VIII CURSO MULTIDISCIPLINAR NACIONAL E INTERNACIONAL DE
CÁNCER COLORRECTAL
del Hospital General Universitario Gregorio Marañón
17 de abril 2026

Innovación en Cáncer Colorrectal y de Canal Anal

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Disclosure

Employment: NO

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Other: Travels: Amgen, Merck, Sanofi, Pierre Fabre, MSD, BMS, Servier, Takeda

Avances recientes más significativos en CCRm y Canal anal

C. Canal Anal
Inmunoterapia en 1ª línea

Terapia Biológica
1. **BRAFmV600E:Breakwather**
2. **KRASG12C**

Inmunoterapia dMMR
1. **CHECKMATE 8HW**
2. **Señales de eficacia en pMMR: STELLAR 303**

Mejoría de la terapia de secuenciación
1. **Fruquintinib (FRESCO)**
2. **Rechallenge**

Cáncer de canal anal

Inmunoterapia en 1ª Línea
Estudio PODIUM 303

Incidence

	U.S.[1]	EU27[2]
Annual incidence rate[a] (per 100,000 persons)	2.0[b]	2.1[e]
Female	2.4[b]	2.3[e]
Male	1.6[b]	1.9[e]
Estimated new cases per year, n	10,930[c]	9,901[e]
Annual growth rate for incidence[a]	+2.2%[d]	

Risk Factors for Anal Cancer

HPV infection[1-4]

- ≈90% of anal cancers are associated with HPV infection
- HPV16 and HPV18 are the most common HPV genotypes associated with anal cancer

Immunosuppression[1-6]

- Immunosuppression is associated with increased incidence of anal cancer
- The risk of being diagnosed with anal cancer is ≈15-35 times higher in people with HIV, compared with the general population[5]
- Although individuals positive for HIV are at greater risk, this group of patients has been historically understudied in, and/or excluded from clinical trials[6]

Other[1-4]

- Older age
- Smoking
- Cervical, vulvar, or vaginal cancer

HPV infection is the strongest risk factor for anal cancer[1,4]

Tratamiento 2021

Stage I-III Cancer of the Anal Canal

- Mitomycin C + 5-FU [I, A] + RT[a] [III, B]
- Capecitabine replacing 5-FU [III, B]

Residual tumor:
- Surgery

Complete response:
- Follow-up

Local relapse:
- Surgery[c]

Distant relapse:
- Management as metastatic disease

Stage IV Anal Cancer[b]

First line:
- Carboplatin/paclitaxel [I, B]

Second line:
- Cisplatin + 5-FU, carboplatin, doxorubicin, taxane, irinotecan ± cetuximab or combinations [III, B]
- In clinical trials: PD-(L)1 inhibitors [III, B]

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2025
Anal Carcinoma

PRINCIPLES OF SYSTEMIC THERAPY – METASTATIC CANCER[a]

First-Line Therapy	
Preferred Regimens	Other Recommended Regimens
• Carboplatin + paclitaxel + retifanlimab-dlwr[a]	• Carboplatin + paclitaxel • FOLFCIS • mFOLFOX6[b] • 5-FU + cisplatin (category 2B) • Modified docetaxel/cisplatin/fluorouracil (DCF) (category 2B)

Study Design[1,2]

Select eligibility criteria

- Locally recurrent or metastatic SCAC
- Inoperable locally recurrent or metastatic SCAC
- No prior chemotherapy except as radiosensitising treatment or (neo) adjuvant therapy ≥6 months prior to study entry
- ECOG PS of 0 to 1
- Patients with HIV and well-controlled infection were eligible
- N patients randomized = 308

Other eligibility criteria

Randomized 1:1

Retifanlimab iv 500 mg q4w (up to 12 months) + standard-dose[a] CP (6 months) n=154

Placebo iv q4w (up to 12 months) + standard-dose[a] CP (6 months) n=154

Stratification:
- PD-L1 expression (<1% vs ≥1%)
- Region (AU/EU/N Am/UK/ROW)
- Extent of disease (locally recurrent vs metastatic)

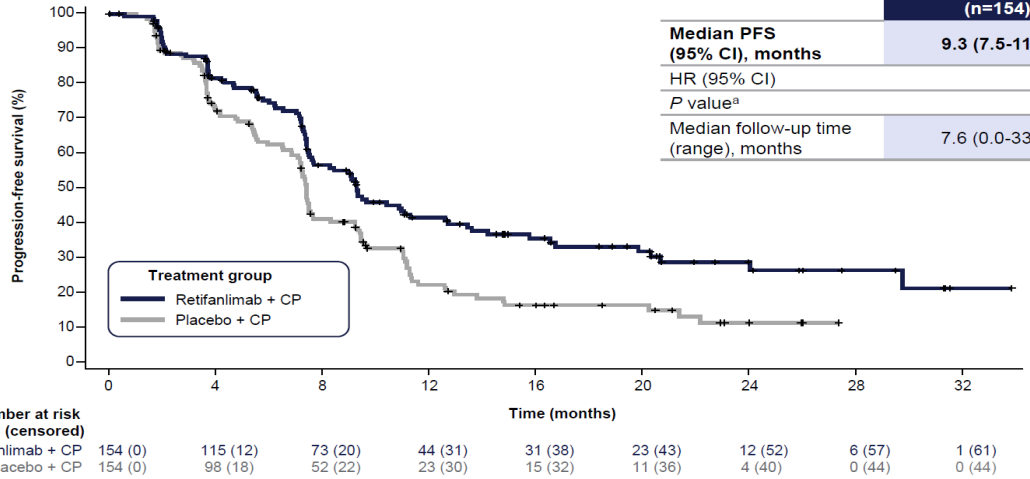
Retifanlimab optional crossover after BICR-verified PD n=77[b,3]

Follow-up disease assessments OS

Primary endpoint: PFS by BICR (projected HR=0.67 at >80% power, alpha=0.025 [1-sided])
Secondary endpoints/objectives: OS (key secondary, alpha=0.025 [1-sided] if PFS is statistically significant), ORR, DOR, safety, PK
Exploratory endpoints/objectives: PROs, HIV control, immunogenicity

POD1UM-303: PFS by BICR

Primary Endpoint



	Retifanlimab + CP (n=154)	Placebo + CP (n=154)
Median PFS (95% CI), months	**9.3 (7.5-11.3)**	**7.4 (7.1-7.7)**
HR (95% CI)	0.63 (0.47-0.84)	
P value[a]	0.0006	
Median follow-up time (range), months	7.6 (0.0-33.9)	7.1 (0.0-27.4)

The primary endpoint was met

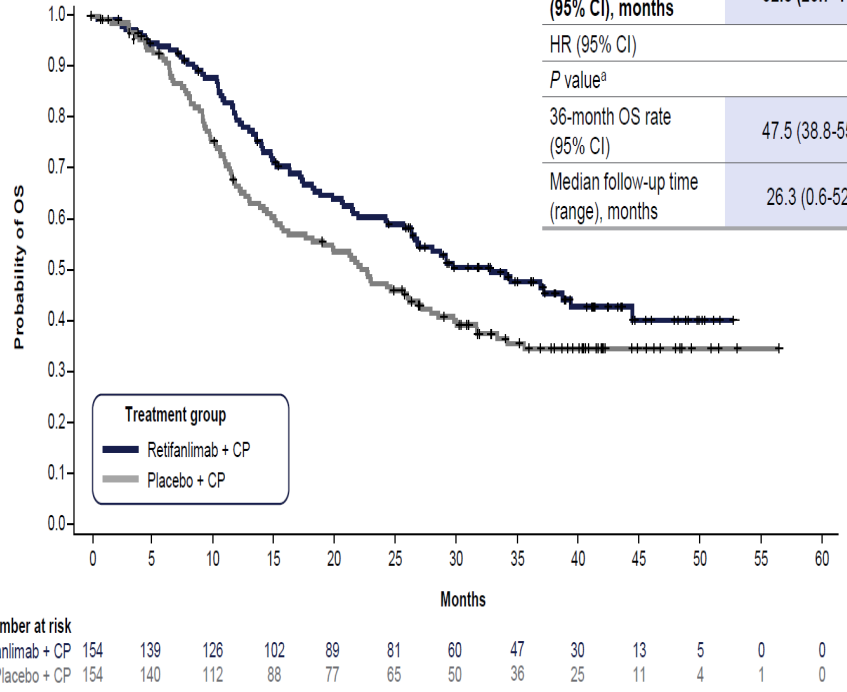
Number at risk (censored)									
Retifanlimab + CP	154 (0)	115 (12)	73 (20)	44 (31)	31 (38)	23 (43)	12 (52)	6 (57)	1 (61)
Placebo + CP	154 (0)	98 (18)	52 (22)	23 (30)	15 (32)	11 (36)	4 (40)	0 (44)	0 (44)

1. Rao S, et al. *Lancet.* 2025;405:2144-2152. 2. ClinicalTrials.gov. Accessed Nov 11, 2025. https://clinicaltrials.gov/study/NCT04472429. 3. Data on file, Incyte Corporation.

POD1UM-303: OS Analysis

Key Secondary Endpoint

	Retifanlimab + CP (n=154)	Placebo + CP (n=154)
Median OS (95% CI), months	**32.8 (25.7-44.5)**	**22.2 (15.7-27.2)**
HR (95% CI)	0.75 (0.55-1.01)	
P value[a]	0.0305	
36-month OS rate (95% CI)	47.5 (38.8-55.6)	34.3 (26.4-42.3)
Median follow-up time (range), months	26.3 (0.6-52.7)	20.6 (0.0-56.5)



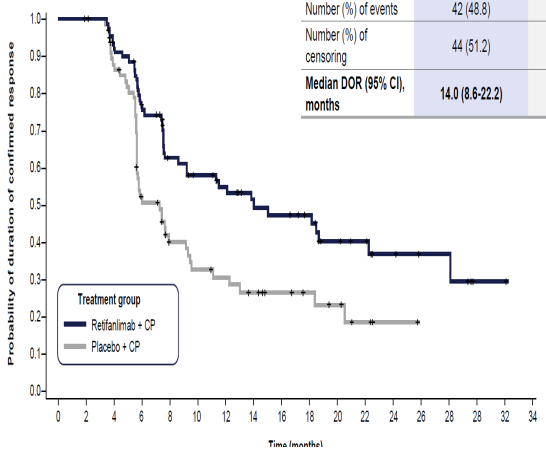
Characteristic	Retifanlimab + CP (n=154)	Placebo + CP (n=154)
ORR (95% CI), %	55.8 (47.6-63.8)	44.2 (36.2-52.4)
Nominal *P* value	0.013	
CR, n (%)	34 (22.1)	21 (13.6)
PR, n (%)	52 (33.8)	47 (30.5)
SD, n (%)	45 (29.2)	52 (33.8)
DCR (95% CI), %	87.0 (80.7-91.9)	79.9 (72.7-85.9)
Median DOR (95% CI), months	14.0 (8.6-22.2)	7.2 (5.6-9.3)

A clinically meaningful improvement in median OS of **10.6 months** was observed with retifanlimab + CP compared with placebo + CP, although the analysis did not cross the prespecified boundary for statistical significance[a]

POD1UM-303: Duration of Response

Kaplan-Meier Curve in the Full Analysis Set

	Retifanlimab + CP (n=86)	Placebo + CP (adjusted; n=68)
Number (%) of events	42 (48.8)	47 (69.1)
Number (%) of censoring	44 (51.2)	21 (30.9)
Median DOR (95% CI), months	**14.0 (8.6-22.2)**	**7.2 (5.6-9.3)**

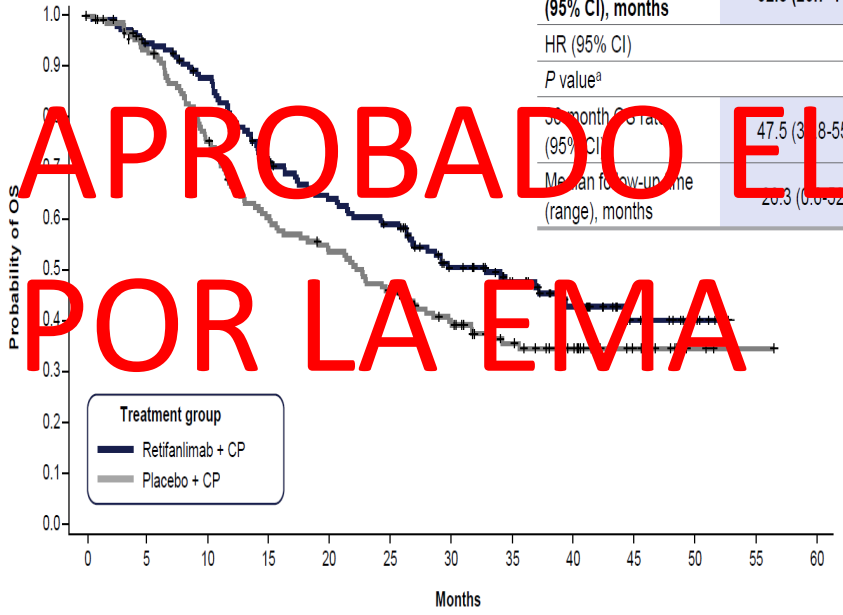


Variable	Retifanlimab + CP (n=154)	Placebo + CP (n=152)	Total (N=306)
Median treatment duration (range), months	7.4 (0.03-14.6)	6.8 (0.03-14.6)	7.2 (0.03-14.6)
Patients with any AEs, n (%)	154 (100)	152 (100)	306 (100)
Patients with grade ≥3 AEs, n (%)	128 (83)	114 (75)	242 (79)
Deaths, n (%)	4 (3)[a]	1 (1)[b]	5 (2)
Patients with SAEs, n (%)	73 (47)	59 (39)	132 (43)

POD1UM-303: OS Analysis

Key Secondary Endpoint

	Retifanlimab + CP (n=154)	Placebo + CP (n=154)
Median OS (95% CI), months	**32.8 (25.7-44.5)**	**22.2 (15.7-27.2)**
HR (95% CI)	0.75 (0.55-1.01)	
P value[a]	0.0305	
36-month OS rate (95% CI)	47.5 (38.8-55.6)	34.3 (26.4-42.3)
Median follow-up time (range), months	20.3 (0.6-52.7)	20.6 (0.0-50.5)



Number at risk

Retifanlimab + CP	154	139	126	102	89	81	60	47	30	13	5	0	0
Placebo + CP	154	140	112	88	77	65	50	36	25	11	4	1	0

A clinically meaningful improvement in median OS of **10.6 months** was observed with retifanlimab + CP compared with placebo + CP, although the analysis did not cross the prespecified boundary for statistical significance[a]

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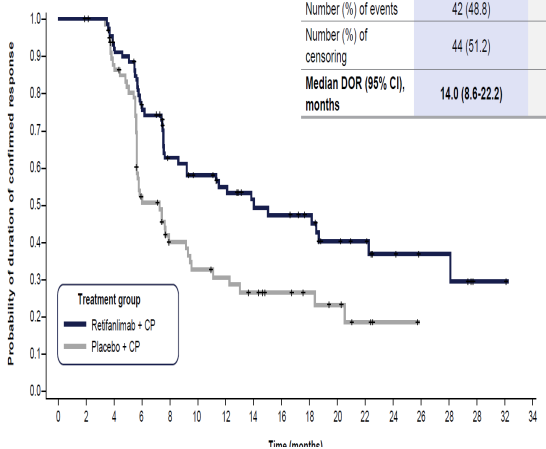

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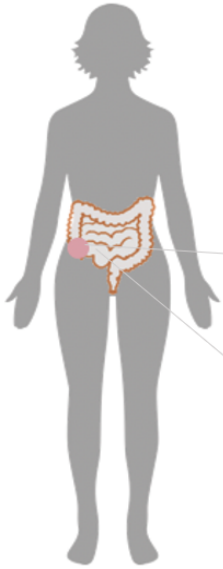
Patients with any AEs, n (%)	154 (100)	152 (100)	306 (100)
Patients with grade ≥3 AEs, n (%)	128 (83)	114 (75)	242 (79)
Deaths, n (%)	4 (3)[a]	1 (1)[b]	5 (2)
Patients with SAEs, n (%)	73 (47)	59 (39)	132 (43)

Terapia Biológica

BRAF V600E Breakwater

Terapia para KRAS G12C

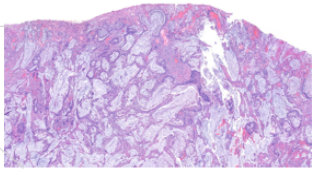
CCRm BRAFV600E



BRAFV600E: 8 to 12% mCRC[1]

Phenotype[2]:

- ✓ Female sex
- ✓ Mucinous right-sided tumors
- ✓ High tumor burden: Peritoneal, lymph node M1
- ✓ <5% M1 achieve liver surgery

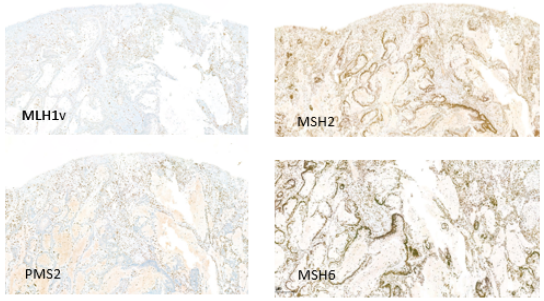


Biomarker role:

Prognostic[4]: mOS 8-24m

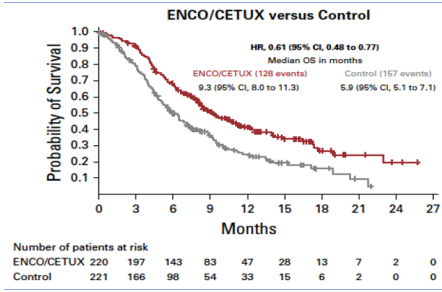
Predictive[5]: No significant benefit from anti-EGFR treatments

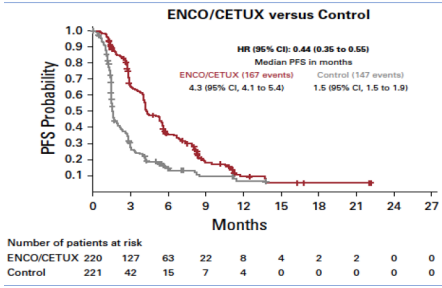
20-30% of BRAFV600E tumors present microsatellite instability (dMMR/MSI-H)[3]



- ✓ The BRAF-V600E mutation is related to the CpG island methylator phenotype[6]
- ✓ MLH1 promoter gene is silenced by hypermethylation (sporadic MSI phenotype)[6]

BEACON





1.Sorbye H et al. PLoS One 2015; 2.Tran B et al. Cancer 2011; 3. Venderbosch S et al. Clin Cancer Res 2014; 4. Seligmann JF et al. Ann Oncol 2017; 5. Rowland A et al. Br J Cancer 2015; 6. Weisenberger DJ et al. Nat Genet 2006; 7. Barras D et al. Clin Cancer Res 2017; 8. Kopetz S et al. J Clin Oncol 39, 2021; 9. Middleton G et al. Clin Cancer Res 20201. Kopetz S et al. N Engl J Med 2019; 2. Tabernero J et al J Clin Oncol 2021

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Encorafenib, Cetuximab, and mFOLFOX6 in *BRAF*-Mutated Colorectal Cancer

E. Elez,[1,2] T. Yoshino,[3] L. Shen,[4] S. Lonardi,[5] E. Van Cutsem,[6,7] C. Eng,[8] T.W. Kim,[9] H.S. Wasan,[10] J. Desai,[11,12] F. Ciardiello,[13] R. Yaeger,[14] T.S. Maughan,[15] V.K. Morris,[16] C. Wu,[17] T. Usari,[18] R. Laliberte,[19] S.S. Dychter,[20] X. Zhang,[21] J. Tabernero,[1,2,22] and S. Kopetz,[16] for the BREAKWATER Trial Investigators*

BREAKWATER: Study Design

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

R 1:1:1[a,b] N=637

- EC (n=158)
- EC + mFOLFOX6 (n=236)
- SOC (n=243)[c]

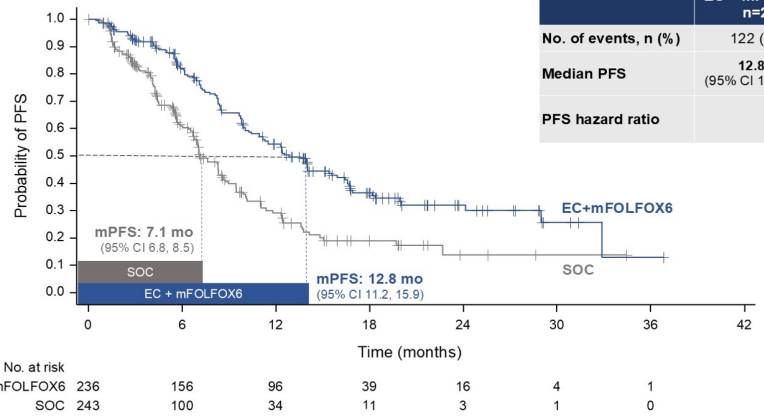
Stratified by regions (US/Canada vs Europe vs Rest of World) and ECOG PS (0 vs 1)

Dual primary endpoints:
PFS by BICR
ORR[d] by BICR

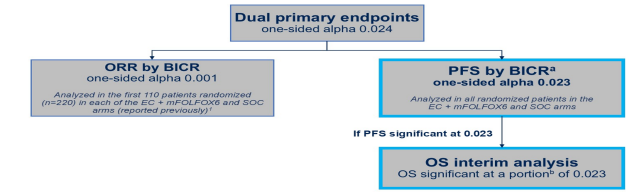
Key secondary endpoint:
OS

We present the primary analysis of PFS by BICR and a second interim analysis of OS in the EC + mFOLFOX6 and SOC arms, the efficacy data in the EC arm, and safety data in all arms

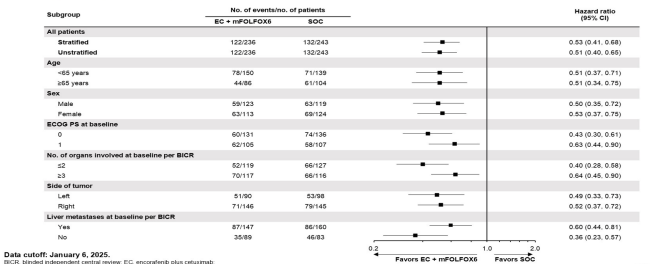
PFS by BICR (EC + mFOLFOX6 and SOC)



	EC + mFOLFOX6 n=236	SOC n=243
No. of events, n (%)	122 (51.7)	132 (54.3)
Median PFS	**12.8 mo** (95% CI 11.2, 15.9)	**7.1 mo** (95% CI 6.8, 8.5)
PFS hazard ratio	**0.53** (95% CI 0.407, 0.677) ***P*<0.0001**	



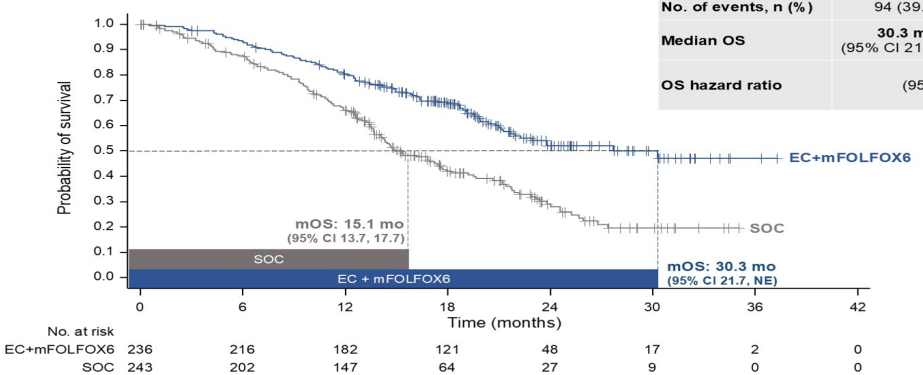
Subgroup Analysis of PFS by BICR (EC + mFOLFOX6 and SOC



Elez E et al, Proc ASCO 2025, NEJM 2025

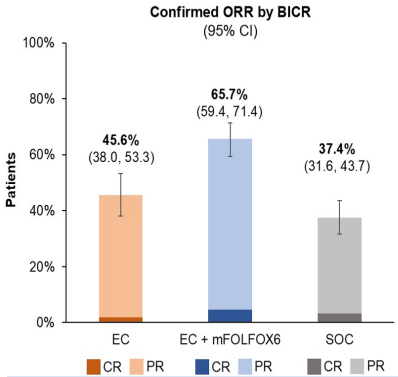
OS (EC + mFOLFOX6 and SOC)

	EC + mFOLFOX6 n=236	SOC n=243
No. of events, n (%)	94 (39.8)	148 (60.9)
Median OS	**30.3 mo** (95% CI 21.7, NE)	**15.1 mo** (95% CI 13.7, 17.7)
OS hazard ratio	**0.49** (95% CI 0.375, 0.632) ***P*<0.0001**[a]	



Data cutoff: January 6, 2025. [a]**Exceeding the threshold for statistical significance in this interim analysis.**
EC, encorafenib plus cetuximab; mFOLFOX6, modified fluorouracil/leucovorin/oxaliplatin; NE, not estimable; SOC, standard of care; mOS, median overall survival

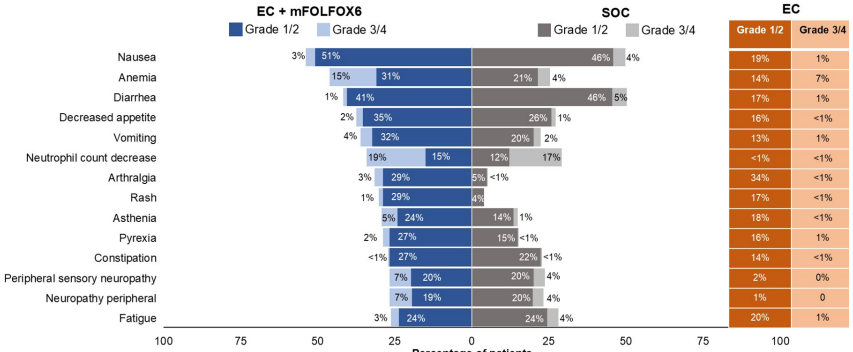
Best Overall Response by BICR (All Randomized Patients)



Confirmed Best Overall Response, TTR, and DOR by BICR

All randomized patients	EC n=158	EC + mFOLFOX6 n=236	SOC n=243
Confirmed best overall response, n (%)[a]			
CR	3 (1.9)	11 (4.7)	8 (3.3)
PR	69 (43.7)	144 (61.0)	83 (34.2)
SD	57 (36.1)	50 (21.2)	85 (35.0)
PD	12 (7.6)	8 (3.4)	21 (8.6)
Responders	**n=72**	**n=155**	**n=91**
TTR, median (range), weeks	6.6 (4.3 to 86.4)	7.0 (5.1 to 103.6)	7.3 (5.4 to 48.0)
DOR, median (95% CI), months	7.0 (4.2, 11.6)	13.9 (10.9, 18.5)	10.8 (7.6, 13.4)
Patients with a DOR of ≥6 months, n (%)	29 (40.3)	110 (71.0)	38 (41.8)
Patients with a DOR of ≥12 months, n (%)	15 (20.8)	54 (34.8)	16 (17.6)

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

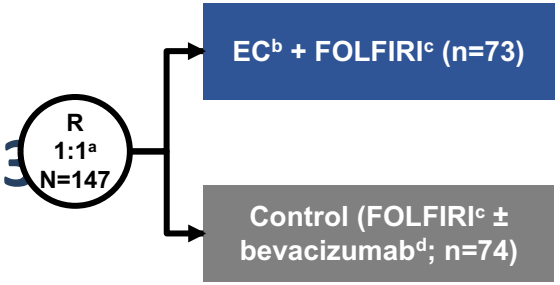


Data cutoff: January 6, 2025.
[a]**Frequency is based on the EC + mFOLFOX6 arm.**
EC, encorafenib plus cetuximab; mFOLFOX6, modified fluorouracil/leucovorin/oxaliplatin; SOC, standard of care; TEAE, treatment-emergent adverse event.

EC + mFOLFOX6 is practice changing as a new SOC for BRAF V600E-mutant mCRC, including in the first-line setting

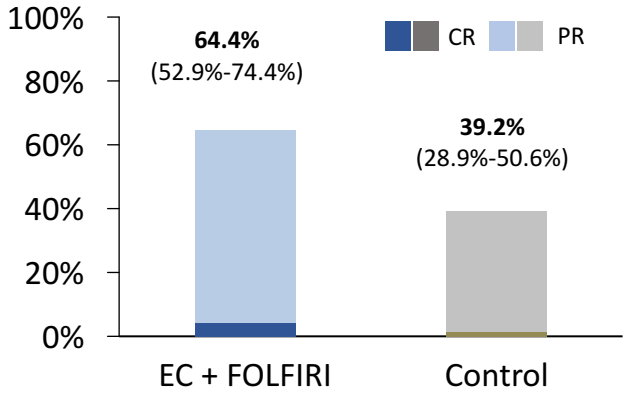
Elez E et al, Proc ASCO 2025, NEJM 2025

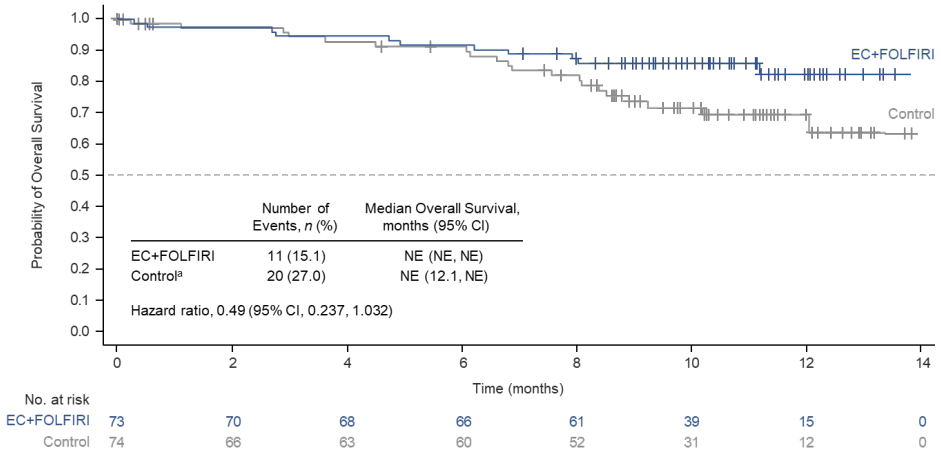
BREAKWATER cohorte 3



Confirmed ORR by BICR

Odds ratio (95% CI): 2.756 (1.420-5.348)
One-sided P-value=0.0011



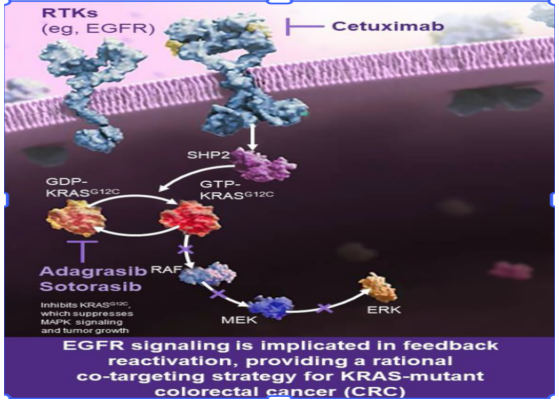


Data are immature but showed a trend for OS improvement with EC + FOLFIRI vs control.

Copete et al, ASCO GI 2026.

CCRm KRAS MUTATED G12C

3-4% de CCRm



Trials showing efficacy of ≥2L anti-EGFR agents + KRAS G12C inhibitors for KRAS G12C mCRC

Phase I/II KRYSTAL-1 trial[1]

	Cetuximab + adagrasib* (n=94)
ORR per BICR (primary endpoint), % (95% CI)	34 (25–45)
ORR per investigators assessment, % (95% CI)	43 (32–53)
mPFS per BICR, months (95% CI)	6.9 (5.6–7.4)
mOS, months (95% CI)	16.0 (13.3–18.8)

Phase III CodeBreaK 300 trial[2]

	960 mg sotorasib + panitumumab (n=53)	Trifluridine/ tipiracil or regorafenib (n=54)	HR (95% CI)
ORR, % (95% CI)	30 (18.3–44.3)	2 (0–9.9)	-
mPFS (primary endpoint), months (95% CI)	5.7 (4.2–7.5)	2.0 (1.9–3.9)	0.45 (0.29–0.72)
mOS, months (95% CI)	NE (8.6–NE)	10.3 (7.0–NE)	0.70 (0.41–1.18)

1. Yaeger R, et al. ASCO GI 2025 (Abstract No. 131 – poster); 2. Pietrantonio F, et al. J Clin Oncol 2025;43:2147–2154.

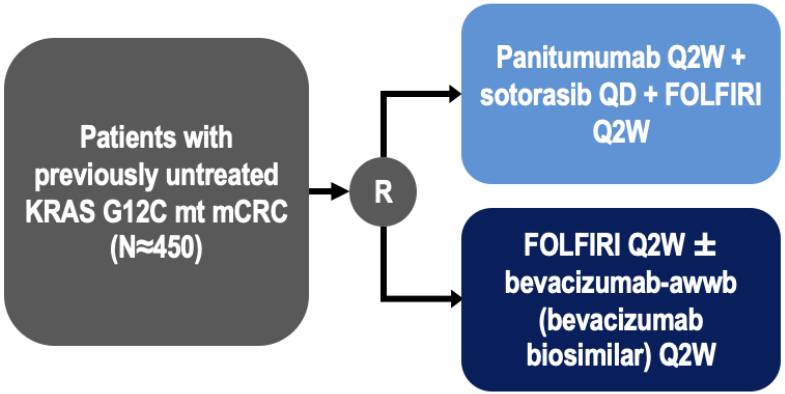
CCRm KRAS MUTATED G12C

Ongoing phase III trials in 1L: anti-EGFR agents + KRAS G12C inhibitors in KRAS G12C mt mCRC

CodeBreaK 301

Phase III trial in 1L KRAS G12C mt mCRC

Primary endpoint: PFS per RECIST v1.1

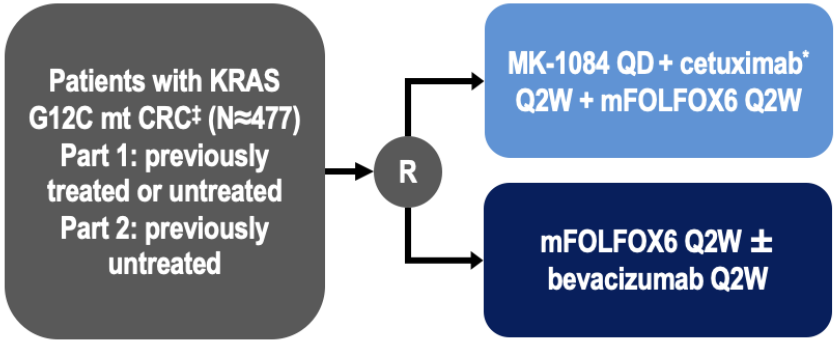


Estimated primary completion: Jan 2028

KANDLELIT-012

Phase III trial in 1L† KRAS G12C mt advanced CRC‡

Primary endpoints: DLTs, AEs,§ and PFS



Estimated primary completion: Aug 2029

1. NCT06252649. 2. NCT06997497.

RAS inhibition: Updated and new results

Long-term safety and efficacy of sotorasib plus panitumumab and FOLFIRI for previously treated *KRAS* G12C-mutated metastatic colorectal cancer: CodeBreaK 101 (phase 1b)

John H. Strickler,[1] Y
Jane Nolte-Hippenm

The KRAS G12C Inhibitor MK-1084 for *KRAS* G12C-Mutated Advanced Colorectal Cancer: Results From KANDLELIT-001

Iwona Ługowska,[1] Matteo S
Joon Oh Park,[7] Victor More
Ruihua Xu,[13] Ruth Perets,[14]
Yewon (Sofia) Choi,[17] Carlo

Efficacy and safety of olomorasib, a second-generation KRAS G12C inhibitor, plus cetuximab in KRAS G12C-mutant advanced colorectal cancer

Antoine Hollebecque[1], Takafumi Koyama[2], Yutaka Fujiwara[3], Yonina R. Murciano-Goroff[4], Philippe Cassier[5], Natraj R. Ammakkanavar[6], Dustin Deming[7], Carlos-Alberto Gomez-Roca[8], Sae-Won Han[9], Mohamedtaki A. Tejani[10], Anthony B. El-Khoueiry[11], Nagla F. Abdel Karim[12], Samantha Bowyer[13], Victor Lin[14], Samuel C. McNeely[15], Xin T. You[15], Aaron Chen[15], Aaron Fink[15], Melinda D. Willard[15], Yasutoshi Kuboki[16]

Strickler JH et al., Lugowska I et al., Houllebecque A et al., all ASCO 2025; #3507 #3508 #3509

CCRm HER-2 +

2-5% CCRm RAS/BRAF WT MSS

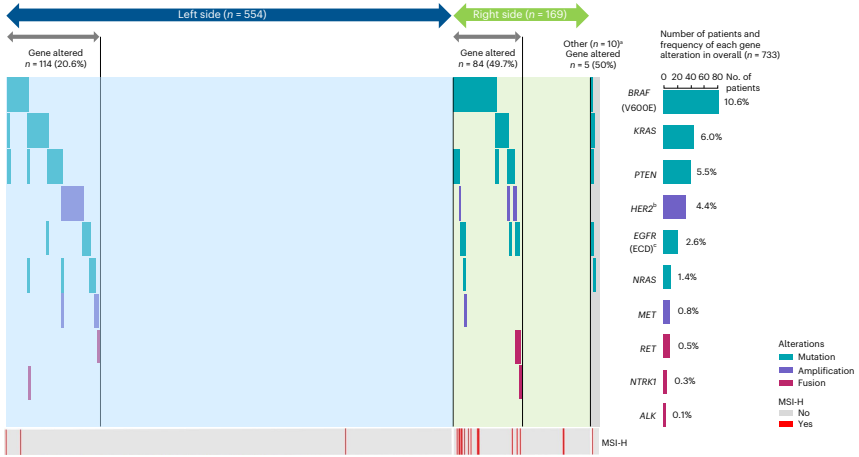
Trial	Treatment	Her2 definition	N	ORR (%)	PFS (m)	OS (m)	Grade ≥ 3 EAs (% of patients)
HERACLES[1-3] (phase II trial)	Trastuzumab + Lapatinib	▪ KRAS wt ▪ HER2 3+ or HER2 2+/FISH+	27	28	4.7	10	Fatigue 15%, rash 4%
HERACLES B[4] (phase II trial)	TDM1 + Pertuzumab	▪ KRAS wt ▪ HER2 3+ or HER2 2+/FISH+	31	10	4.8	NR	Thrombocytopenia 6.5%
MyPathway[5] (phase II trial)	Trastuzumab + Pertuzumab	▪ HER2 amplif (ISH or NGS) ▪ HER2 3+ (IHC)	56 KRASwt 43	32 KRASwt: 40	2.9 KRASwt: 5.3	11.5 KRASwt: 14	Gastrointestinal 8%, left ventricular dysfunction 2%
Mountaineer[6] (phase II trial)	Trastuzumab + Tucatinib	▪ RAS wt ▪ HER2 3+ or HER2 2+/FISH+ ▪ HER2 amplif (NGS)	84	38.1	8.2	24.1	Hypertension 7%, Diarrhea 3%
Destiny-CRC01[7,8] (phase II trial)	Trastuzumab deruxtecan	▪ RAS / BRAF wt ▪ HER2 3+ or HER2 2+/FISH+ (Coh A) ▪ HER2 2+ /FISH- (Coh B) ▪ HER2 1+ (Coh C)	78 Coh A: 53 Coh B: 7 Coh C: 18	Coh A: 45.3 * Coh B y C: no responses	6.9	15.5	Thrombocytopenia 48.7%, fatigue 10%, nausea 2%, interstitial lung disease 3.9% (incluiding two treatment-related deaths).
Destiny-CRC02[9] (phase II trial)	Trastuzumab deruxtecan	▪ RAS wt + **mut** ▪ HER2 3+ or HER2 2+/FISH+	82 (5.4mg/Kg) 40 (6.4mg/Kg)	37.8 (5.4mg/Kg) 27.5 (6.4mg/Kg)	5.8 (5.4mg/Kg) 5.5 (6.4mg/Kg)	13.4 (5.4mg/Kg) NE (6.4mg/Kg)	Neutropenia 16% y 26%, anemia 7% y 21%, thrombocitopenia 5% y 10%, nausea 7% y 0% (5.4 y 6.4 mg/kg, respectively) ^

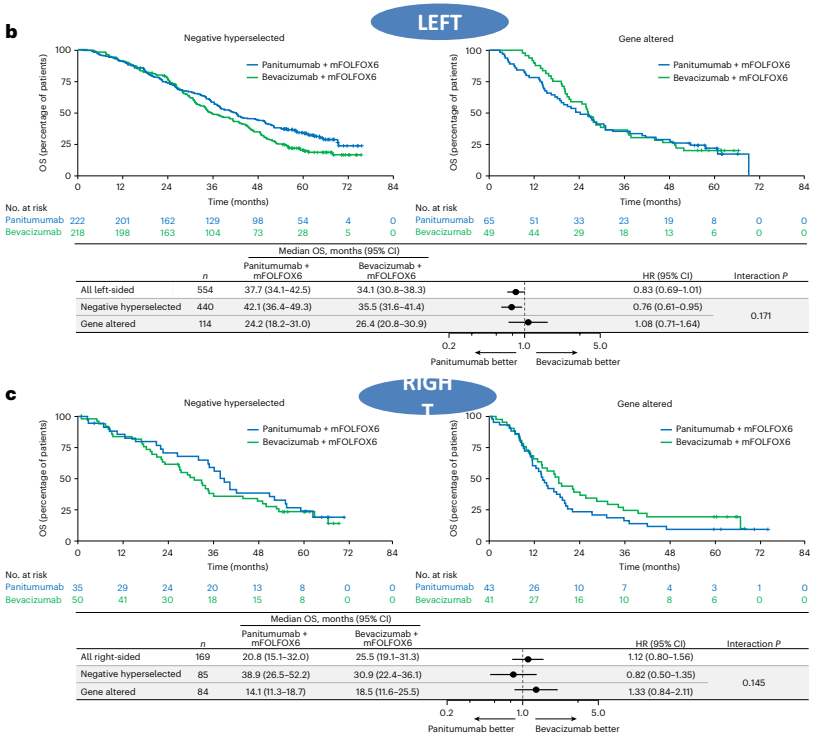
ORR: objetive response rate. PFS: progression-free survival. m: months. OS: overall survival. EAs: adverse events. wt: wild type. Amplif: amplification. Coh A: cohort A. Coh B: cohort B. Coh C: cohort C. NR: not reported. NE: not estimable.
* 43.8% in patients previously treated with Her2-target therapy. ^. Pneumonitis gr 1-2: 8.4% y 12.8% (5.4 y 6.4 mg/kg respectively), there was no grade ≥ 3 pneumonitis.

1-Sartore- Bianchi, A. et al. Lancet Oncol. 17, 738–746 (2016), 2. Siravegna, G. et al. Clin. Cancer Res. 25, 3046–3053 (2019), 3. Tosi, F. et al. Clin. Colorectal Cancer 19, 256 262.e2 (2020), 4. Sartore- Bianchi, A. et al. ESMO Open 5, e000911 (2020), 5. Meric- Bernstam, F. et al. Lancet Oncol. 20, 518–530 (2019), 6. Strickler JH, et al. Lancet Oncol. 24:496-508 (2023), 7. Siena, S. et al. Lancet Oncol:779-789 (2021), 8. Yoshino T, et al. Nature Communications. 14:3332 (2023), 9. Raghav K et al. Lancet Oncol 2014;25:1147-62.

Tabla de elaboración propia. No se pretende hacer una comparación directa de los estudios.

PARADIGM: Hiperselección de RAS nativos





Shitara et al, Nat Med 2024.

Hiper/ultraselección en 1L a través del ADNtc

	POPULATION	STRATEGY of HYPERSELECTION	mOS (months)
PRESSING[1]	1st line anti-EGFR (N: 94) *RAS/BRAF WT*	*HER 2/MET* amp, *PIK3CA* exon 20 mut, *NTRK/ROS1/ALK/RET* fus, pMMR	17.3 vs 15.2 (NS)
PRESSING 2[2]	Anti-EGFR any line (N: 650) *RAS / BRAF* WT, MSS, *POLE* ED WT, PRESSING negative	*NTRKs*, *ERBB3*, *NF1*, *MAP2K1/2/4*, *AKT2* mut; *PTEN/NF1* loss; *ERBB3*, *FGFR2*, *IGF1R*, *KRAS*, *ARAF*, and *AKT1-2* ampl; *EGFR* rearrangements.	49.9 vs 22.6
PANDA[3]	Phase II. FOLFOX –Pani vs 5FU-Pani (N: 147) *RAS/BRAF* WT. Elderly population	PRESSING PANEL + *MAP2K1*, *PTEN* mut	29.5 vs 20
PANAMA[4]	Phase III. mFOLFOX6 + Pani -> 5FU +/- Pani (N: 202) *RAS* WT. Maintenance	*KRAS, NRAS, BRAF* (V600E), *AKT1*, *ERBB2*, *PIK3CA* exon 9/20, *PTEN*, *ALK1* mut, *HER2/neu* amp (IHC)	28.7 vs 22.2
FIRE 3[5]	Fase III. FOLFIRI –Cet vs FOLFIRI – Bev (N: 171) RAS / BRAF WT, pMMR	PRESSING-1 / PRESSING-2 (+ 7.6% alterations in PRESSING -1 neg)	38.5 vs 27.5
PARADIGM[6]	Phase III FOLFOX-Pani vs FOLFOX-Beva (N: 733) *RAS* WT (basal tissue)	*PTEN/EGFR/ KRAS /BRAF* mut, *HER 2 /MET* amp, *ALK/RET/NTRK1* fus, MMR	41.4 vs 18.7

1. Cremolini, Ann Oncol 2017; 2. Randon, JCO Prec Oncol 2022; 3. Lonardi, J Clin Oncol 2023; 4. Stahler, Clin Can Res 2024; 5. Weiss, Eur J Cancer 2025; 6. Shitara, Nat Med 2024

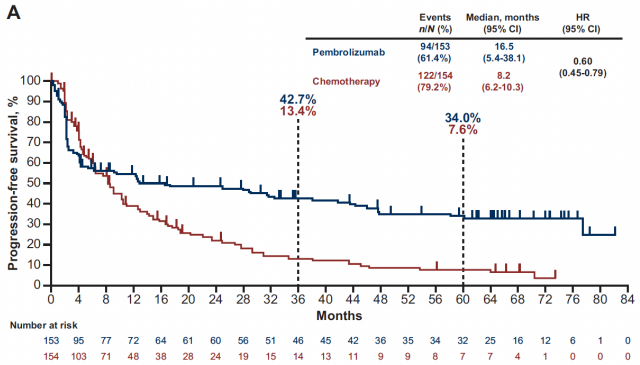
Mulet N, Simposio TTD 2025 (por cortesía de la Dra Mulet).

Inmunoterapia en dMMR/MSI

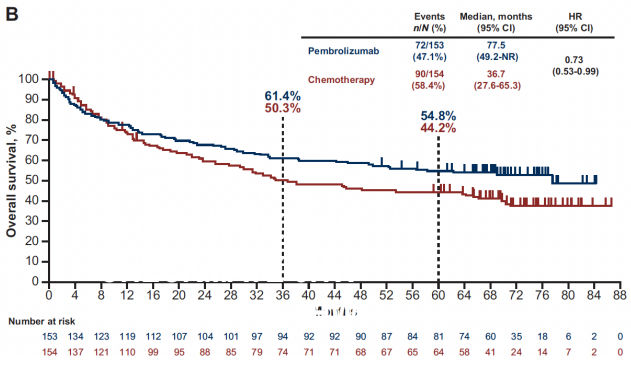
Inmunoterapia en pMMR

KEYNOTE-177: 1L Pembrolizumab vs CT +/- MAb (INV choice) in MSI mCRC

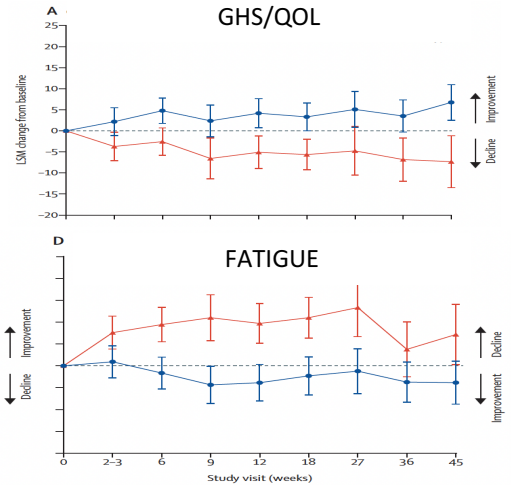
Progression-Free Survival



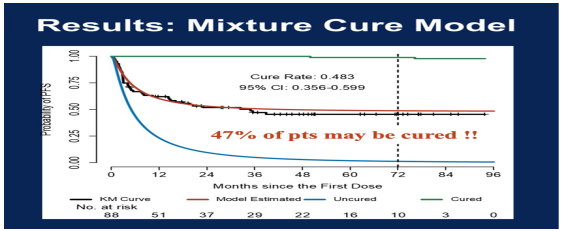
Overall Survival



HR-QoL



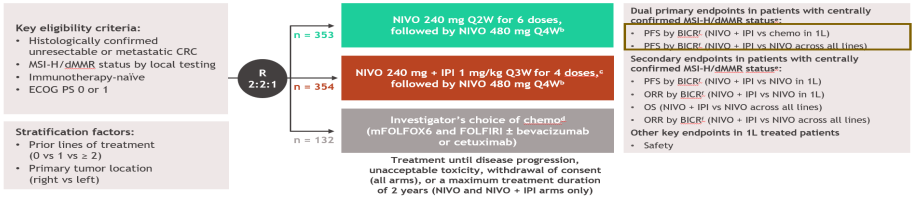
- ✓ Long-term improvement in PFS (34% vs 8% progression-free at 5y)
- ✓ Strong trend towards improved OS (▲10%) despite >60% crossover
- ✓ Lower toxicity (22% vs 67% G3-5 AEs) and improved QoL

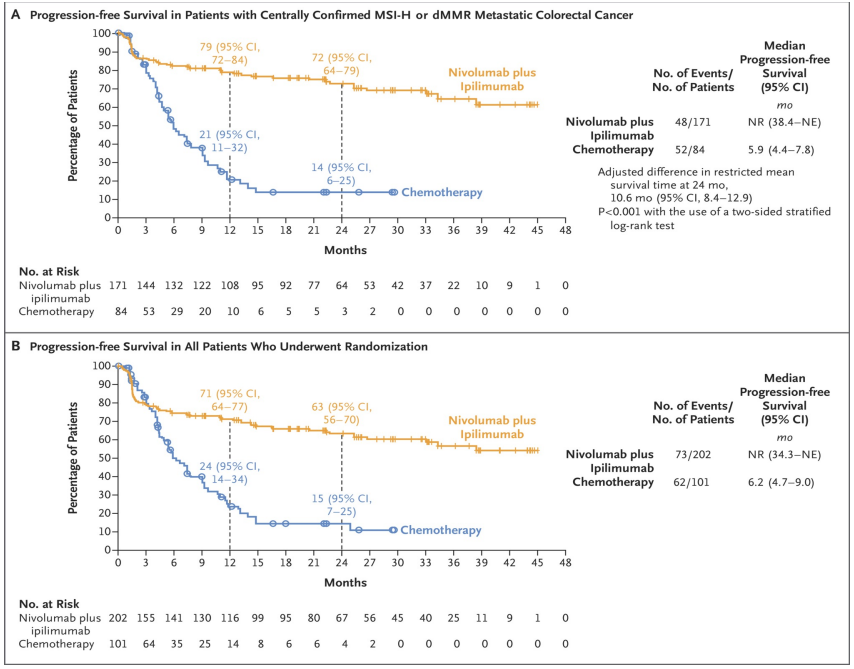


Andre T, NEJM 2020 & Lancet 2021 & Ann Oncol 2025; Diaz L, Lancet 2022; Beber K ASCO 2025

Study design: CheckMate 8HW

- CheckMate 8HW is a randomized, multicenter, open-label phase 3 trial[a]



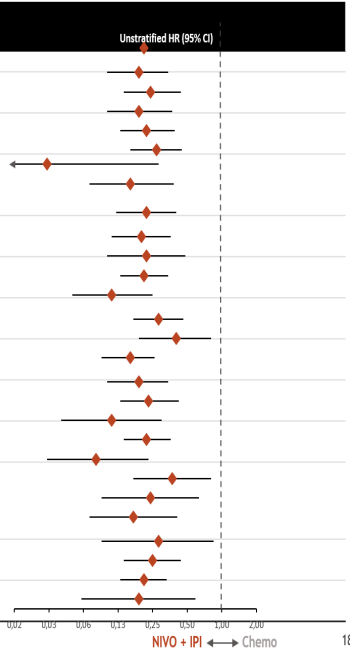


Andre T, ASCO GI 2024, NEJM 2024

Primary Endpoint: NIVO + IPI vs Chemotherapy in the 1L setting; PFS by BICR in centrally confirmed dMMR/MSI mCRC

1L all treated patients	NIVO + IPI (n = 200)		Chemo (n = 88)	
	Any grade	Grade 3/4	Any grade	Grade 3/4

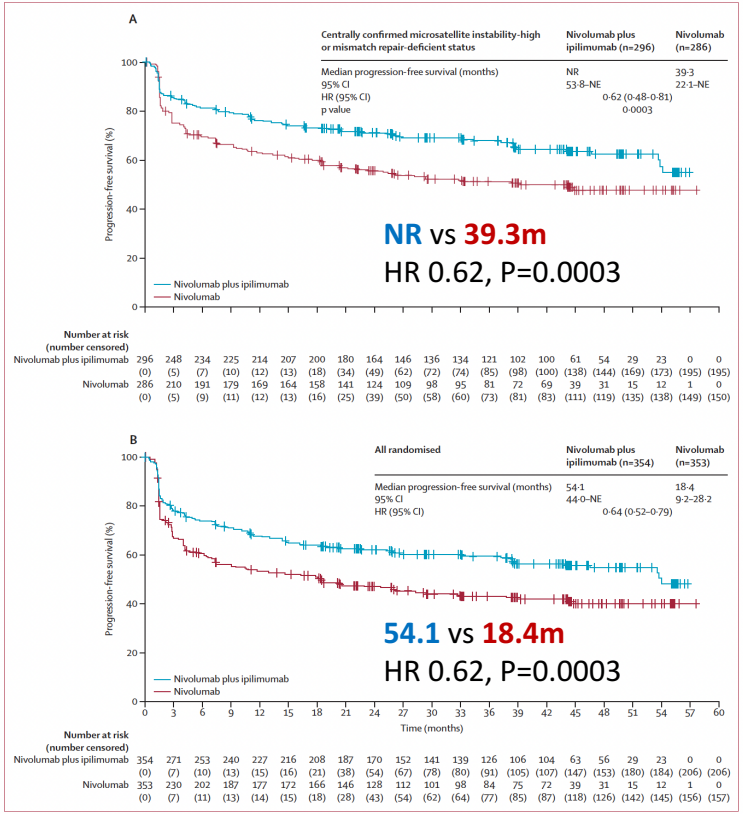
Category (1L centrally-confirmed MSI-H/dMMR)	Subgroup	Median PFS,[a] months NIVO + IPI	Median PFS,[a] months Chemo	Unstratified HR
Overall (N = 255)		NR	5.9	0.21
Age, years	< 65 (n = 138)	NR	5.7	0.19
	≥ 65 (n = 117)	NR	5.9	0.24
Sex	Male (n = 117)	NR	5.9	0.19
	Female (n = 138)	NR	6.2	0.22
Region	US/Canada/Europe (n = 167)	NR	5.7	0.27
	Asia (n = 28)	NR	7.4	0.03
	Rest of world (n = 60)	NR	6.2	0.16
ECOG PS	0 (n = 142)	NR	9.0	0.22
	≥ 1 (n = 113)	NR	4.2	0.20
Tumor sidedness	Left (n = 70)	NR	4.4	0.22
	Right (n = 185)	NR	7.1	0.21
Liver metastases[a]	Yes (n = 87)	NR	5.9	0.11
	No (n = 166)	NR	5.4	0.28
Lung metastases[a]	Yes (n = 53)	13.2	4.9	0.40
	No (n = 200)	NR	6.2	0.16
Peritoneal metastases[a]	Yes (n = 115)	NR	4.4	0.19
	No (n = 138)	NR	7.4	0.23
Tumor cell PD-L1 expression	≥ 1% (n = 55)	NR	3.4	0.11
	< 1% (n = 191)	NR	6.5	0.22
BRAF/KRAS/NRAS mutation status	*BRAF/KRAS/NRAS* all wild type (n = 58)	34.3	5.4	0.08
	BRAF mutant (n = 72)	NR	9.2	0.37
	KRAS or *NRAS* mutant (n = 45)	NR	5.7	0.24
	Unknown (n = 74)	NR	4.9	0.17
Lynch syndrome	Yes (n = 31)	NR	7.4	0.28
	No (n = 152)	NR	6.2	0.25
Prior surgery	Yes (n = 222)	NR	7.1	0.21
	No (n = 33)	NR	3.0	0.19

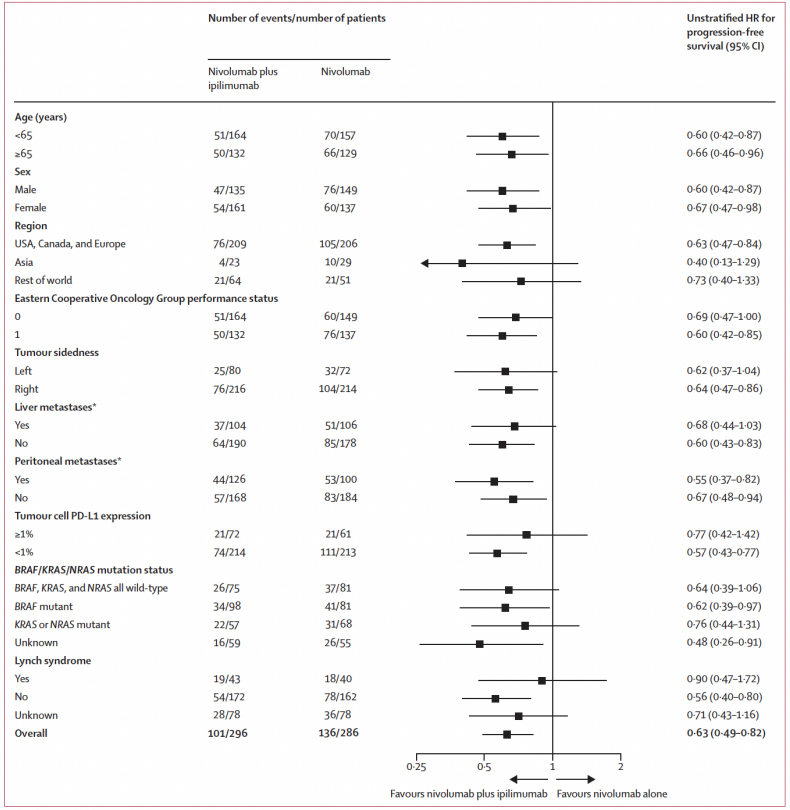


HRs not computed for subgroups with less than 10 patients per treatment arm. [a]Per BICR.

Primary Endpoint: NIVO + IPI vs Nivolumab across all lines

PFS by BICR in centrally confirmed dMMR/MSI mCRC





Andre T, ASCO GI 2025, Lancet 2025

At data cutoff (Aug 2024), median follow-up was 47 months

STELLAR-303 (NCT05425940) Study Design

Patient Population

- Aged ≥18 years
- Documented to not have MSI-H or dMMR status
- mCRC that radiographically progressed on or was refractory or intolerant to prior standard-of-care therapy, which had to include all the following (if approved and available in the country where the patient is randomized):
  - Fluoropyrimidine, irinotecan and oxaliplatin ± anti-VEGF antibody
  - Anti-EGFR antibody (if *RAS* wild type)
  - BRAF inhibitor (if known *BRAF* V600E mutation)

R 1:1
N=901

- Zanzalintinib 100 mg PO QD + Atezolizumab 1200 mg IV Q3W (n=451)*
- Regorafenib 160 mg PO QD (days 1–21 of each 28-day cycle) (n=450)*

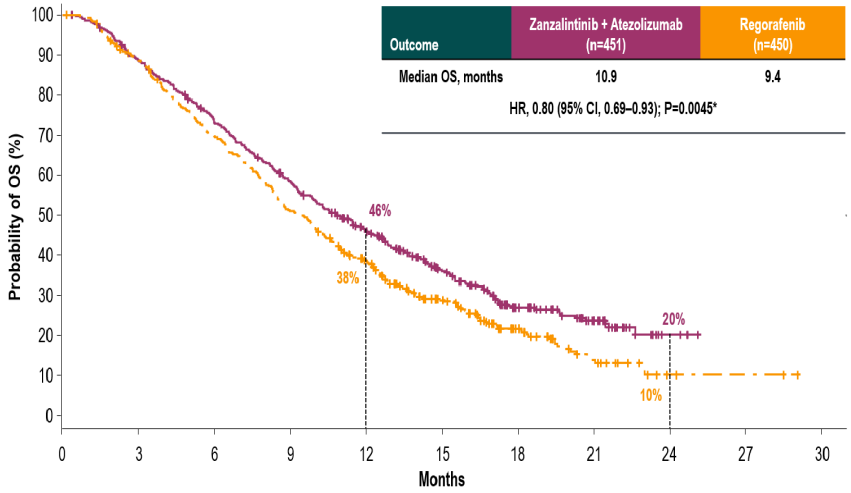
Stratification Factors

- Geographic region (Asia/rest of the world)
- *RAS* status (wild type/mutant)

Endpoints

Dual primary	OS in the ITT population
	OS in patients without liver metastases (nImITT)

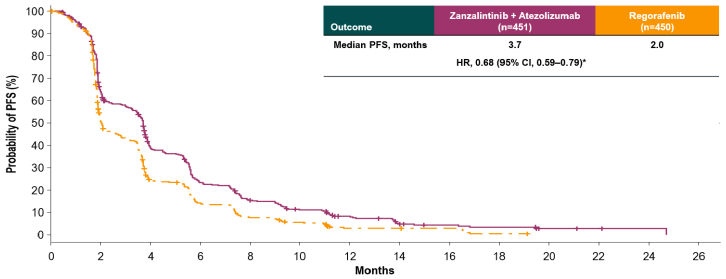
OS Analysis (ITT Population)



Outcome	Zanzalintinib + Atezolizumab (n=451)	Regorafenib (n=450)
Median OS, months	10.9	9.4
HR, 0.80 (95% CI, 0.69–0.93); P=0.0045*		

No. at Risk											
anzalintinib + Atezolizumab	451	396	324	256	189	117	65	33	4	0	0
Regorafenib	450	392	307	225	156	90	47	19	4	2	0

PFS (ITT Population)



Outcome	Zanzalintinib + Atezolizumab (n=451)	Regorafenib (n=450)
Median PFS, months	3.7	2.0
HR, 0.68 (95% CI, 0.59–0.79)*		

No. at Risk														
Zanzalintinib + Atezolizumab	451	265	151	89	57	39	25	12	9	7	3	2	1	0
Regorafenib	450	213	97	55	30	20	7	7	6	1	0	0	0	0

Tox g ¾: Zanzalintinib/Atezo 59% vs Regorafenib 37%

Phase III STELLAR-303 trial

Efficacy data for zanzalintinib + atezolizumab in pretreated MSS/pMMR mCRC[3]

Outcome	Overall population (ZZ-atz vs Reg)	Without liver metastases
mOS, months	10'9 vs 9'4 (HR 0'8, p 0'0045)	15'9 vs 12'8 m (HR 0'79, p 0'0875)
mPFS, months	3'7 vs 2'0 (HR 0'68)	–
ORR, %	4% vs 1%	–

1. Saeed A, et al. Future Oncol 2024;20:1733–1743; 2.Saeed A et al. ESMO 2025

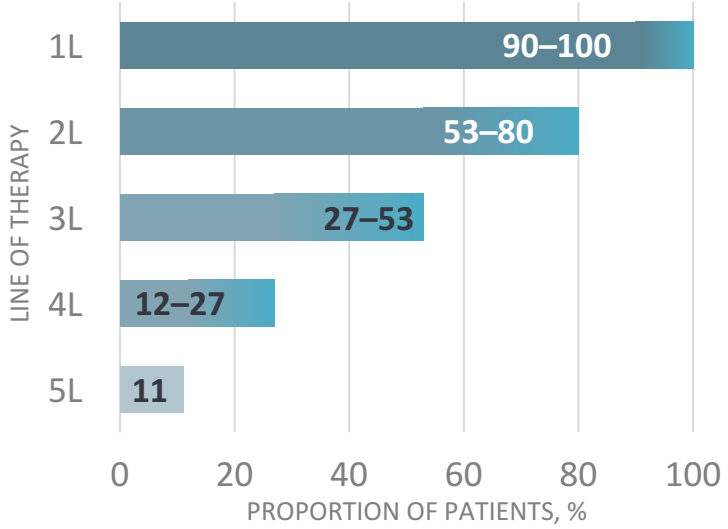
Mejoría de la terapia de secuenciación

1. Fruquintinib (FRESCO)
2. Rechallenge

The proportion of patients receiving therapy and survival rates decline with each successive line of treatment in mCRC

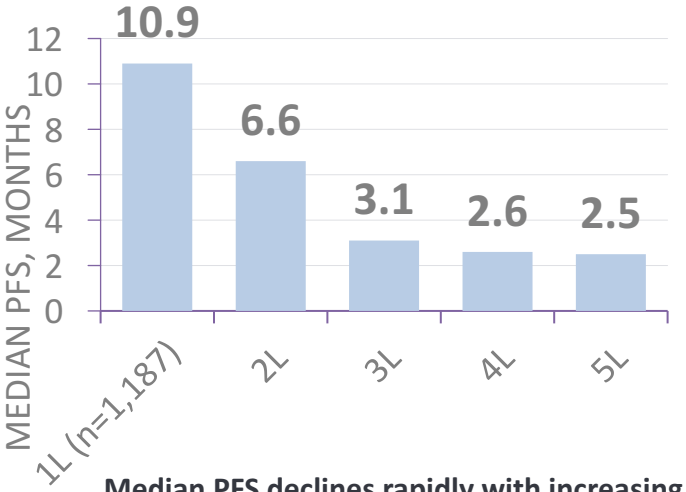
Few patients receive later-line treatment, and survival is generally poor in those who do[1–5]

Patients receiving systemic therapy for mCRC at each line[1-4,*]



The proportion of patients receiving therapy decreases with each line of therapy[1-4]

PFS in patients with mCRC receiving standard treatment by line of therapy[1,†]



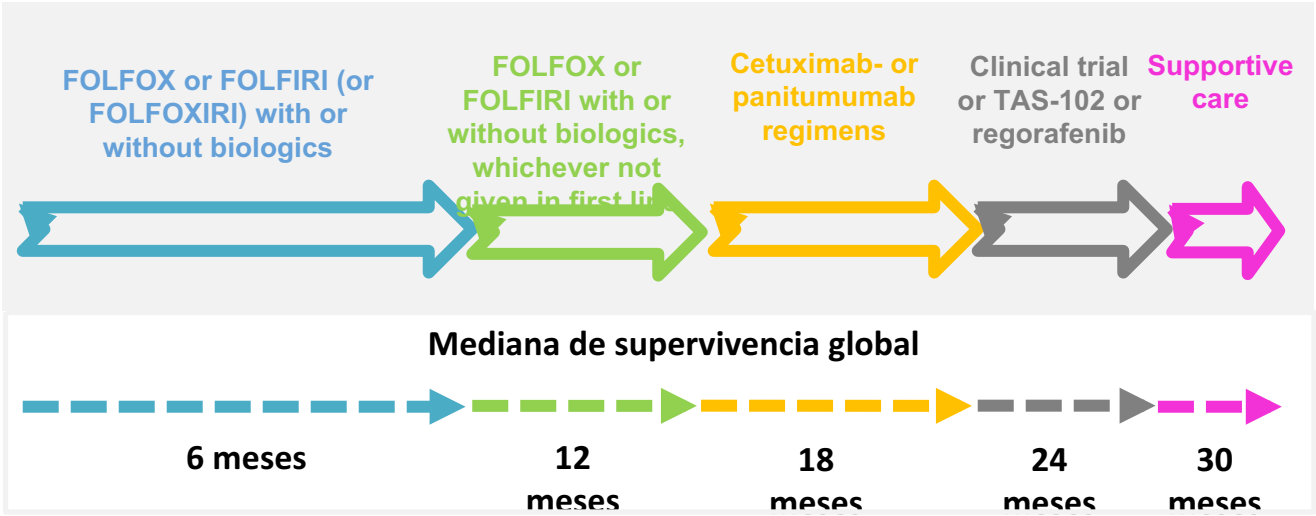
Median PFS declines rapidly with increasing lines of therapy in mCRC[1]

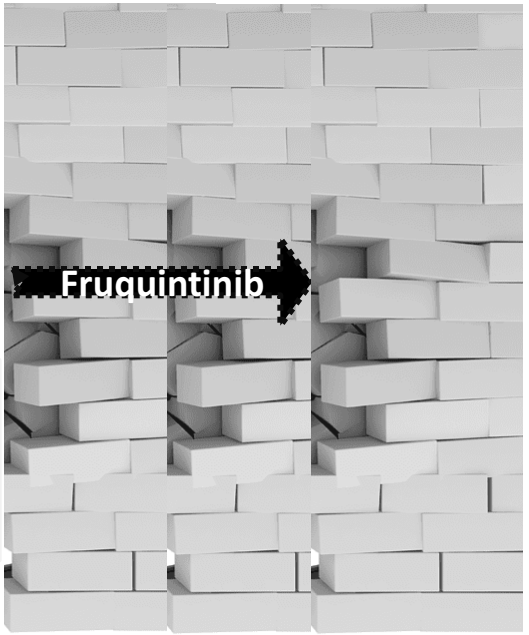
* Data from Italy, Canada, Spain, and the US; †Post hoc analysis of TRIBE/TRIBE2 studies of 1,187 patients with mCRC who received 1L treatment with FOLFOXIRI + bevacizumab, or doublets + bevacizumab

#L, # line; CRC, colorectal cancer; FOLFOXIRI, folinic acid + fluorouracil + oxaliplatin + irinotecan; mCRC, metastatic colorectal cancer; PFS, progression free survival

1. Rossini D, et al. Eur J Cancer 2022;170:64–72; 2. Kennecke H, et al. Curr Oncol 2019;26:e748–54; 3. Aranda E, et al. Clin Transl Oncol 2020;22:1455–62; 4. Abrams TA, et al. J Natl Cancer Inst 2014;106:dji371; 5. Cicero G, et al. Onco Targets Ther 2018;11:3059–63

Secuenciación Terapéutica





Delphi consensus for the third-line treatment of metastatic colorectal cancer

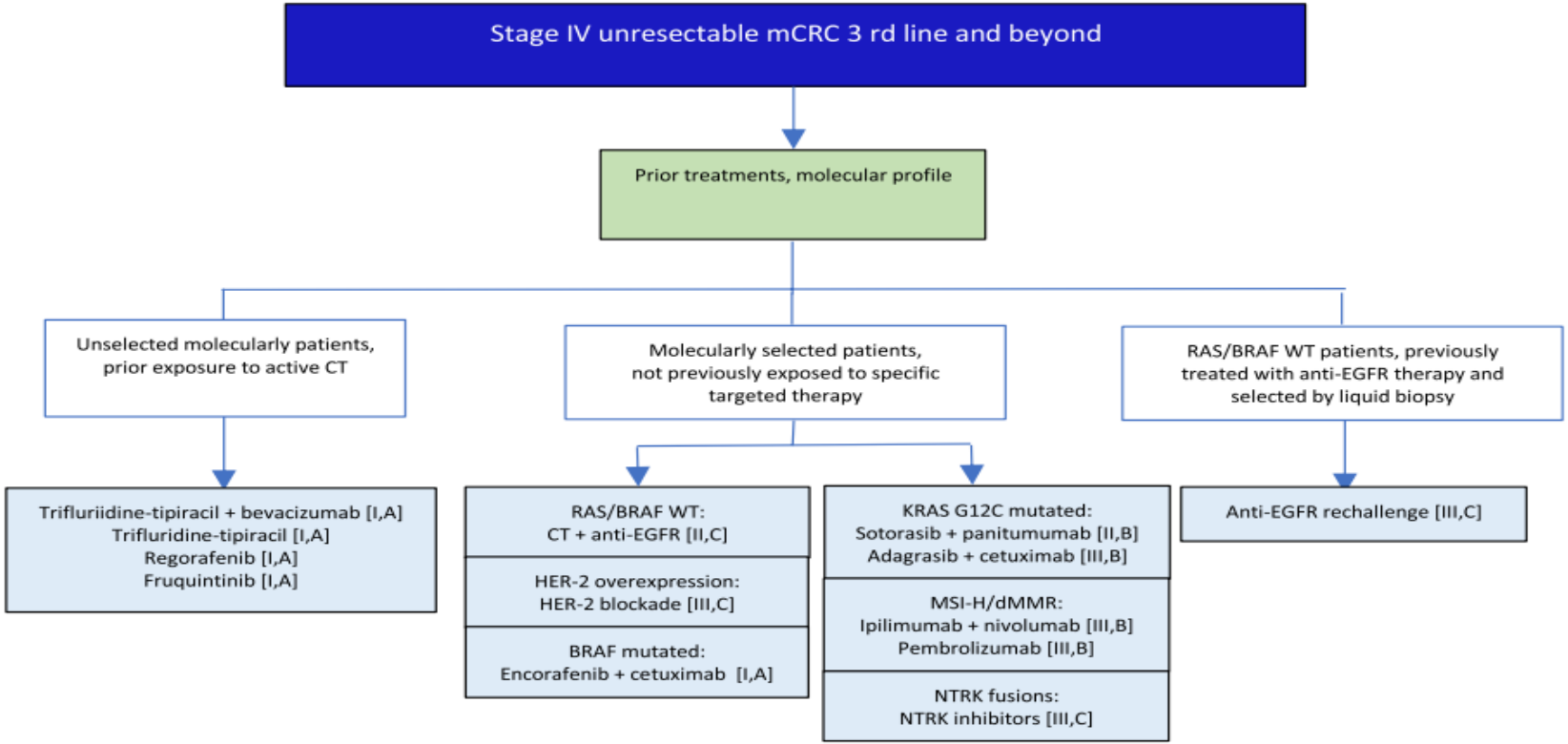
*Mediante un **método Delphi modificado**, **un grupo de 67 expertos** debatió sobre el tratamiento en 3L de pacientes con CCRm*

The objective of 3L is to equally increase survival and improve the quality of life of patients

Patients with mCRC in 3L mostly prefer to receive active treatment rather than only symptomatic treatment

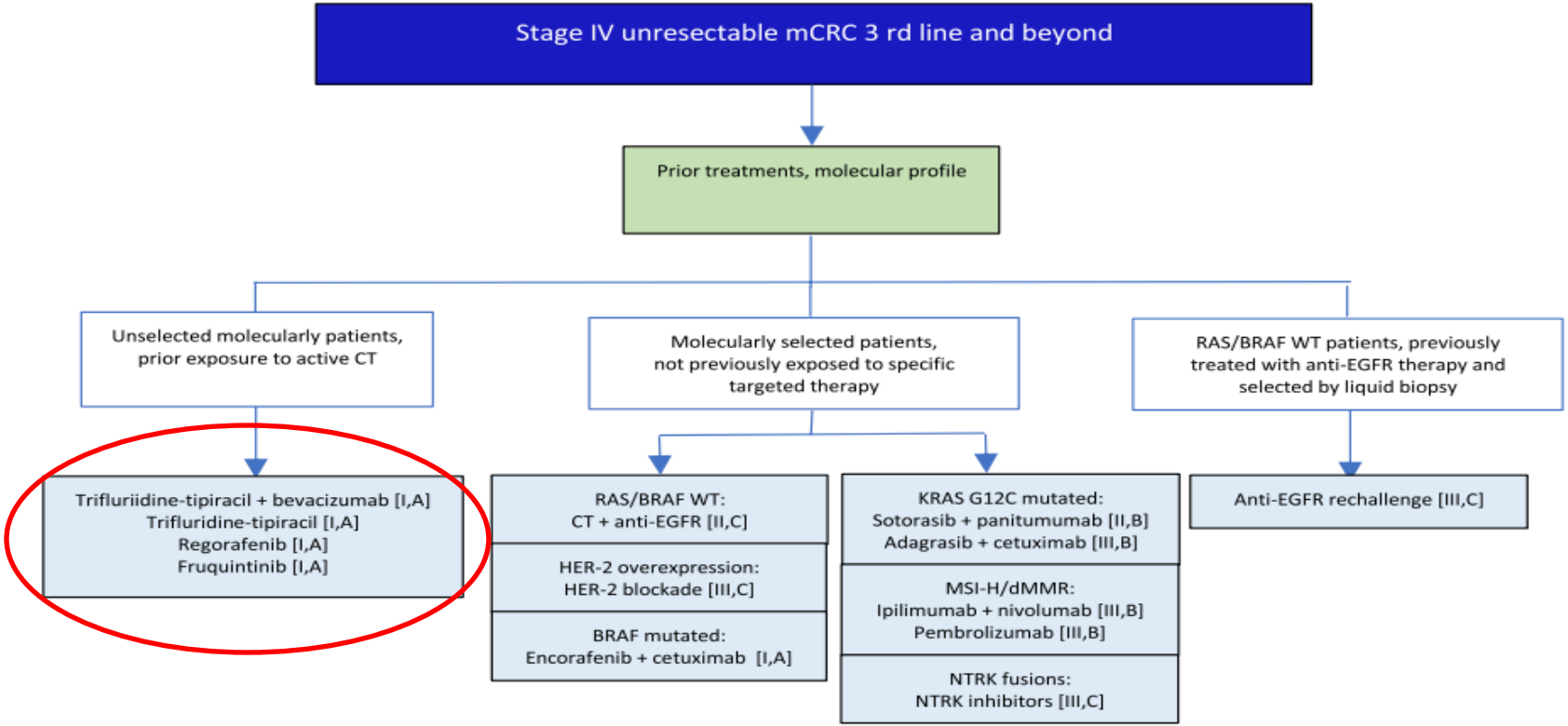
Pilar García Alfonso. Clinical and Translational Oncology 2024

GUIAS SEOM CANCER COLORRECTAL METASTASICO



Clinical and Translational Oncology (2025) 27:1845–1850
https://doi.org/10.1007/s12094-025-03860-x

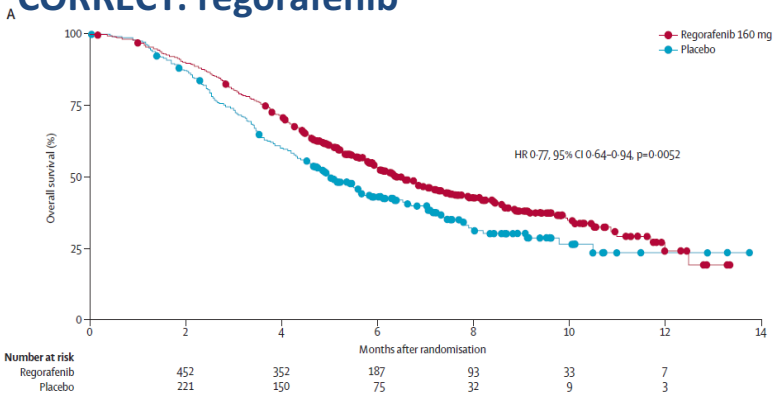
GUIAS SEOM CANCER COLORRECTAL METASTASICO



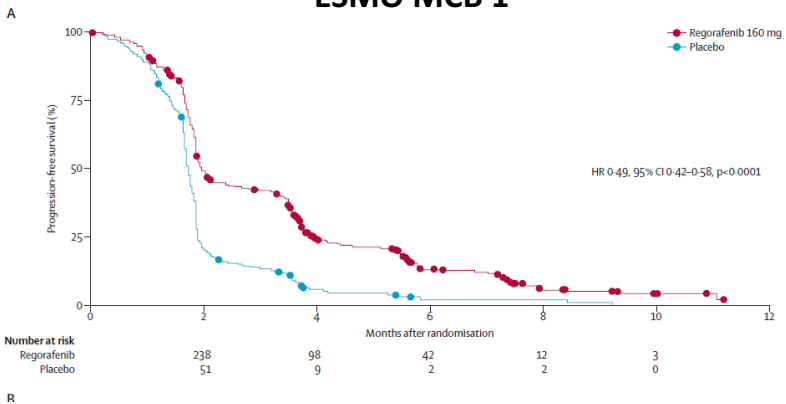
Clinical and Translational Oncology (2025) 27:1845–1850
https://doi.org/10.1007/s12094-025-03860-x

Regorafenib and trifluridine/tipiracil in refractory mCRC

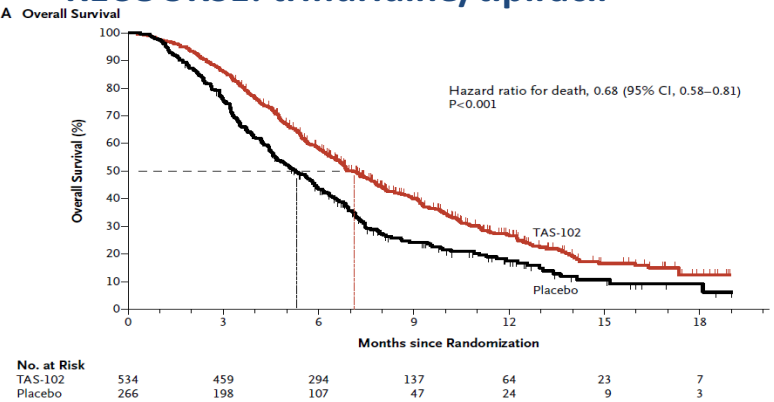
CORRECT: regorafenib



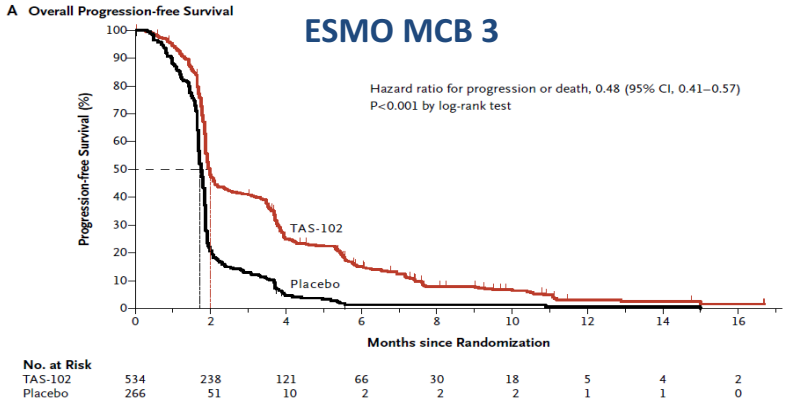
ESMO MCB 1



RECOURSE: trifluridine/tipiracil



ESMO MCB 3



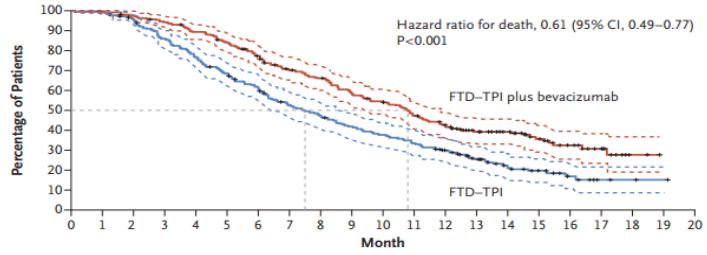
Grothey, Van Cutsem E et al, Lancet 2013; Mayer R, Van Cutsem E, Ohtsu A et al NEJM, 2015

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

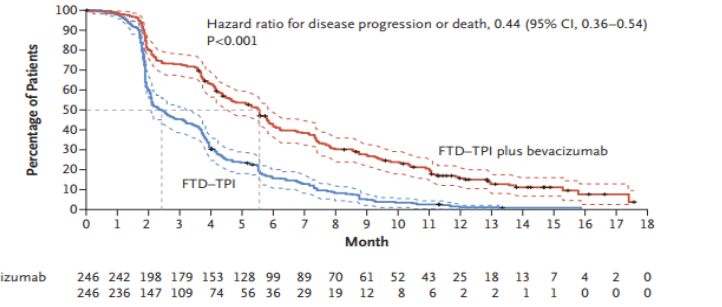
Trifluridine–Tipiracil and Bevacizumab in Refractory Metastatic Colorectal Cancer

A Overall Survival



10,8 vs 7,5
HR 0.68(0,4-0,7
p< 0.001)

B Progression-free Survival



5,6 v 2.4
HR 0,4(0,3-0,5
ps)

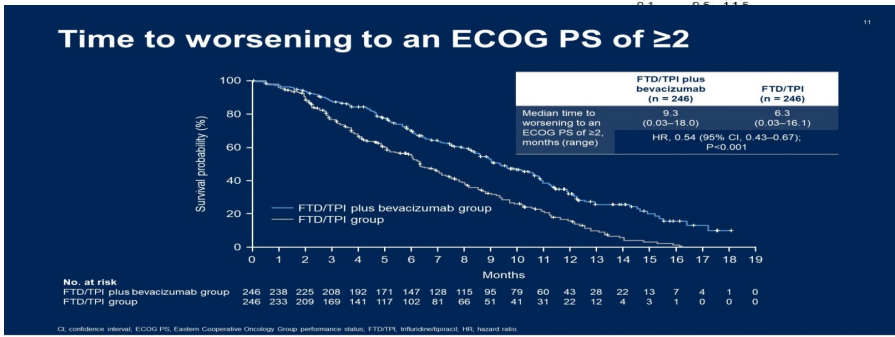
Figure 2. Overall Survival and Progression-free Survival (Intention-to-Treat Population).

The widths of the confidence intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing. The intention-to-treat population included all the patients who had undergone randomization. The dashed gray lines indicate the median values in each panel. The dashed red and blue lines in each panel indicate the upper and lower boundaries of the 95% confidence intervals. The tick marks indicate censored data.

ESMO MCB 4

Figure S1: Overall Survival by Subgroup

Subgroup	FTD/TPI Plus Bevacizumab Group	FTD/TPI Group	FTD/TPI Plus Bevacizumab Group	FTD/TPI Group	Hazard Ratio
	No. of events/total no.		Median overall survival (95% CI)		
Region					
European Union	97/158	121/157	10.6 (9.0–11.8)	7.0 (6.0–8.5)	0.61 (0.47–0.80)
North America	0/8	4/8	—	6.0 (4.2–NE)	<0.01 (<0.01–NE)
Rest of the world	51/80	58/81	10.7 (8.5–14.2)	8.5 (6.3–10.7)	0.70 (0.48–1.02)
Time from diagnosis of first metastasis					
<18 months	65/104	82/105	10.8 (8.8–12.5)	6.1 (5.1–7.4)	0.52 (0.37–0.72)
≥18 months	83/142	101/141	10.8 (9.0–12.1)	8.6 (7.2–10.6)	0.70 (0.53–0.94)
RAS status					
Mutant	103/171	128/170	10.6 (9.0–11.3)	7.5 (6.3–8.6)	0.62 (0.48–0.81)
Wild	45/75	55/76	11.9 (9.0–14.9)	7.1 (5.9–10.9)	0.64 (0.43–0.96)
Location of primary disease					
Left	108/184	120/169	10.7 (9.3–12.2)	8.2 (6.7–9.3)	0.65 (0.50–0.85)
Right	40/62	63/77	10.8 (8.5–11.9)	6.2 (5.2–8.0)	0.59 (0.40–0.87)
ECOG PS					
0	70/119	74/106	10.8 (8.8–14.5)	9.3 (7.7–11.6)	0.74 (0.53–1.02)
≥1	78/127	109/140	10.8 (9.0–11.9)	6.3 (5.4–7.5)	0.54 (0.41–0.73)
Sex					
Female	79/124	85/112	10.7 (9.0–11.4)	6.9 (6.0–9.0)	0.62 (0.46–0.85)
Male	69/122	98/134	10.8 (9.0–14.6)	7.8 (6.5–9.4)	0.62 (0.45–0.84)
Age, years					
<65	89/146	94/129	10.7 (8.5–12.1)	7.5 (6.3–9.3)	0.65 (0.48–0.87)
≥65	59/100	89/117	11.0 (9.4–12.9)	7.2 (6.0–8.8)	0.69 (0.42–0.81)
No. of metastatic sites					
1 or 2	83/152	97/141	11.9 (10.7–15.1)	8.8 (7.5–10.5)	0.62 (0.46–0.83)
≥3	65/94	86/105	8.5 (6.7–10.6)	6.0 (5.2–7.1)	0.66 (0.47–0.91)
Neutrophil:lymphocyte ratio					
<3	66/128	75/115	14.2 (10.8–16.4)	11.0 (8.7–12.5)	0.67 (0.48–0.93)
≥3	81/117	108/131	9.0 (7.5–10.6)	6.0 (5.1–6.8)	0.58 (0.44–0.78)
No. of prior metastatic drug regimens					
1	6/11	11/15	9.9 (8.1–NE)	5.1 (3.9–8.0)	0.35 (0.12–1.0)
≥2	142/235	172/1231	10.8 (9.4–11.9)	7.8 (6.5–8.9)	0.64 (0.51–0.80)
BRAF status					
Mutant	4/8	7/11	11.4 (4.7–NE)	5.9 (3.2–NE)	0.69 (0.20–2.41)
Wild	91/159	116/156	10.8 (9.0–12.2)	7.8 (6.3–9.1)	0.59 (0.45–0.78)
MMR/MSI status					
MSI high/MMR deficient	6/13	7/8	NE (8.6–NE)	5.5 (2.3–13.3)	0.33 (0.11–0.99)
MSI stable or low/MMR proficient	85/139	114/145	10.7 (9.0–11.4)	7.0 (6.0–8.2)	0.57 (0.43–0.76)
Prior bevacizumab					
No	30/68	48/69	15.1 (12.1–NE)	8.1 (6.3–9.7)	0.40 (0.25–0.63)
Yes	118/178	135/177	9.0 (8.3–10.8)	7.1 (6.0–8.5)	0.72 (0.56–0.92)
Prior surgical resection					
No	99/153	113/152	9.0 (8.3–10.8)	6.3 (5.6–7.9)	0.67 (0.51–0.87)
Yes	49/93	70/94	11.9 (10.9–16.4)	9.0 (7.2–10.7)	0.54 (0.37–0.78)
Overall	148/246	183/246	10.8 (9.4–11.8)	7.5 (6.3–8.6)	0.62 (0.50–0.77)



Clinical outcomes of treatments for patients with refractory metastatic colorectal cancer: a systematic literature review and network meta-analysis

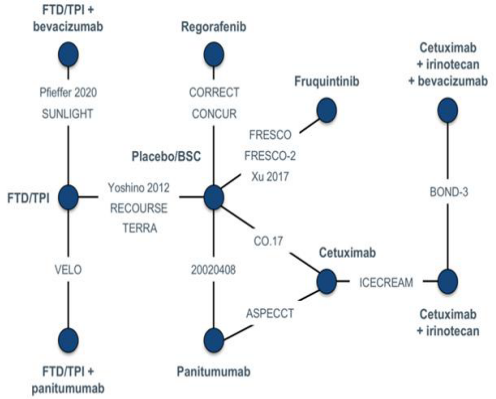


Figure 1. Network of evidence for OS and PFS.
OS, overall survival; PFS, progression-free survival.

Conclusion: NMA results suggest that FTD/TPI + bevacizumab confers clinically relevant improvements in OS and PFS compared with other treatment regimens for refractory mCRC patients, supporting the use of this combination therapy in the third-line treatment setting.

Table 1. Trial characteristics.

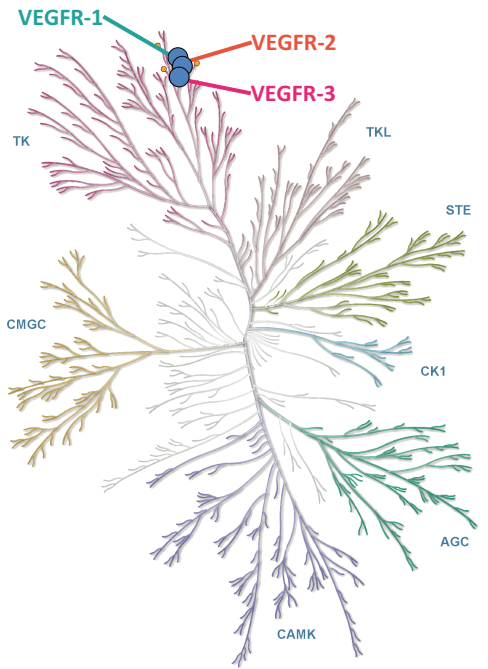
Trial ID	Phase	Masking	Geographical region	Multi-center	Treatments	*N*
20020408 (NCT00113763)[34–42]	II	Open-label	Multinational	Yes	Panitumumab + BSC vs BSC	463
ASPECCT[40–44]	III	Open-label	Multinational	Yes	Panitumumab vs Cetuximab	999
BOND-3 (NCT02292758)[45]	II	Double-blind	US	Yes	Cetuximab + irinotecan + bevacizumab vs Cetuximab + irinotecan + placebo	36
CO.17[46–53]	III	Open-label	Multinational	Yes	Cetuximab + BSC vs BSC	572
CONCUR[54,55]	III	Triple-blind	Asia	Yes	Regorafenib vs Placebo	136
CORRECT (NCT01103323)[56–59]	III	Quadruple-blind	Multinational	Yes	Regorafenib vs Placebo	760
FRESCO[60–63]	III	Double-blind	China	Yes	Fruquintinib vs Placebo	416
FRESCO-2 (NCT04322539)[64,65]	III	Double-blind	Multinational	Yes	Fruquintinib vs Placebo	691
ICECREAM[66]	II	Open-label	Multinational	Yes	Cetuximab vs Cetuximab + irinotecan	53
Pfeiffer 2020[14,67]	II	Open-label	Denmark	Yes	FTD/TPI vs FTD/TPI + bevacizumab	93
RECOURSE (NCT01607957)[12,27–30]	III	Double-blind	Multinational	Yes	FTD/TPI vs Placebo	800
SUNLIGHT[15,68–70]	III	Open-label	Multinational	Yes	FTD/TPI + bevacizumab vs FTD/TPI	492
TERRA (NCT01955837)[71]	III	Double-blind	Asia	Yes	FTD/TPI vs Placebo	406
VELO[72–75]	II	Open-label	Italy	Yes	FTD/TPI + panitumumab vs FTD/TPI	62
Xu 2017 (NCT02196688)[76]	II	Double-blind	China	Yes	Fruquintinib + BSC vs Placebo + BSC	71
Yoshino 2012[77]	II	Double-blind	Japan	Yes	FTD/TPI vs Placebo	169

BSC, best supportive care; FTD/TPI, trifluridine/tipiracil; US, United States.

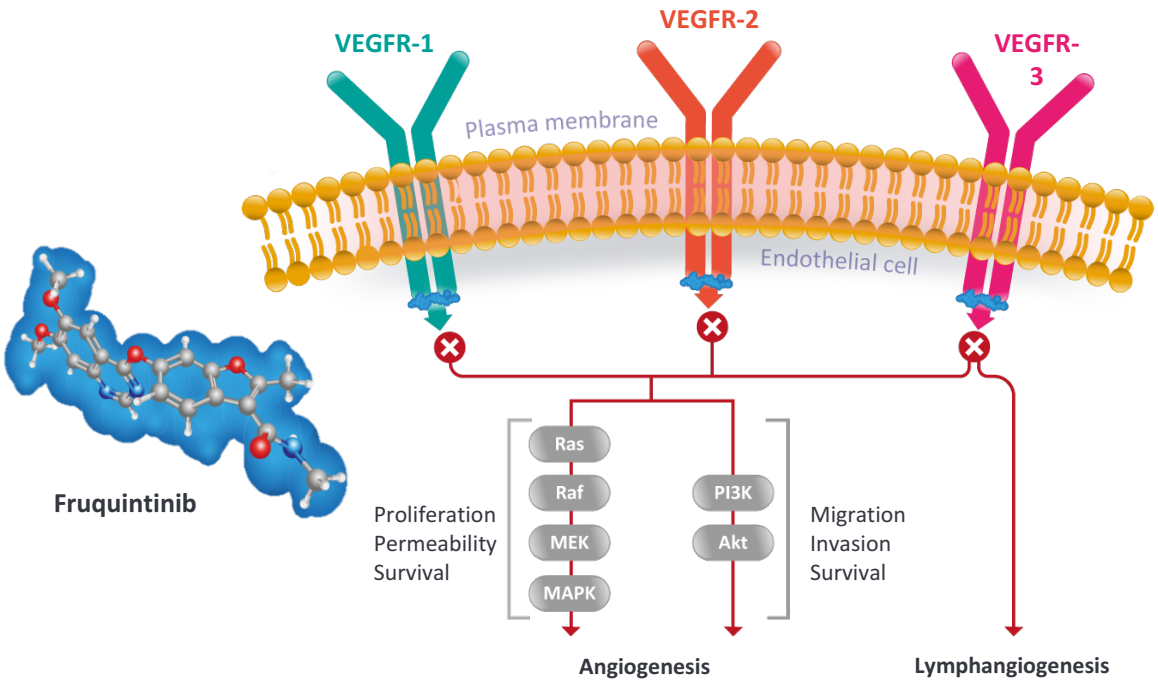
Taieb J, et al. Ther Adv Med Oncol 2026

Fruquintinib selectively inhibits all three VEGF receptors, restricting tumor growth by inhibiting angiogenesis

Fruquintinib selectively binds to all three VEGF receptors[1,*]



Fruquintinib-mediated VEGFR inhibition[2,3]



3 Illustration reproduced courtesy of Cell Signalling Technology, Inc (www.cellsignal.com)

4 See slide notes for abbreviations

1. Sun QL, et al. Cancer Biol Ther 2014;15:1635–45; 2. Qin S, et al. J Hematol Oncol 2019;12:27; 3. Zhang Y, et al. Cancer Manag Res 2019;11:7787–803

Fruquintinib efficacy: FRESCO-2: Overall survival

FRESCO-2 (NCT04322539): Study design

Global, multicenter, randomized, double-blind, placebo-controlled Phase 3 trial

PATIENT ELIGIBILITY
- Aged ≥18 years (≥20 in Japan)
- Confirmed mCRC
- ECOG PS 0–1
- Prior treatment with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, anti-VEGF therapy, and, if *RAS* wild type, anti-EGFR therapy
- Progression on, or intolerance to, TAS-102 and/or regorafenib*
- Prior treatment with an ICI or BRAF inhibitor if indicated

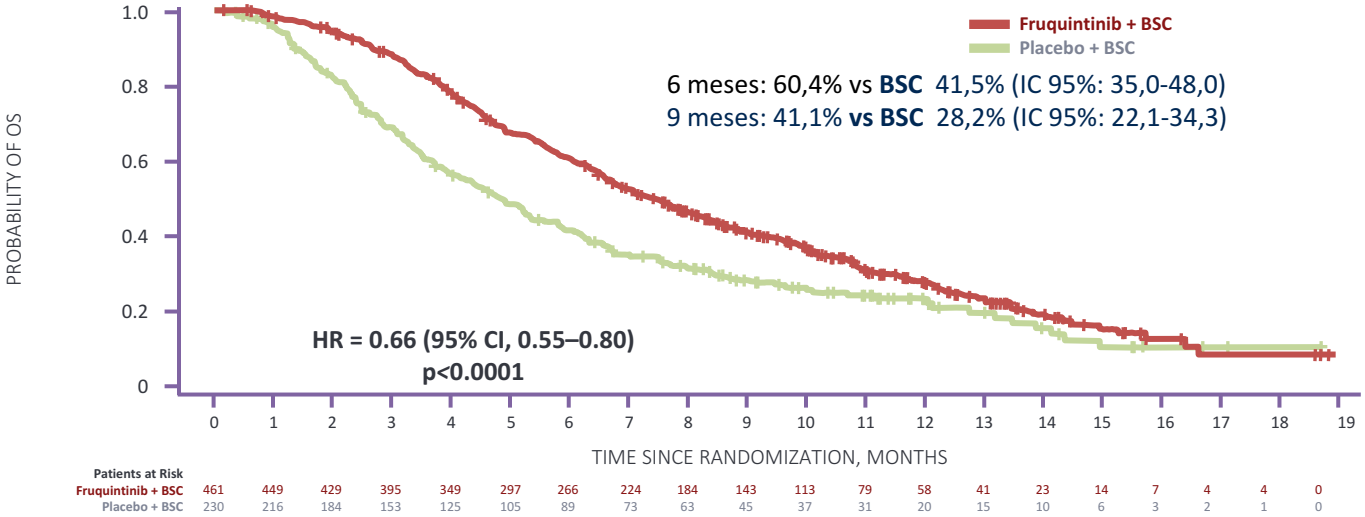
N=691 → R 2:1

FRUQUINTINIB ARM (n=461)
Fruquintinib 5 mg PO, QD (3 weeks on, 1 week off) + BSC

Stratification Factors
- Prior therapy (TAS-102 vs regorafenib vs TAS-102 and regorafenib)
- *RAS* mutational status (wild type vs mutant)
- Duration of metastatic disease (≤18 months vs >18 months)

PLACEBO ARM (n=230)
Placebo 5 mg PO, QD (3 weeks on, 1 week off) + BSC

Treatment until progression or unacceptable toxicity



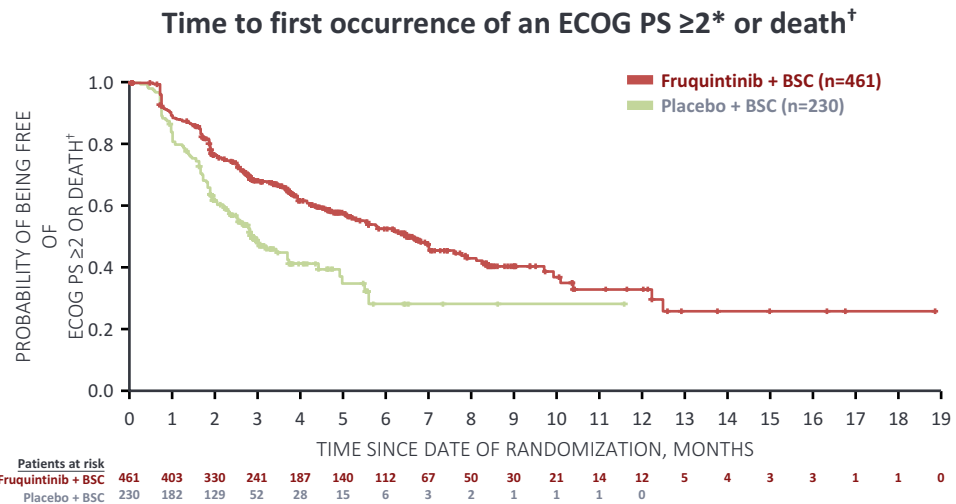
	FRUQUINTINIB + BSC (n=461)	PLACEBO + BSC (n=230)
Median follow-up, months	11.3	11.2
Median OS (95% CI), months	7.4 (6.7–8.2)	4.8 (4.0–5.8)
Median OS difference, months	2.6	
Stratified HR (95% CI); p-value	0.66 (0.55–0.80); <0.0001	
Received subsequent therapies, %	29	34

	FRUQUINTINIB + BSC (n=461)	PLACEBO + BSC (n=230)
Median PFS (95% CI), months	3.7 (3.5–3.8)	1.8 (1.8–1.9)
Median PFS difference, months	1.9	
Stratified HR (95% CI); p-value	0.32 (0.27–0.39); <0.0001	

BSC, best suppnnn ve care; CI, confidence interval; HR, hazard ratio; OS, overall survival

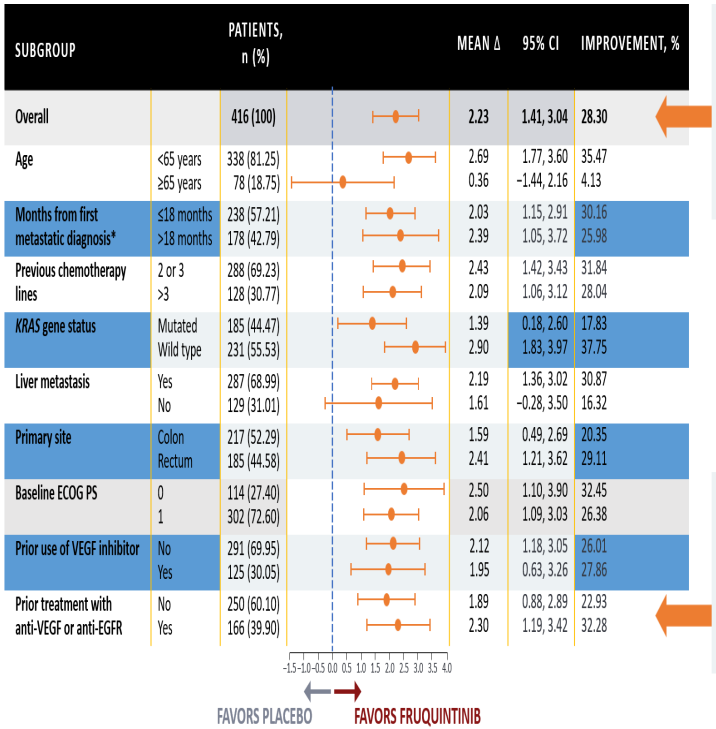
1. Li J, et al. JAMA 2018;319:2486–96; 2. Dasari A, et al. Lancet 2023;402:41–53

QOL with fruquintinib: FRESCO-2 Time to worsening of ECOG PS (ad hoc analysis)



	FRUQUINTINIB + BSC (n=461)	PLACEBO + BSC (n=230)
Events, n (%)	208 (45.1)	121 (52.6)
ECOG PS ≥2	169 (36.7)	82 (35.7)
Death	39 (8.5)	39 (17.0)
Median time to ECOG PS ≥2 or death† (95% CI), months	6.6 (5.5–7.9)	2.9 (2.5–3.7)
Median difference, months	3.7	
Stratified HR (95% CI)	0.551 (0.436–0.697)	
Two-sided p-value	<0.001	

azard ratio; QOL, quality of life



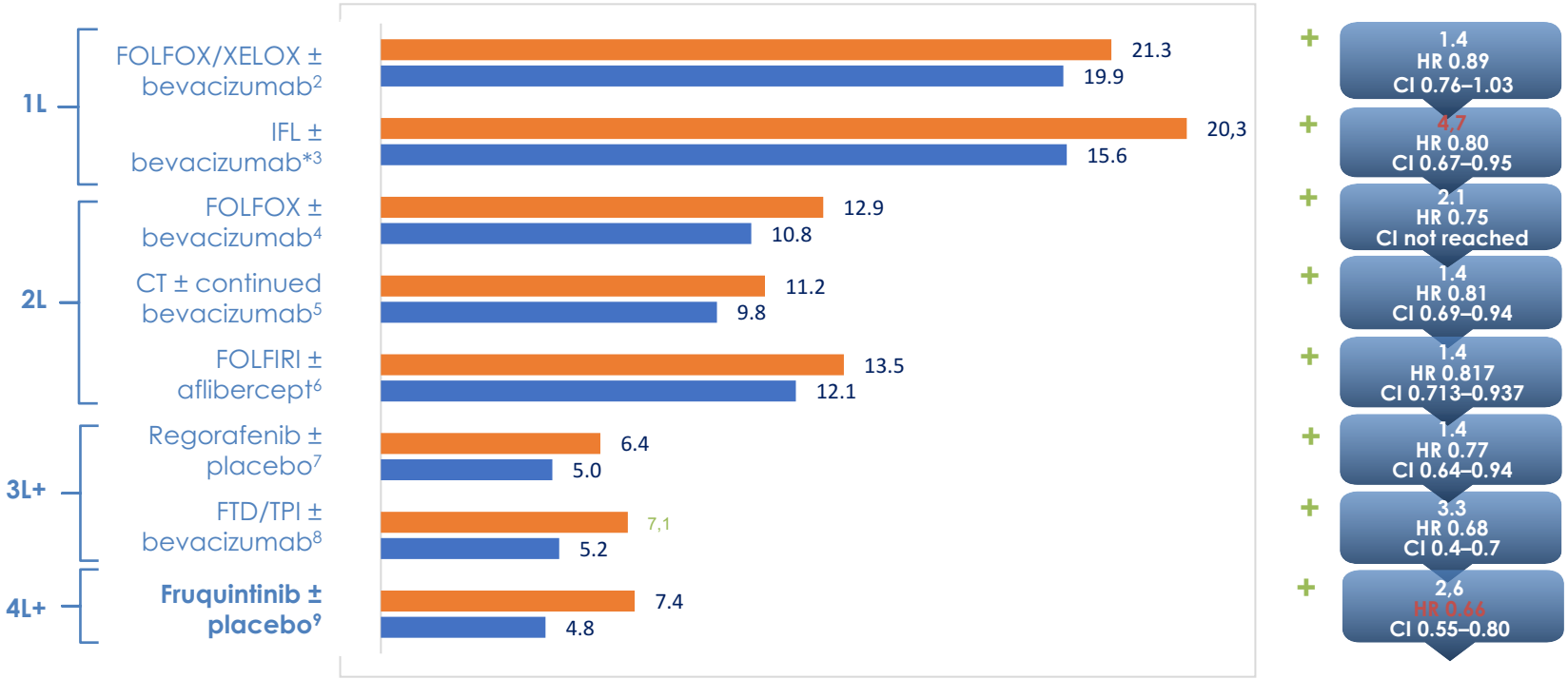
Fruquintinib significantly improved patients' Q-TWiST vs placebo by 2.23 months, representing a **28.3%** relative gain

Q-TWiST was longer for fruquintinib vs placebo regardless of prior treatment with anti-VEGF or anti-EGFR therapy

Qin S, et al. Future Oncol 2021;17:1923–31

Impact of Antiangiogenesis in Colorectal Cancer

Continuum of care across lines of treatments and gain in median OS (months) :



*KRAS wt subset; p-value not significant; 1L, first line; 2L, second line; 3L, third line; CI, Confidence interval; CT, chemotheray; FOLFOX, folinic acid + fluorouracil + oxaliplatin; FOLFIRI, irinotecan + infusional fluorouracil + folinic acid; FTD/TPI, trifluridine/tipiracil; HR, relative risk; OS, Overall survival ; XELOX, oxaliplatin + capecitabine.

1. Van Cutsem E, et al. Ann Oncol. 2016;27:1386–422. 2. Saltz LB, et al. J Clin Oncol 2008;26:2013–9; 3. Hurwitz H, VaNew England Journal of Medicine. 2004;350(23):2335–42. 4. Giantonio BJ, et al. J Clin Oncol 2007;25:1539–44; 5. Arnold D, et al Future Medicine Ltd Colorect. Cancer 2012; 6. Van Cutsem E, et al. J Clin Oncol 2012;30:3499–506; 7. Grothey A, et al. Lancet 2013;381:303–12; 8.Tabernero JM, et al. N Engl J Med 2023;388:1957–67; 9. Dasari N.A. LBA 25 FRESCO-2.

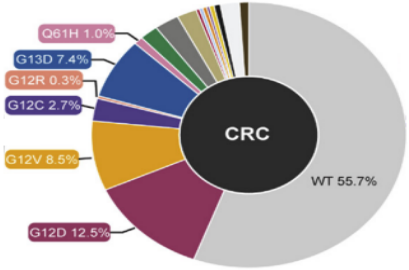
Rechallenge guiado por biopsia líquida

Trial*	Phase	Treatment	Patients (n)	mOS (months)	mPFS (months)	ORR (%)
FIRE4[1] (n=87)	Phase III	**(FOLF)IRI-Cetuximab** vs. Investigator Choice	45 vs. 42	**17.6 vs. 15.1** HR 0.77 (p=0.005)	**5.8 vs. 4.6** HR 0.86 (p=0.54)	**26.7 vs. 11.9**
CITRIC[2] (n=58)	Phase II	**Irinotecan-cetuximab** vs. Investigator Choice	31 vs. 27	**11.3 vs. 7.3** HR 0.8 (p=0.6)	**4.64 vs. 2** HR 0.6 (p=0.1)	**9.7 vs. 3.7**
PARERE[3] (n= 213)	Phase II	**Panitumumab->Regorfenib Vs.** Regorafenib->Panitumumab	106 vs. 107	**11.6 vs. 11.7** HR 1.13 (p=0.44)	**4.2->2.7 vs. 2.4->3.9** (p=0.103) & (p=0.019)	**16->0 vs. 2->18**

*The majority of ongoing studies do **not** incorporate TAS102 + Bevacizumab as a standard-of-care comparator arm.

Weiss L, et al. ASCO 2025. Montagut C, et al, ESMO 2025. Cirari P, et al. Ann. Oncol 2026

Futuro: Nuevos Fármacos



The promising KRAS G12D and pan-RAS inhibitors

Anti-EGFR + KRAS G12D inhibitor*

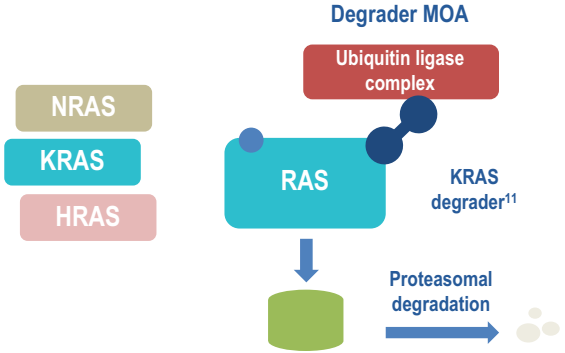
- KRAS G12Di LY3962673 ± cetuximab (MOONRAY-01)[1]
- KRAS G12Di AZD0022 ± cetuximab (ALAFOSS-01)[2]
- KRAS G12Di INCB161734 ± cetuximab[3]
- KRAS G12D degrader ASP3082 ± cetuximab[4]
- KRAS G12Di GDC-7035 ± panitumumab[5,6]

Anti-EGFR + pan-RAS inhibitor + KRAS G12D inhibitor†

- Cetuximab + Pan-RASi ± KRAS G12Di/mFOLFOX6[7]

Anti-EGFR + pan-RAS inhibitor†

- Pan-KRASi LY4066434 ± cetuximab[8]
- Pan-RASi AMG 410 ± panitumumab[9]
- Pan-RAS degrader ASP5834 ± panitumumab[10]



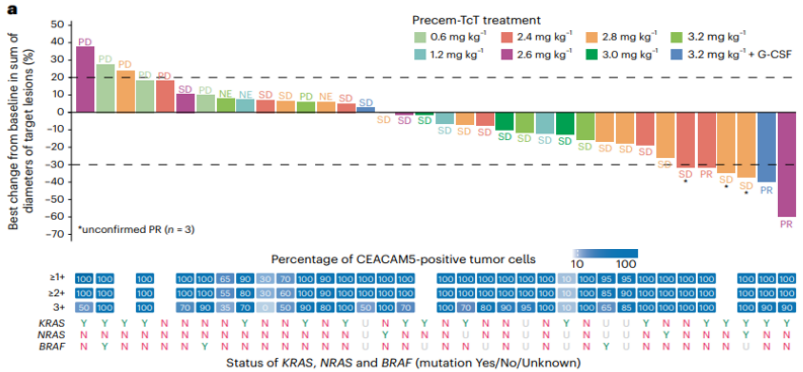
KRAS G12D

1.https://clinicaltrials.gov/study/NCT06586515;2.https://clinicaltrials.gov/study/NCT06599502;3.https://clinicaltrials.gov/study/NCT06179160;4.https://clinicaltrials.gov/study/NCT05382559;5.https://www.clinicaltrials.gov/study/NCT06619587;6.8.https://www.clinicaltrials.gov/study/NCT06607185;9.https://www.clinicaltrials.gov/study/NCT07094113;10.https://www.clinicaltrials.gov/study/NCT07094204; 11. Tolcher AW, et al. J Clin Oncol 2023;41:TPS764

Ac Conjugados

Precombat tocentecan

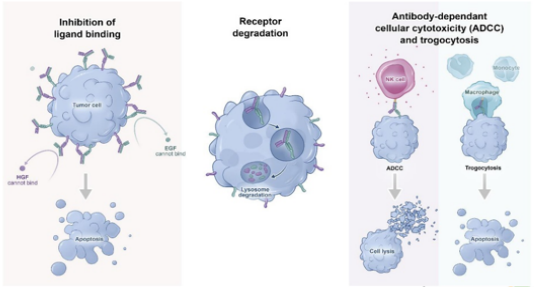
CEACAM5 is overexpressed in ~90% of CRCs, with limited expression in healthy tissues



Kopetz S. et al. Nature Medicine 2025

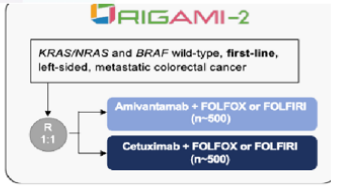
Ac Biespecíficos

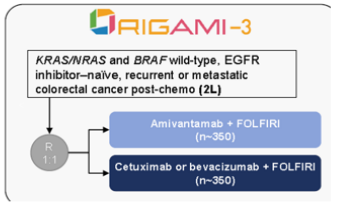
Amivantamab: Ac biespecífico EGFR-MET



ORIGAMI-1: Phase Ib/II, 1-2L
Amivantamab + FOLFOX/ FOLFIRI

	Total (N=43)
ORR[a,b]	49% (95% CI, 33–65)
ORR in 1st line (26%)	64%
ORR in 2nd line (74%)	44%
Median PFS	7.5 months (95% CI, 7.4–NE)





Pietrantonio et al, ESMO 2024.

ADC en Tumores Gastrointestinales

ADC	mAb target	Payload	Trial phase	Therapy line
Trastuzumab deruxtecan	HER2	Topoisomerase I inhibitor	Phase II ongoing	≥2L
HLX43	PD-L1	Topoisomerase I inhibitor	Phase II ongoing	≥2L
Disitamab vedotin	HER2	Anti-mitotic agent	Phase II ongoing	≥2L
HS-20093	B7-H3	Topoisomerase I inhibitor	Phase Ib ongoing	≥2L (dose escalation), 1L (dose expansion)
Precemtabart tocentecan	CEACAM5	Topoisomerase I inhibitor	Phase I ongoing	≥2L
AGX101	TM4SF1	Anti-mitotic agent	Phase I ongoing	≥2L
ALX2004	EGFR	Topoisomerase I inhibitor	Phase I ongoing	≥3L

1.Raghav K, et al. Lancet Oncol 2024;25:1147–1162; 2. NCT07106892. 3. NCT05578287. 4. Usan Council, 5. NCT06825624 6. Kopetz S, et al. ASCO 2025 7. NCT06440005. 8. NCT07085091. 9. Kopetz S, et al. ASCO 2024

Otros Ac biespecíficos (MSS/pMMR):

Volrustomig (MEDI-5752)	PD-1 y CTLA-4	CANTOR	II	Volrustomig + FOLFIRI + beva vs Bevacizumab + FOLFIRI	1L, No mts hep
Ivonescimab (AK112)	PD-1 y VEGF-A	HARMONi-GI3	III	Ivonescimab + mFOLFOX6 vs Bevacizumab + mFOLFOX6	1L, BRAF wt
PF-08634404 (SSGJ-707)	PD-1 y VEGF	Symbiotic-GI-03	III	PF-08634404 + QT vs Bevacizumab + QT	1L, BRAF wt
Pumitamig (BNT 327)	PD-L1 y VEGF-A	ROSETTA CRC-203	II/III	Pumitamig+ QT vs Bevacizumab + QT	1L, BRAF wt
BNT 314 (GEN1059)	4-1BB (agonista) y EpCAM	NCT07079631	I/II	BNT314 + pumitamig + QT Bevacizumab + QT Pumitamig + QT	1-2L (y 2L+)
Petosemtamab (MCLA-158)	EGFR y LGR5	MCLA-158-CL01	I/II	Petosemtamab + mFOLFOX6 o FOLFIRI	1-2L (y 3L+), RAS-RAF wt, EGFRi naïve.

Raghav K et al., *Lancet Oncol* 2024; Kopetz S et al., *Nature Medicine* 2025; ASCO 2024–2025; ClinicalTrials.gov (NCT07106892, NCT05578287, NCT06825624, NCT06440005, NCT07085091).

¡Gracias!