III JORNADA TRASLACIONAL DE ONCOLOGÍA DE PRECISIÓN:

A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN

SEVILLA, 12 Y 13 DE FEBRERO DE 2026

NUEVOS ENFOQUES TERAPÉUTICOS EN CÁNCER DIGESTIVO: BRAF, CLAUDINA

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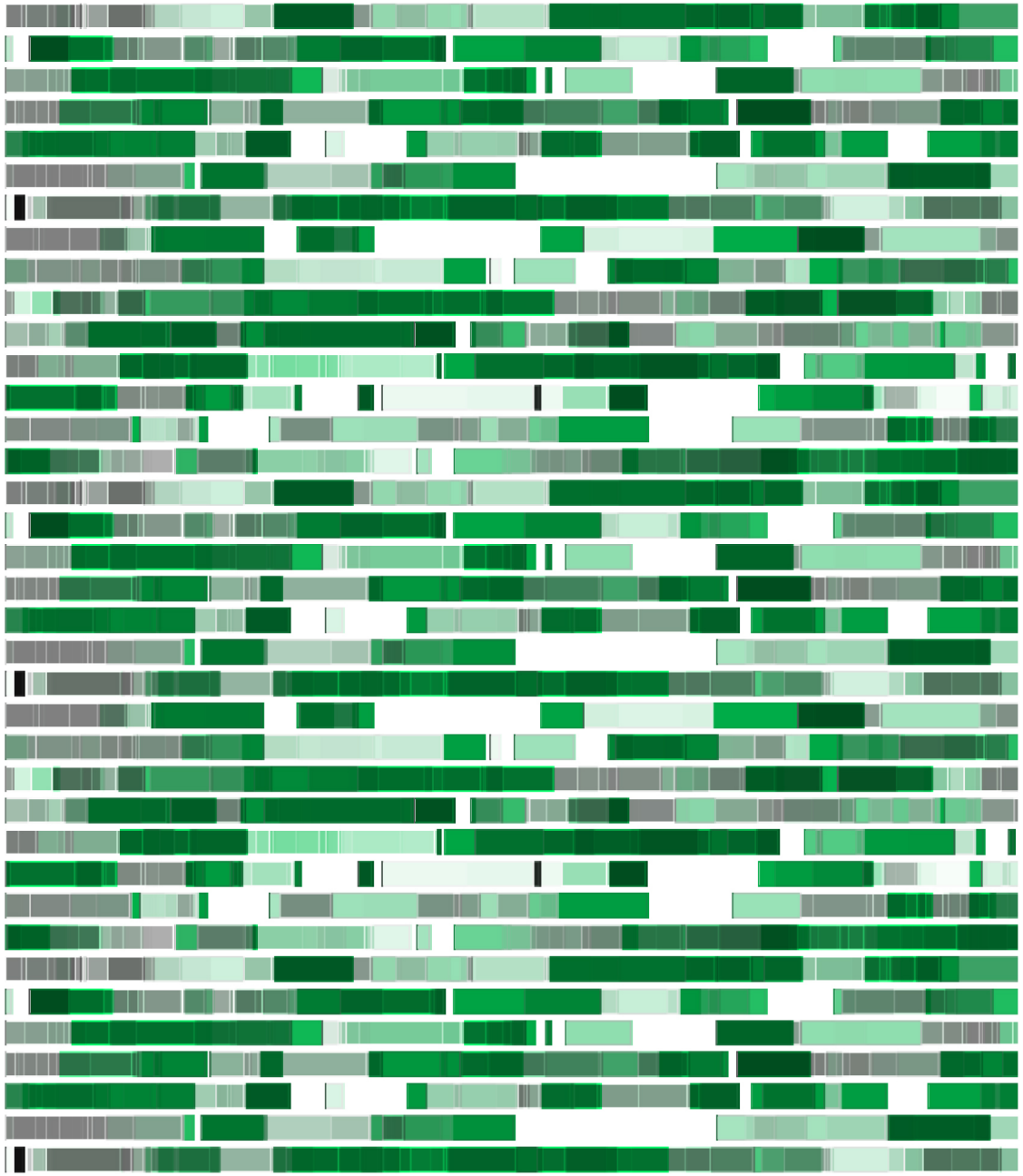
Oncología Médica – Hospital Universitario Virgen del Rocío Sevilla

Organizador por:

HENDERE HEALTHCARE



CONFLICTOS DE INTERES

Contratos de investigación, honorarios personales AMGEN

honorarios de consultoría / asesorías de AMGEN, SERVIER, Merk y SANOFI;

ponencias: MSD, Bristol-Myers y Merck; Takeda; MSD; Pierre-Fabre

apoyo para asistir a reuniones y viajes: Merck, SERVIER y AMGEN

NUEVAS DIANAS:

- **“Oncogenic drivers”: Impulsores oncogénicos:** alteraciones genéticas que causan y mantienen el crecimiento tumoral.

- **Dianas no oncogénicas:** moléculas que no inician el cáncer, pero favorecen la proliferación, supervivencia o evasión inmune del tumor.
  Ej.: **VEGF, PD-L1, TROP2…**

MINISTERIO DE SANIDAD

Castellano | Buscar

Ministerio | Áreas | Prensa y comunicación | Sanidad en datos | Servicios a la Ciudadanía | Participación Pública

Webs temáticas | Sede Electrónic@

HERRAMIENTAS DE ACCESIBILIDAD

> Áreas > Farmacia > Información de medicamentos > Buscadores de medicamentos

> BIFIMED: Buscador de la Información sobre la situación de financiación de los medicamentos - Nomenclátor de FEBRERO - 2026

Quiénes somos

Información de medicamentos

Comisión interministerial de precios

BIFIMED: Buscador de la Información sobre la situación de financiación de los medicamentos - Nomenclátor de FEBRERO - 2026

Cáncer colorrectal (CCRm)

Encorafenib en combinación con cetuximab, está indicado para el tratamiento de pacientes adultos con cáncer colorrectal metastásico con mutación BRAF V600E, que han recibido terapia sistémica previa.

Indicaciones autorizadas

Indicación autorizada	Situación expediente indicación	Resolución expediente de financiación indicación
En combinación con cetuximab, para el tratamiento de pacientes adultos con cáncer colorrectal metastásico con mutación BRAF V600E, que han recibido terapia sistémica previa (ver las secciones 4.4 y 5.1).	Resuelto	No incluida

Código nacional	Principio activo o asociación*	Nombre del medicamento	Situación de financiación	Tipo de medicamento	Más Información
765859	ZOLBETUXIMAB	VYLOY 100 MG POLVO PARA CONCENTRADO PARA SOLUCION PARA PERFUSION, 1 vial	Estudio o sin petición financiación	Biológico Huérfano	⊞

4.1 Indicaciones terapéuticas

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

Indicaciones autorizadas

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

"ONCOGENIC DRIVERS"

- **BRAF V600E**

BRAF V600E MUTATED MCRC

- In GI cancers, the ***BRAF* V600E** (**class-I**) mutation accounts for up to 12% of mCRC and small bowel cancers, 5–7% of cholangiocarcinoma, and 0–3% of gastric, esophageal, neuroendocrine, and ampullary tumors.
- ***BRAF*-V600E** constitutes the 95% of *BRAF* mutations in CRC
  - Old patients, females
  - Right-sided
  - High-grade, mucinous tumors
  - Co-occurrence with MSI (30%), MLH
  - CpG island methylator phenotype
  - Nodal, brain and peritoneal spread

PLOS ONE

Prognostic role of *KRAS* and *BRAF* mutations in stage II/III colorectal cancer

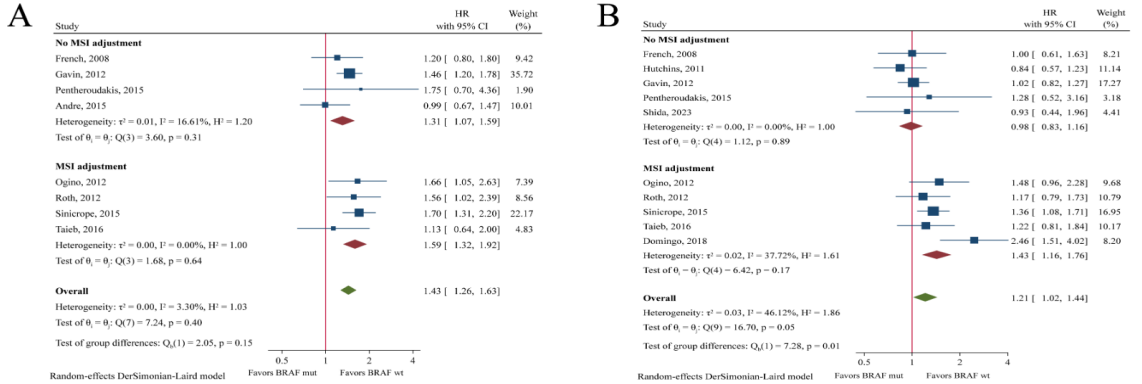
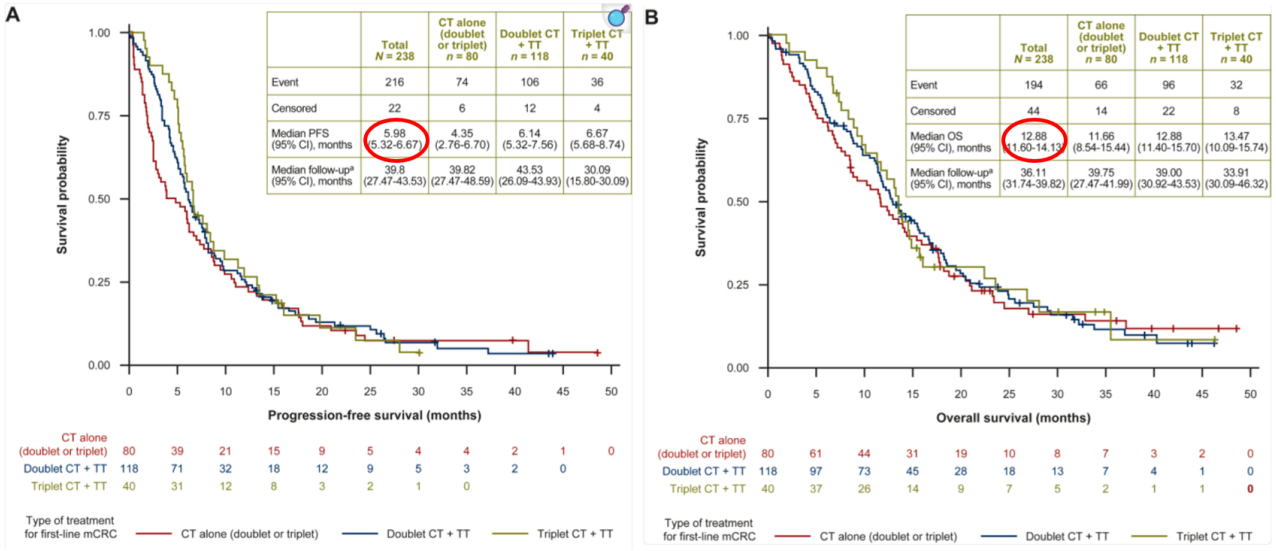


Fig 5. Forest plot of meta-analysis of the association between *BRAF* mutation and overall survival (A) and disease-free survival (B).

https://doi.org/10.1371/journal.pone.0320783.g005

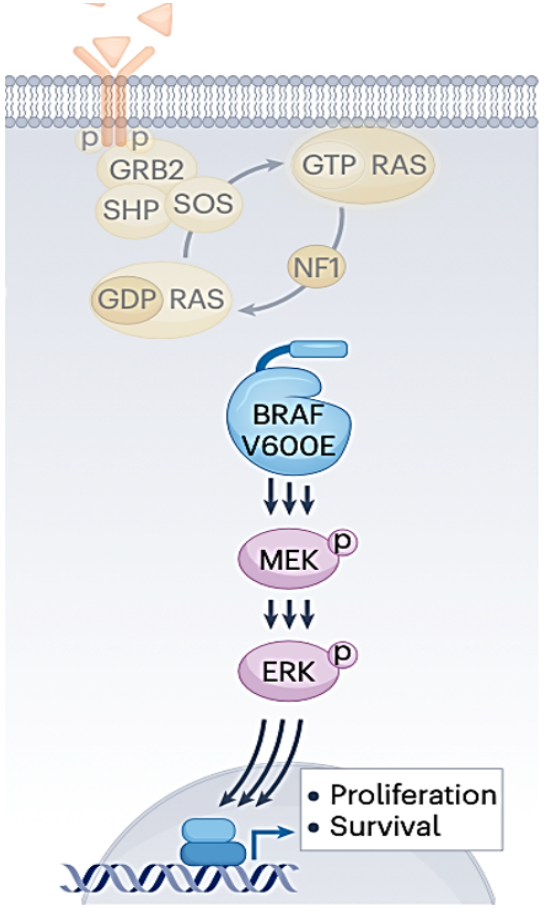


Median duration of first-line treatment was 4.9 months.
Overall, 52.5% received second-line treatment.

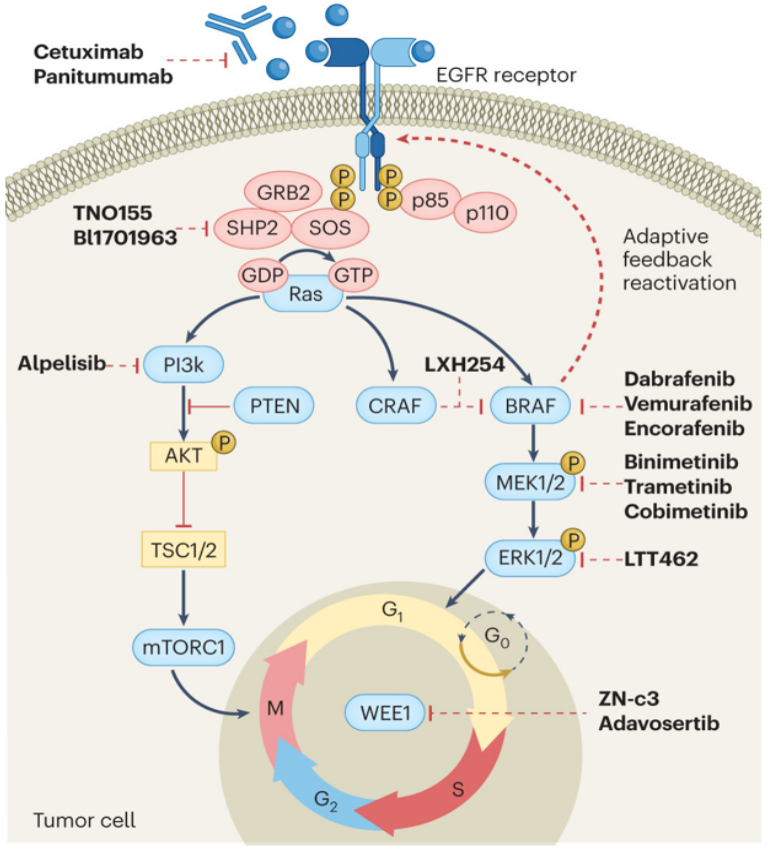
Kaplan–Meier estimates for (A) PFS and (B) OS according to first-line mCRC treatment (*N* = 238).

Martinelli E, Cremolini C, Mazard T, et al. CAPSTAN CRC study. ESMO Open. 2022 Dec;7(6):100603.

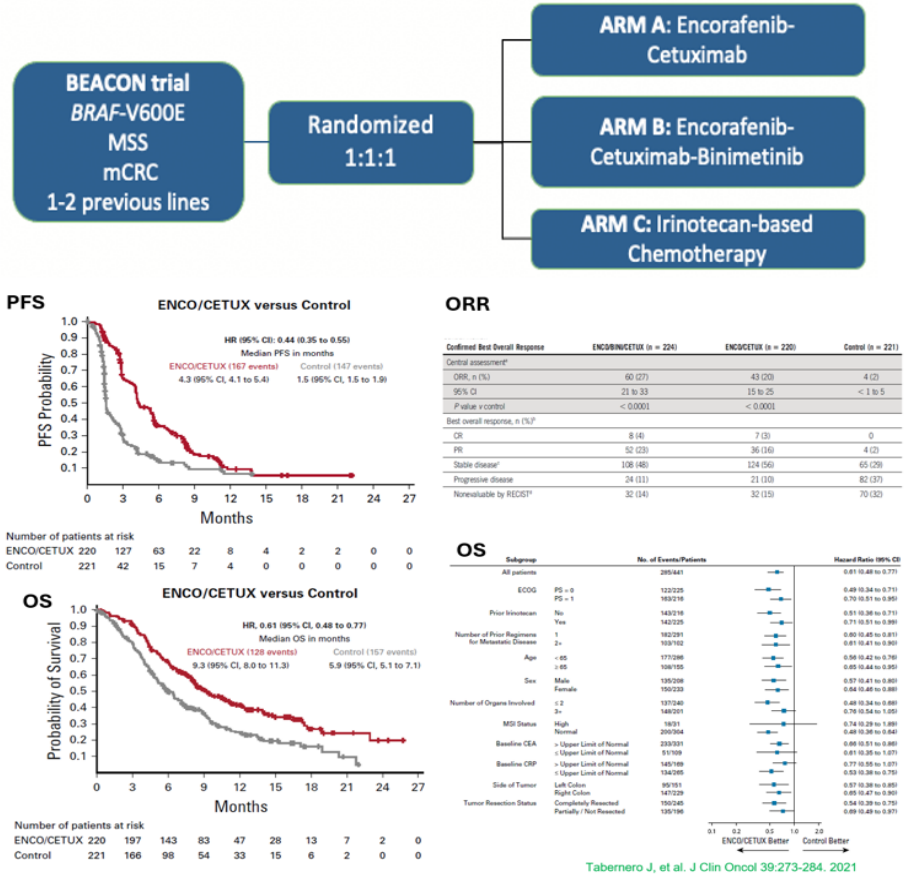
BRAFV600E MUTATED MCRC: TARGETED TREATMENT



Class I BRAF mut (V600E)
Signal as high-activity, RAS-independent monomers under conditions of low RAS activity



Single-agent BRAF inhibition does not achieve clinical benefit because of signal upregulation via the EGFR, and an anti-EGFR treatment should therefore be added.



Tabernero J, et al. J Clin Oncol 39:273-284. 2021

Encorafenib/cetuximab is the standard of care for BRAFV600E mCRC patients after prior therapy **(no reembolsado en España)**

Subbiah V, et al. *CA Cancer J Clin*. 2024;74(5):433-452 Adashek JJ, et al. Mol Cancer Ther. 2022;21(6):871-878
Hanrahan AJ. Nat Rev Clin Oncol. 2024;21(3):224-247
Elez E et al. Nat Med. 2023 Feb;29(2):307-308, Adapted from Tabernero J et al, ASCO Educational Book 2022, https://www.fda.gov/drugsatfda, Tabernero J et al. J Clin Oncol. 2021 Feb 1;39(4):273-284

THE SOONER, THE BETTER: THE BREAKWATER TRIAL, FIRST LINE

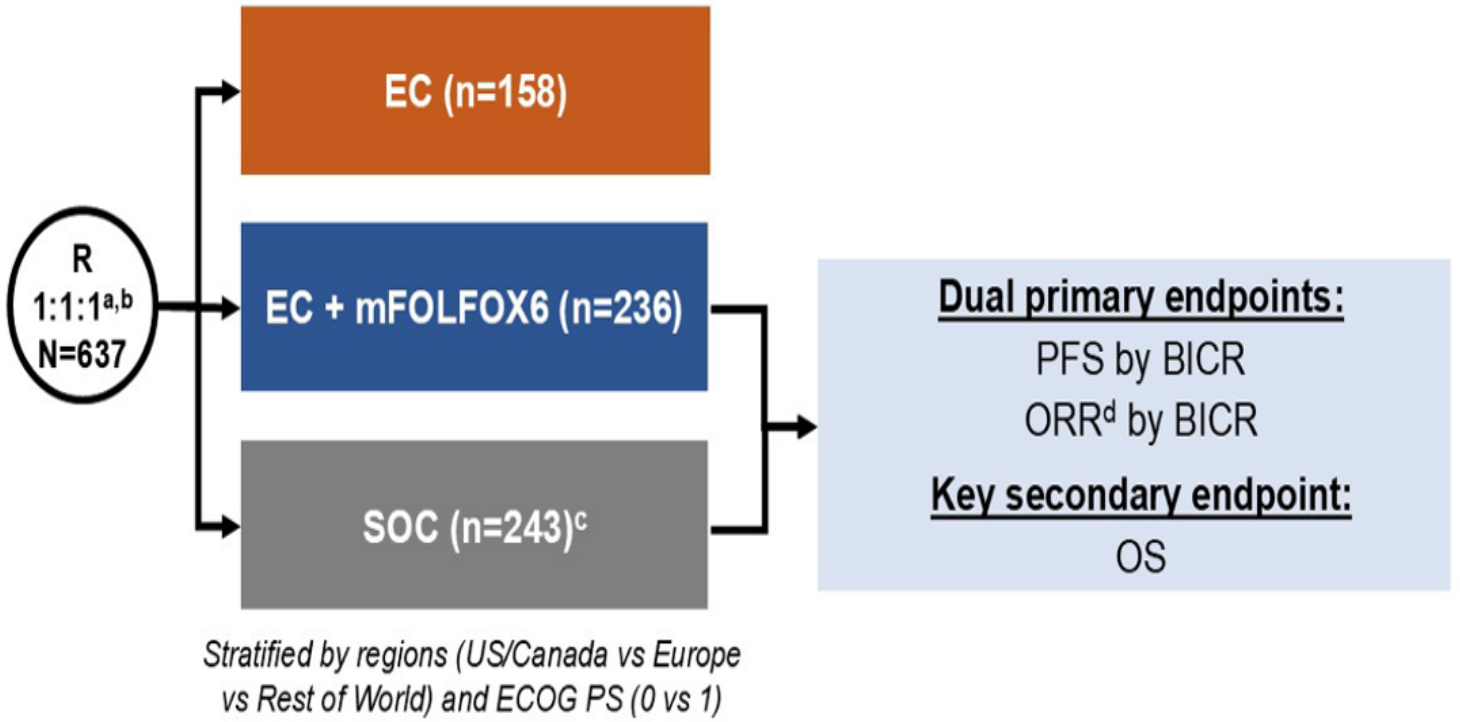
BREAKWATER (NCT04607421) is an open-label, multicenter, phase 3 study in first-line BRAF V600E-mutant mCRC

Inclusion criteria

- Age ≥16 years (or ≥18 years based on country)
- No prior systemic treatment for metastatic disease
- Measurable disease (RECIST 1.1)
- BRAF V600E-mutant mCRC by local or central laboratory testing
- ECOG PS 0 or 1
- Adequate bone marrow, hepatic, and renal function

Exclusion criteria

- Prior BRAF or EGFR inhibitors
- Symptomatic brain metastases
- MSI-H/dMMR tumors (unless patients were ineligible to receive immune checkpoint inhibitors due to a pre-existing medical condition)
- Presence of a *RAS* mutation

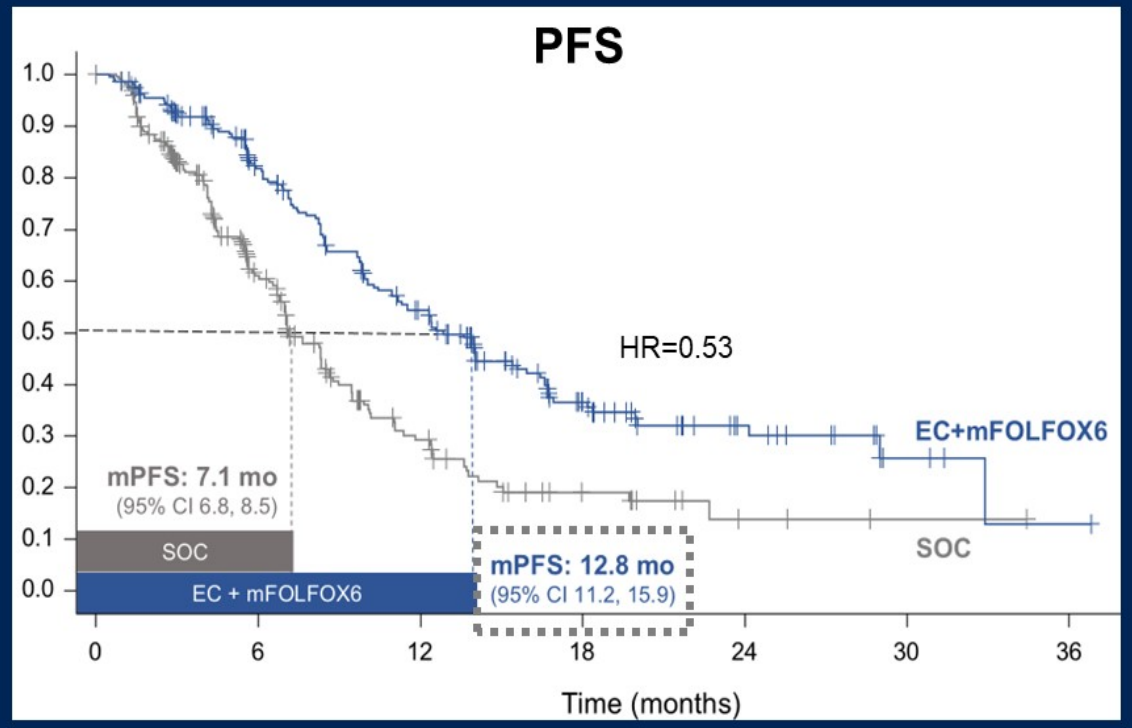


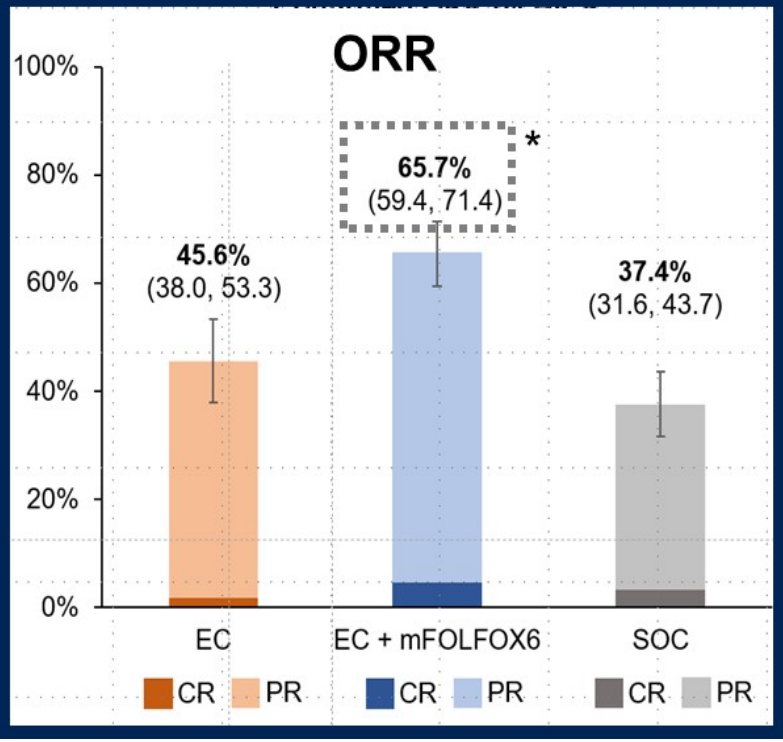
Elez E et al. N Engl J Med. 2025 Jun 26;392(24):2425-2437

THE SOONER, THE BETTER: THE BREAKWATER TRIAL, FIRST LINE

- **Results**

Dual primary endpoints:

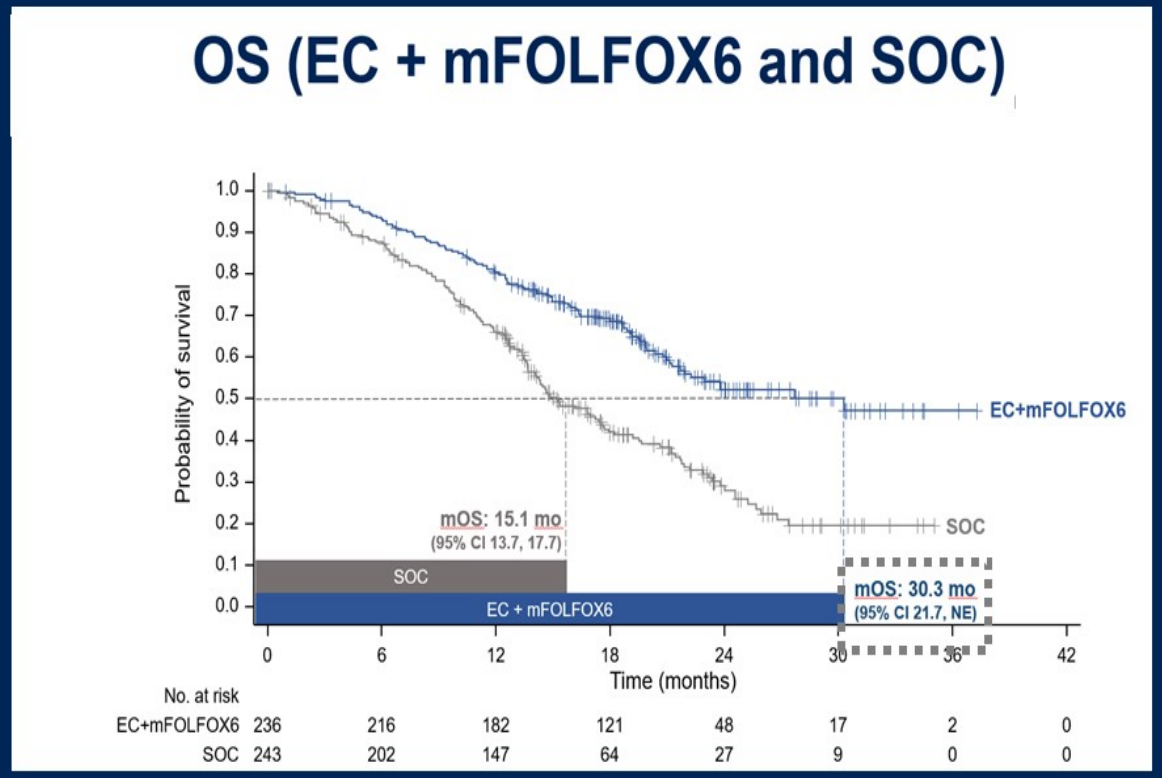




- **PFS robust delta** >5 months →usually poor prognostic setting (only 50% receive 2L)
- **Enhanced ORR** (+20%) *updated in all randomized pts → often symptomatic patients requiring shrinkage

Elez E et al. N Engl J Med. 2025 Jun 26;392(24):2425-2437

THE SOONER, THE BETTER: THE BREAKWATER TRIAL, FIRST LINE



Elez et al, ASCO 2025

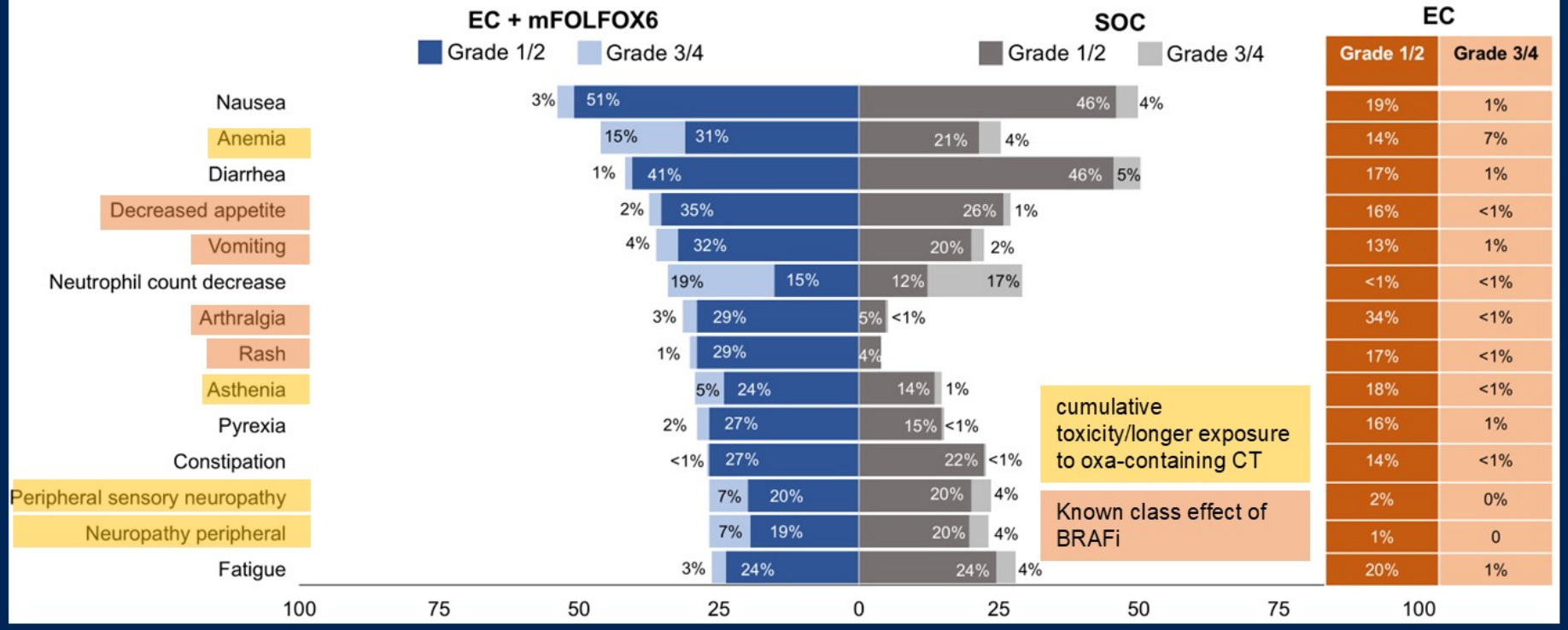
OS of patients with BRAF V600E mutated mCRC treated in the 1L setting with CT doublet/triplet + bev

Study (reference)	Population	Median OS (months)
FOLFOXIRI+Bev, meta-analysis of 5 studies (Cremolini et al. *J Clin Oncol* 2020)	BRAF mut	**13.6**
Doublet+Bev, meta-analysis of 5 studies (Cremolini et al. *J Clin Oncol* 2020)	BRAF mut	**14.5**
FOLFIRI+Bev, FIRE-3 trial (Stintzing et al *Eur J Cancer* 2017)	BRAF mut	**13.7**

Elez E et al. N Engl J Med. 2025 Jun 26;392(24):2425-2437

THE BREAKWATER TRIAL, FIRST LINE: SAFETY

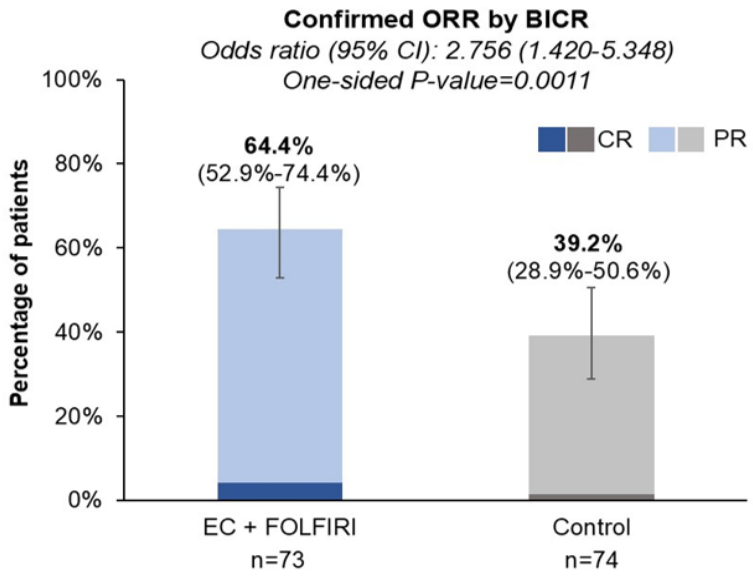
Most Frequent (≥25%)[a] All-Causality TEAEs



- Tolerability confirmed with **expected additive toxicity to FOLFOX**: G≥3 anemia/asthenia and GI AEs, also reflecting **longer treatment exposure** due to improved efficacy
- → no substantial increase in chemotherapy dose reduction or discontinuation, around 15% discontinuation of E and/or C

Elez et al, ASCO 2025

THE BREAKWATER TRIAL, FIRST LINE: FOLFIRI + ENCORAFENIB + CETUXIMAB

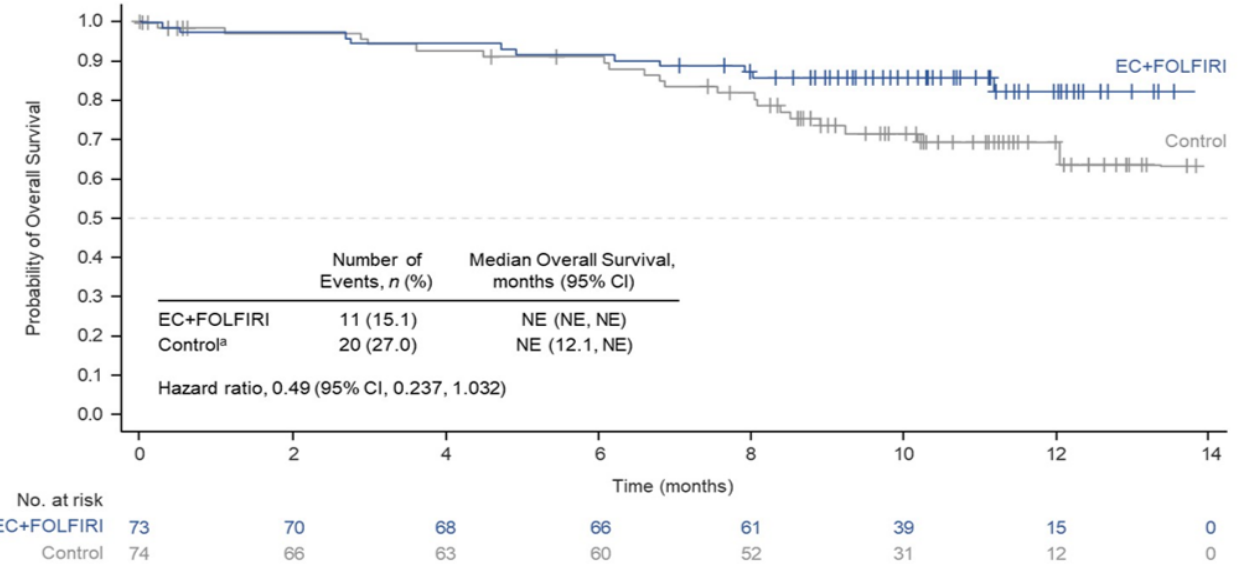


Confirmed Best Overall Response, TTR, and DOR by BICR

	EC + FOLFIRI n=73	Control[a] n=74
Confirmed best overall response, n (%)		
CR	3 (4.1)	1 (1.4)
PR	44 (60.3)	28 (37.8)
SD	15 (20.5)	25 (33.8)
Non-CR/non-PD[b]	1 (1.4)	0
PD	1 (1.4)	8 (10.8)
Not evaluable	9 (12.3)	12 (16.2)
TTR, median (range), weeks	6.9 (5.4-36.1)	7.1 (5.9-25.3)
Estimated DOR, median (range), months	NE (NE-NE)	NE (7.0-NE)
Patients with a DOR of ≥6 months, n (%)	27 (57.4)	10 (34.5)
Patients with a DOR of ≥12 months, n (%)	2 (4.3)	0

Overall Survival

Data are immature but showed a trend for OS improvement with EC + FOLFIRI vs control

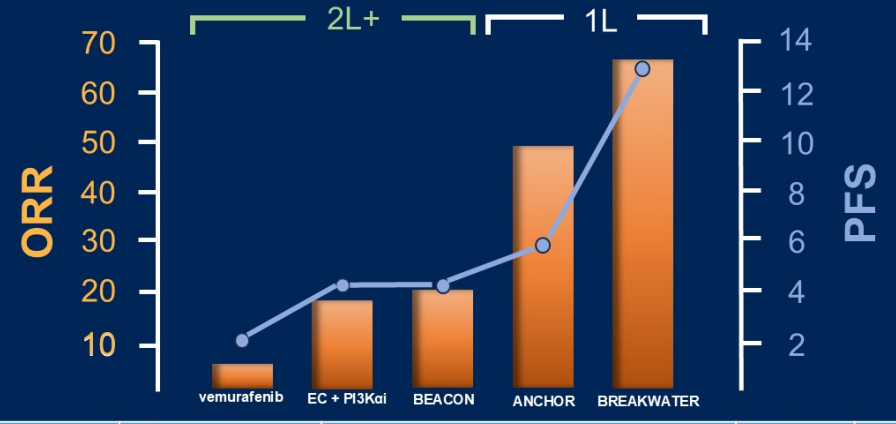


l ± bevacizumab.
ifenib plus cetuximab; FOLFIRI, fluorouracil/leucovorin/irinotecan; NE, not estimable.

Abstract 13. Presented by S Kopetz. Saturday 1:30 CRC oral abstract session ASCO GI 2026.

THE EVOLUTION OF BRAF TARGETING

IN MCRC



Study	Phase/Line	Regimen	ORR	PFS	OS
Prahallad et al (2012)	Preclinical	Discovery of EGFR feedback activation	-	-	-
Kopetz et al (2015)	I/advanced	Vemurafenib monotherapy	5%	2.1 mo	-
Van Geel et al (2017)	I/II/advanced	Encorafenib + Cetuximab ± Alpelisib	18%	4.2 mo	-
BEACON CRC (2020)	III/2L+	Encorafenib + Cetuximab	20%	4.2 mo	8.4 mo
ANCHOR CRC (2021)	II/1L	Encorafenib + Binimetinib + Cetuximab	47.4%	5.8 mo	18.3 mo
BREAKWATER (2025)	III/1L	Encorafenib + Cetuximab + mFOLFOX6	65.7%	12.8 mo	30.3 mo

SARTORE BIANCHI, A. ASCO 2025

FUTURE:

1. Paradox brakers: mosperafenib
2. Cooperativity between BRAF-targeting and immunotherapy
    i) Combining PD1/BRAF/MEK in BRAFV600E mCRC MMR
    ii) MSI-H/dMMR: Phase Ib/II Combining PD 1/ BRAF/EGFRi
3. BRAF degraders
4. Targeting BRAF in other digestive tumours

Tian J, Nat Med. 2023;29(2):458-466;Russo M, et al. Science. 2019;366(6472):1473-148Elez. , Morris VK et al. Cancer Cell. 2025. E et al. Future Oncol 2024 Apr,20(11):653-663. Vieito M et al. ESMO 2024. Fontana E et al. ASCO 2025

QUIMIO MÁS CETUXIMAB MÁS ENCORAFENIB EN 1ª LÍNEA

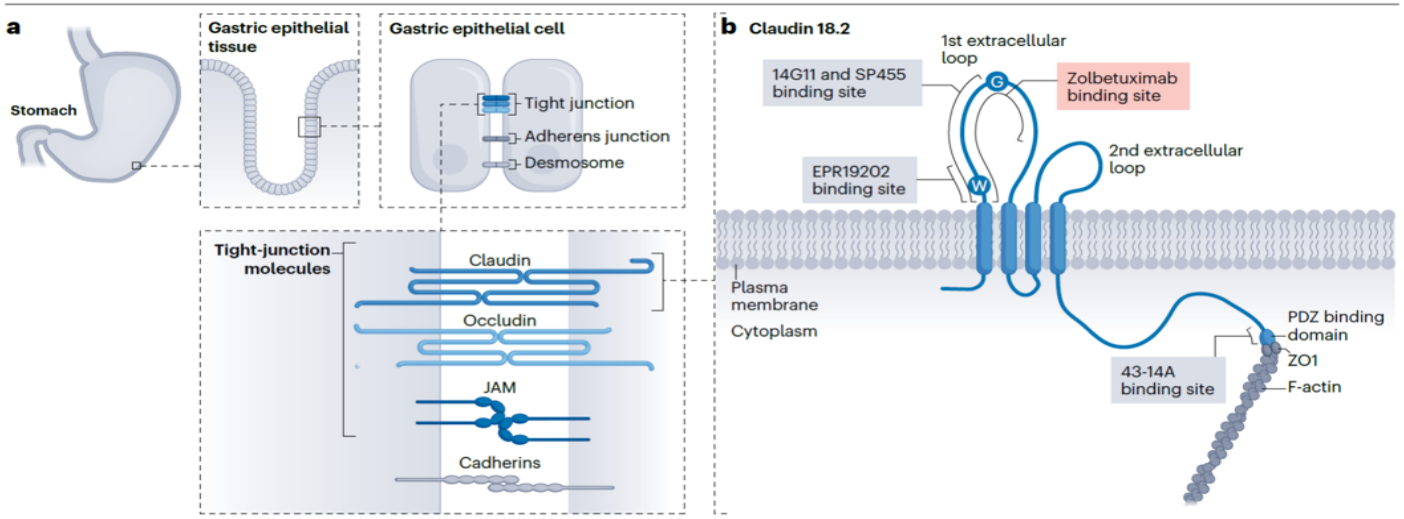
- BREAKWATER demonstrates that combining EC with chemotherapy provides meaningful clinical benefit for patients with *BRAF*^{V600E}–mutant mCRC with a tolerable safety profile

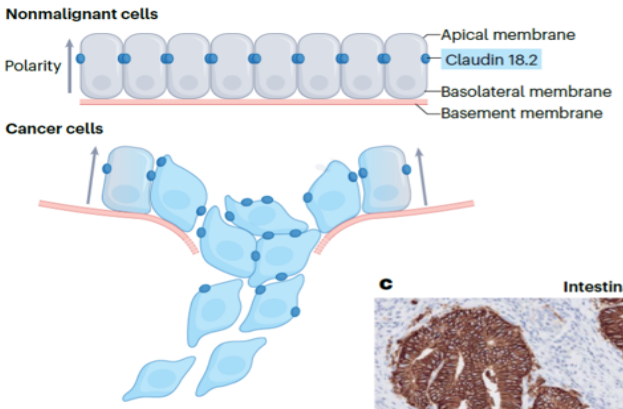
- EC + mFOLFOX6 showed clinically meaningful improvement in ORR (by BICR) and statistically significant, clinically meaningful improvement in PFS (by BICR) and OS vs SOC
- Cohort 3 confirmed a statistically significant and clinically relevant improvement in ORR with EC + FOLFIRI vs FOLFIRI ± bevacizumab, with responses that were rapid and durable
- Together, these data support EC-based combinations as a potential new standard of care in the first-line setting for *BRAF*^{V600E}–mutant mCRC

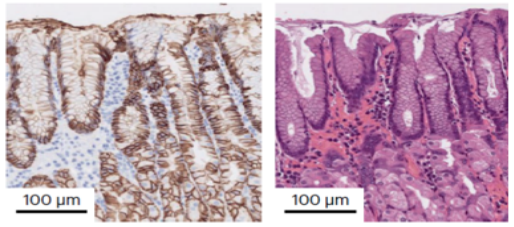
NUEVAS DIANAS:

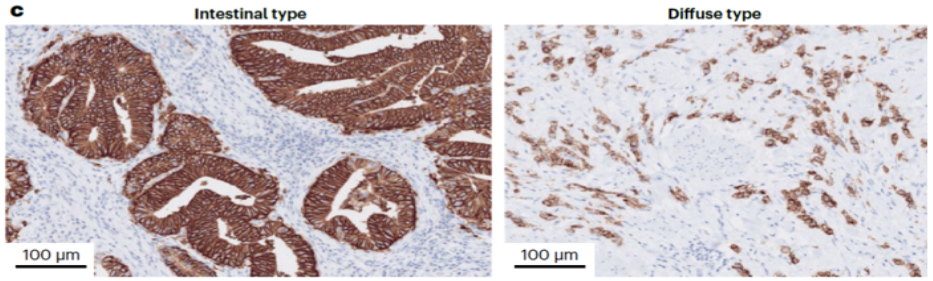
- **Dianas no oncogénicas:** moléculas que no inician el cáncer, pero favorecen la proliferación, supervivencia o evasión inmune del tumor:
  - CLAUDINA 18.2

CLAUDIN 18.2









Differences in polarity between nonmalignant cells and tumour cells

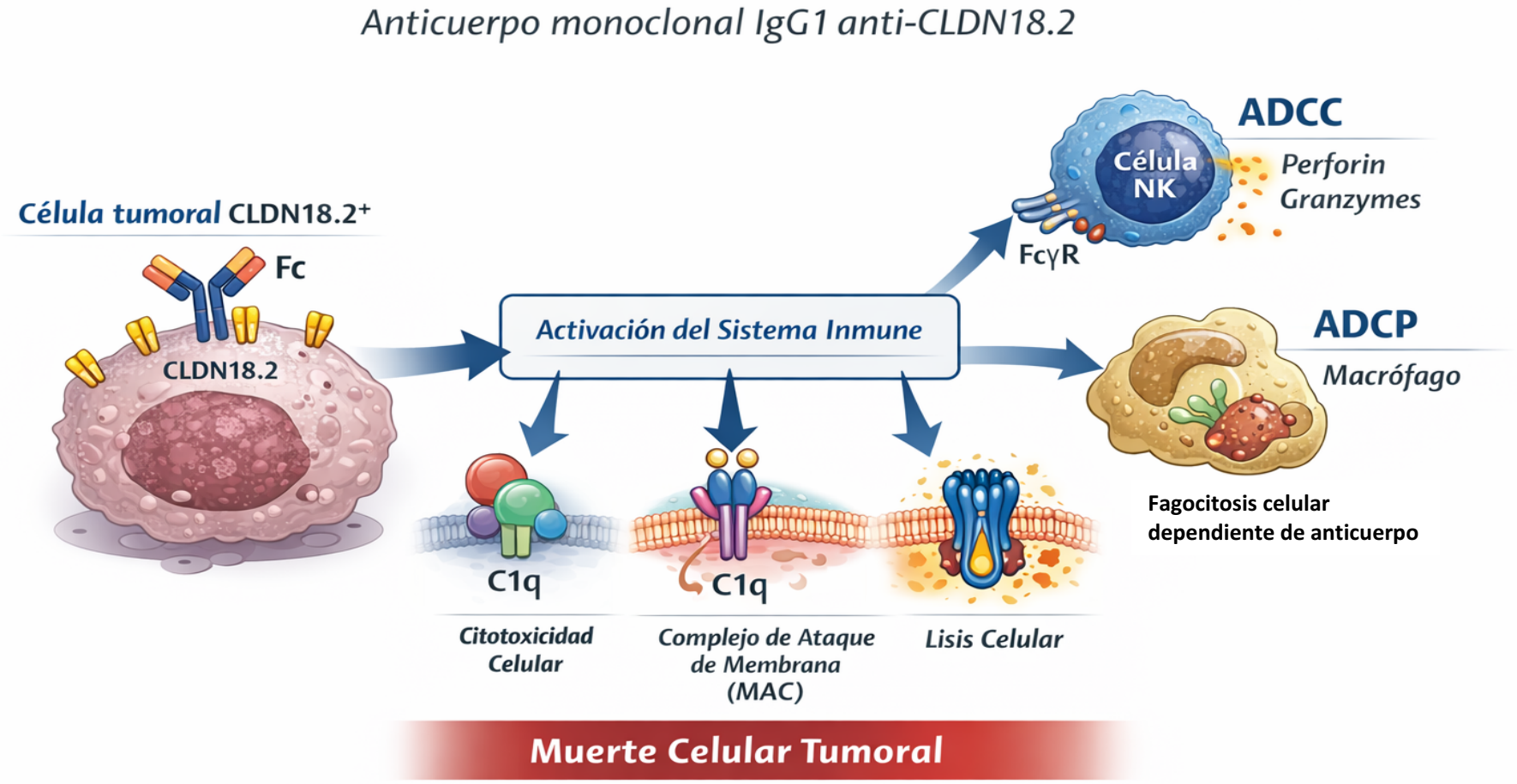
The resultant changes in the distribution of claudin 18.2 expression, from tight junctions to expresión on cell membranas

Claudin 18.2 is known to be overexpressed / ectopic expressed in various other cancer types, including other gastrointestinal tract cancers (such as oesophageal, pancreatic and colorectal cancer)

Also in other non-gastrointestinal solid tumours

Nakayama I, Qi C, Chen Y, Nakamura Y, Shen L, Shitara K. Claudin 18.2 as a novel therapeutic target. Nat Rev Clin Oncol. 2024 May;21(5):354-369.

ZOLBETUXIMAB: MECANISMO DE ACCIÓN



1. Túreci O, et al. Oncoimmunology. 2019;8:e1523095.
2. Sahin U, et al. Clin Cancer Res. 2018:24:559–568.
3. Jiang H, et al. Biomark Res. 2022;10:58.

PHASE II AND III CLINICAL TRIAL TESTING ZOLBETUXIMAB

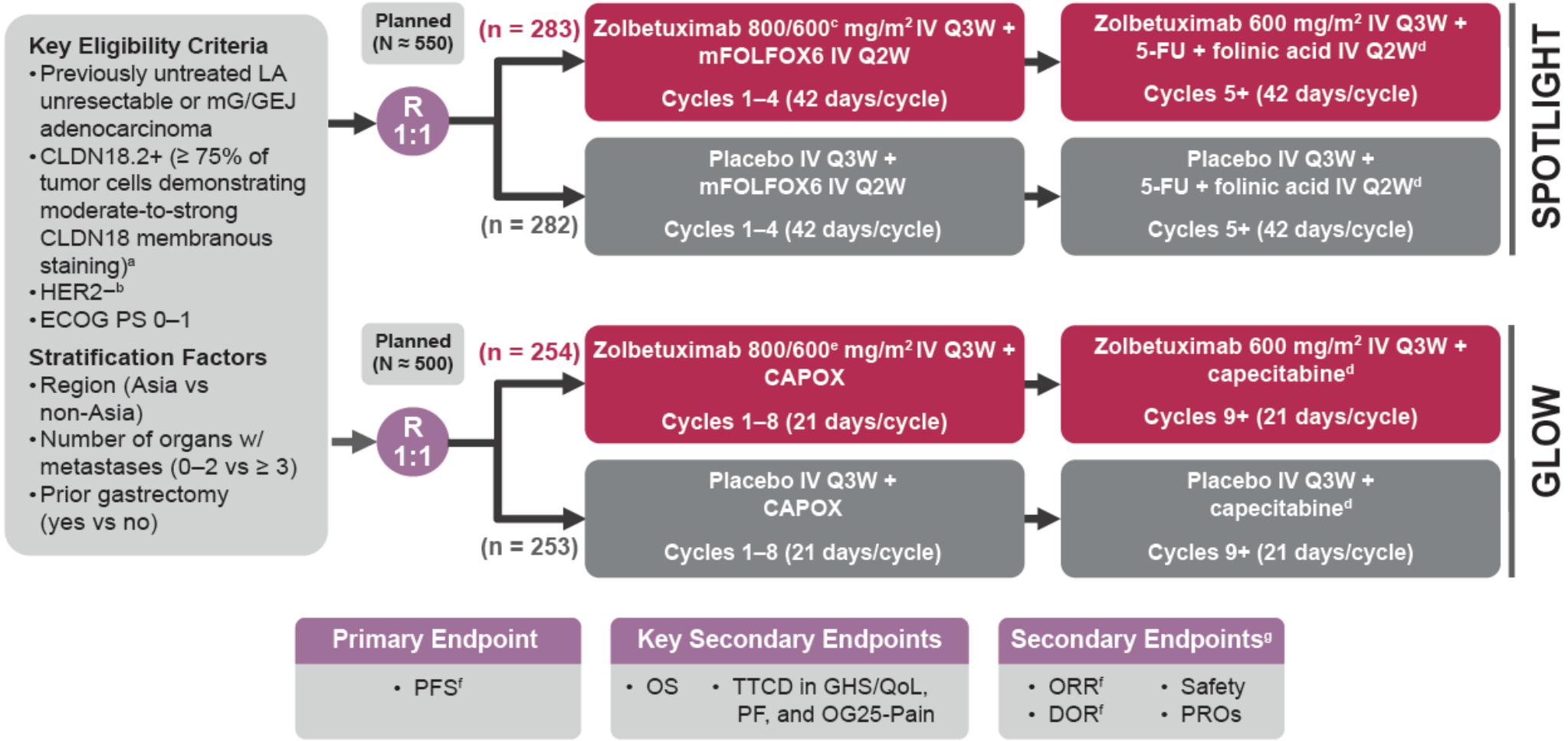
Study details	Intervention	Outcomes	Adverse events
MONO phase IIa (2019)[148]	Zolbetuximab 300 mg/m² (*n*=4) or 600 mg/m² (*n*=50) as second-line or later-line therapy for patients with claudin 18.2-positive[a] recurrent gastric, GEJ or oesophageal adenocarcinoma	ORR 9%	Common grade 3–4 TEAEs included vomiting (22%), nausea (15%) and dyspnoea (11%)
FAST phase II (2021)[28]	**enrichment of benefit in patients with claudin 18.2 expression on ≥70% of tumour cells** plus EOX line therapy 8.2-positive[b] l adenocarcinoma	ORR 39% vs 25%; mPFS 7.5 vs 5.3 months, HR 0.44, 95% CI 0.29–0.67, *P*<0.0005; mOS 13.0 vs 8.3 months, HR 0.55, 95% CI 0.39–0.77, *P*<0.0005	Common grade 3–4 TEAEs included vomiting (10.4% vs 3.6%), nausea (6.5% vs 4.8%) and decreased appetite (0% vs 2.4%)
SPOTLIGHT phase III (2023)[9]	Zolbetuximab 800 mg/m² then 600 mg/m² plus mFOLFOX6 (*n*=283) vs placebo plus mFOLFOX6 (*n*=282) as first-line therapy for patients with claudin 18.2-positive[c] locally advanced, unresectable and/or metastatic gastric or GEJ adenocarcinoma	ORR 48% vs 48%; mPFS 10.61 vs 8.67 months, HR 0.75, 95% CI 0.60–0.94, *P*=0.0066; mOS 18.23 vs 15.54 months, HR 0.75, 95% CI 0.60–0.94, *P*=0.0053	Common grade 3–4 TEAEs included vomiting (16% vs 6%), nausea (16% vs 6%) and decreased appetite (6% vs 3%)
GLOW phase III (2023)[10]	Zolbetuximab plus CAPOX (*n*=254) vs placebo plus CAPOX (*n*=253) as first-line therapy for patients with claudin 18.2-positive[c] locally advanced, unresectable and/or metastatic gastric or GEJ adenocarcinoma	ORR 53.8% vs 48.8%; mPFS 8.21 vs 6.8 months, HR 0.69, 95% CI 0.54–0.87, *P*=0.0007; mOS 14.39 vs 12.16, HR 0.77, 95% CI 0.62–0.97, *P*=0.012	Common grade 3–4 TEAEs included vomiting (12.2% vs 3.6%), nausea (8.7% vs 2.4%) and decreased appetite (6.7% vs 1.6%)

CAPOX, capecitabine plus oxaliplatin; CI, confidence interval; EOX, epirubicin plus oxaliplatin and capecitabine; GEJ, gastro-oesophageal junction; HR, hazard ratio; mFOLFOX6, modified 5-fluorouracil, leucovorin and oxaliplatin; mOS, median overall survival; mPFS, median progression-free survival; ORR, objective response rate; TEAEs, treatment-emergent adverse events; vs, versus. [a]Immunohistochemistry (IHC) score ≥2+ on ≥50% of tumour cells with the 43-14A antibody. [b]IHC score ≥2+ on ≥40% of tumour cells stained with the 43-14A antibody. [c]IHC score ≥2+ on ≥75% of tumour cells stained with the 43-14A antibody.

Nature Reviews Clinical Oncology | Volume 21 | May 2024 | 354–369

Nakayama I, Qi C, Chen Y, Nakamura Y, Shen L, Shitara K. et al.

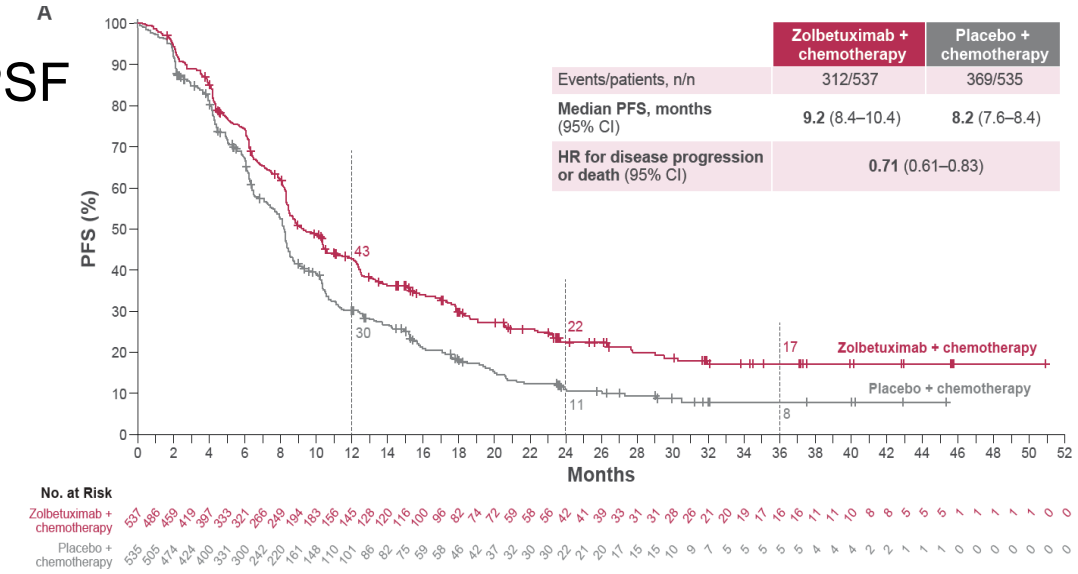
PHASE III CLINICAL TRIAL TESTING ZOLBETUXIMAB



References
1. Shitara K et al. Lancet. 2023;401(10389):1655–1668; 2. Shah MA et al. Nat Med. 2023;29(8):2133–2141; 3. Ajani JA et al. Ann Oncol. 2023;34(2):S1322; 4. Lordick F et al. Ann Oncol. 2023;34(2):S1321.

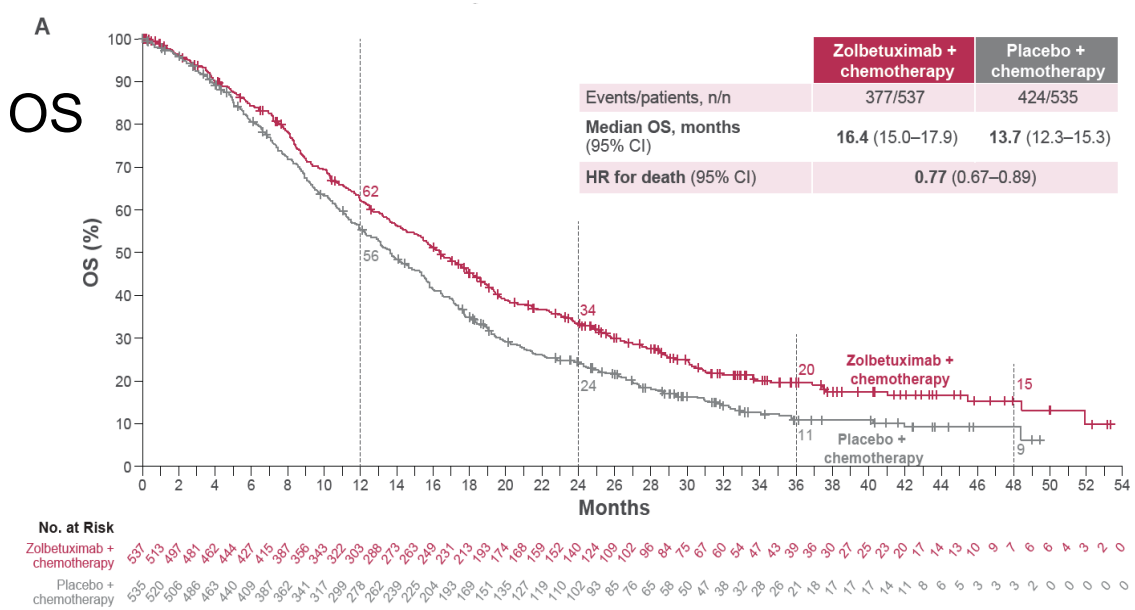
PHASE III CLINICAL TRIAL TESTING ZOLBETUXIMAB: COMBINED ANALYSIS

PSF



	Zolbetuximab + chemotherapy	Placebo + chemotherapy
Events/patients, n/n	312/537	369/535
Median PFS, months (95% CI)	**9.2** (8.4–10.4)	**8.2** (7.6–8.4)
HR for disease progression or death (95% CI)	**0.71** (0.61–0.83)	

OS



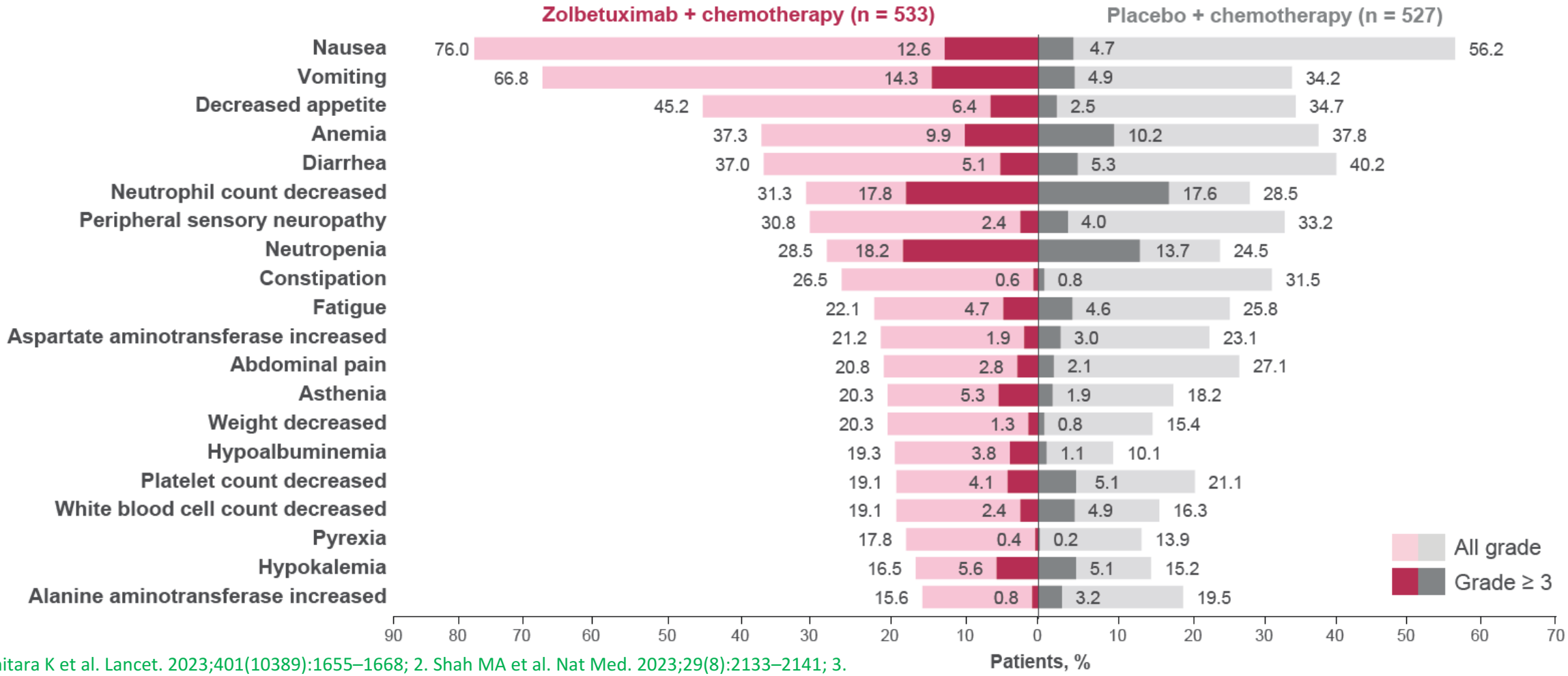
	Zolbetuximab + chemotherapy	Placebo + chemotherapy
Events/patients, n/n	377/537	424/535
Median OS, months (95% CI)	**16.4** (15.0–17.9)	**13.7** (12.3–15.3)
HR for death (95% CI)	**0.77** (0.67–0.89)	

ORR

	Full analysis set[a]		Patients with measurable disease	
	Zolbetuximab + chemotherapy (n = 537)	Placebo + chemotherapy (n = 535)	Zolbetuximab + chemotherapy (n = 406)	Placebo + chemotherapy (n = 414)
ORR[b], n (%)	244 (45.4)	233 (43.6)	233 (57.4)	229 (55.3)
95% CI	41.2–49.8	39.3–47.9	52.4–62.3	50.4–60.2
BOR[c,d], n (%)				
CR	32 (6.0)	17 (3.2)	21 (5.2)	13 (3.1)
PR	212 (39.5)	216 (40.4)	212 (52.2)	216 (52.2)
SD	91 (16.9)	108 (20.2)	91 (22.4)	108 (26.1)
PD	27 (5.0)	45 (8.4)	24 (5.9)	39 (9.4)
Median DOR[b,e] months (95% CI)	8.1 (6.4–9.0)	6.5 (6.2–7.7)	7.7 (6.3–8.9)	6.5 (6.2–7.9)

References
1. Shitara K et al. Lancet. 2023;401(10389):1655–1668; 2. Shah MA et al. Nat Med. 2023;29(8):2133–2141; 3. Ajani JA et al. Ann Oncol. 2023;34(2):S1322; 4. Lordick F et al. Ann Oncol. 2023;34(2):S1321.

ZOLBETUXIMAB: TEAES OCURRING IN >= 15% OF PATIENTS IN EITHER TREATMENT GROUP



1. Shitara K et al. Lancet. 2023;401(10389):1655–1668; 2. Shah MA et al. Nat Med. 2023;29(8):2133–2141; 3. Ajani JA et al. Ann Oncol. 2023;34(2):S1322; 4. Lordick F et al. Ann Oncol. 2023;34(2):S1321.

ONCOLOGIA DE PRECISIÓN EN CÁNCER GÁSTRICO

Biomarcador	% aproximado de pacientes	DELTA OS (meses)	EC
HER2 positivo	~20–22 %	2,7	TOGA
CLDN18.2 positivo	~30–38 %	2,7	SPOTLIGHT Y GLOW
PD-L1 CPS ≥5	~29–31 %		
	PD-L1 >= 5%	3,3	CHECKMATE 649 (NIVOLUMAB)
	PD-L1 >= 1%	1,4	PEMBROLIZUMAB KEYNOTE 859
	TAP >= 5%	3,6	TISLELIZUMAB
HER2 Y PD-L1 positivos	4 - 9 %	3,8	KEYNOTE 811 PEMBRO TRASTU
IMS	8-10%	48-55% a 36 meses	KEYNOTE 59-61-62
CLDN18.2 + PD-L1 CPS ≥5	~17–21 % de CLDN18.2 +		EN MARCHA

Ajani JA, D'Amico TA, Bentrem DJ, et al. *J Natl Compr Canc Netw.* 2022;20:167-192. Bang YJ, Van Cutsem E, Feyereislova A, et al. *Lancet.* 2010;376:687-697. Shitara K, Lordick F, Bang YJ, et al. *N Engl J Med.* 2023;388:1689-1699. Pellino A, Riello E, Nappo F, et al. *Gastric Cancer.* 2021;24:737-746. Cancer Genome Atlas Research Network. Nature. 2014
Chao J, et al. JAMA Oncol 2021; 7: 895-902
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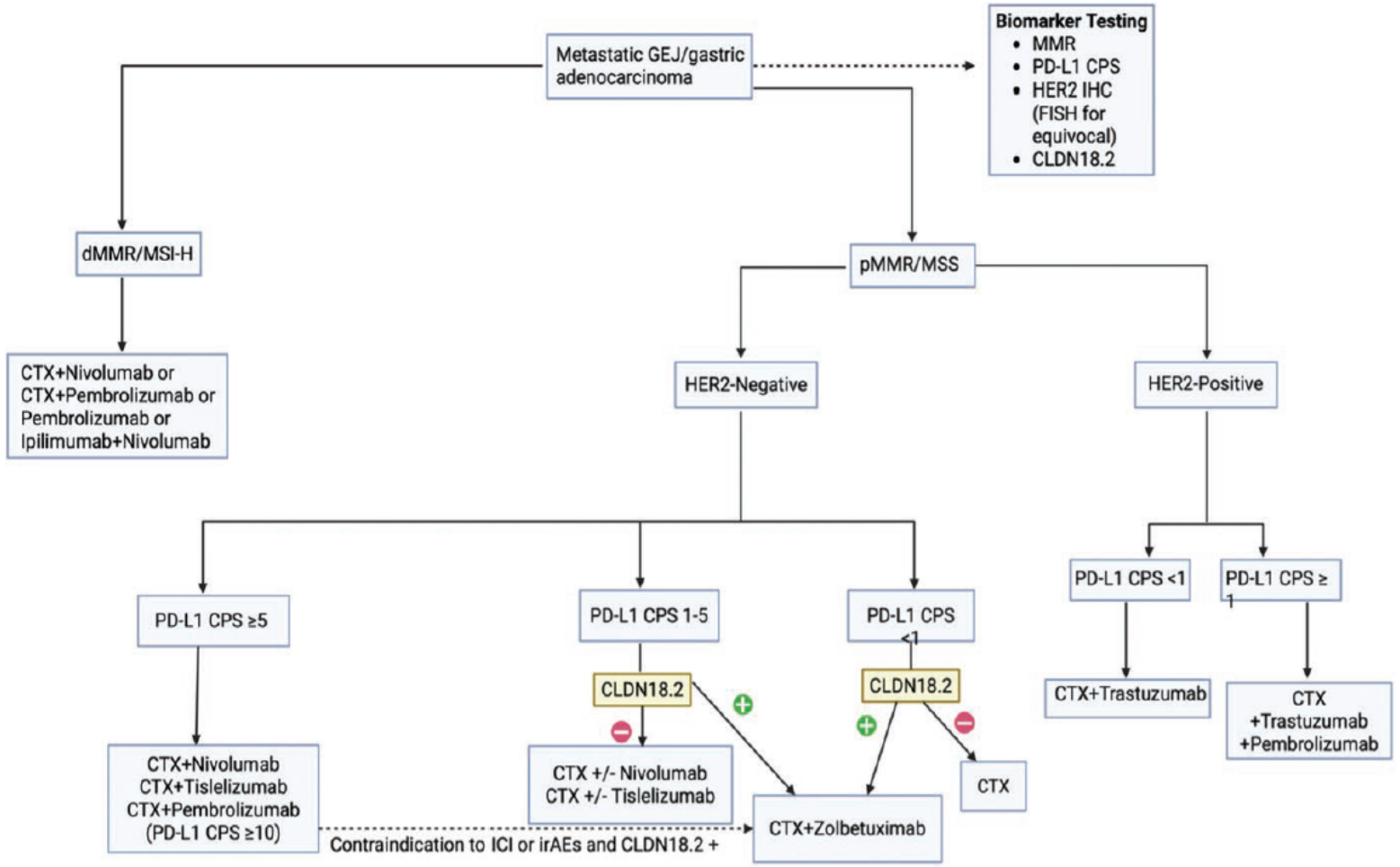
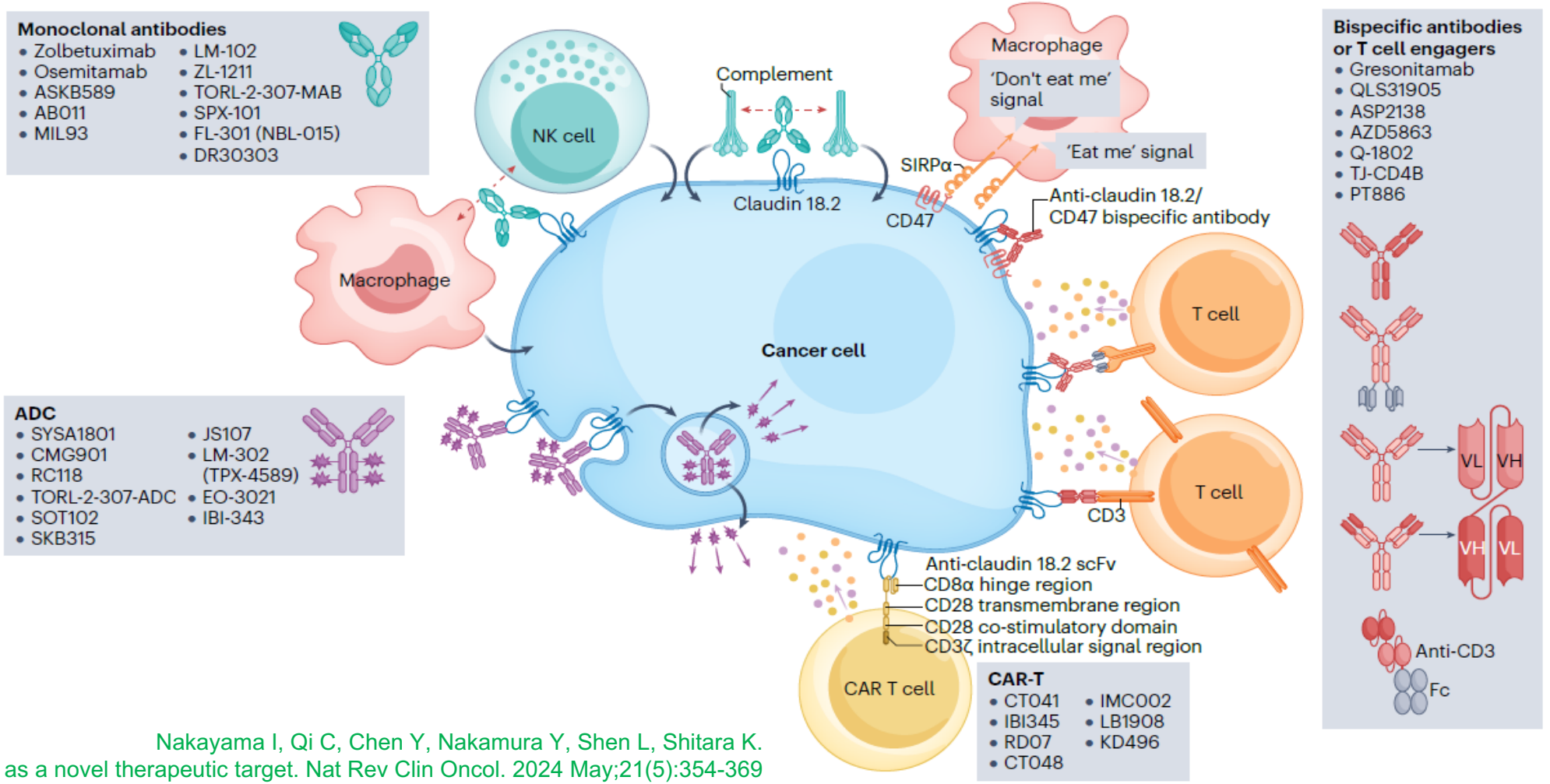


Udhayvir S. Grewal, Timothy J. Brown
The Oncologist, 2025, 30, oyaf185
https://doi.org/10.1093/oncolo/oyaf185

CLAUDINA 18.2 COMO DIANA



Nakayama I, Qi C, Chen Y, Nakamura Y, Shen L, Shitara K.
Claudin 18.2 as a novel therapeutic target. Nat Rev Clin Oncol. 2024 May;21(5):354-369

ZOLBETUXIMAB

Zolbetuximab plus chemotherapy continued to demonstrate a clinically meaningful improvement in PFS and OS versus placebo plus chemotherapy, with no new safety signals

These results support zolbetuximab plus chemotherapy as a global standard for 1L treatment of patients with HER2−, LA unresectable or mG/GEJ adenocarcinoma whose tumors are CLDN18.2+

CLDN18.2+

Nueva diana para tratamiento

GRACIAS!

III JORNADA TRASLACIONAL DE ONCOLOGÍA DE PRECISIÓN:

A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN
SEVILLA, 12 Y 13 DE FEBRERO DE 2026

Manuelj.valladares.sspa@juntadeandalucia.es