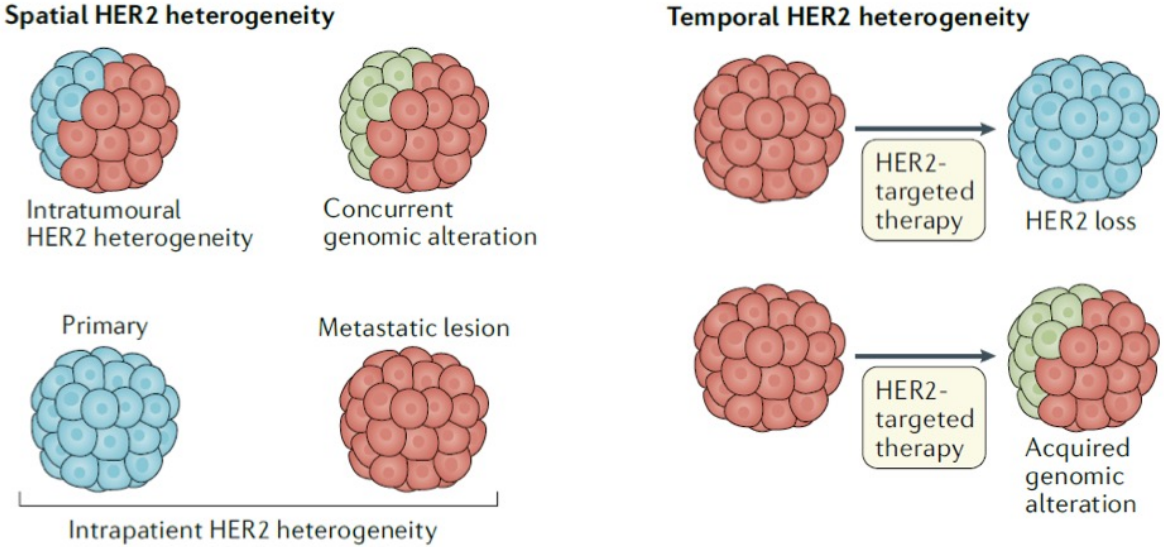
Vall d'Hebron Barcelona Campus Hospitalari

Geoffrey Ku, et al. ESMOParis2022.

# Challenges and opportunities in HER2-positive disease




Gastroesophageal tumors are **heterogeneus (spatial and temporal)**



Nakamura Y et al. Nat Rev Clin Oncol. 2021;18:473-487.

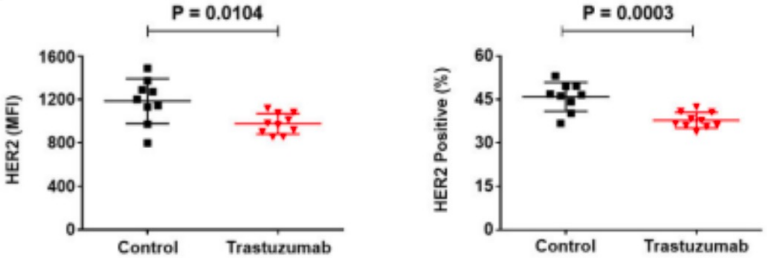
# Challenges and opportunities in HER2-positive disease

## HER2 and PD-L1

Published in final edited form as:
*Cancer Lett.* 2018 August 28; 430: 47–56. doi:10.1016/j.canlet.2018.05.009.

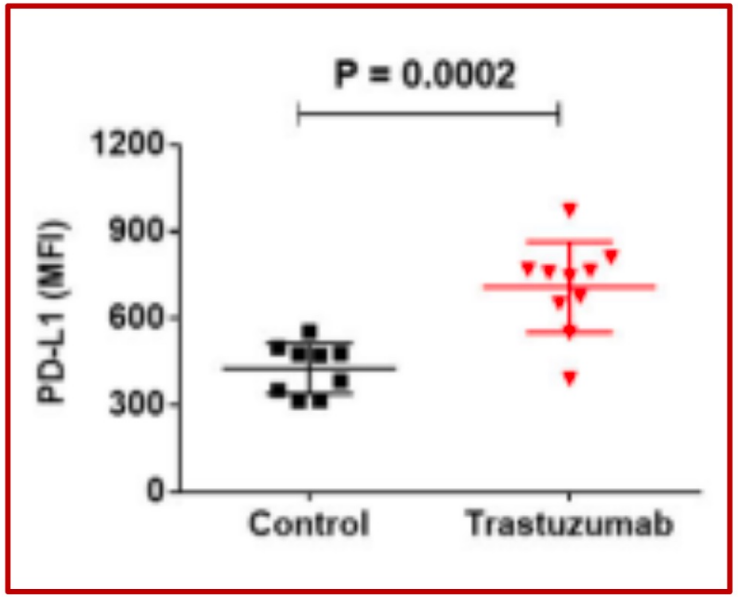
**Trastuzumab upregulates PD-L1 as a potential mechanism of trastuzumab resistance through engagement of immune effector cells and stimulation of IFNγ secretion**

### Her2 downregulated during Trastuzumab exposure




Upregulation of MHC-I, T-cell co-stimulatory molecules, and PD-L1 through interferon-gamma production mainly by NK cells and downregulation of HER2 by trastuzumab in HER2-overexpressing tumors in vivo.

### PD-L1 upregulated during Trastuzumab exposure




Chaganti BKR et al. Cancer Lett. 2018 Aug 28; 430:47-56

# Future directions…(HER2 disease)

**I line**

ToGA 2010

KEYNOTE 811 2023, 2024

**2/3 line**

Destiny-Gastric 01 2020 / 02 2023

**So what about the FUTURE?**

**OR present…**

# Future directions…(HER2 disease)

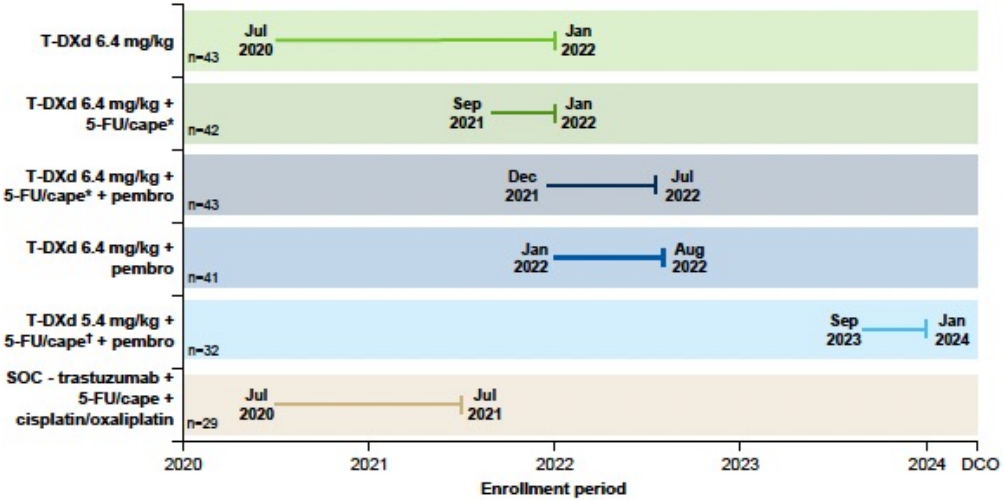
BARCELONA 2024 ESMO congress

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

Yelena Y Janjigian,[1] Hanneke van Laarhoven, Sun Young Rha, Vadim Kozlov, Do-Youn Oh, Adriano Gravina, Liane Rapatoni, Hirokazu Shoji, Ralf-Dieter Hofheinz, Li-Tzong Chen, Hugo Ford, Maxime Chénard-Poirier, Saeed Raoufmoghaddam, Caron Lloyd, Cuihong Zhang, Carla Mateo Mohedano, Jeeyun Lee

[1]Memorial Sloan Kettering Cancer Center, New York, NY, US

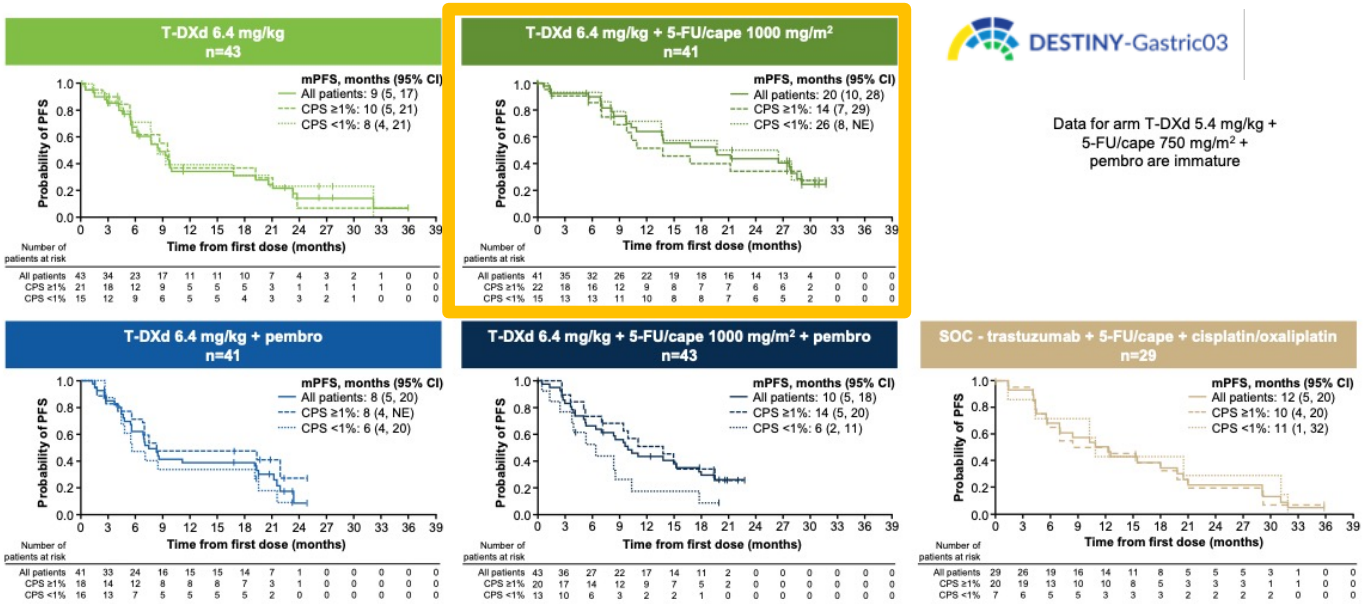
DESTINY-Gastric03




**Phase 1b/2 trial (NCT04379596), with non-contemporaneous and non-randomized arms**

# Future directions…(HER2 disease)

## DESTINY-Gastric03: Progression-free survival in all patients and by PD-L1 status




For PFS analyses (assessed by investigator per RECIST 1.1), patients without progression or who died, or who had progression or died after two or more missed visits, were censored at the latest evaluable RECIST assessment, or at Day 1 (randomization/treatment assignment) if there were no evaluable visits or no baseline assessment (unless the patient died within 13 weeks of baseline assessment). PD-L1 status was centrally assessed. Patients with CPS missing/pending status were not included in the PFS subgroup analyses.

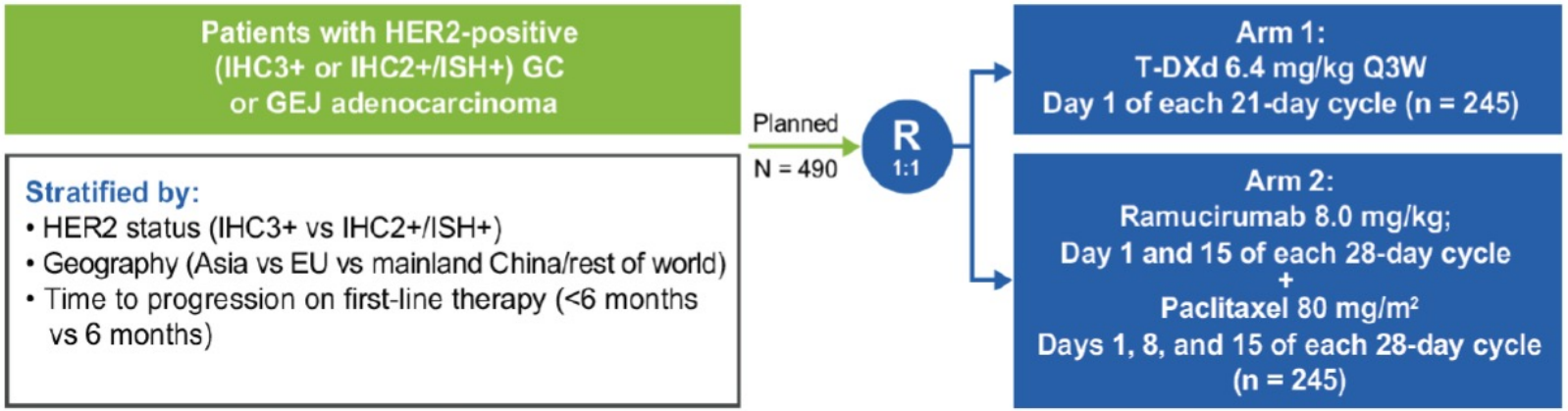
**5Fu/CPC → BACKBONE**

Higher toxicity 5-Fu/CPC-TDXd-pembrolizumab

Yelena Y, et al. ESMOBarcelona2024

# Future directions…(HER2 disease)

## DESTINY-Gastric04: T-DXd vs pac + ram




EU, European Union; GC, gastric cancer; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan.

Press Release

**ENHERTU® Demonstrated Statistically Significant and Clinically Meaningful Improvement in Overall Survival in Patients with HER2 Positive Metastatic Gastric Cancer at Interim Analysis of DESTINY-Gastric04 Phase 3 Trial**

- Phase 3 results confirm the efficacy of Daiichi Sankyo and AstraZeneca's ENHERTU in second-line metastatic gastric cancer
- DESTINY-Gastric04 will be unblinded at interim analysis based on the superior efficacy of ENHERTU
- Results will be shared with global regulatory authorities

**Tokyo and Basking Ridge, NJ – (March 3, 2025)** – Positive topline results from the DESTINY-Gastric04

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

LBA4002 - Trastuzumab deruxtecan (T-DXd) vs ramucirumab (RAM) + paclitaxel (PTX) in second-line treatment of patients (pts) with human epidermal growth factor receptor 2-positive (HER2+) unresectable/metastatic gastric cancer (GC) or gastroesophageal junction adenocarcinoma (GEJA): Primary analysis of the randomized, phase 3 DESTINY-Gastric04 study.

Shitara K, et al. ESMO 2021. NCT04704934.

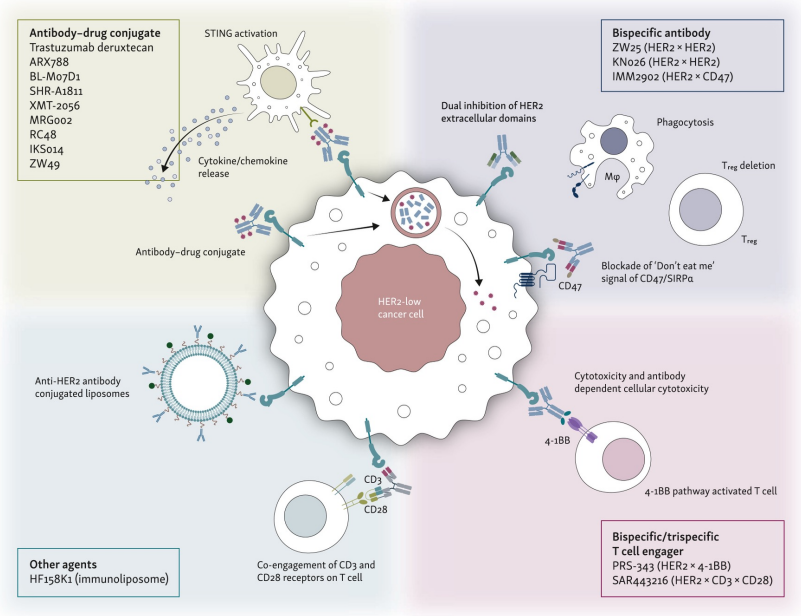
# Future directions…(HER2 disease)

## Redefinition of HER2 expression…
## HER2-low

**Table 3. Clinical trials targeting for HER2-low gastric cancer.**

| Drug | NCT | Phase | Inclusion criteria for the HER2-low group | Types of agents | Summary of the mechanisms of action, preclinical data, and clinical trial results |
|---|---|---|---|---|---|
| Trastuzumab deruxtecan | 03329690 (DESTINY-Gastric01[37]) | II | Cohort 1: IHC 2+/ISH− Cohort 2:1+ | ADC | • ORR: 26.2% (cohort 1), 9.5% (cohort 2)<br>• Median PFS: 4.4 months (cohort 1), 2.8 months (cohort 2)<br>• Median OS: 7.8 months (cohort 1), 8.5 months (cohort 2) |
| | 04379596 (DESTINY-Gastric03[41]) | Ib/II | IHC 2+/ISH− or IHC 1+ | | • T-DXd plus fluoropyrimidine and volrustomig (arm 3B)<br>• T-Dxd plus fluoropyrimidine and rilvegostomig (arm 4B) |
| | 05894824 | I/II | IHC 2+/ISH− or IHC 1+ | | • T-DXd plus ramucirumab for second line |
| | NA (EPOC2203) | I/II | IHC 2+/ISH− or IHC 1+ | | • T-DXd plus CAPOX and nivolumab for first line |
| SHR-A1811 | 04513223 | I/II | IHC 2+/ISH− or IHC 1+ | ADC | • Payload: SHR9265 (DNA topoisomerase 1 inhibitor)[44]<br>• 4/12 Patients achieved PR[45] |
| BL-M07D1 | 06031584 | Ib/II | IHC 2+/ISH− or IHC 1+ | ADC | • Payload: Ed-04 (DNA topoisomerase 1 inhibitor)[46] |
| RC48 | 05980481 | II/III | IHC 2+/ISH− or IHC 1+ | ADC | • Payload: monomethyl auristatin E[50]<br>• Potentially promotes STING pathway activation<br>• RC48 plus toripalimab: ORR 46%[19]<br>• RC48 plus toripalimab plus CAPOX for first line[50] |
| MRG002 | 05141747 | II | IHC 2+/ISH− or IHC 1+ | ADC | • Payload: monomethyl auristatin E[51]<br>• Antibody component MAB802 reduces antibody-dependent cell-mediated cytotoxicity with increased fucosylation of the Fc region of the antibody |
| IKS014 | 05872295 | I | IHC 2+/ISH− or IHC 1+ | ADC | • Payload: monomethyl auristatin F[52] |
| PRS-343 | 05190445[58] | II | Arm B: IHC 2+/ISH− or IHC 1+ | Bispecific T-cell engager antibody | • HER2 binding domain and a CD137 binding domain[57,86]<br>• Preliminary efficacy and safety profile in monotherapy and in combination with atezolizumab for HER2+ solid tumors[58]<br>• PRS-343 in combination with tucatinib was investigated |
| SAR443216 | 05013554[60] | Ib | Dose expansion cohort: IHC 2+/ISH− or 1+, *ERRB2* activating mutation | Trispecific T-cell engager antibody | • HER2 binding domain, a CD3 binding domain and a CD28 binding domain[59,61]<br>• Activating T cells and inducing T-cell-mediated cytotoxic activity |
| HF-K1 | 05861895 | I | IHC 2+/ISH− or IHC 1+ | Immunoliposome | • Immunoliposome of doxorubicin encapsulated by lipid membranes containing TL01[62]<br>• TL01 is a fragment conjugated lipid of trastuzumab Fab lesion |

ADC, antibody–drug conjugate; CAPOX, capecitabine and oxaliplatin; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, *in situ* hybridization; NA, not available; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; STING, stimulator of interferon genes; T-DXd, trastuzumab deruxtecan.

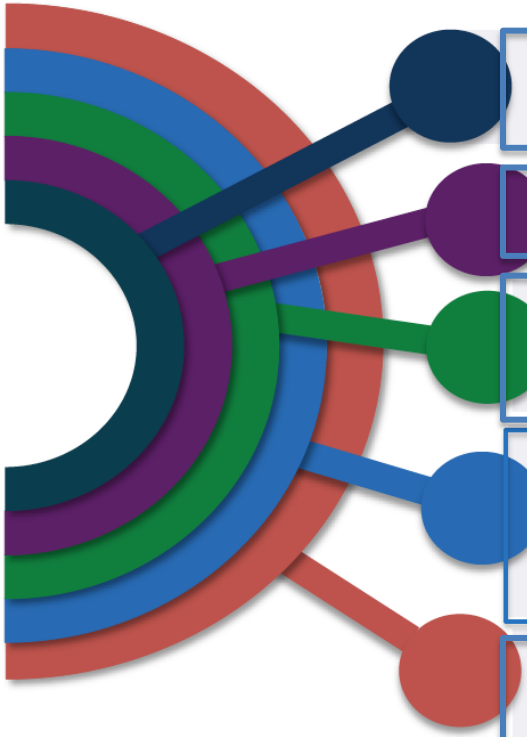



| Tumor types | Gastric | |
|---|---|---|
| Trial name | DESTINY-Gastric01[37,38] | |
| NCT | 03329690 | |
| Phase | II | |
| Line | ≥3 | |
| HER2 | 2+/ISH− | 1+ |
| ORR | 26.3% | 9.5% |
| Median PFS, months (95% CI) | 4.4 (2.7-7.1) | 2.8 (1.5-4.3) |
| Median OS, months (95% CI) | 7.8 (4.7-NE) | 8.5 (4.3-10.9) |

Shimozaki K, et al. ESMO Open. 2024 Sep;9(9):103679

# Future directions…(HER2 disease)

**Artemide-Gastric**
**DestinyGastric05**



**Combination with PD-1 blockade**
- With durvalumab, nivolumab, and pembrolizumab
- KN811 study is awaited

**Tyrosine kinase inhibitor**
- Tucatinib (+chemotherapy, tras, and ramucirumab)

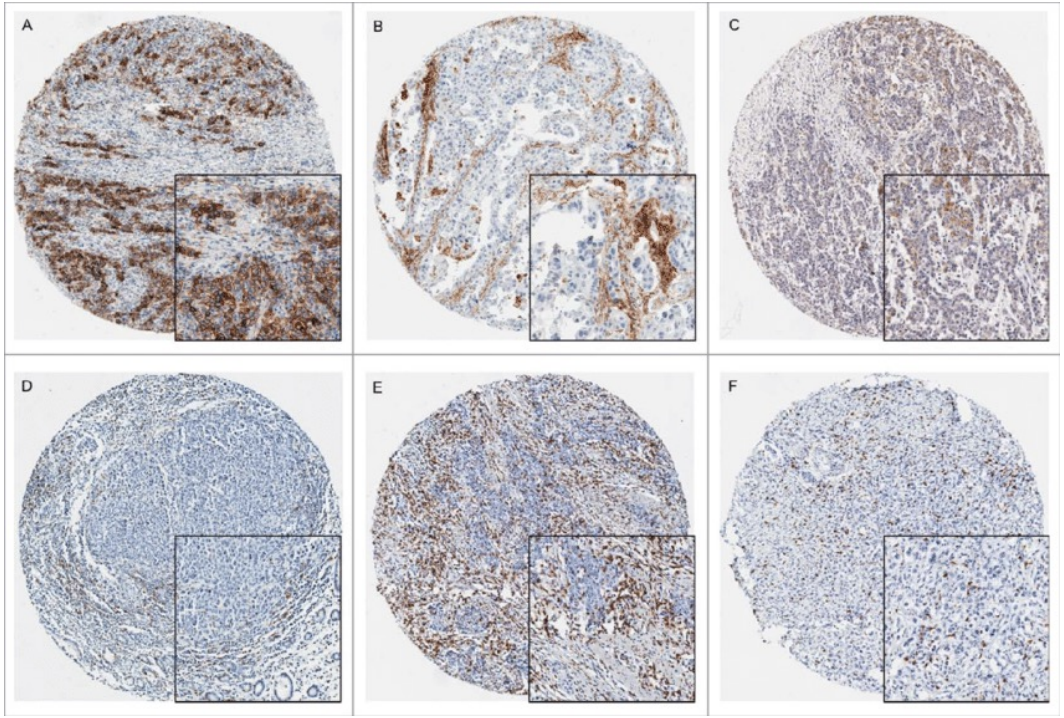
**Antibody-drug conjugate**
- Trastuzumab deruxtecan (T-Dxd)
- RC48-ADC, Trastuzumab duocarmazine etc.
- NJH 395 and SBT6050 with toll-like receptor agonists

**Monoclonal/bispecific antibodies**
- Margetuximab (+ PD-1 inhibitor):enhanced ADCC
- ZW25 or KN026; targets two epitopes on HER2
- CD47 inhibition with trastuzumab
- HER2-41BB (PRS-343)or HER2-CD3 bispecific (BTRC4017A)

**Newer Immunotherapy**
- Cellular therapy for HER2: CT-0508 and CYNK-101
- Vaccination against Her-2/neu

# Second stop 📍

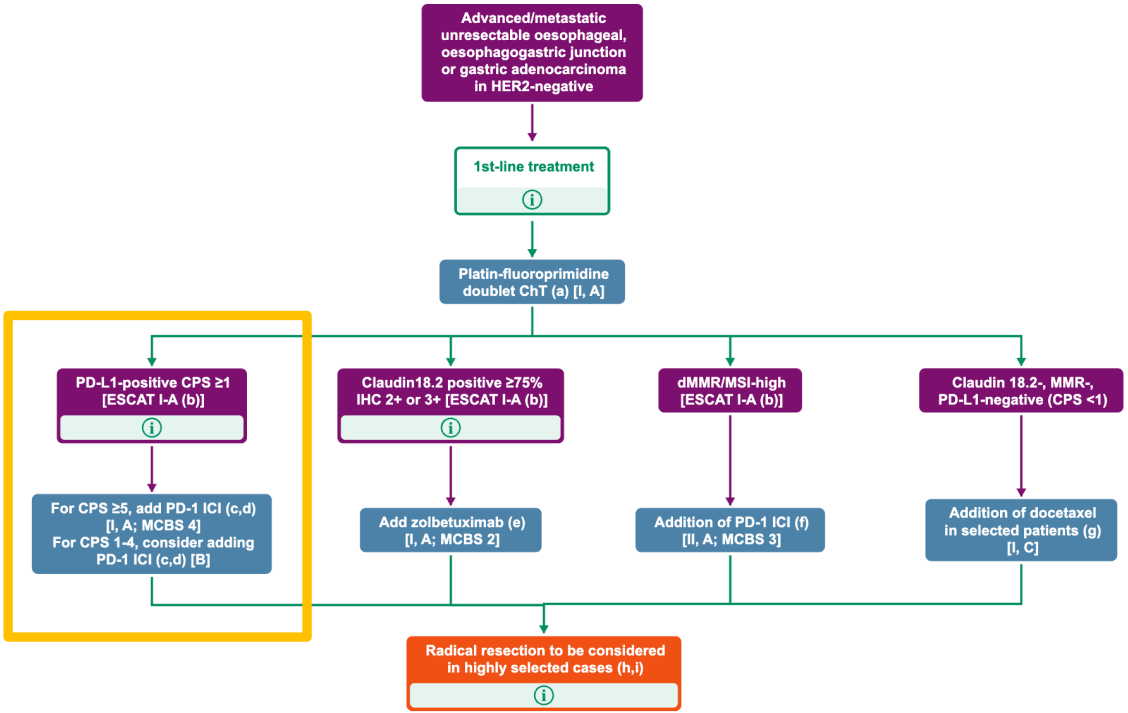
# PDL1






Xing X, et al. Oncoimmunology. 2017 Dec 21;7(3):e1356144. doi: 10.1080/2162402X.2017.1356144.

# Looking our guidelines…



# Data from pivotal Phase III trials: EMA approved therapy

| | |
|---|---|
| **Tislelizumab** | GC or GEJ unresectable/metastatic HER2 negative PDL1 TAP score ≥ 5% |

***Rationale 305***

| | |
|---|---|
| **Pembrolizumab** | GC or GEJ unresectable/metastatic HER2 negative PDL1 CPS ≥ 1 |
| | GC or GEJ unresectable/metastatic HER2 positive PDL1 CPS ≥ 1 |
| | EAC or GEJ unresectable/metastatic HER2 negative PDL1 CPS ≥ 10 |

***Keynote 859, Keynote 811, Keynote 590***

| | |
|---|---|
| **Nivolumab** | EAC, GEJ or GC, unresectable/metastatic HER2 negative PDL1 CPS≥ 5 |

***Checkmate 649***

MINISTERIO DE SANIDAD

| | |
|---|---|
| Resuelto | Sí, con restricción a la indicación autorizada: Se restringe a pacientes cuyos tumores expresen PD-L1 con una CPS>=10 |
| En estudio | |

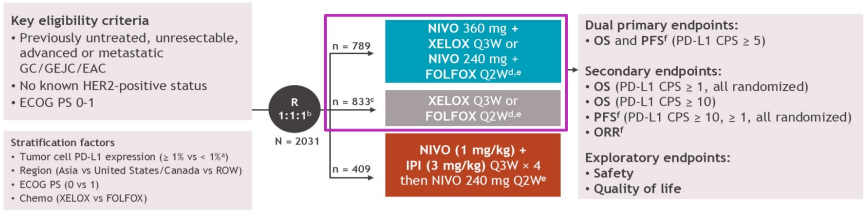
# Data from pivotal Phase III trials: EMA approved therapy

## Checkmate 649: Nivolumab

CheckMate 649

### Figure 1. CheckMate 649 study design[1]

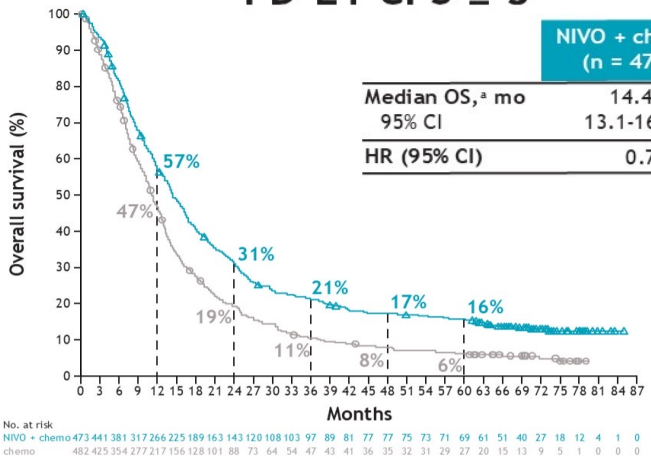
- CheckMate 649 (NCT02872116) is a randomized, open-label, global phase 3 trial (**Figure 1**)
- Patients were enrolled from 175 hospitals and cancer centers in 29 countries




- At data cutoff (May 28, 2024), the minimum follow-up (time from concurrent randomization of the last patient to clinical data cutoff) was 60.1 months
- No patients in the NIVO + chemo or chemo arms were receiving ongoing study treatment at data cutoff

[a]Less than 1% includes indeterminate tumor cell PD-L1 expression. [b]During concurrent randomization period. [c]Includes patients concurrently randomized to chemo vs NIVO + IPI (October 2016-June 2018) and to NIVO + chemo (April 2017-April 2019). [d]XELOX: oxaliplatin 130 mg/m² IV (day 1) and capecitabine 1000 mg/m² orally twice daily (days 1-14); FOLFOX: oxaliplatin 85 mg/m², leucovorin 400 mg/m², and FU 400 mg/m² IV (day 1) and FU 1200 mg/m² IV daily (days 1-2). [e]Until documented disease progression (unless consented to treatment beyond progression for NIVO + chemo or NIVO + IPI), discontinuation due to toxicity, withdrawal of consent, or study end. NIVO is given for a maximum of 2 years. [f]BICR assessed. BICR, blinded independent central review; CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; FU, fluorouracil; ORR, objective response rate; PD-L1, programmed death ligand 1; Q × W, every × weeks; R, randomization; ROW, rest of world.

### PD-L1 CPS ≥ 5




| | NIVO + chemo (n = 473) | Chemo (n = 482) |
|---|---|---|
| Median OS,[a] mo | 14.4 | 11.1 |
| 95% CI | 13.1-16.2 | 10.1-12.1 |
| HR (95% CI) | 0.71 (0.61-0.81) | |

**Improvement in PFS and OS in PDL1 CPS ≥ 5**



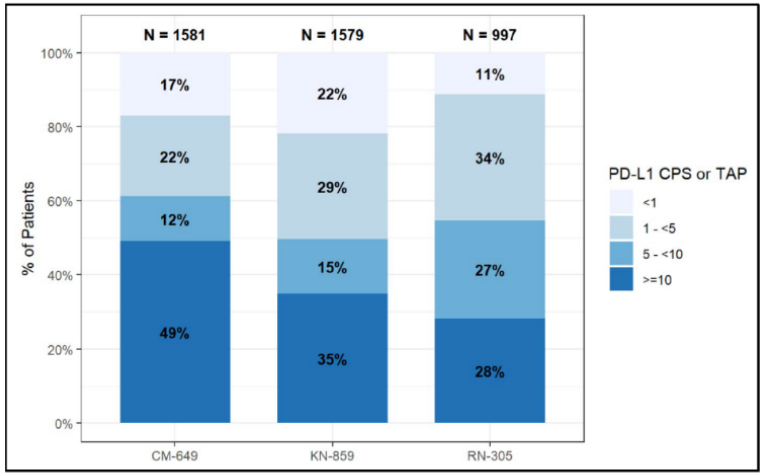
Janjigian Y Y, et al. Presented at the American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium; January 23–25, 2025; San Francisco, CA and Online

# Data from pivotal Phase III trials: EMA approved therapy

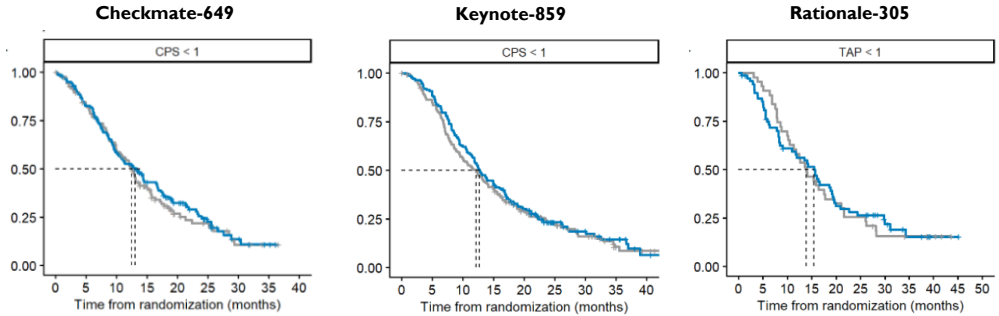
## How do we choose a candidate for IO in 1st line?
## PD-L1 CPS as biomarker

## Efficacy in PD-L1<1

Figure 4: PD-L1 Distribution Across Studies (FDA Analysis)




Abbreviations: CM-649: CheckMate-649; CPS: Combined Positive Score; KN-859: KEYNOTE-859; PD-L1: Programmed Death Ligand-1; TAP: Tumor Area Positivity. Note: 20 patients with missing PD-L1 status in Study CM-649 were not included in this figure.

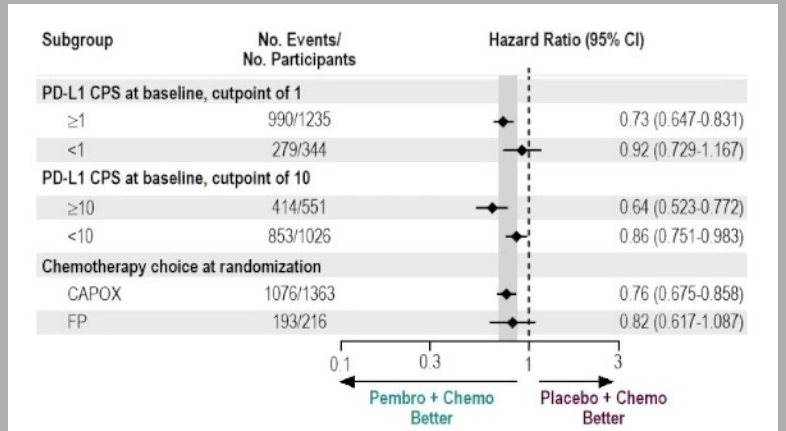



**No benefit in PDL1 < 1 patients**

# Data from pivotal Phase III trials: EMA approved therapy

## How do we choose a candidate for IO in 1st line?
## PD-L1 CPS as biomarker

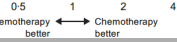
### KN-859




HR: 0.78 ⇒ 0.73 ⇒ 0.64
CPS: All ⇒ ≥ 1 ⇒ ≥ 10

### CM-649

| Population* | Median overall survival, months | | Unstratified hazard ratio for death (95% CI) | Interaction test p value |
|---|---|---|---|---|
| | Nivolumab plus chemotherapy | Chemotherapy | | |
| **Overall** (N=1581) | 13·8 | 11·6 | 0·79 (0·70–0·89) | |
| **PD-L1 CPS <1** (n=265) | 13·1 | 12·5 | 0·92 (0·70–1·23) | |
| **PD-L1 CPS ≥1** (n=1296) | 14·0 | 11·3 | 0·76 (0·67–0·87) | 0·2041 |
| **PD-L1 CPS <5** (n=606) | 12·4 | 12·3 | 0·94 (0·78–1·13) | |
| **PD-L1 CPS ≥5** (n=955) | 14·4 | 11·1 | 0·70 (0·60–0·81) | 0·0107† |



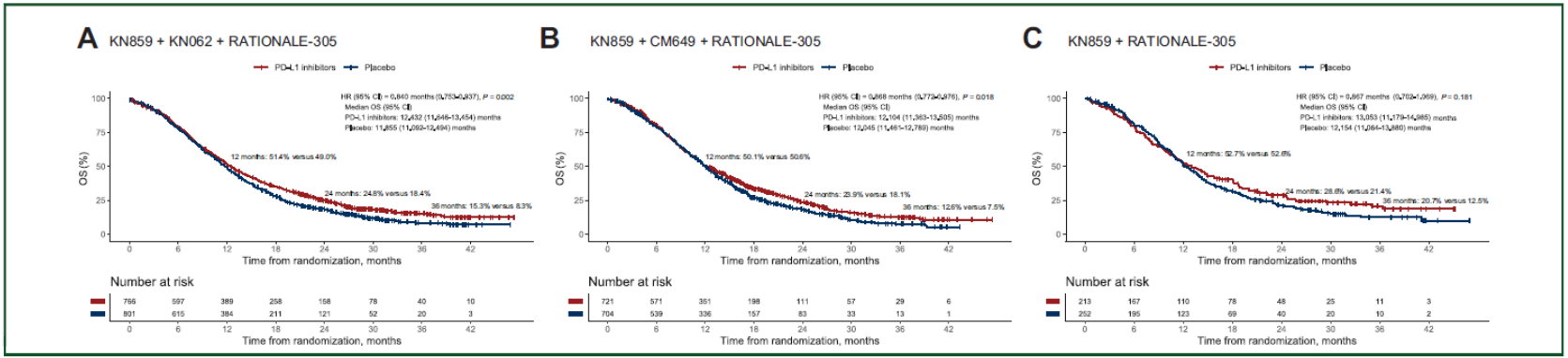

HR: 0.79 ⇒ 0.76 ⇒ 0.70
CPS: All ⇒ ≥ 1 ⇒ ≥ 5

## Magnitude of benefit was greater with increasing PD-L1 CPS values

# Data from pivotal Phase III trials: EMA approved therapy

## How do we choose a candidate for IO in 1st line?
## PD-L1 CPS as biomarker

CPS 1-9 | CPS 1-4 | CPS 5-9




PD-L1 low

CPS 1-9: modest OS benefit

CPS 1-4: modest OS benefit

CPS 5-9: no significant OS benefit

PD-L1 high

CPS >=10: Significant OS benefit

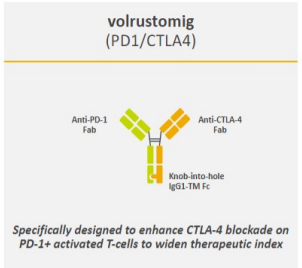
**Further translational research is needed to better select patients who could benefit from immunotherapy in PD-L1low**

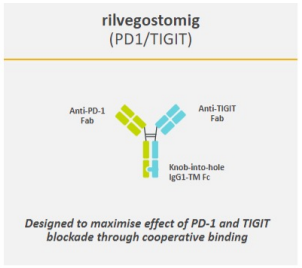
# Future approaches: Immunotherapy

Article | Published: 22 January 2025

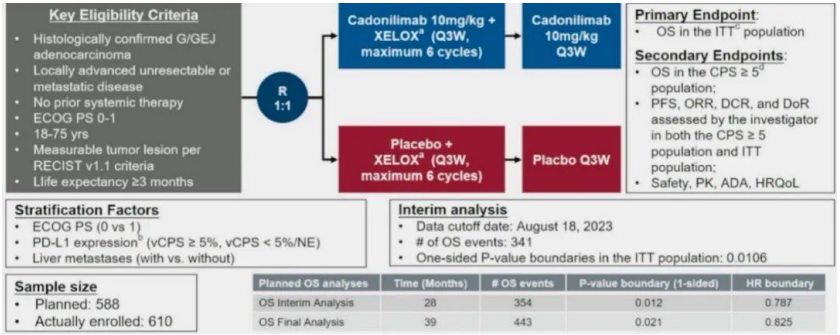
## First-line cadonilimab plus chemotherapy in HER2-negative advanced gastric or gastroesophageal junction adenocarcinoma: a randomized, double-blind, phase 3 trial

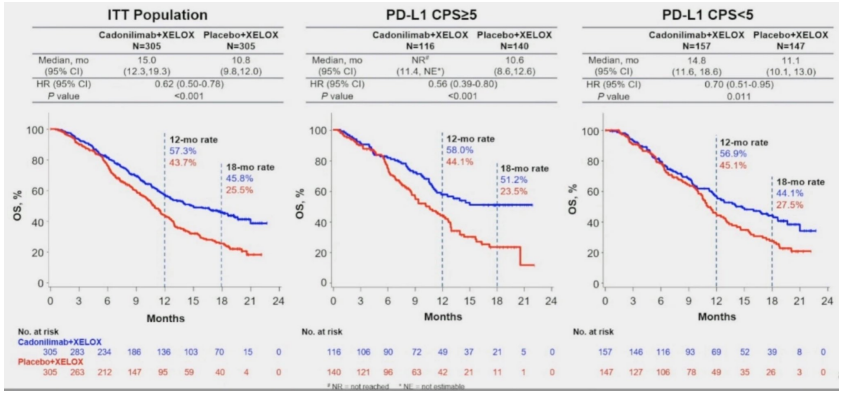
Cadonilimab (PD-1/cytotoxic T lymphocyte antigen-4 (CTLA-4) bispecific antibody)




**AACR 2024 (Plenary) - Cadonilimab plus chemotherapy versus chemotherapy as first-line treatment for unresectable locally advanced or metastatic gastric or gastroesophageal junction (G/GEJ) adenocarcinoma (COMPASSION-15): A randomized, double-blind, phase 3 trial**



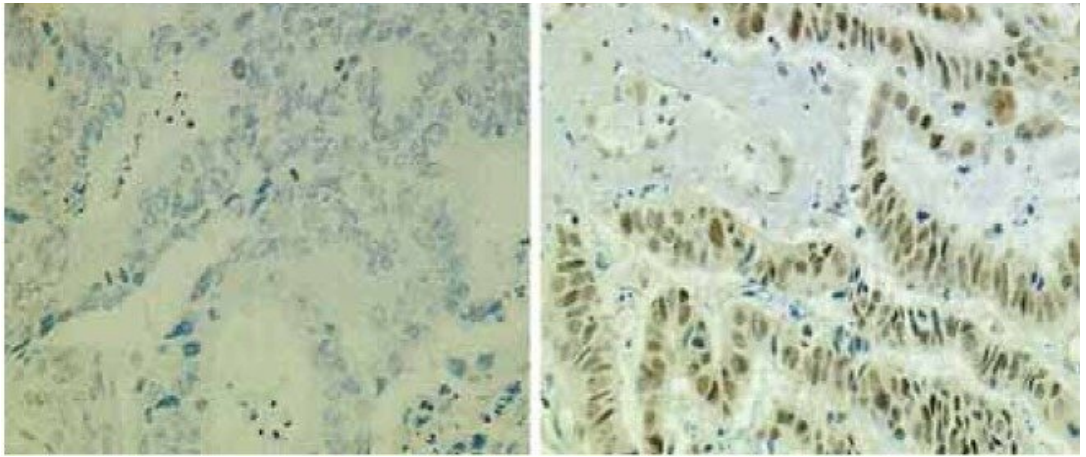




Shen L, et al. Nat Med. 2025 Apr;31(4):1163-1170. doi: 10.1038/s41591-024-03450-4.

# Third stop 📍

## dMMR / MSI-H

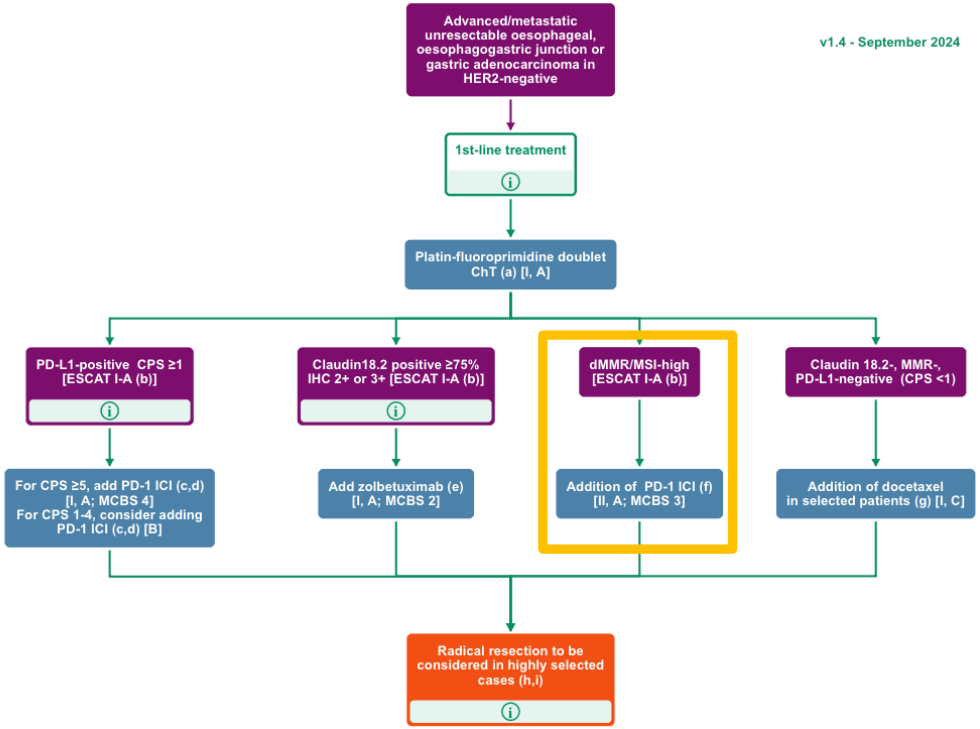
8–22%





Choe WH, et al. Korean J Intern Med. 2005 Jun;20(2):116-22. doi: 10.3904/kjim.2005.20.2.116.

# MSI-H/dMMR: manegement in advanced disease




*"(f) Subgroup analyses from first-line randomised trials…, consistently demonstrate a large benefit if PD-1 ICIs are used first-line for dMMR/MSI-high oesophagogastric cancer.*

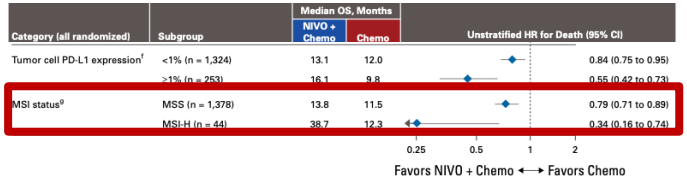
*Whether ChT should be combined with PD-1 or PD-1 ICI should be given alone is an open question. If fast response is needed due to high symptom burden, involvement of vital organs etc., an initial phase of combination therapy should be considered."*

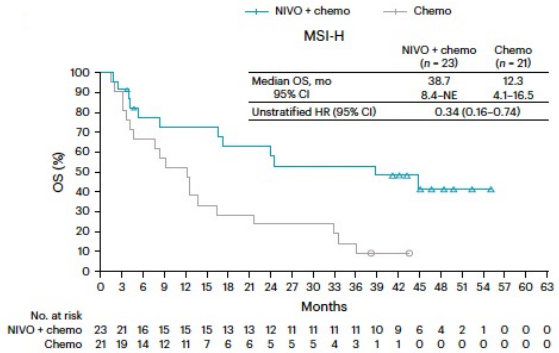
# MSI-H/dMMR: manegement in advanced disease

## Chemo-immunotherapy in metastatic setting

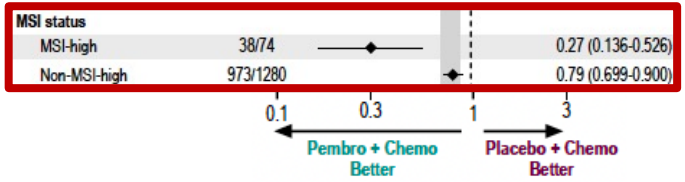
Subgroup analyses from…

### CM649 (1L)

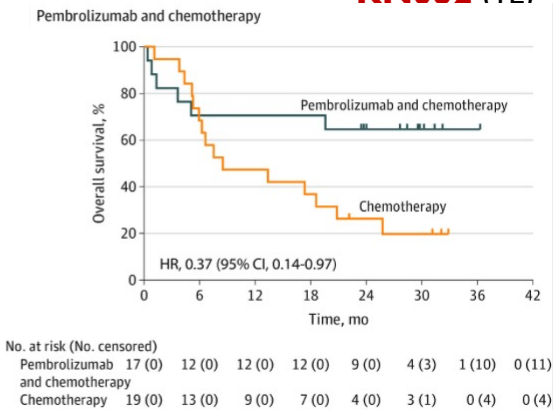



### KN859 (1L)




### KN062 (1L)




Great benefit of adding **IO to Chemotherapy in 1L treatment**

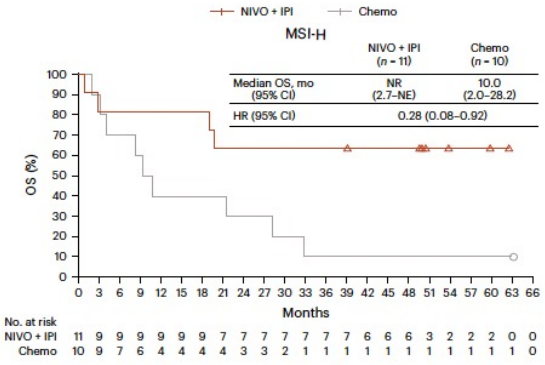
Janjigian YY, et al. J Clin Oncol. 2024 Jun 10;42(17):2012-2020. doi: 10.1200/JCO.23.01601.
Rha SY, et al. Lancet Oncol. 2023 Nov;24(11):1181-1195. doi: 10.1016/S1470-2045(24)00650-8. PMID: 37875143.
Shitara K, et at. JAMA Oncol. 2020 Oct 1;6(10):1571-1580. doi: 10.1001/jamaoncol.2020.3370.

# MSI-H/dMMR: manegement in advanced disease

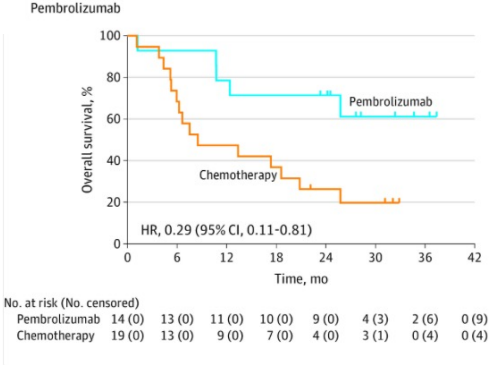
## Immunotherapy in metastatic setting

Subgroup analyses from…

### CM649 (1L)




### KN062 (1L)




**IO mono or IO-combo feasible option in 1L or pretreated MSI/dMMR gastric cancer**

### KN158 (>1L)

| Tumor Type | No. | CR, No. | PR, No. | ORR, % (95% CI) | Median PFS, Months (95% CI) | Median OS, Months (95% CI) | Median DOR, Months (range) |
|---|---|---|---|---|---|---|---|
| Endometrial | 49 | 8 | 20 | 57.1 (42.2 to 71.2) | 25.7 (4.9 to NR) | NR (27.2 to NR) | NR (2.9 to 27.0+) |
| Gastric | 24 | 4 | 7 | 45.8 (25.6 to 67.2) | 11.0 (2.1 to NR) | NR (7.2 to NR) | NR (6.3 to 28.4+) |
| Cholangiocarcinoma | 22 | 2 | 7 | 40.9 (20.7 to 63.6) | 4.2 (2.1 to NR) | 24.3 (6.5 to NR) | NR (4.1+ to 24.9+) |
| Pancreatic | 22 | 1 | 3 | 18.2 (5.2 to 40.3) | 2.1 (1.9 to 3.4) | 4.0 (2.1 to 9.8) | 13.4 (8.1 to 16.0+) |
| Small intestine | 19 | 3 | 5 | 42.1 (20.3 to 66.5) | 9.2 (2.3 to NR) | NR (10.6 to NR) | NR (4.3+ to 31.3+) |
| Ovarian | 15 | 3 | 2 | 33.3 (11.8 to 61.6) | 2.3 (1.9 to 6.2) | NR (3.8 to NR) | NR (4.2 to 20.7+) |
| Brain | 13 | 0 | 0 | 0.0 (0.0 to 24.7) | 1.1 (0.7 to 2.1) | 5.6 (1.5 to 16.2) | – |

…

**NO LIMIT** (1L)
**KN061** (2L)
**KN059** (3L)

Janjigian YY, et al. J Clin Oncol. 2024 Jun 10;42(17):2012-2020. doi: 10.1200/JCO.23.01601. Shitara K, et al. JAMA Oncol. 2020 Oct 1;6(10):1571-1580. doi: 10.1001/jamaoncol.2020.3370
Marabelle A, et al. J Clin Oncol. 2020 Jan 1;38(1):1-10. doi: 10.1200/JCO.19.02105. Shitara K, et al. Nat Med. 2025 Mar 7. doi: 10.1038/s41591-025-03575-0.

# MSI-H/dMMR: manegement in advanced disease

## Chemo-immunotherapy vs IO-mono vs IO-combo in metastatic setting

**Patient features**
Age
Comorbidities
Patient`s preferences

**Disease features**
Volume of disease
Ascites
Disease heterogeinity

**Objectives**
Time to response
Toxicity manegement
QoL

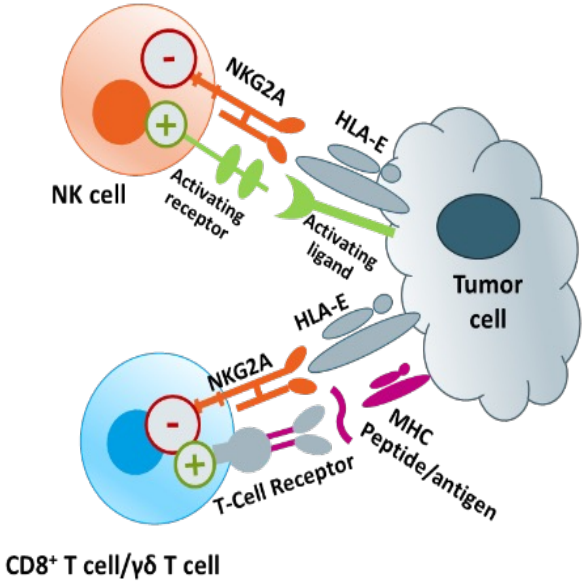
**Reinbursment issues**
FDA, EMA...



Chao J, et al. JAMA Oncol. 2021 Jun 1;7(6):895-902. doi: 10.1001/jamaoncol.2021.0275.

# MSI-H/dMMR: manegement in advanced disease

## New treatment approaches in dMMR/MSI-H GEA




## CL1-95029-002

Ph 1b/2 trial investigating the safety, tolerability, and antitumor activity of **S095029 (anti-NKG2A antibody) + pembrolizumab** in unresectable/metastatic MSI-H/dMMR gastroesophageal junction /gastric cancer.

**S095029**-mechanism of action: blockade of HLA-E interaction with NKG2A/CD94 which releases the breaks on various immune cell subsets.

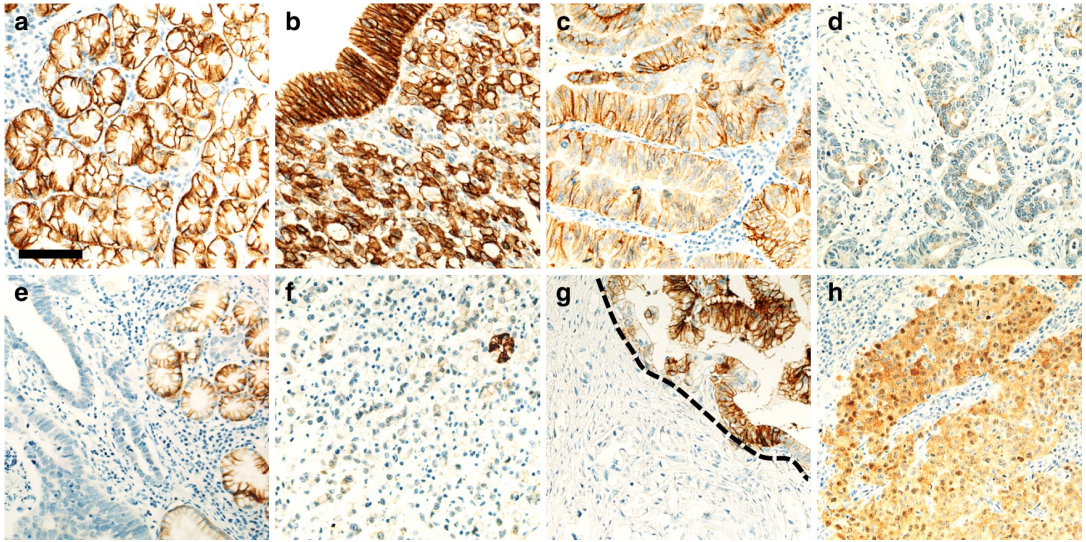
**NOW RECRUITING!**
**3pts ongoing

**Chemo-free option with good safety profile!**

# Forth stop 📍

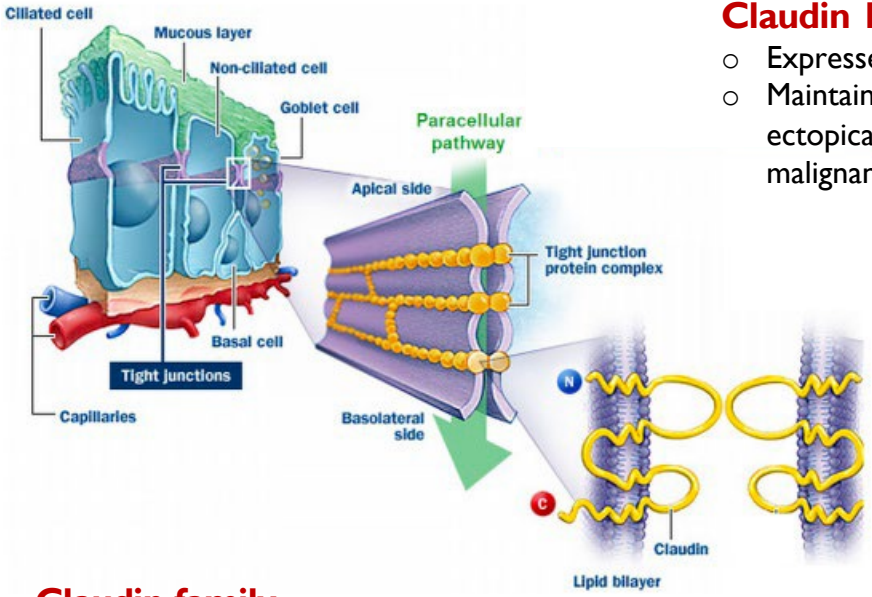
# CLDN-18.2

30–40%




Coati I, et al. Br J Cancer. 2019 Jul;121(3):257-263. doi: 10.1038/s41416-019-0508-4.

# CLDN-18.2: a novel therapeutic target

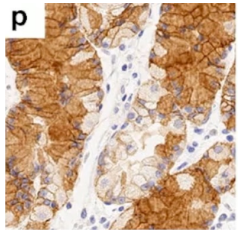



## Claudin family

- Member proteins in tight junctions.
- Fence function and regulation of permeability.

## Claudin 18 isoform 2 (CLDN 18.2)

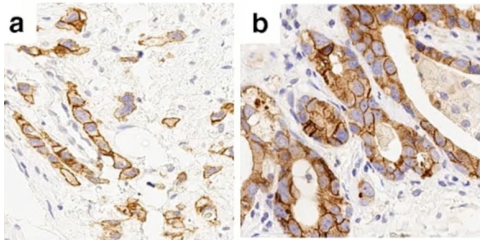
- Expressed ONLY in stomach mucosa.
- Maintained in GC/GEJ cancer and ectopically expressed in other malignancies (PDAC, etc.).




Normal stomach

Apical side of tight junctions

Celular Surface

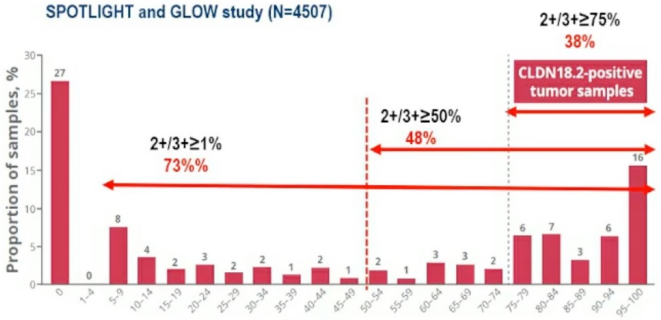



Gastric adenocarcinoma



Deliv Rev 2021: Tsukita S, et al. Trends Biochem Sci 2019: Zihni C, et al. Nat Rev Mol Cell Biol, 2016; Kyuno D, et al. Tissue Barriers 2022.

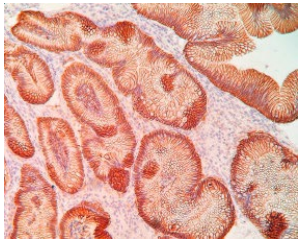
# CLDN-18.2: a novel therapeutic target

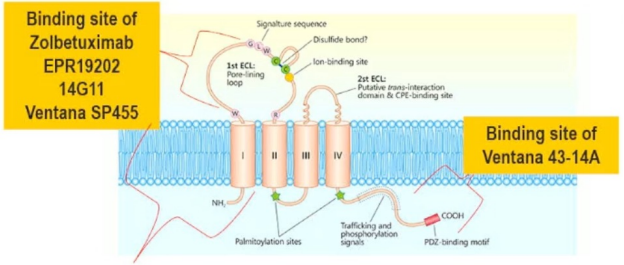



## CLDN-18.2 in GC/GEJC

- 25~40% with high expression (>75% with 2/3+).
- Low incidence of low CLDN expression.

**CLDN18 (43-14A)** Leipzig Lab recognize both 18.1 and 18.2






CLDN18 (43-14A) less specific but more sensitive (compared to EPR19202/ab222512)

Prof. Dr. Ugur Sahin, Dr. Özlem Türeci and Prof. Dr. Christoph Huber. **GERMAN AWARD 2021**

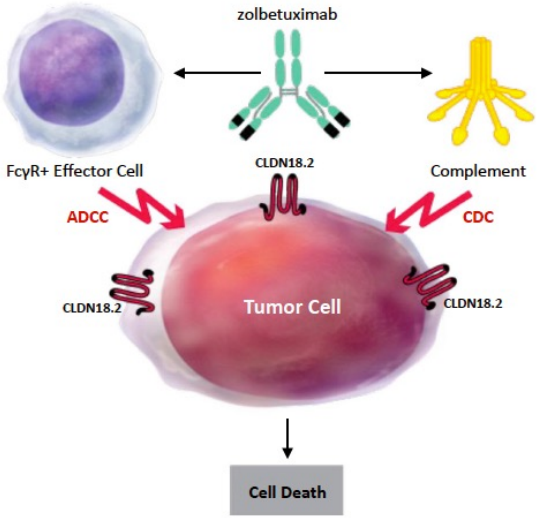


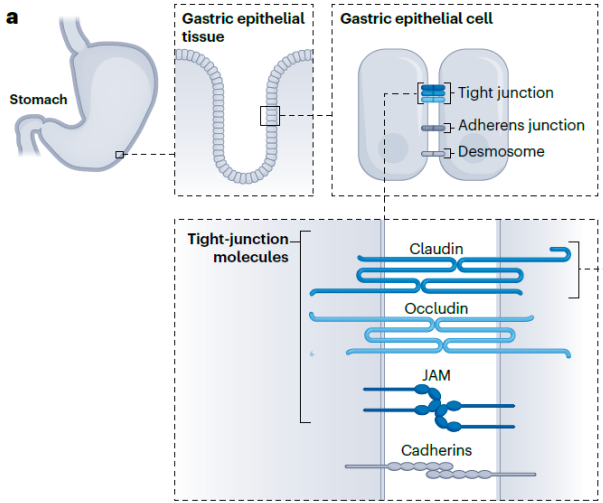
Konnno H, et al. Cancer Res Com 2022; Arnold A, et al. Clinical and Translational Oncology 2020.

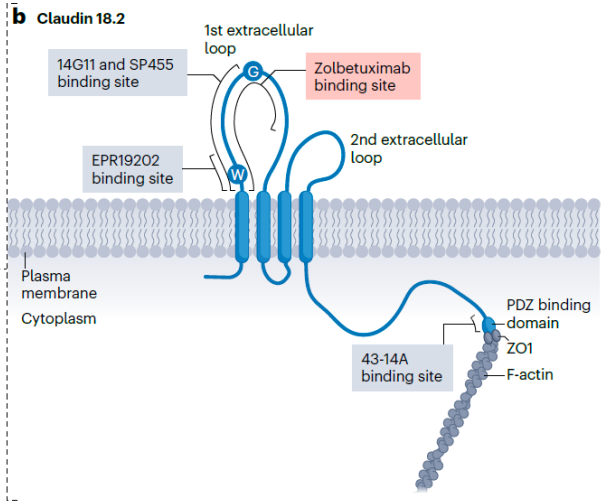
# Zolbetuximab – CLDN-18.2 directed monoclonal antibody

## Mechanism of Action of Zolbetuximab

Chimeric IgG1 antibody
Minimal apoptosis induction upon cross linking and proliferation inhibition
Strong ADCC/CDC for CLDN+ tumor cells




1. Pro-Inflammatory and Chemoattractant Environment.
2. Cross presentation by APCs.
3. T Cell Infiltration.
4. Induction of Adaptive T cell immunity.



Sahin U et al. Ann Oncol. 2021 May;32(5):609-619.Nakayamaal et al. Nat Rev Clin Oncol. 2024 Mar 19.

# Zolbetuximab – CLDN-18.2 directed monoclonal antibody

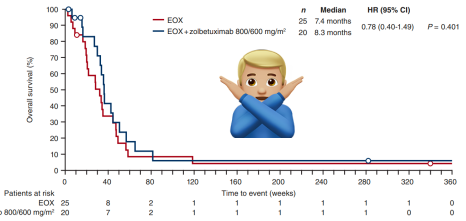
**Clinical trials of Zolbetuximab for CLDN 18.2+ GC**

**Ph 1/2 MONO** 2/3+ ≥50% (later lines)
Modest single agent activity ≈ 10% ORR
GI toxicities were common: Nausea, vomiting…
Less GI toxicity after gastrectomy

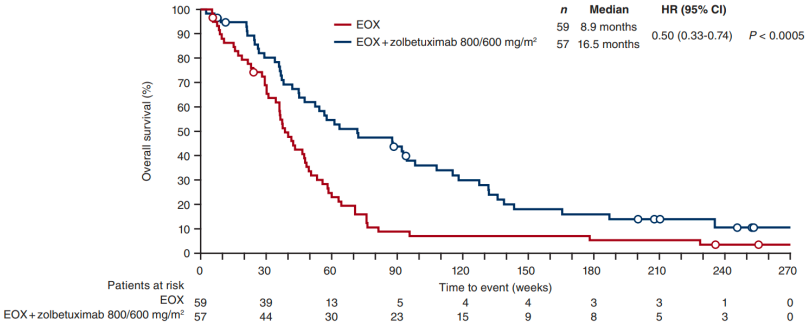
**rPh 2 FAST** 2/3+ ≥40% (1st line)
PFS/OS benefit combined with chemo
Enriched benefit in CLDN >70%

## FAST - Ph II study of Zolbetuximab

CLDN18.2+ 40-69% of tumor cells




**CLDN18.2+ ≥ 70% of tumor cells**

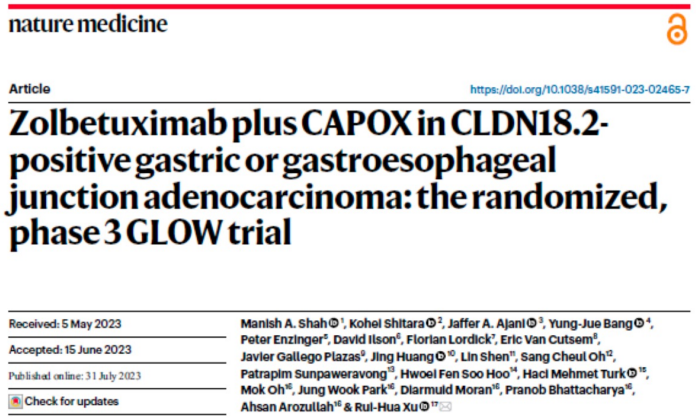





Sahin U, et al. EJC 2018: Türeai O, et al. Ann Oncol 2019; Sahin U, et al. Ann Oncol 2021.

# Zolbetuximab – CLDN-18.2 directed monoclonal antibody

## GLOW and SPOTLIGHT - Ph 3 studies of Zolbetuximab



nature medicine

Article

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

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

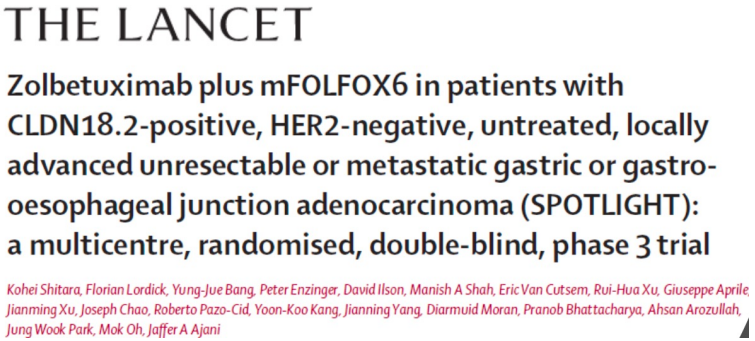
Received: 5 May 2023

Accepted: 15 June 2023

Published online: 31 July 2023

Check for updates

Manish A. Shah[1], Kohei Shitara[2], Jaffer A. Ajani[3], Yung-Jue Bang[4], Peter Enzinger[5], David Ilson[6], Florian Lordick[7], Eric Van Cutsem[8], Javier Gallego Plazas[9], Jing Huang[10], Lin Shen[11], Sang Cheul Oh[12], Patrapim Sunpaweravong[13], Hwoei Fen Soo Hoo[14], Haci Mehmet Turk[15], Mok Oh[16], Jung Wook Park[16], Diarmuid Moran[16], Pranob Bhattacharya[16], Ahsan Arozullah[16] & Rui-Hua Xu[17]



THE LANCET

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

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

**GLOW** (CAPOX-Zolbetuximab)

**SPOTLIGHT** (FOLFOX-Zolbetuximab)

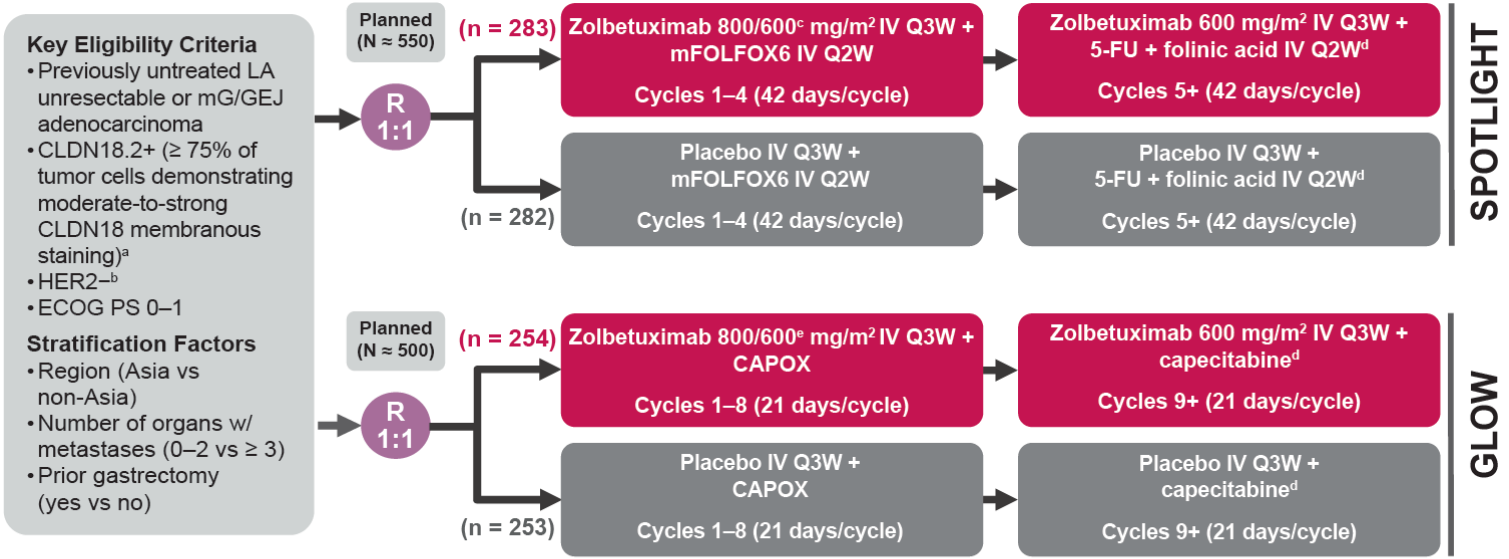
**CLDN18.2+ IHC 2+/3+ in ≥75%**



Shitara K, Lordick F et al. Lancet 2023; Apr 14:S0140-6736(23)00620-7. Shah M, Lordick F et al. Nat Med. 2023 Aug;29(8):2133-2141.

# Zolbetuximab – CLDN-18.2 directed monoclonal antibody

## GLOW and SPOTLIGHT – Combined Data

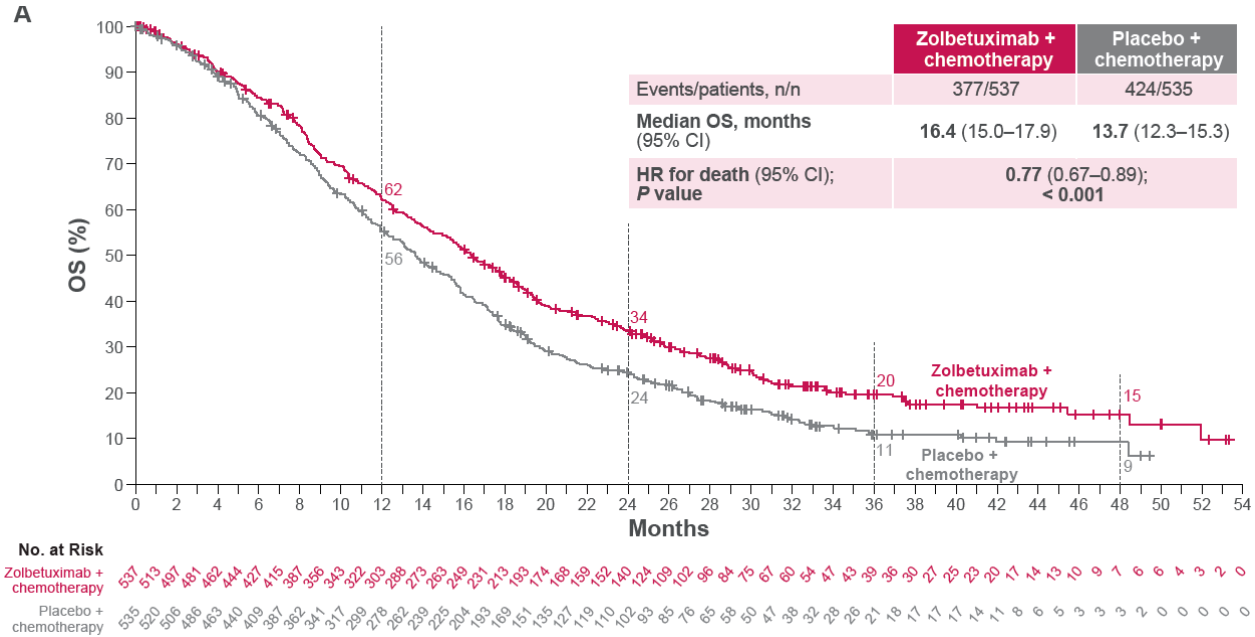



| Primary Endpoint | Key Secondary Endpoints | Secondary Endpoints[g] |
|---|---|---|
| • PFS[f] | • OS<br>• TTCD in GHS/QoL, PF, and OG25-Pain | • ORR[f]<br>• DOR[f]<br>• Safety<br>• PROs |

ESMO2024. Y. Kang, et al. Annals of Oncology (2024) 35 (suppl_2): S878-S912. 10.1016/annonc/annonc1603.

# Zolbetuximab – CLDN-18.2 directed monoclonal antibody

## GLOW and SPOTLIGHT – Combined Data




| | Zolbetuximab + chemotherapy | Placebo + chemotherapy |
|---|---|---|
| Events/patients, n/n | 377/537 | 424/535 |
| Median OS, months (95% CI) | **16.4** (15.0–17.9) | **13.7** (12.3–15.3) |
| HR for death (95% CI); *P* value | **0.77** (0.67–0.89); **< 0.001** | |

**Improvement of PFS and OS in both studies**

**Approved**

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

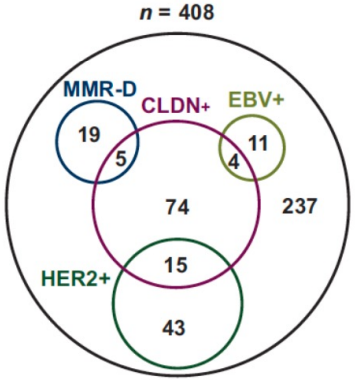
FDA

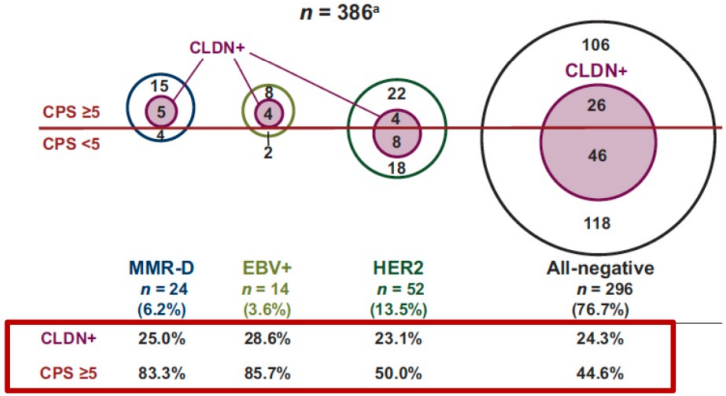
VHIO Vall d'Hebron Instituto de Oncología

Vall d'Hebron Barcelona Campus Hospitalari

# Today and tomorrow. Current limitations and future perspectives (CLDN-18.2)

## CLDN-18.2 could be a target regardless of the molecular subtype




| | MMR-D n = 24 (6.2%) | EBV+ n = 14 (3.6%) | HER2 n = 52 (13.5%) | All-negative n = 296 (76.7%) |
|---|---|---|---|---|
| CLDN+ | 25.0% | 28.6% | 23.1% | 24.3% |
| CPS ≥5 | 83.3% | 85.7% | 50.0% | 44.6% |

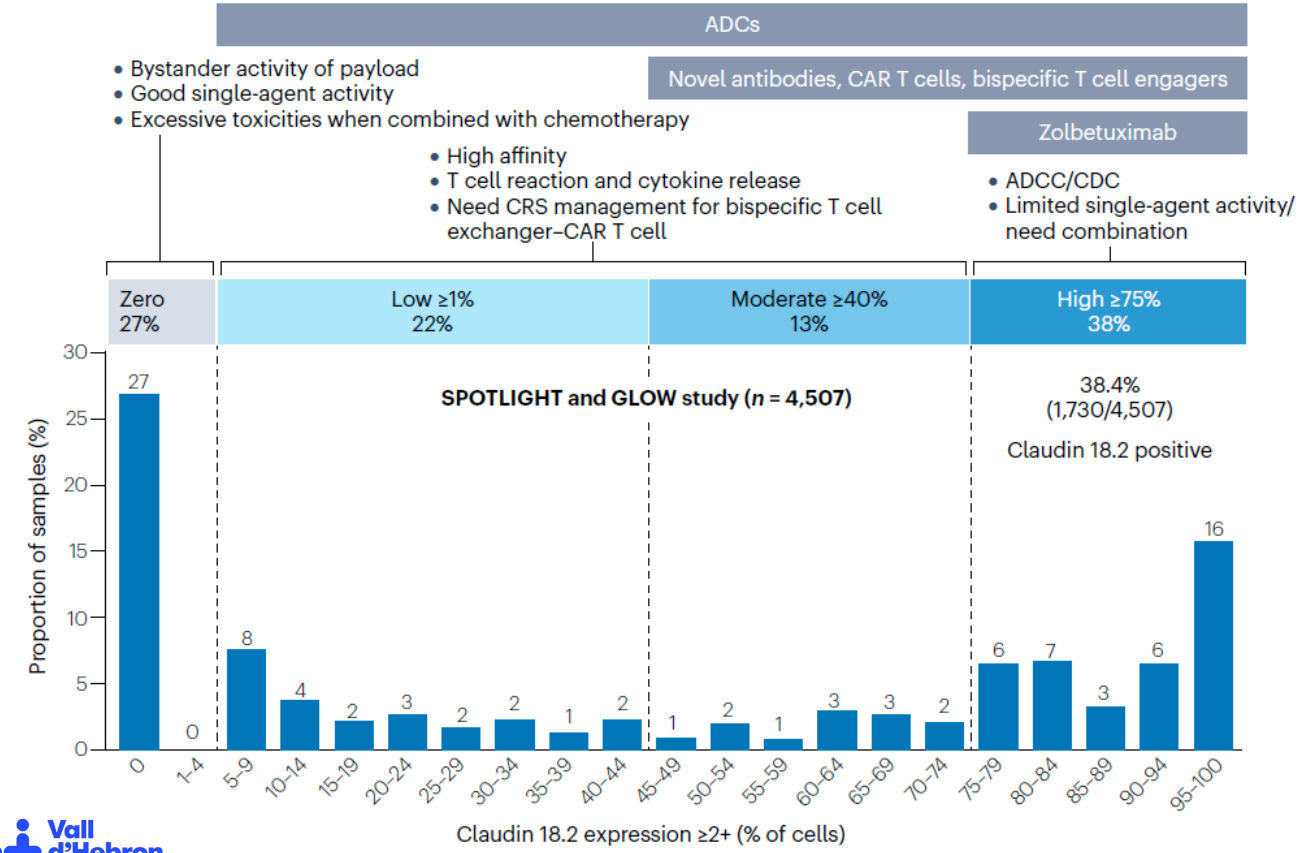
Almost **equal distribution of moderate-to-high CLDN 18.2 expression (≥ 75%)** in **all molecular subtypes (24%)**

**Claudin 18.2 expression in gastroesophageal adenocarcinoma: biomarker overlap and association with immunotherapy outcomes – a multicenter study**

**Authors:** E. Terán[1], C. Blanco[2], M. Reboredo[3], L. Visa[4], A. Calvo[5], A. López[6], R. Vidal[7], C. Agra[8], I. Alés[9], S. Foti[10], B. Paredes[11], L. Fornaro[12], T. Sauri[13], E. Martínez[14], J. Martínez[15], L. Caritá[16], S. Landolfi[17], D. Acosta[1], T. Tian[18] and T. Macarulla[1].


Kubota, Y., et al. "Comprehensive clinical and molecular characterization of claudin 18.2 expression in advanced gastric or gastroesophageal junction cancer."ESMO open8.1 (2023): 100762.

# Today and tomorrow. Current limitations and future perspectives (CLDN-18.2)



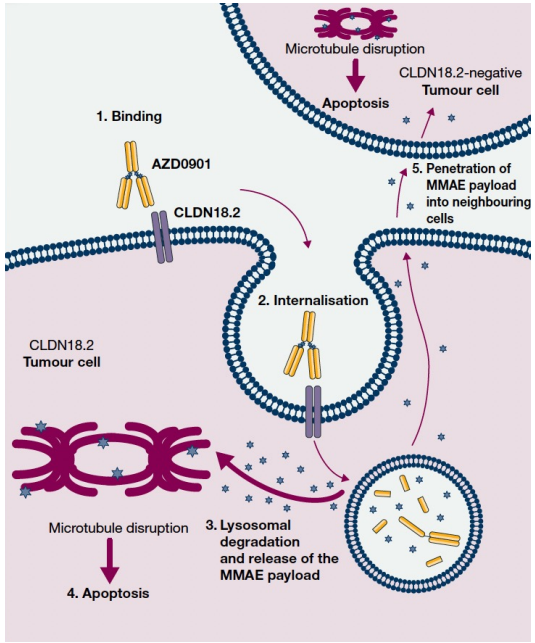

**Redefine CLDN cut-off?**

**CLNDlow?**

Nakayamal et al. Nat Rev Clin Oncol. 2024 Mar 19.

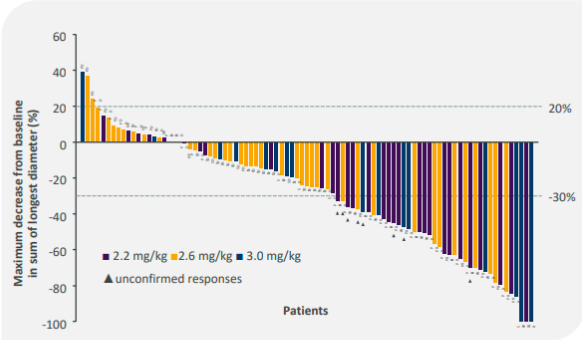
# Today and tomorrow. Current limitations and future perspectives (CLDN-18.2)

## CLDN-18.2 – Antibody-drug-conjugate




**AZD0901** is a potential first-in-class CLDN18.2-targeted antibody-drug conjugate (ADC) carrying monomethyl auristatin E (MMAE).

**Robust ORR of 48% in 2.2 mg/kg cohort**




**Promising efficacy** and manageable safety
Ph I **GC/GEJC**

**Cut-off ≥ 25%**

**ONGOING**

**CLARITY-Gastric01 // Ph 3**
2/3L GC/GEJC CLDN18.2 +
**CLARITY-PanTumor01 // Ph1/2:**
1L PDAC /2L+GC/GEJC CLDN18.2+
**GEMINI-SS4 // Ph2**
1L GC/GEJC CLDN18.2 +

Zhang Q et al, Abstract 4019 presented at American Society of Clinical Oncology 2024. K. Shitara, et al. 495TiP - CLARITY-Gastric 01. Annals of Oncology (2024) 35 (suppl_1): S162-S204. 10.1016/annonc/annonc1482. Alexander G, et al. CLARITY-PanTumor01: Journal of Clinical Oncology https://doi.org/10.1200/JCO.2024.42.16_suppl.TPS3163.

# New biomarkers on the horizon

# New biomarkers on the horizon: FGFR2b

- FGFR2 amplifications, leading to overexpression of FGFR2b epithelial splice variant, occurs in **20-30%** of GC/EGJ, and are associated with more advanced stage and **poor prognosis**[1]
- **Bemarituzumab:** monoclonal Ab that inhibits FGFR2b

## Phase II FIGHT trial

**Key Eligibility Criteria**

- No prior therapy for unresectable, locally advanced or metastatic gastric/GEJ adenocarcinoma
- RECIST v1.1 evaluable disease
- FGFR2b overexpression and/or *FGFR2* gene amplification
- Not HER2-positive

**Stratification Factors**

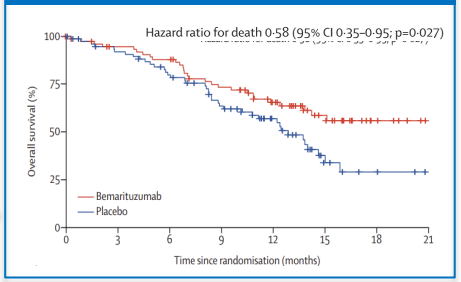
- Geographic region
- Single dose of FOLFOX while screening
- Prior perioperative chemotherapy

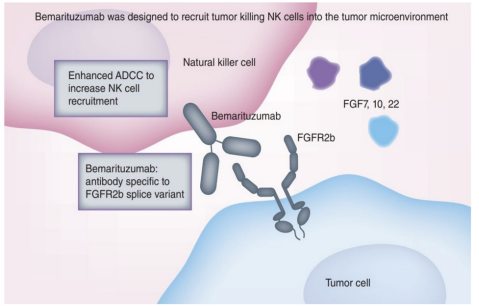
Randomization 1:1

- Bemarituzumab* + mFOLFOX6 (n = 77)
- vs
- Placebo + mFOLFOX6 (n = 78)

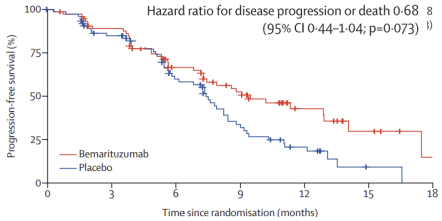
Treatment may continue until progression, unacceptable toxicity, or the patient meets other withdrawal criteria

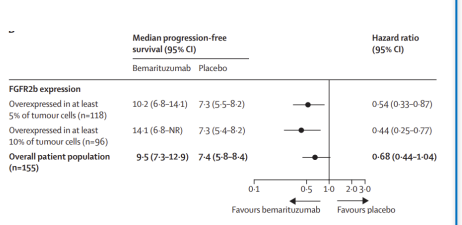
## OS (2º EP)




## PFS (1º EP)




**Phase 2/3 clinical trials of Bemarituzumab in GC/GEJ (1L)**

- Previously untreated, advanced GC/GEJ
- HER2 non-positive
- FGFR2b overexpression (IHC 2/3+ ≥10% of TC)

→ **FORTITUDE-101 TRIAL:** mFOLFOX6 +- Bemarituzumab

→ **FORTITUDE-102 TRIAL:** mFOLFOX6+Nivolumab +- Bemarituzumab

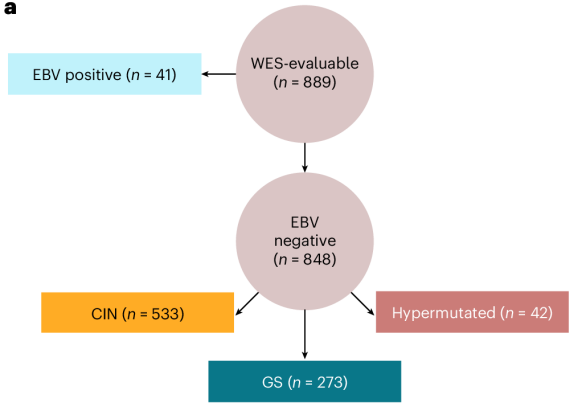
*Pending results*



Su, X. et al. Br. J. Cancer 110, 967–975 (2014

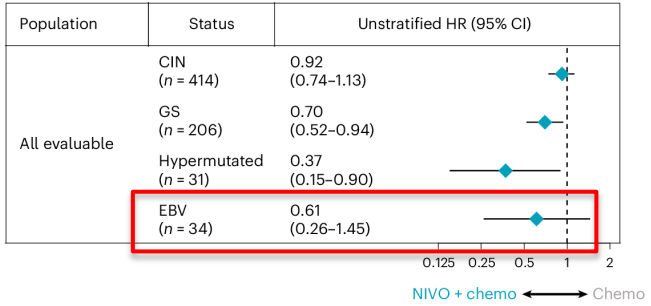
# New biomarkers on the horizon: EBV

**a**

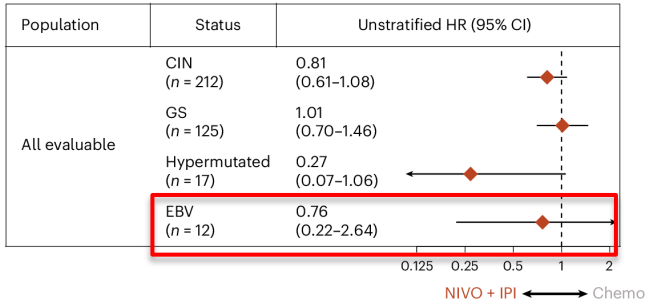



| WES cluster, n (%) | CIN | GS | Hypermutated | EBV | Total |
|---|---|---|---|---|---|
| MSS | 528 (63) | 271 (32) | 5 (1) | 40 (5) | 844 (100) |
| MSI-H | 3 (7) | 0 (0) | 37 (90) | 1 (2) | 41 (100) |
| NA | 2 (50) | 2 (50) | 0 (0) | 0 (0) | 4 (100) |
| Total | 533 (60) | 273 (31) | 42 (5) | 41 (5) | 889 (100) |

**c**

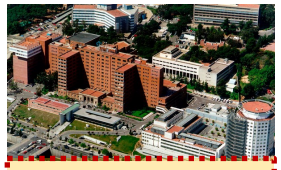



**d**




**<5% GC**

*ARID1A*, *PIK3CA* and *AR* genes more frequently in **EBV-positive GC**



**8 patients treated with IO**
**50% ORR**

**EBV derive benefit from IO. Lack of prospective data.**



Shitara, K et al Nat Med (2025)

# Take-home messages

**Gastroesophageal cancer diagnosis**

Biopsy!
Biopsy!!
Biopsy!!!

**Think about heterogeneity, several biomarkers, clinical trials, NGS…**

**Know your opponent's weaknesses**

- MMR/MSI
- HER2
- PDL1
- CLDN-18.2

**Validated biomarkers**

**Choose your weapons**

* Consider clinical trial

**CT doublet PF**

+

**Target treatment**

**Preferences**
**Experience**
**Safety profile**
**Flexibility**

**Set your goals**

=

**Extend survival**
**Symptom control**
**Quality of life**

**Personalized medicine**

**TREAT PATIENTS, NOT TUMORS!**

**Predict treatment response**
**Minimize side effects**
**Optimize resources**

# Thanks for your attention
# Any questions?


eduardoteran@vhio.net
eduardo.teran.brage@gmail.com

@EduardoTB94