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

Cáncer colorrectal: Subgrupos Moleculares

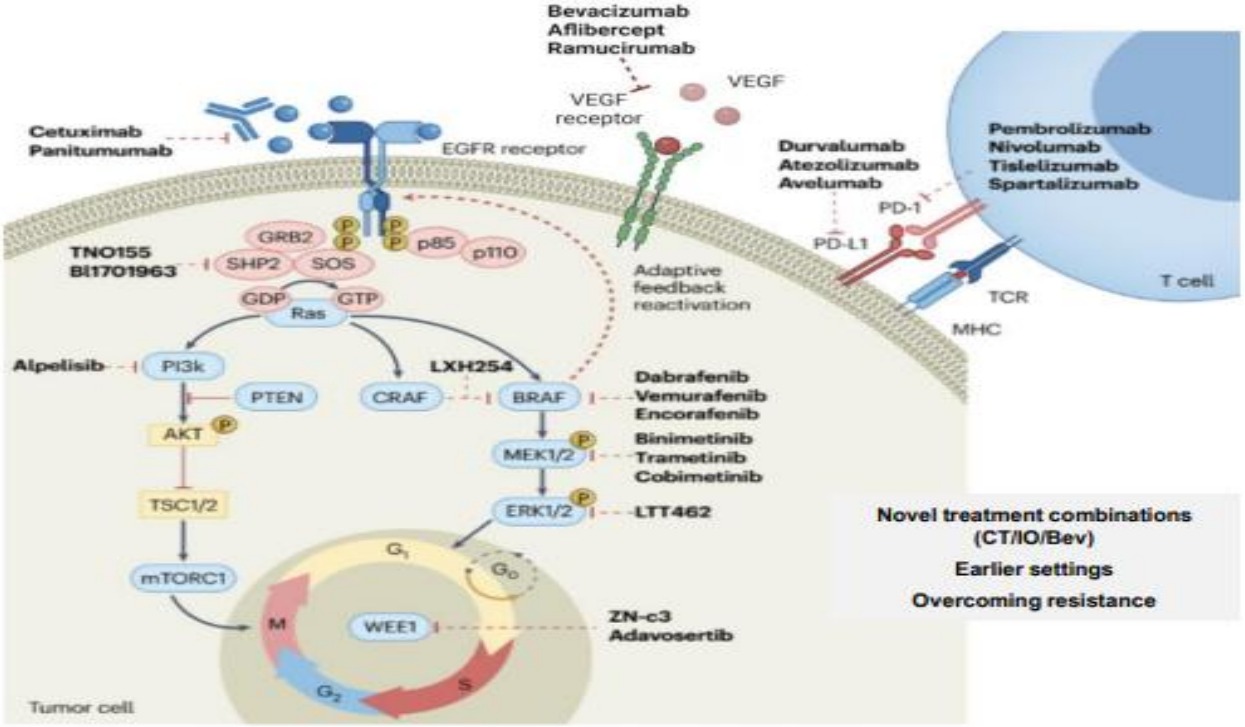
Pilar García Alfonso

Profesor titular UCM
H.G.U. Gregorio Marañón

DISCLOSURE

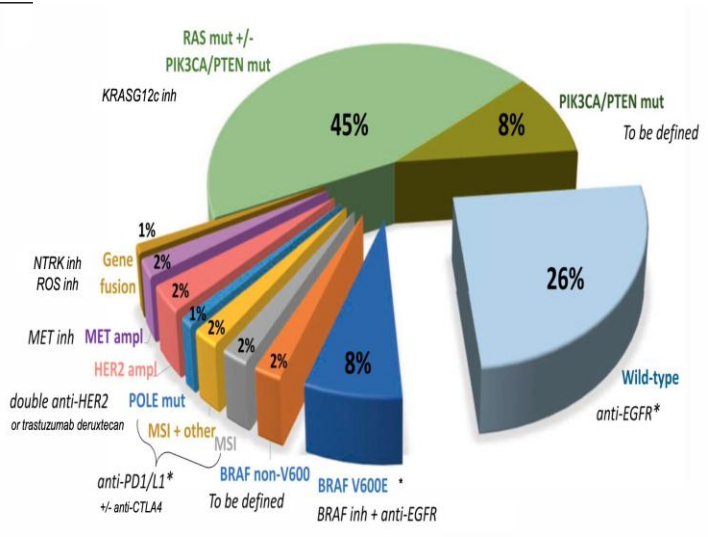
Receipt of honoraria or consultation fees for speaker, consultancy or advisory roles:

Amgen, Bayer, Bristol, Merck Serono, MSD, Lilly, Roche, Sanofi, Servier, Pierre Fabre


Bevacizumab
Aflibercept
Ramucirumab
VEGF
VEGF receptor
Cetuximab
Panitumumab
EGFR receptor
Durvalumab
Atezolizumab
Avelumab
Pembrolizumab
Nivolumab
Tislelizumab
Spartalizumab
PD-1
PD-L1
T cell
TCR
MHC
GRB2
p85
p110
SHP2
SOS
TNO155
BI1701963
GDP
GTP
Ras
Adaptive feedback reactivation
Alpelisib
PI3k
PTEN
AKT
LXH254
CRAF
BRAF
Dabrafenib
Vemurafenib
Encorafenib
MEK1/2
Binimetinib
Trametinib
Cobimetinib
ERK1/2
LTT462
TSC1/2
mTORC1
G1
G0
M
WEE1
ZN-c3
Adavosertib
G2
S
Tumor cell
Novel treatment combinations (CT/IO/Bev)
Earlier settings
Overcoming resistance

Update of the recommendations for the determination of biomarkers in colorectal carcinoma: National Consensus of the Spanish Society of Medical Oncology and the Spanish Society of Pathology

Biomarker	Technique	Indication
CRC—universal		
MSI	IHC and/or MSI analysis by qPCR, bPCR, NGS	Required
Immunoscore or immunodensity	IHC and/or digital score	Optional
CRC—localized		
MSI	IHC and/or PCR and MSI analysis	Required
Immunoscore or immunodensity	IHC and/or digital score	Optional
CRC—advanced		
MSI	IHC and/or PCR and MSI analysis	Required
Extended *RAS*	KRAS, NRAS	Required
B-RAF	V600E V600E2/K/D/R or M	Required Optional
HER2	IHC / FISH / SISH	Optional
Rearrangements of: NTRK1; NTRK2; NTRK3	IHC and FISH, NGS, RT-PCR, NanoString®	Optional in MSI, *MLH1* hyper-methylation and *RAS WT*
Liquid biopsy	qPCR, dPCR, NGS, cfDNA Idylla	Optional for patient monitoriza



Garcia-Alfonso et al., Clin Transl Oncol 2020
Cohen et al., Cancers 2020

Adaptada de Dienstmann et al, ASCO Educ. Book 2018 by Chalabi , ESMO 2023

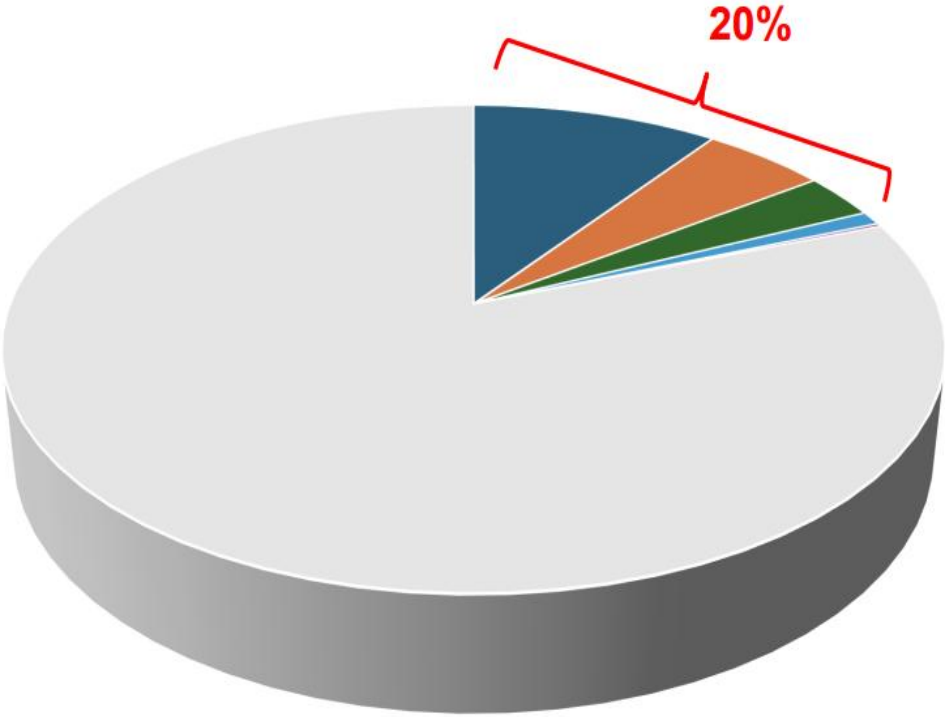
10% BRAF V600E mutation[1]

3-5% HER 2 overexpression/amplification[2]

2-3% KRAS G12C mutation[3]

0.9% NTRK Fusion[4]

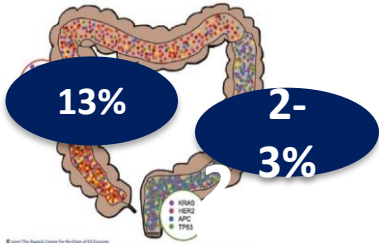
0.2% RET Fusion[5]



. De Roock W et al. Lancet Oncol. 2010 Aug;11(8):753-62.
. Bertotti A, et al. *Cancer Discov*. 2011 Nov;1(6):508-23.
. Chida K et al. Oncologist. 2021 Oct;26(10):845-853.
4. Okamura R et al. JCO Precis Oncol. 2018:2018:PO.18.00183.
5. Le Rolle AF et al. Oncotarget. 2015 Oct 6;6(30):28929-37.

BRAF V600E mutado

BRAF V600E Mutation



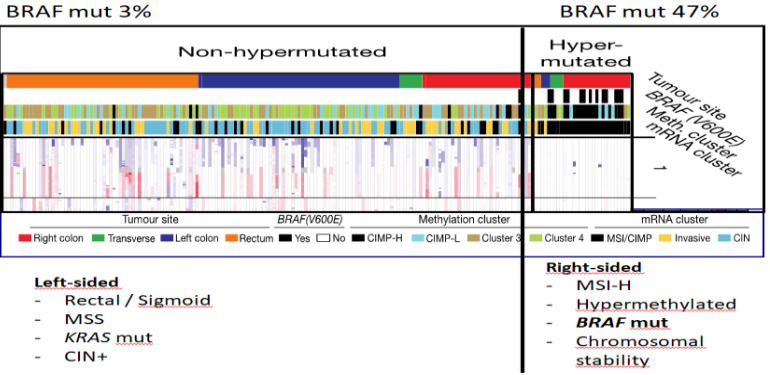
8 to 12% CRC[1]

96% V600E (Exon 15, T1799 point mutation (valine->glutamine) codon 600

Asociación de BRAF y MSI esporádico en 30% casos.

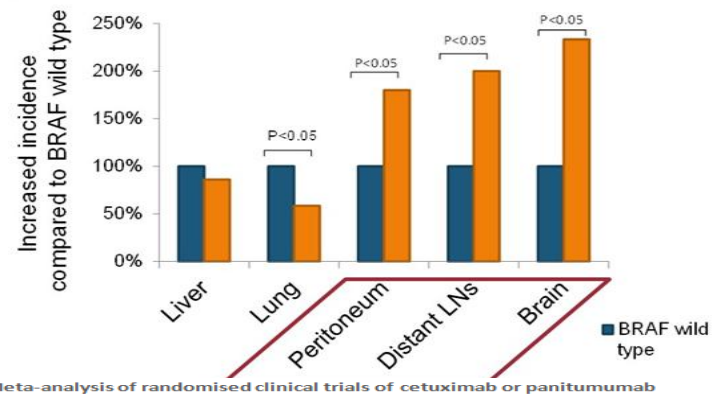
Mal pronostico. T. mucinosos más frecuentes en mujeres,

Ancianos y colon derecho

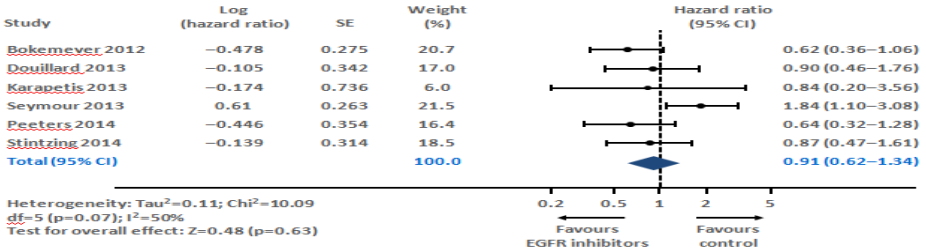


Left-sided
- Rectal / Sigmoid
- MSS
- *KRAS* mut
- CIN+

Right-sided
- MSI-H
- Hypermethylated
- ***BRAF* mut**
- Chromosomal stability



Meta-analysis of randomised clinical trials of cetuximab or panitumumab



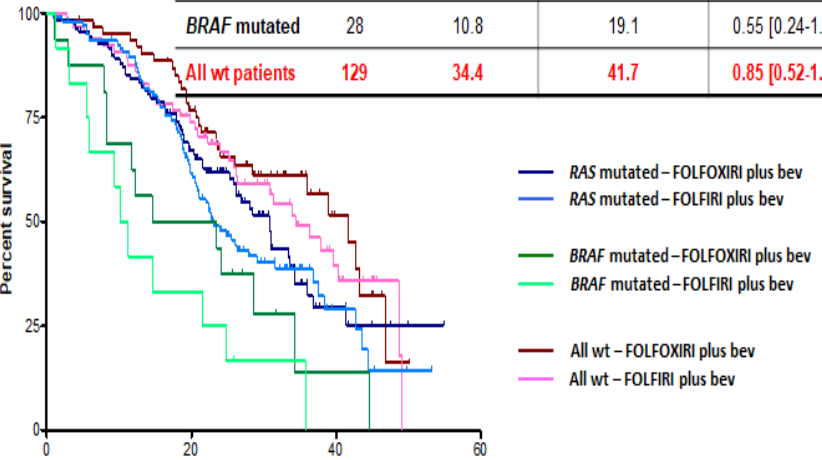
EGFR inhibitors are authorised only for RAS WT mCRC

Pietrantonio, et al. Eur J Cancer 2015

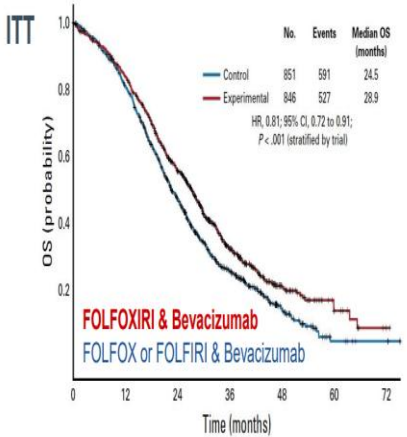
. Davies 2002 Nature

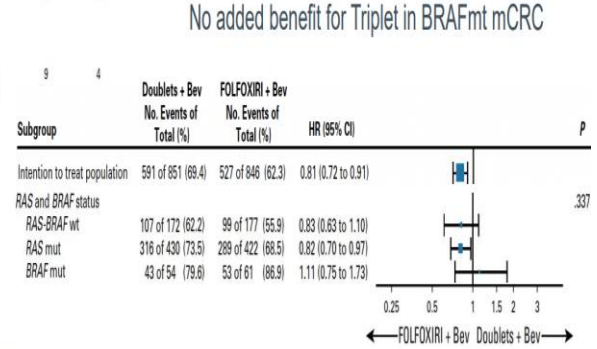
Tratamiento del CCRm BRAF mutado

	N	FOLFIRI + bev Arm A Median OS	FOLFOXIRI + bev Arm B Median OS	HR [95% CI]
ITT population	508	25.8	31.0	0.79 [0.63-1.00]
R&B evaluable	375	25.8	31.0	0.86 [0.65-1.12]
RAS mutated	218	23.1	30.8	0.86 [0.60-1.22]
BRAF mutated	28	10.8	19.1	0.55 [0.24-1.23]
All wt patients	129	34.4	41.7	0.85 [0.52-1.39]



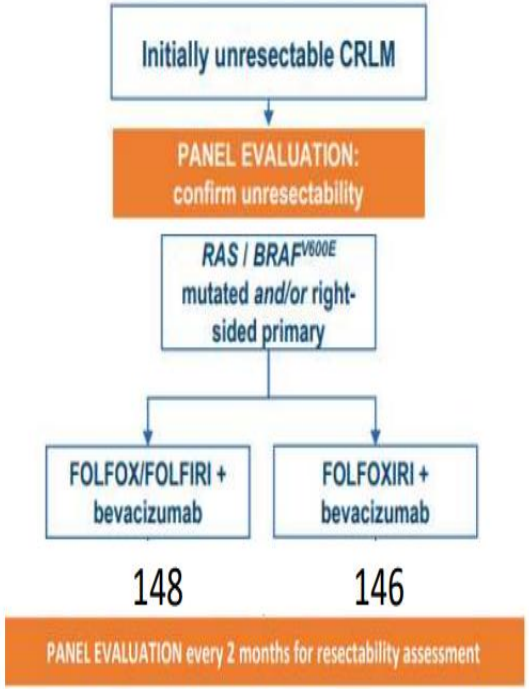
Cremolini et a. Lancet Oncol 2015



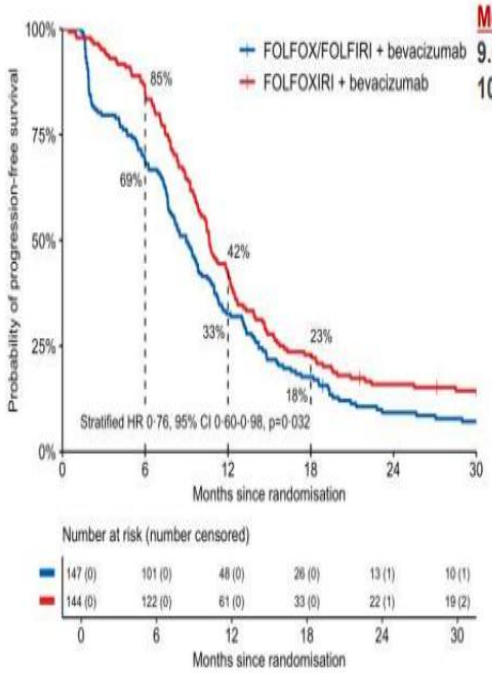


Cremolini C et al. J Clin Oncol. 2020 Aug 20;JCO2001225

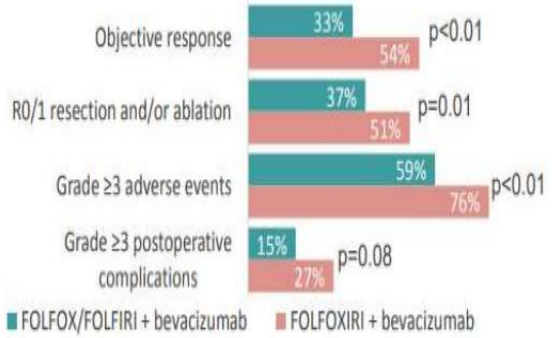
CAIRO5



Objetivo principal: SLP

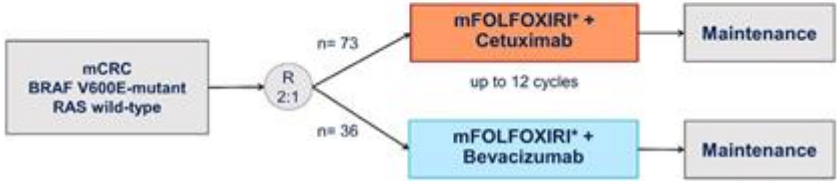


Median PFS
9.0 months
10.6 months
HR 0.76, p 0.03

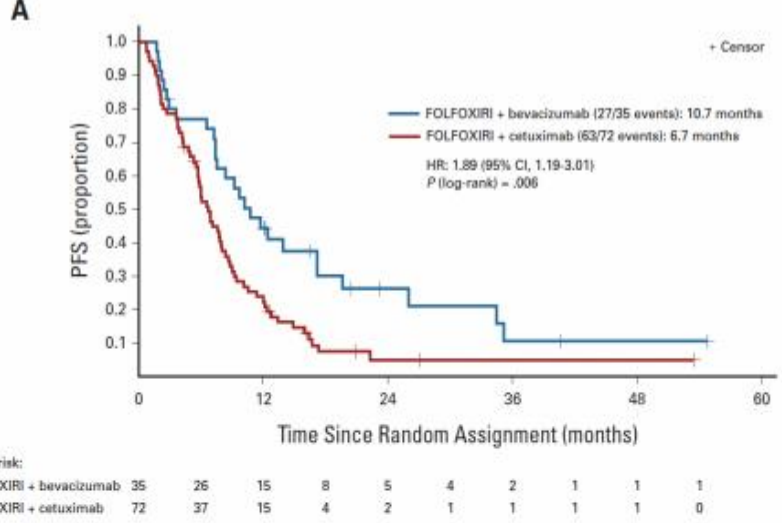


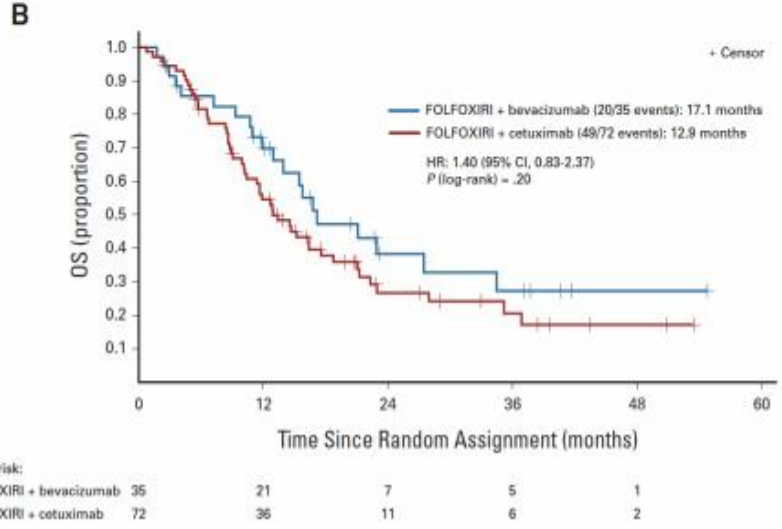
BRAFV600E mut: 7-8%

FIRE-4.5 Study Design
AIO KRK-0116



	Cetuximab Arm N=72	Bevacizumab Arm N=35
ORR (per BICR)	**41.7%**	**57.1%**
CR	4.2%	5.7%
PR	37.5%	51.4%
SD	26.4%	20.0%
DCR	68.1%	77.1%
median PFS	6.7 months	10.7 months
median OS	12.9 months	17.1 months





Stintzing S et al. J Clin Oncol. 2023 Sep 1;41(25):4143-4153.

BEACON

Final Study Design

Results of Safety Lead-In led to the introduction of an additional primary endpoint of ORR and an interim OS analysis to allow for early assessment

Patients with *BRAF*^{V600E} mCRC with disease progression after 1 or 2 prior regimens; ECOG PS of 0 or 1; and no prior treatment with any RAF inhibitor, MEK inhibitor, or EGFR inhibitor

Phase 3

Safety Lead-in

ENCO + BINI + CETUX
N = 30

Encorafenib 300 mg PO daily
Binimetinib 45 mg PO bid
Cetuximab standard weekly dosing

A separate Safety Lead-in cohort of n=7 in Japan was enrolled subsequently. Results will be reported at a later time.

R 1:1:1

- Triplet therapy ENCO + BINI + CETUX n = 205
- Doublet therapy ENCO + CETUX n = 205
- Control arm FOLFIRI + CETUX, or irinotecan + CETUX n = 205

Overall Survival

Primary Endpoints:

- Triplet vs Control
- OS
- ORR (Blinded Central Review)

Secondary Endpoints: Doublet vs Control OS & ORR, PFS, Safety

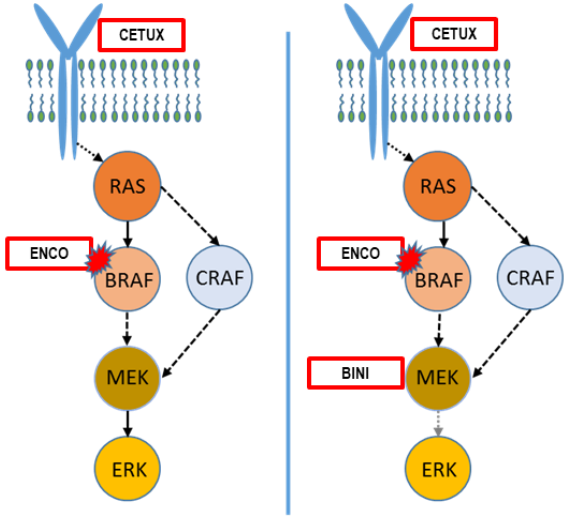
Randomization was stratified by ECOG PS (0 vs. 1), prior use of irinotecan (yes vs. no), and cetuximab source (US-licensed vs. EU-approved).

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Encorafenib, Binimetinib, and Cetuximab in *BRAF* V600E–Mutated Colorectal Cancer

S. Kopetz, A. Grothey, R. Yaeger, E. Van Cutsem, J. Desai, T. Yoshino, H. Wasan, F. Ciardiello, F. Loupakis, Y.S. Hong, N. Steeghs, T.K. Guren, H.-T. Arkenau, P. Garcia-Alfonso, P. Pfeiffer, S. Orlov, S. Lonardi, E. Elez, T.-W. Kim, J.H.M. Schellens, C. Guo, A. Krishnan, J. Dekervel, V. Morris, A. Calvo Ferrandiz, L.S. Tarpgaard, M. Braun, A. Gollerkeri, C. Keir, K. Maharry, M. Pickard, J. Christy-Bittel, L. Anderson, V. Sandor, and J. Tabernero



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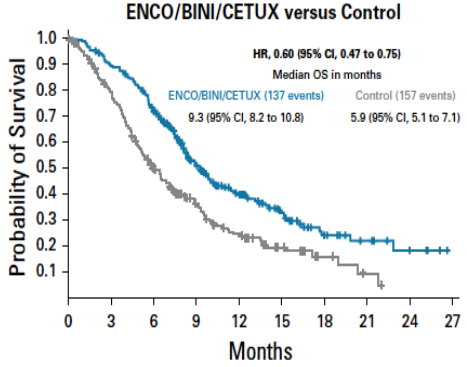

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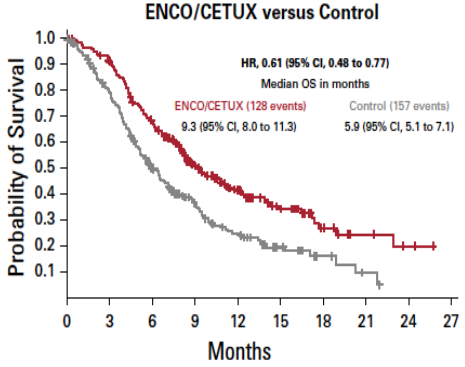
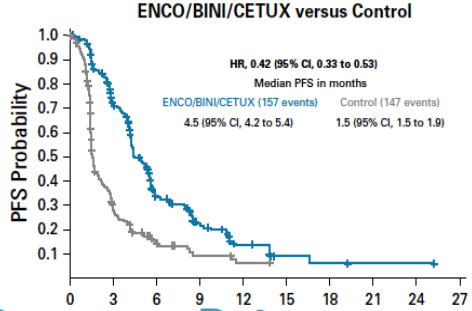


Number of patients at risk
ENCO/BINI/CETU
Control

Number of patients at risk

A



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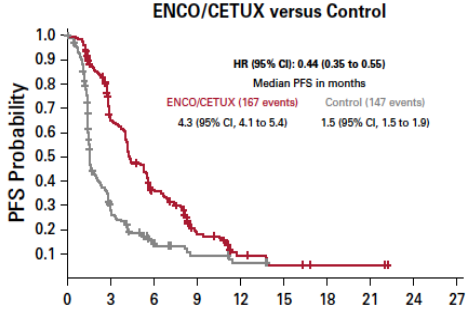


Objective Response Rate (First 331 Randomized Patients)

Confirmed Response by blinded central review	Triplet N=111	Doublet N=113	Control N=107
Objective Response Rate	**26%**	**20%**	**2%**
95% (CI)	(18%, 35%)	(13%, 29%)	(<1%, 7%)
p-value vs. Control	<0.0001	<0.0001	

J Clin Oncol 2021

BREAKWATER – Safety Lead In

Safety Lead-In

Participants who have received ≤1 prior treatment for mCRC

Cohort 1 (n=30)
Encorafenib 300 mg QD
+ cetuximab 500 mg/m² Q2W
+ FOLFIRI Q2W in 28-day cycles

Cohort 2 (n=27)
Encorafenib 300 mg QD
+ cetuximab 500 mg/m² Q2W
+ mFOLFOX6 Q2W in 28-day cycles

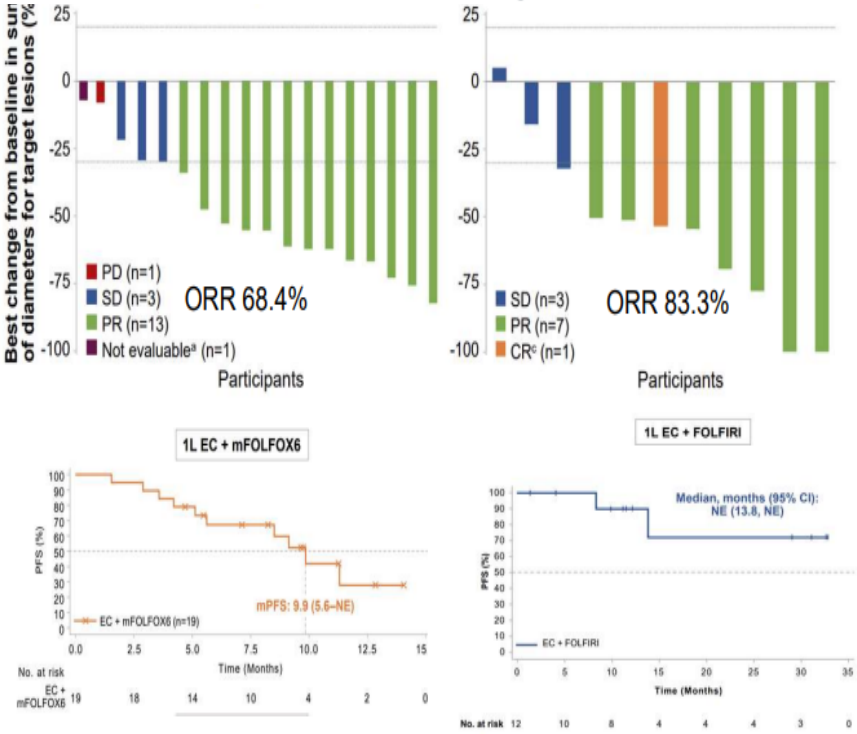
Primary Endpoint

- Safety (frequency of DLTs)

Secondary Endpoints

- Safety (AEs, dose interruptions/ modifications/discontinuations)
- PKs
- Antitumor activity by investigator (ORR, DOR, TTR, PFS, OS)

Inclusion Criteria	Exclusion Criteria
• *BRAF*^{V600E} mCRC (blood or tumor tissue) • ≤1 prior systemic treatment for mCRC • Evaluable disease (RECIST 1.1) • ECOG PS 0 or 1 • Adequate BM, hepatic, and renal function	• Prior treatment with BRAFi/EGFRi or both oxaliplatin and irinotecan • Symptomatic brain metastases • MSI-H or dMMR tumors[a]



≈28 months after the last patient was enrolled

Tabernero J et al. ESMO 2022, 2024

CEBRRA

Study design:

open-label, multicenter, non-randomized, single arm phase II clinical trial to assess the efficacy of EBC as induction therapy in BRAF-V600E-mutant MSS Acrc

Included patients will be treated with oral encorafenib and binimetinib daily together with biweekly intravenous cetuximab, for 12 or 24 weeks depending upon eligibility for surgical treatment.

Study endpoints:

Primary endpoint:

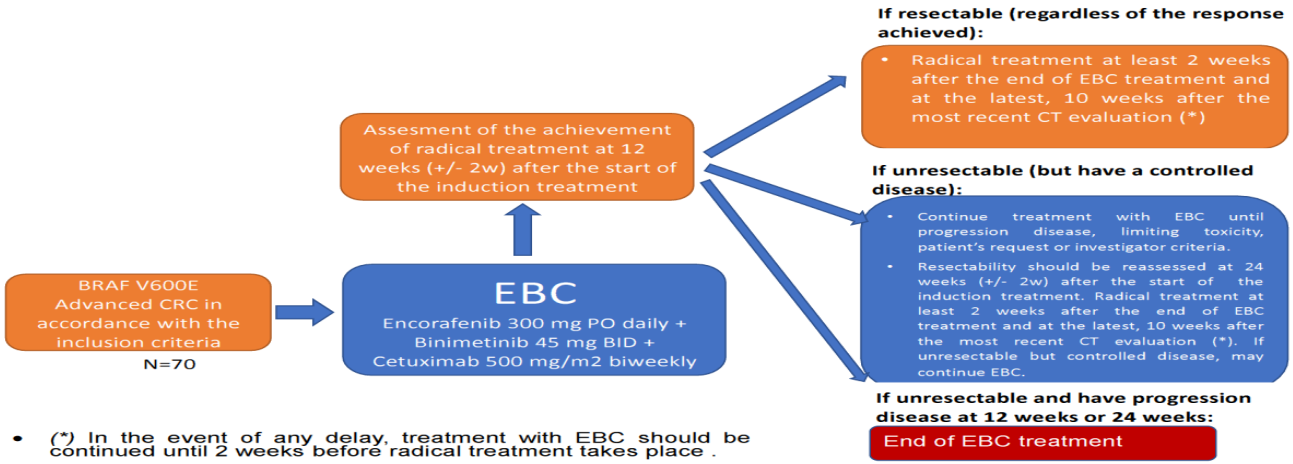
- Efficacy of cetuximab in combination with encorafenib plus binimetinib (EBC)

Secondary endpoints:

- ORR, TRG, PFS, OS and DFS in BRAF-V600E-mutated MSS aCRC patients treated with EBC.
- Safety and tolerability of EBC treatment.
- To assess complications related to surgery

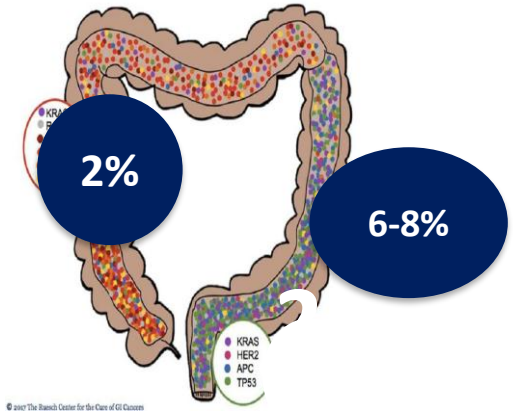
'adical

N=70

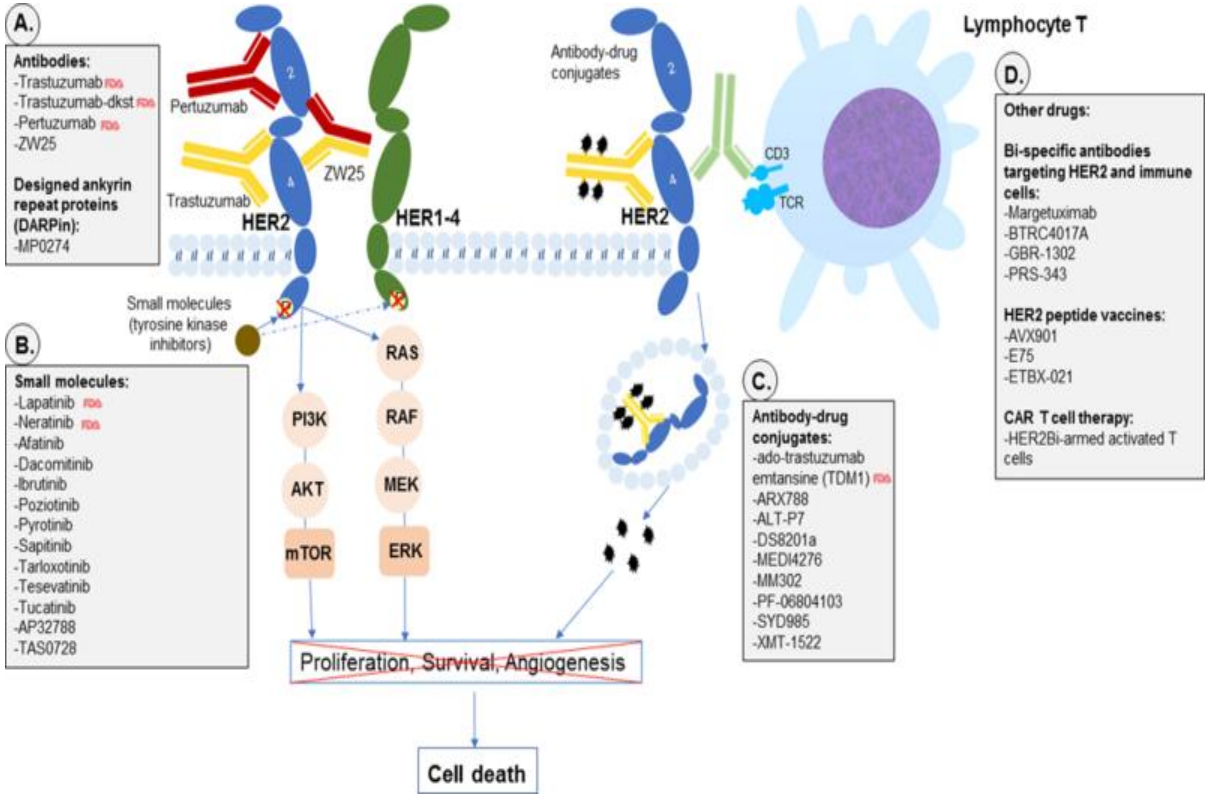


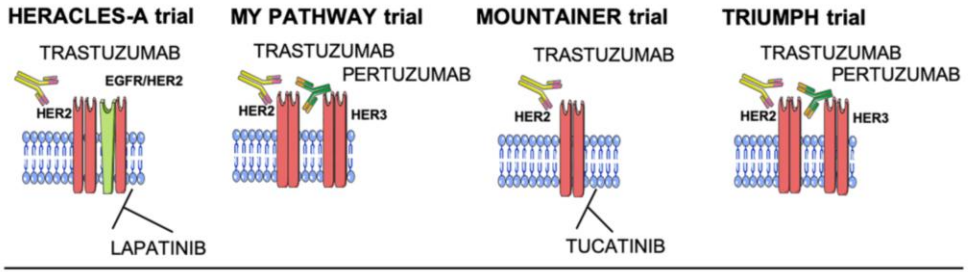
Her-2

HER-2



Her2: Sobreexpresión en el 2-3% de CCR
En el 5% en el Lado izdo
Avidez por afectación SNC
Enriquecido RAS wt
Predictor negativo de respuesta a antiEGFR





ESTUDIOS FASE II

	HERACLES	MY PATHWAY	MOUNTAINER
RESPUESTAS	30%	38%	55%

No está claro el aumento de la PFS y SG: HACEN FALTA ESTUDIOS FASE III

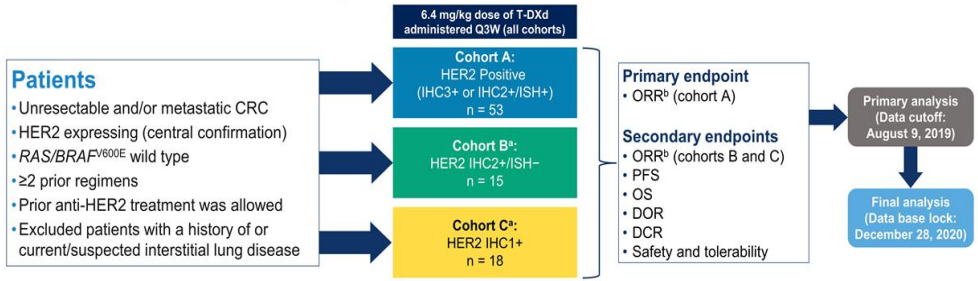
Giulia Martini, Rodrigo Dietsmann et al.- Ther Adv Med Oncol 2020

Trial name	Phase	Treatment line	Number	Regimen	ORR (%)	DCR (%)	Median PFS (months)	Median overall survival (months)
Ramanathan et al.[184]	II	Second or later	9	Trastuzumab plus irinotecan	71	Not reported	Not reported	Not reported
HERACLES-A[20,112] (NCT03225937)	II	Third or later	32	Trastuzumab plus lapatinib	28	69	4.7	10.0
HERACLES-B[185] (NCT03225937)	II	Third or later	30	Pertuzumab plus trastuzumab emtansine	10	80	4.9	Not reported
MyPathway[113]	II	Second or later	57 (*RAS* wild type: 43)	Trastuzumab plus pertuzumab	32 (*RAS* wild type: 40)	Not reported	2.9 (*RAS* wild type: 5.3)	11.5 (*RAS* wild type: 14.0)
TAPUR Group 8 (NCT02693535)	II	Any lines	28	Trastuzumab plus pertuzumab	14	Not reported	Not reported	Not reported
TRIUMPH[111] (UMIN000027887)	II	Second or later	27 (tissue) 25 (ctDNA)	Trastuzumab plus pertuzumab	30 28	Not reported	4.0 3.1	10.1 8.8
MOUNTAINEER[186] (NCT03043313)	II	Third or later (*RAS* wild type)	23	Trastuzumab plus tucatinib	52	Not reported	8.1	18.7
Yuan et al.[187] (NCT04380012)	II	Any lines	11	Trastuzumab plus pyrotinib	27	45	Not reported	Not reported
DESTINY-CRC01 (ref. [116]) (NCT03384940)	II	Third or later	53 (IHC3+ or IHC2+ and ISH+) 15 (IHC2+ and ISH–) 18 (IHC1+)	Trastuzumab deruxtecan	45.3 0 0	83 60 22.2	6.9 2.1 1.4	15.5 7.3 7.7
Clark et al.[188]	II	Second or third	21 (IHC2+/IHC3+)	5-FU–leucovorin plus oxaliplatin plus trastuzumab	24	Not reported	Not reported	Not reported
Bekaii-Saab et al.[189]	I	Second or later	6	Paclitaxel plus trastuzumab plus IL-12	0	33.3	Not reported	Not reported
Meric-Bernstam et al.[190] (NCT02892123)	I	Salvage	26 (IHC3+ or IHC2+ and ISH+)	Zanidatamab (ZW25)	38	77	6.8	Not reported

5-FU, fluorouracil; ctDNA, circulating tumour DNA; DCR, disease control rate; IHC, immunohistochemistry; ISH, in situ hybridization; ORR, overall response rate; PFS, progression-free survival.

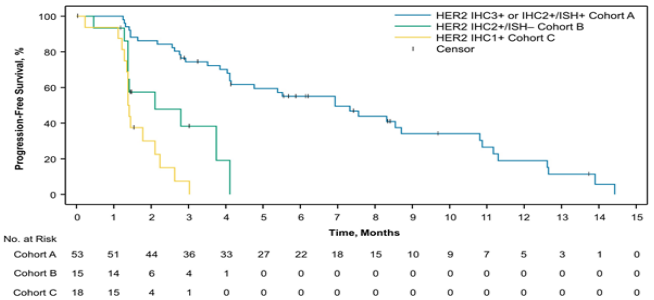
DESTINY-CRC01 Study Design

An open-label, multicenter, phase 2 study (NCT03384940)



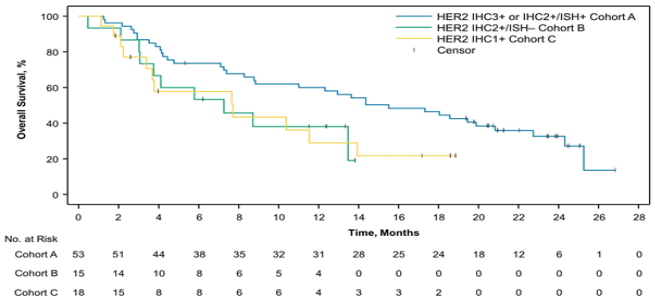
	HER2 IHC3+ or IHC2+/ISH+ Cohort A (n = 53)	HER2 IHC2+/ISH− Cohort B (n = 15)	HER2 IHC1+ Cohort C (n = 18)
Confirmed ORR by ICR, n (%) [95% CI]	24 (45.3) [31.6-59.6]	0 [0.0-21.8]	0 [0.0-18.5]
CR	0	0	0
PR	24 (45.3)	0	0
SD	20 (37.7)	9 (60.0)	4 (22.2)
PD	5 (9.4)	5 (33.3)	10 (55.6)
Not evaluable[a]	4 (7.5)	1 (6.7)	4 (22.2)
Disease control rate, % (95% CI)	83.0 (70.2-91.9)	60.0 (32.3-83.7)	22.2 (6.4-47.6)
Median duration of response, (95% CI) months	7.0 (5.8-9.5)	NE (NE-NE)	NE (NE-NE)
Median treatment duration, (95% CI) months	5.1 (3.9-7.6)	2.1 (1.4-2.6)	1.4 (1.3-1.5)

Progression-Free Survival



	HER2 IHC3+ or IHC2+/ISH+ Cohort A (n = 53)	HER2 IHC2+/ISH− Cohort B (n = 15)	HER2 IHC1+ Cohort C (n = 18)
mPFS (95% CI), months	6.9 (4.1-8.7)	2.1 (1.4-4.1)	1.4 (1.3-2.1)

Overall Survival



	HER2 IHC3+ or IHC2+/ISH+ Cohort A (n = 53)	HER2 IHC2+/ISH− Cohort B (n = 15)	HER2 IHC1+ Cohort C (n = 18)
mOS (95% CI), months	15.5 (8.8-20.8)	7.3 (3.0-NE)	7.7 (2.2-13.9)

Interstitial Lung Disease

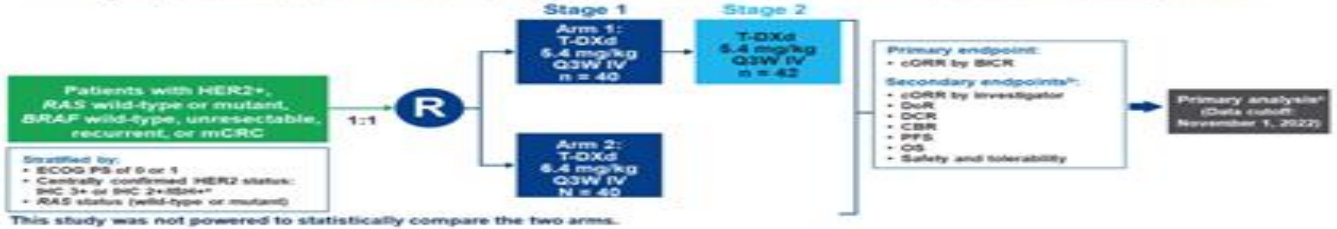
All Patients (N=86)	n (%)
Grade 1	0
Grade 2	4 (4.7)
Grade 3	1 (1.2)
Grade 4	0
Grade 5	3 (3.5)[a]
Any Grade/Total	8 (9.3)[b,c]

Yoshino T, et al. ASCO 2021. Siena S, et al. Lancet Oncol 2021;22:779

DESTINY-CRC02 Study Design

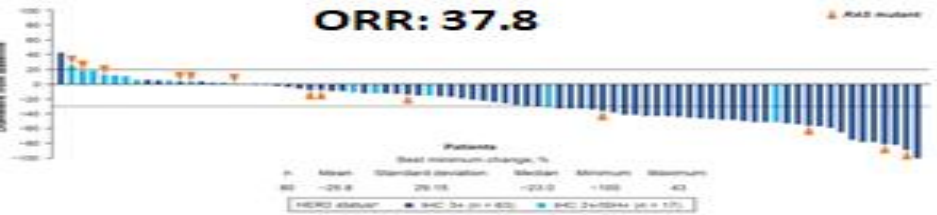
A randomized, blinded, 2-stage, 2-arm, multicenter, global, phase 2 study (NCT04744831)

- Stage 1 (randomized) was followed by Stage 2 (nonrandomized), which enrolled an additional 42 patients



T-DXd 5.4 mg/kg Q3W Total (N = 82)

ORR: 37.8



Median PFS
5.8 months (95% CI, 4.6-7.0)

Median OS
13.4 months (95% CI, 12.5-16.8)

T-DXd 6.4 mg/kg Q3W Stage 1 (N = 40)

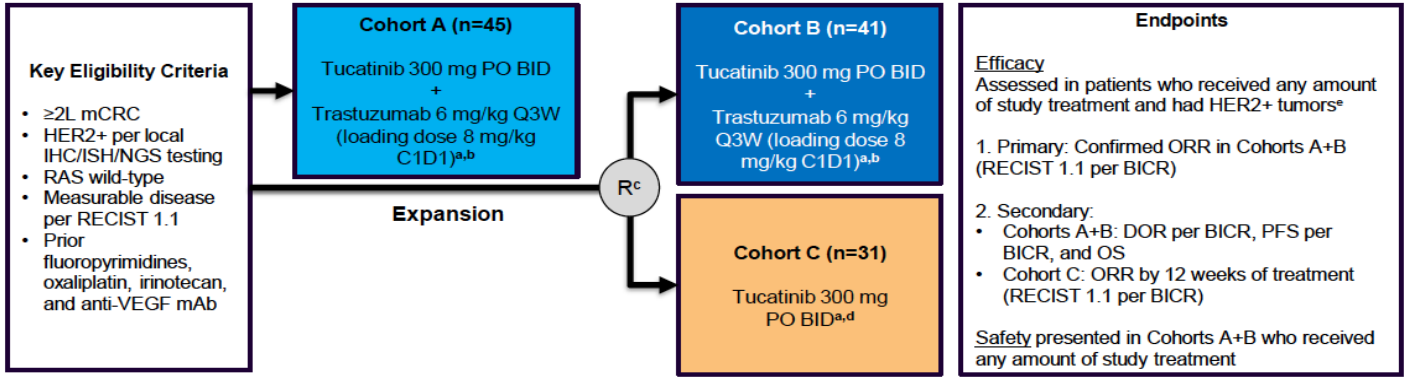
ORR: 27.5

Median PFS
5.5 months (95% CI, 4.2-7.0)

Median OS
NE (95% CI, 9.9 months-NE)

Raghav K, et al. ASCO 2023.

Tucatinib plus trastuzumab for chemotherapy-refractory, HER2-positive, *RAS* wild-type unresectable or metastatic colorectal cancer (MOUNTAINEER): a multicentre, open-label, phase 2 study



	Tucatinib plus trastuzumab (cohorts A and B; n=84)
Confirmed objective response rate (95% CI)	**38.1%** (27.7-49.3)
Median duration of response, months (IQR)	**12.4** (8.3-25.5)
Median PFS, months (95% CI)	**8.2** (4.2-10.3)

2 prior therapies: 42%
≥3 prior therapies: 37%

ADVERSE EVENTS	Most common AEs	≥ G3 AEs
Cohort A and B	Diarrhoea (64%)	Hypertension (7%)
Cohort C	Diarrhoea (33%)	Increased ALT (7%) Increased AST (7%)

Strickler. Lancet Oncol 2023

Final results of a pase 2 study of tucatinib and trastuzumab for HER2-positive mCRC (MOUNTAINEER)

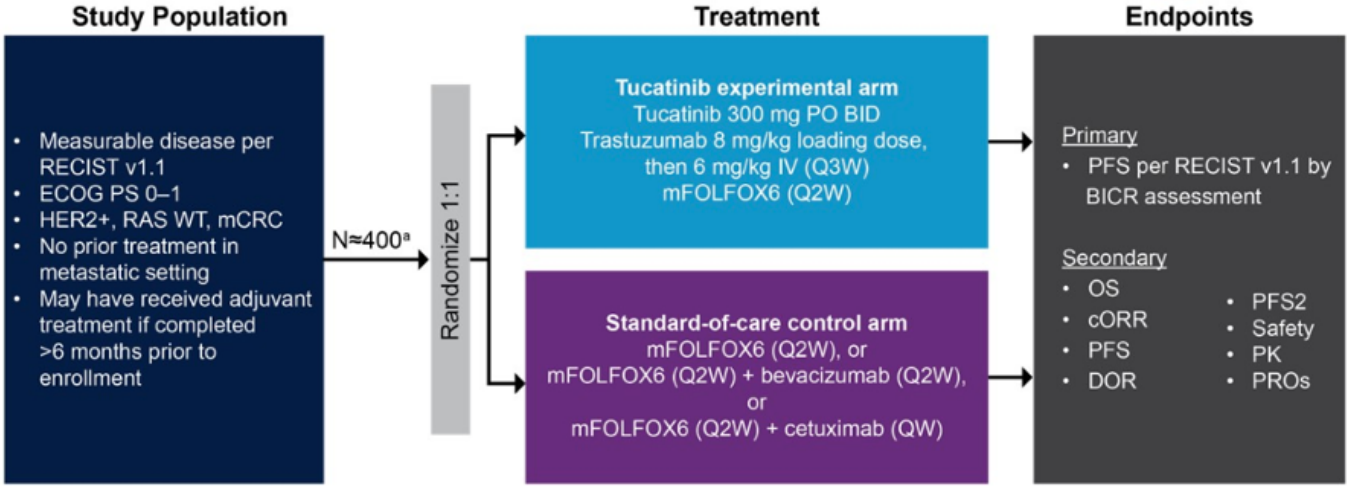
- Median follow-up: 32.4-months

cORR, % (95% CI)	**39.3** (28.8-50.5)
Median DOR, mo (95% CI)	**15.2** (8.9-20.5)
Median PFS, mo (95% CI)	**8.1** (4.2-10.2)
Median OS, mo (95% CI)	**23.9** (18.7-28.3)

- **Clinical efficacy was similar across 3 central HER2 testing methods** (Tissue IHC/FISH, Tissue NGS, Blood NGS)
- 23 of 84 (**27%**) patients had **Long-term response**, defined as having > 12 months duration of treatment with CR/PR/SD
- Tucatinib in combination with trastuzumab continued to have a good safety profile and be well-tolerated with longer follow-up

Strickler. ASCO 2024

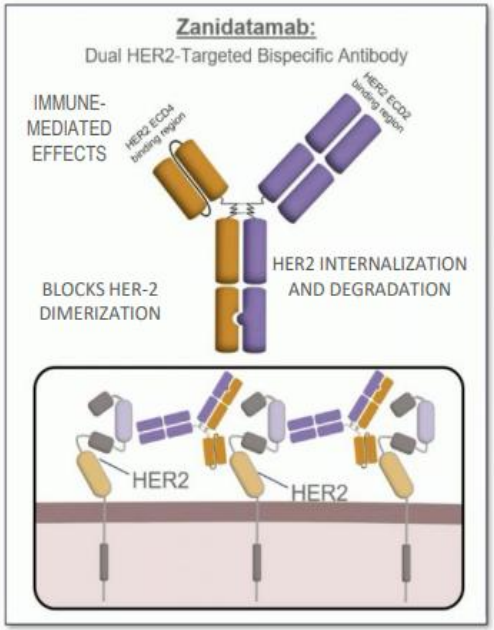
A Study of Tucatinib With Trastuzumab and mFOLFOX6 Versus Standard of Care Treatment in First-line HER2+ Metastatic Colorectal Cancer (MOUNTAINEER-03)



a Stratification by both primary tumor location (left-sided versus all other) and liver metastases (presence or absence)

NCT05253651

HER2 amplified mCRC patients



Phase 2 Study of Zanidatamab + Chemotherapy for First-Line Treatment of HER2-Positive Metastatic CRC

Key eligibility criteria:

- Unresectable, locally advanced, recurrent or metastatic CRC
- HER2-expressing/amplified tumours (IHC 3+; or *HER2* gene amplified) based upon central assessment
- Extended *RAS*- and *BRAF*-wildtype based on local or central assessment
- ECOG PS ≤1
- No prior HER2-targeted agents
- No prior systemic therapy for metastatic disease
  - ✓ One prior cycle of 5-FU based chemotherapy for was permitted

Physician's choice of chemotherapy regimen (≥6 cycles):[a]

28-day cycle: **Zanidatamab + mFOLFOX6-2**
(Zanidatamab 1200/1600 mg[b] + mFOLFOX6-2: Leucovorin 400 mg/m² and oxaliplatin 85 mg/m² on days 1 and 15; 5-FU 1200 mg/m²/day on days 1-2 and 15-16)

OR

28-day cycle: **Zanidatamab + mFOLFOX6-2 + bevacizumab**
(Zanidatamab 1200/1600 mg[b] + mFOLFOX6-2 + bevacizumab: 5 mg/kg on days 1 and 15)

Tumour assessment Q6W per RECIST v1.1[1]

DLTs evaluated during the first 28-week cycle

Mandatory premedication for IRR[c] and antidiarrhoeal[d] prophylaxis

Primary endpoints (Part 1):
- DLTs
- AEs and SAEs
- Laboratory abnormalities
- Dose reductions

Secondary endpoints (Part 1):
- Objective response rate
- Disease control rate
- Duration of response
- Progression-free survival

CRC patients treated (Part 1) N=13

DLT evaluable[e] n=12

Response evaluable n=11

Data cut-off: 31 October 2023

ClinicalTrials.gov: NCT03929666

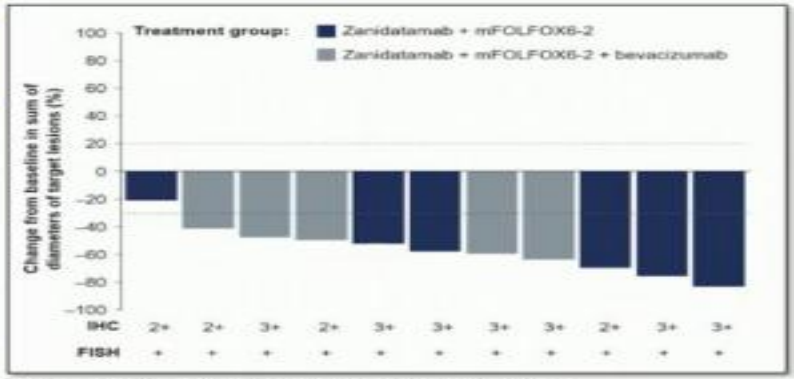
Rha SY et al. ESMO 2024 mini oral sesión

HER2 amplified mCRC patients

11 response-evaluable patients[a]

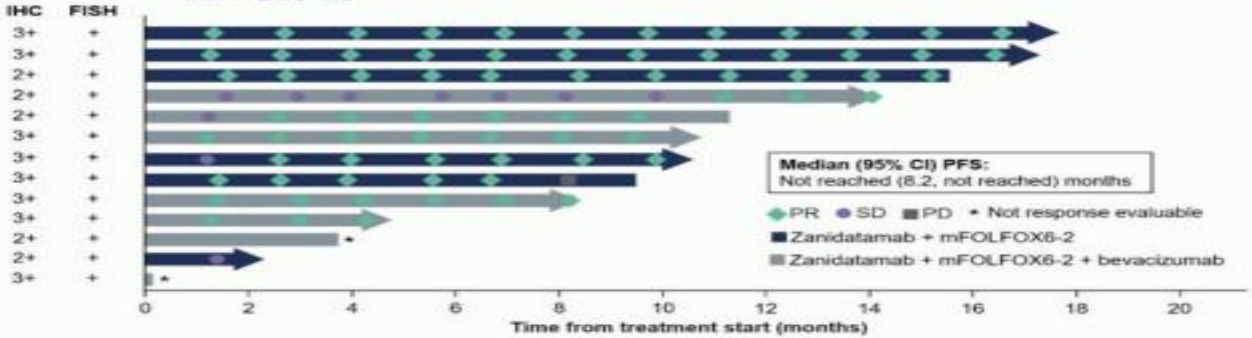
	Zanidatamab + mFOLFOX6-2 (n=6)	Zanidatamab + mFOLFOX6-2 + bevacizumab (n=5)	Total (N=11)
cORR			
n (%)	5 (83.3)	5 (100)	10 (90.9)
95% CI	35.9, 99.6	47.8, 100	58.7, 99.8
cBOR, n (%)			
CR	0 (0)	0 (0)	0 (0)
PR	5 (83.3)	5 (100)	10 (90.9)
SD	1 (16.7)	0 (0)	1 (9.1)
PD	0 (0)	0 (0)	0 (0)
DCR[b]			
n (%)	6 (100)	5 (100)	11 (100)
95% CI	54.1, 100	47.8, 100	71.5, 100

Median (range) duration of response:
Not reached (2.9+-16.7+) months



Dotted lines indicate 20% increase or 30% decrease in sum of diameters of target tumours

All Patients

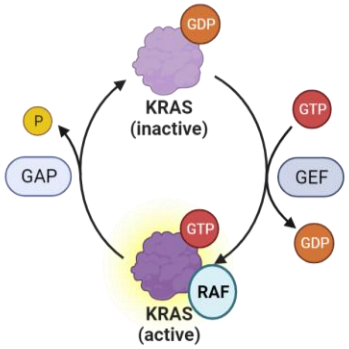


Median (range) duration of follow-up: 15.4 (4-19) months

KRAS G12C

KRAS G12C mutations drive tumour growth and occur in a subset of mCRC patients

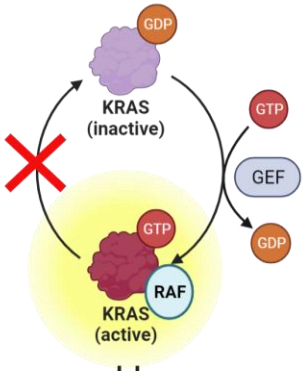
KRAS^{WT} signalling[1]



Downstream signalling

Cell growth and differentiation

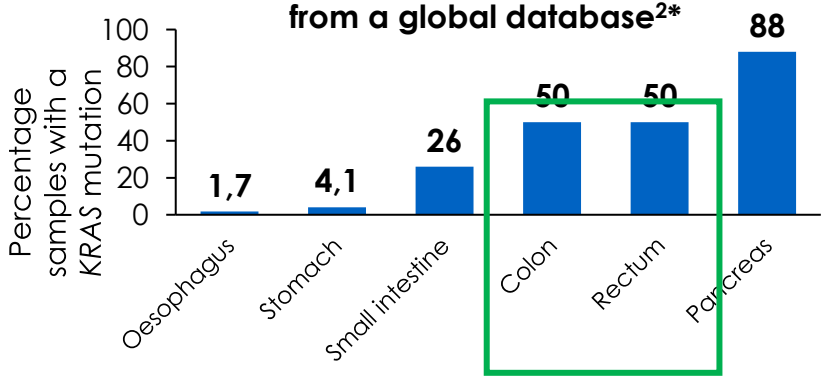
KRAS^{G12C} signalling[1]



Downstream signalling

Cancer progression

Frequency of *KRAS* mutations in GI cancers from a global database[2]*



- ***KRAS* G12C mutations are present in ~3–4% of CRC cases[3]**
- **RWD have suggested that *KRAS* G12C mutations may be associated with a poor prognosis[†4,5]**

*Images created with Biorender.com. *Mutation frequencies are based on COSMIC data, together with selected publicly available colon, rectal, and pancreatic data from the Foundation Medicine database;*
[†]Some real-world data publications have not shown a difference in prognosis between patients with KRAS G12C-mutated mCRC and those with other KRAS variants.[6,7]
GDP, guanosine diphosphate; GEF, guanine nucleotide exchange factor; GTP, guanosine triphosphate; RAF, rapidly accelerated fibrosarcoma; RWD, real-world data.
1. Zhang J, et al. Pharmacol Ther 2022;229:108050; 2. Prior I, et al. Cancer Res 2020;80:2969–74; 3. Strickler JH, et al. Oncologist 2023;28:e981–94; 4. Schirripa M, et al. Clin Colorectal Cancer 2020;19:219–25; 5. Taieb J, et al. Presented at ESMO Congress 2023, abstract 5530; 6. Osterlund E, et al. Front Oncol 2022;12:826073; 7. Koulouridi A, et al. Cancers (Basel) 2022;14:3320.

KRAS^{G12C} inhibitors and anti-EGFR antibodies in mCRC

Rationale for sotorasib and panitumumab combination therapy

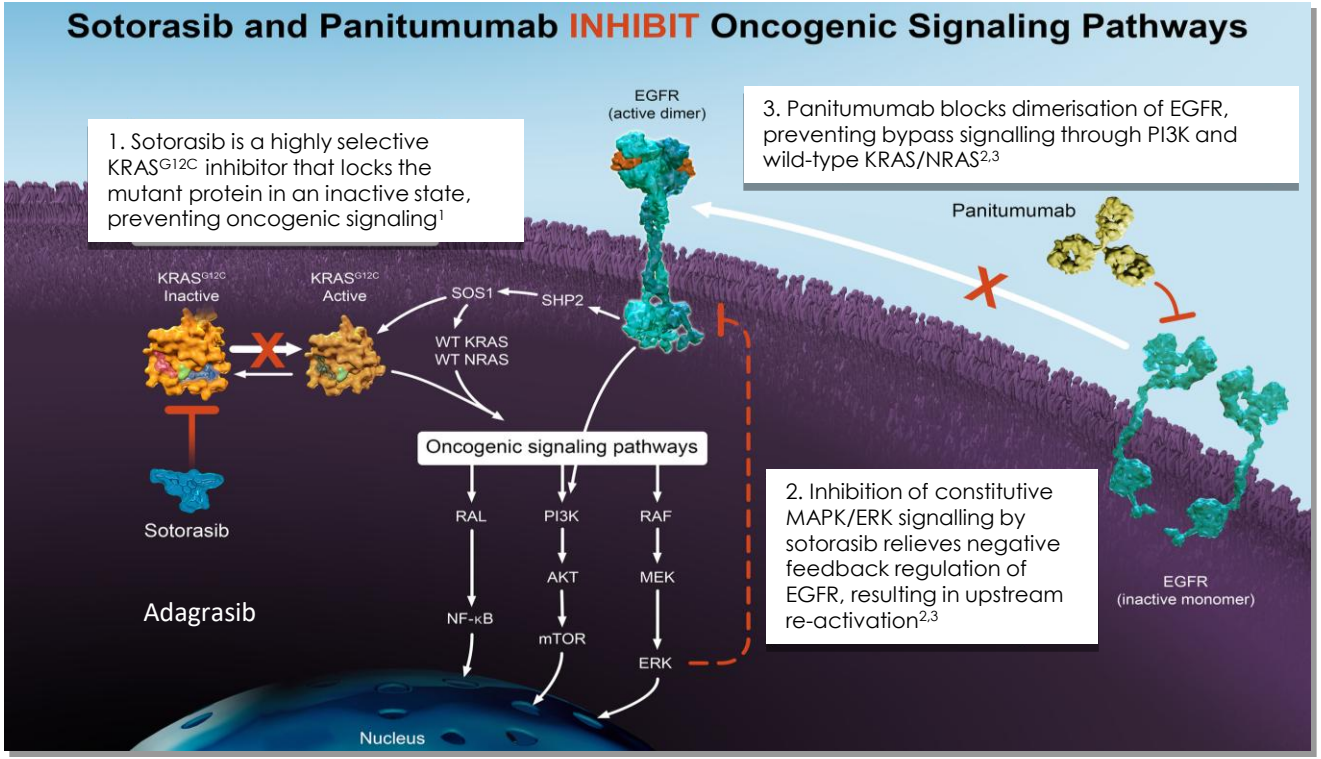


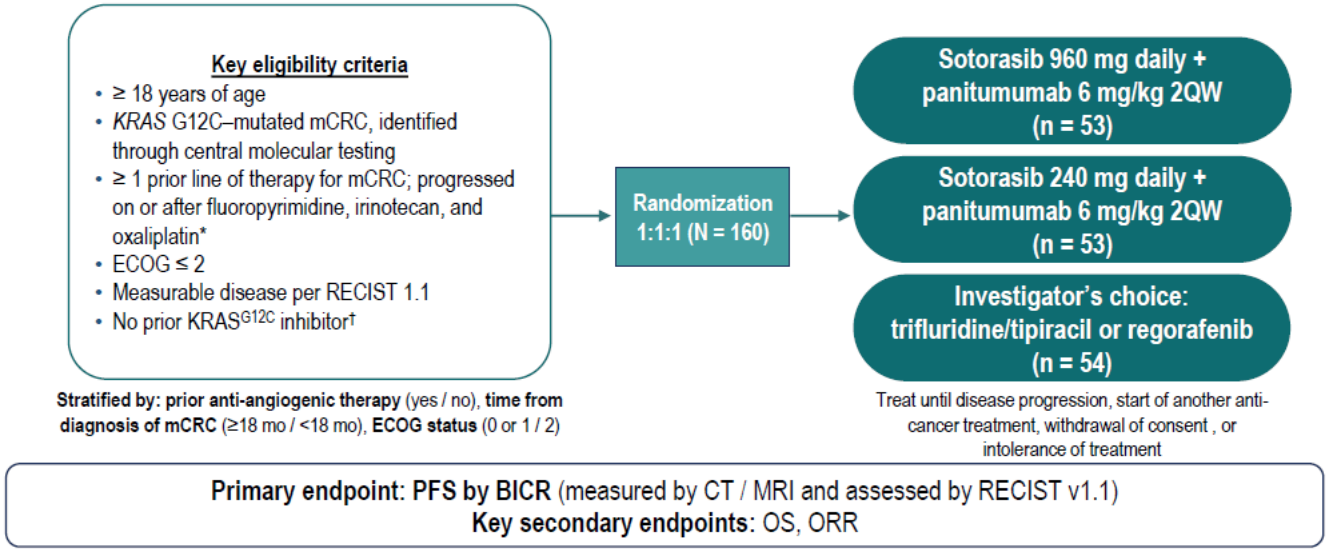
Figure courtesy of Amgen.

1. Canon J, et al. Nature 2019;575:217–23; 2. Berg M, Soreide K. Discov Med 2012;14:207–14; 3. Amodio V, et al. Cancer Discov 2020;10:1129–39.

Sotorasib plus Panitumumab in Refractory Colorectal Cancer with Mutated KRAS G12C

CodeBreaK 300 Phase 3 Study Design

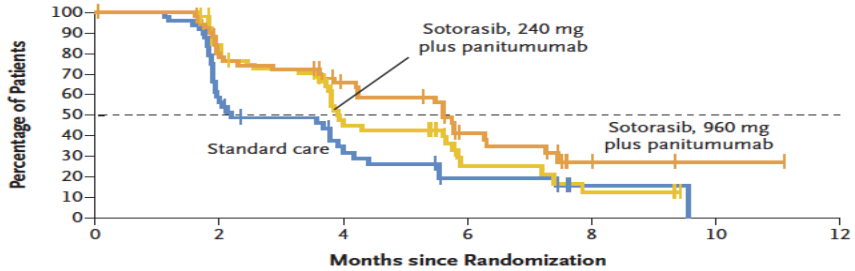
Global, randomized, open-label, active-controlled study of sotorasib + panitumumab in mCRC (NCT05198934)



≥ 2 prior lines: >80%

Fakih. N Eng J Med 2023

Primary Endpoint: PFS in Intent-to-Treat Population



No. at Risk							
Sotorasib, 960 mg plus panitumumab	53	40	28	13	2	1	0
Sotorasib, 240 mg plus panitumumab	53	43	20	6	3	0	
Standard care	54	24	12	5	1	0	

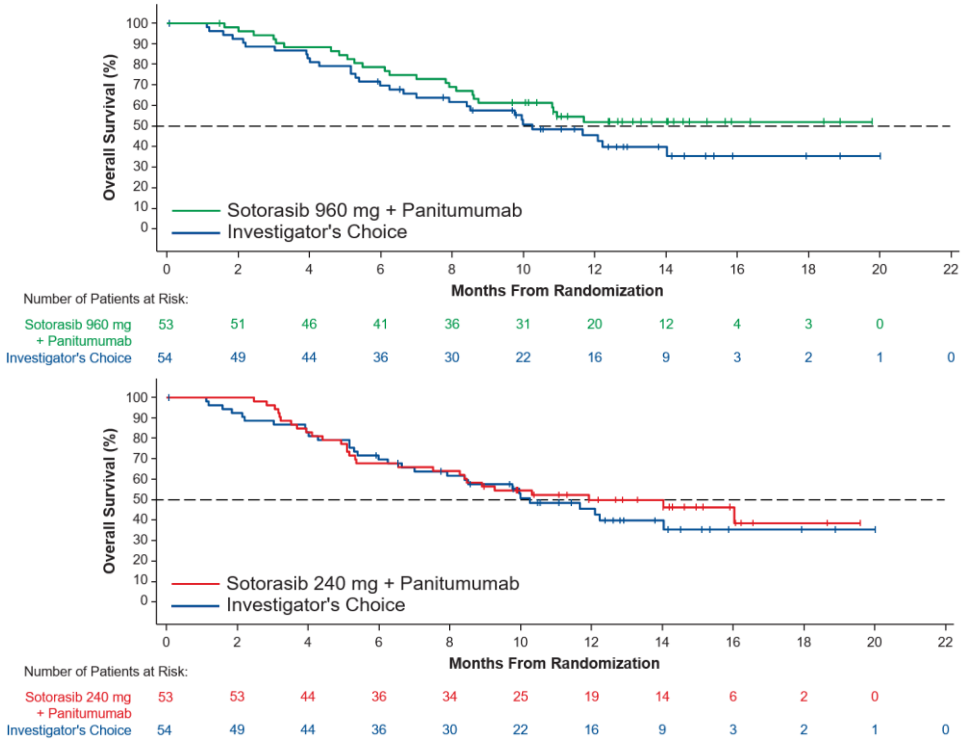
	Median Progression-free Survival	Hazard Ratio for Disease Progression or Death (95% CI)	Two-Sided P Value
	mo		
Sotorasib, 960 mg plus Panitumumab	5.62	0.49 (0.30–0.80)	0.006
Sotorasib, 240 mg plus Panitumumab	3.91	0.58 (0.36–0.93)	0.03
Standard Care	2.20		

	Sotorasib 960 mg + Panitumumab	Sotorasib 240 mg + Panitumumab	Investigator's Choice
OBJECTIVE RESPONSE	**26.4%** (95% CI, 15.3 to 40.3)	5.7% (95% CI, 1.2 to 15.7)	0% (95% CI, 0.0 to 6.6)

	Sotorasib 960 mg + PNT	Sotorasib 240 mg + PNT	Investigator's Choice
Grade ≥3 events	**35.8%** Dermatitis acneiform 11.3% Hypomagnesemia 5.7% Rash 5.7%	**30.2%** Hypomagnesemia 7.5% Diarrhea 5.7%	**43.1%** Neutropenia 23.5% Anemia 5.9% Hypertension 5.9%

Fakih. N Eng J Med 2023

Secondary Endpoint: Protocol-Specified Final OS in Intent-to-Treat Population



	Sotorasib 960 mg + Panitumumab (n = 53)	Sotorasib 240 mg + Panitumumab (n = 53)	Investigator's Choice (n = 54)
Median (95% CI) OS, months*	NE (8.6–NE)	11.9 (7.5–NE)	10.3 (7.0–NE)
HR (95% CI)†	0.70 (0.41–1.18)	0.83 (0.49–1.39)	–
P-value (2-sided)‡	0.20	0.50	–
Number of deaths (%)	24 (45)	28 (53)	30 (56)

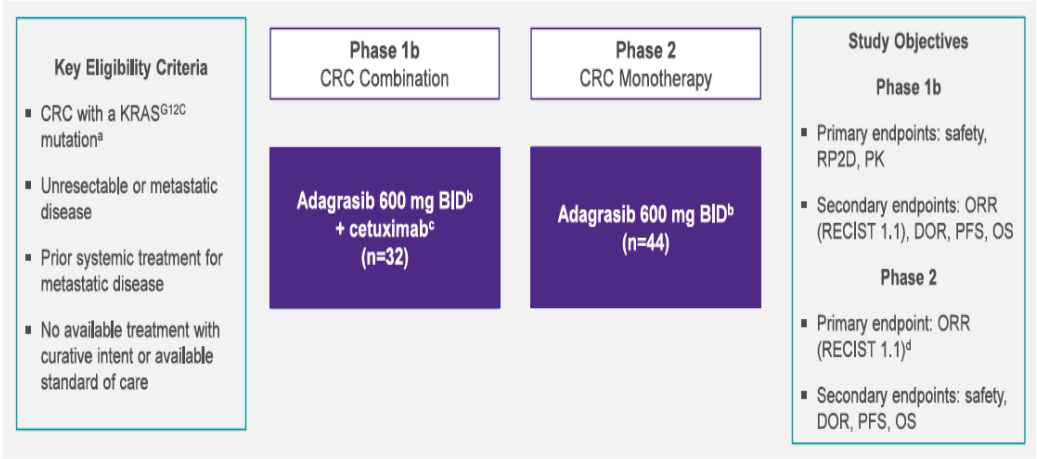
- **After a median follow-up of 13.6 months, sotorasib (240 mg and 960 mg) + panitumumab showed a trend of improved OS versus investigator's choice, with 30% reduction in risk of death for sotorasib 960 mg + panitumumab**

*Estimated using the Kaplan-Meier method, 95% CIs from log-log transformation. †HRs and 95% CIs from stratified Cox proportional hazards model. HR < 1.0 indicates a lower risk and a longer OS for [sotorasib + panitumumab] versus [trifluridine and tipiracil or regorafenib]. ‡*P*-value from stratified log-rank test. Data cutoff, 18 December 2023. CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival.

Fakih MG et al ASCO 2024

Adagrasib with or without Cetuximab in Colorectal Cancer with Mutated KRAS G12C

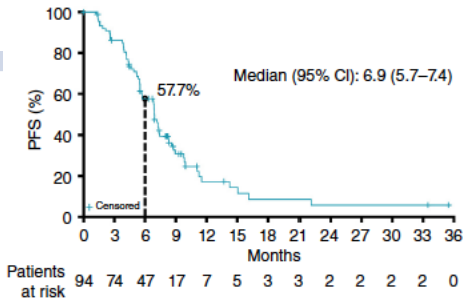
KRYSTAL-1 (849-001) Phase 1b/2 CRC Cohorts Study Design



Prior lines of systemic anticancer therapy, % 1 / 2 / 3 / ≥4	9% / 25% / 34% / 31%	18% / 21% / 25% / 36%

	ADAGRASIB 600mg BID	ADAGRASIB 600mg BID + CTX
Grade ≥3 events	34% Anemia 9% Diarrhea 7%	16% Diarrhea 3% Maculopapular rash 3% Dermatitis acneiform 3%

	ADAGRASIB 600mg BID (N=32)	ADAGRASIB 600mg BID + CETUXIMAB (Pooled data from the phase I and phase II cohorts , N=94)
ORR	19% (95% CI, 8-33)	**34%** (95% CI, 24.6-44.5) **DCR: 85.1%** (95% CI, 76.3-91.6)
mPFS	5.6 m (95% CI, 4.1-8.3)	**6.9 m** (95% CI, 5.7-7.4)



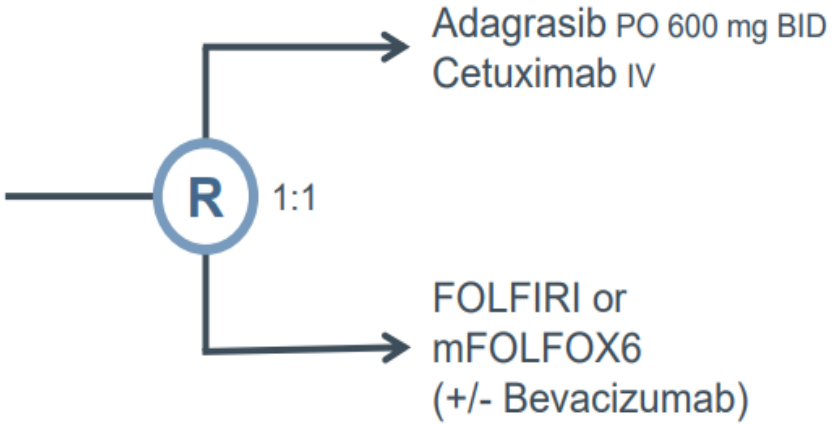
Yaeger. N Eng J Med 2023
Yaeger. Cancer Discov 2024

KRYSTAL-10 – Study Design

Phase 3 RCT

mCRC, **KRAS G12C** mutated
2L setting (progression on 1L FOLFOX or FOLFIRI)
N=461

1° end point
- PFS, OS



NCT04793958

CodeBreaK 101 Subprotocol H phase 1b, multicenter, open-label study*: sotorasib + panitumumab + FOLFIRI in first-line *KRAS* G12C–mutated mCRC

Key eligibility criteria

- *KRAS* G12C–mutated mCRC, identified through local molecular testing
- $KRAS^{G12C}$ inhibitor-naive
- No prior systemic treatment for metastatic disease

→ **Part 1: Cohort B Dose exploration† (N = 6)**

Dose Level 1:
Sotorasib: 960 mg
PO daily
+
Panitumumab: 6 mg/kg
IV Q2W
+
FOLFIRI IV
Q2W

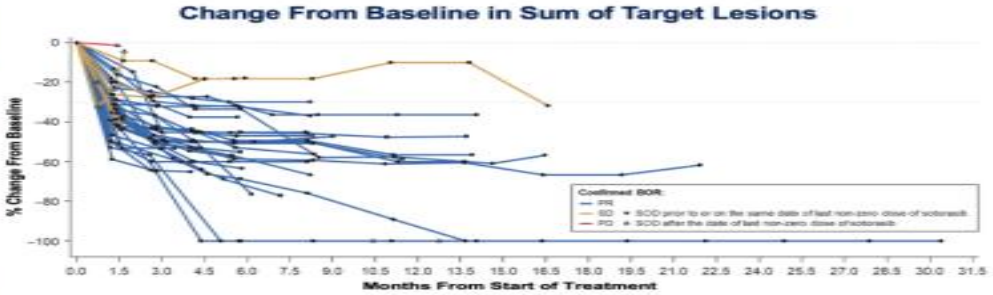
→ **No DLTs were observed, and dose level 1 was declared the RP2D‡**

→ **Part 2: Cohort F Dose expansion† (N = 40)**

Sotorasib: 960 mg
PO daily
+
Panitumumab: 6 mg/kg
IV Q2W
+
FOLFIRI IV
Q2W

Primary endpoint: Safety and tolerability
Secondary endpoints: Anti-tumor efficacy (ORR, DCR, DOR, TTR, PFS per RECIST v1.1, and OS) and PK

ORR by investigator assessment*	Sotorasib + Panitumumab + FOLFIRI (N = 40)
ORR, n (%)	31 (78)
Complete response†	0
Partial response	31 (78)
Stable disease	7 (18)
Progressive disease	1 (3)
Not evaluable / not done	1 (3)
Patients with liver metastasis only, n / N (%)	7/7 (100)
Left-sided tumor, n / N (%)	22 / 27 (82)
Right-sided tumor, n / N (%)	6 / 10 (60)

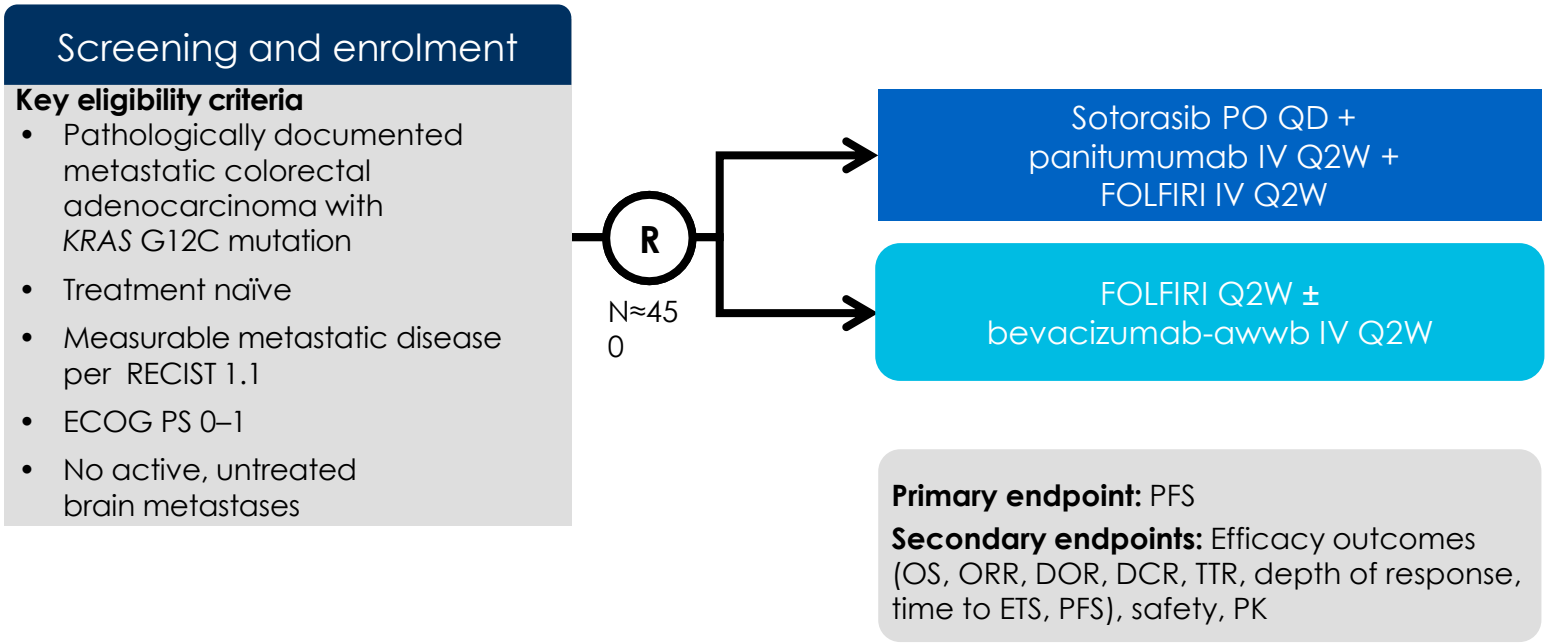


- A total of 38 patients (95%) achieved disease control, and all patients had reduction in target lesions

1. Ros J et al. Int J Mol Sci. 2024 Mar 14;25(6):3304, 2. Siena S et al. ESMO 2024 proffered paper session

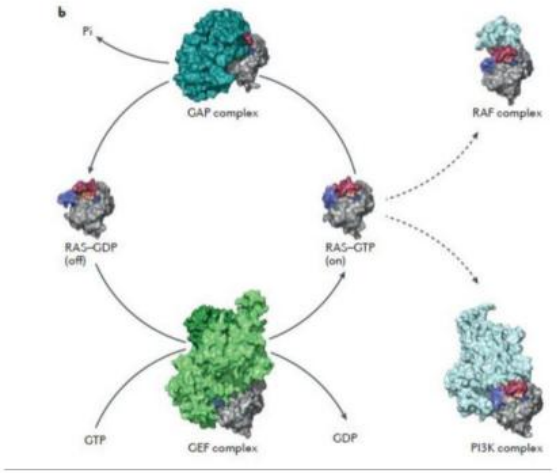
CodeBreaK 301: Phase 3 sotorasib + panitumumab + FOLFIRI in the 1L treatment setting

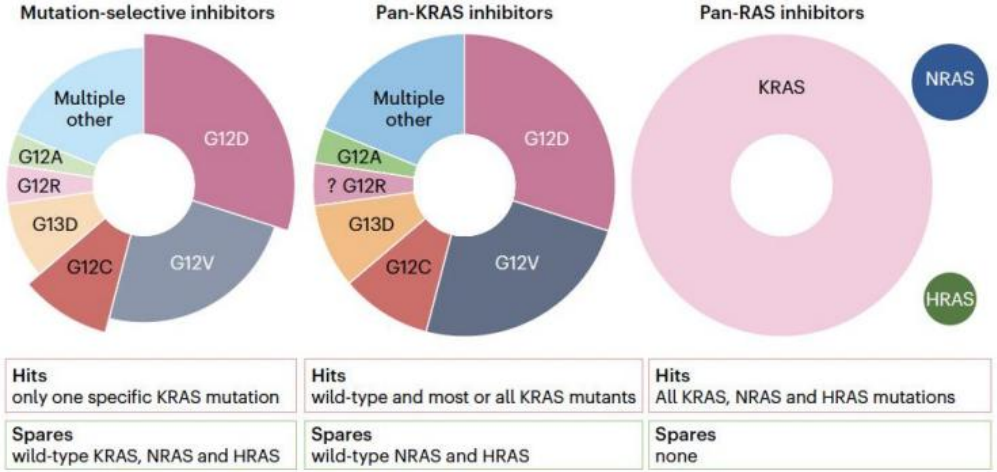
Study design



NCT06252649. Available at: https://www.clinicaltrials.gov/study/NCT06252649?term=CodeBreaK%20301&rank=1 (accessed June 2024).

INHIBIDORES DE RAS

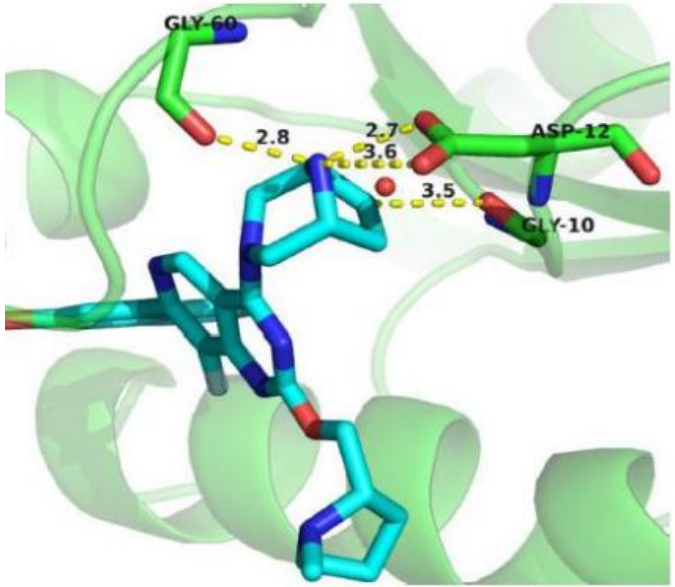


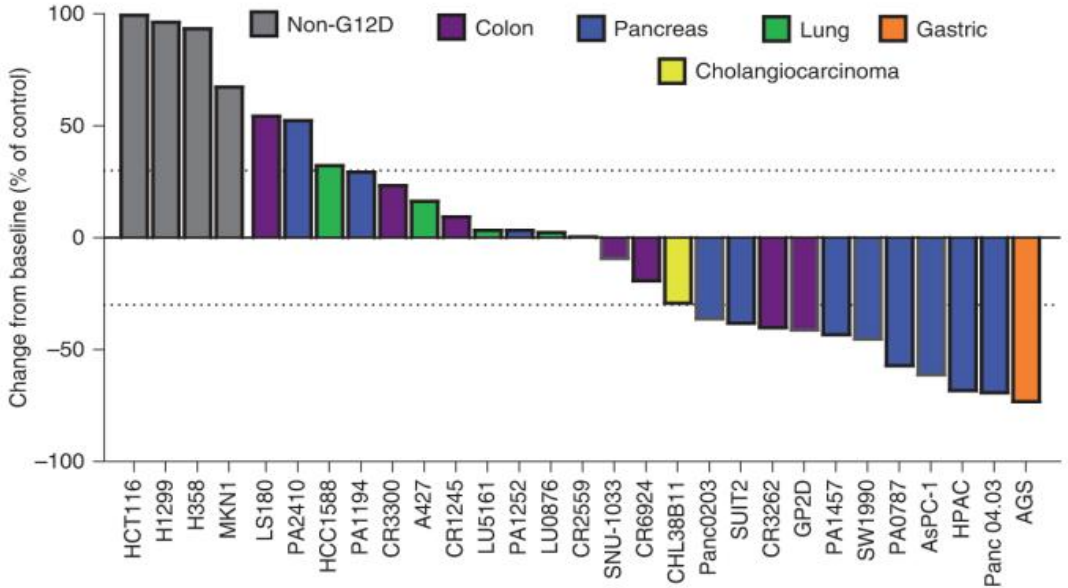


1. Jungwirth J et al. Sci Rep. 2022 Feb 16;12(1):2570. 2. Mullard A. Nat Rev Drug Discov. 2023 Mar;22(3):167-171, 3. Punekar SR et al. Nat Rev Clin Oncol. 2022 Oct;19(10):637-655, 1. Hallin J et al. Cancer Discov 2020; 10(1): 54-71,
2. Sai-Hong Ignatius Ou et al. J Clin Oncol 2022 Aug 10;40(23):2530-2538, 3. Hong DS et al. N Engl J Med. 2020 Sep 24;383(13):1207-1217, 4. Corcoran RB. Nat Cancer. 2023 Aug;4(8):1060-1062.

Mutant-selective inhibition of KRAS G12D

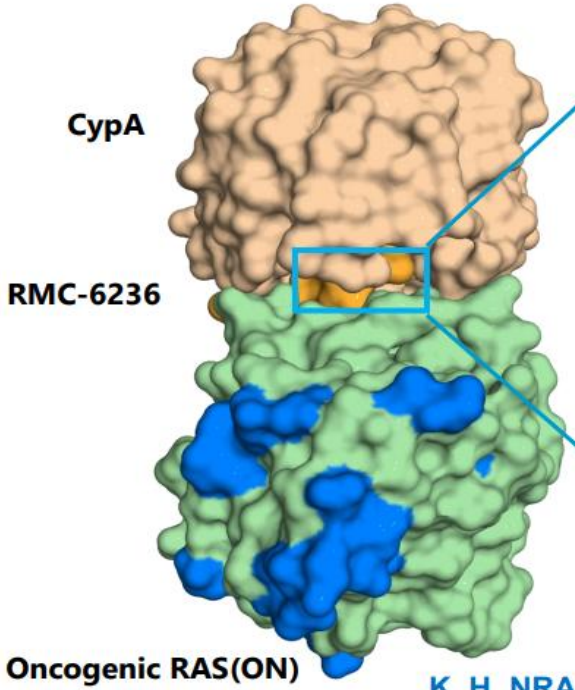
MRTX1133

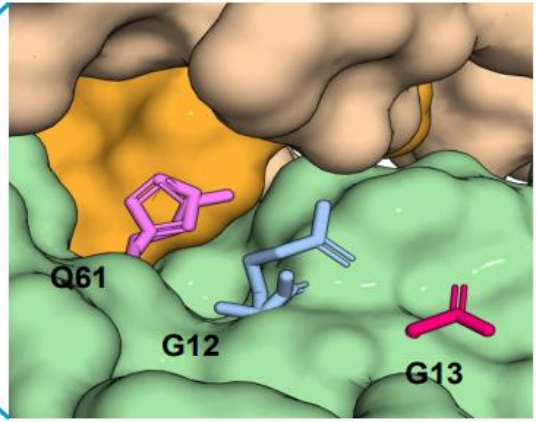




Wang et al, JMC 2021
Hallen et al, Nat Med 2022

RMC-6236: the first panRAS inhibitor

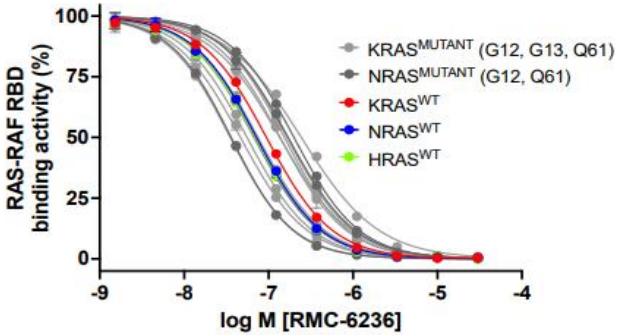




TCI binding mode leaves a groove along Q61-G12-G13 axis in RAS(ON) un-occupied

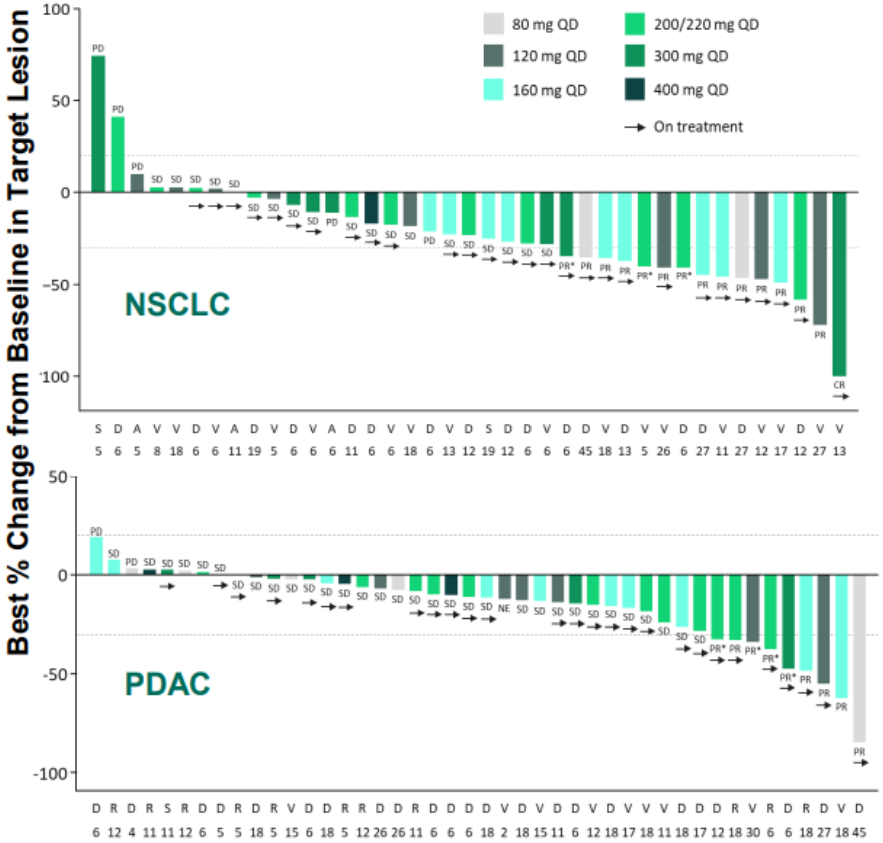
K, H, NRAS divergent residues

Biochemical RAS-RAF RBD Disruption



Koltun et al, AACR 2024

Initial clinical efficacy of RMC-6236



Data Extracted 12 Oct 2023
Arbour et al. Presented at ESMO 2023

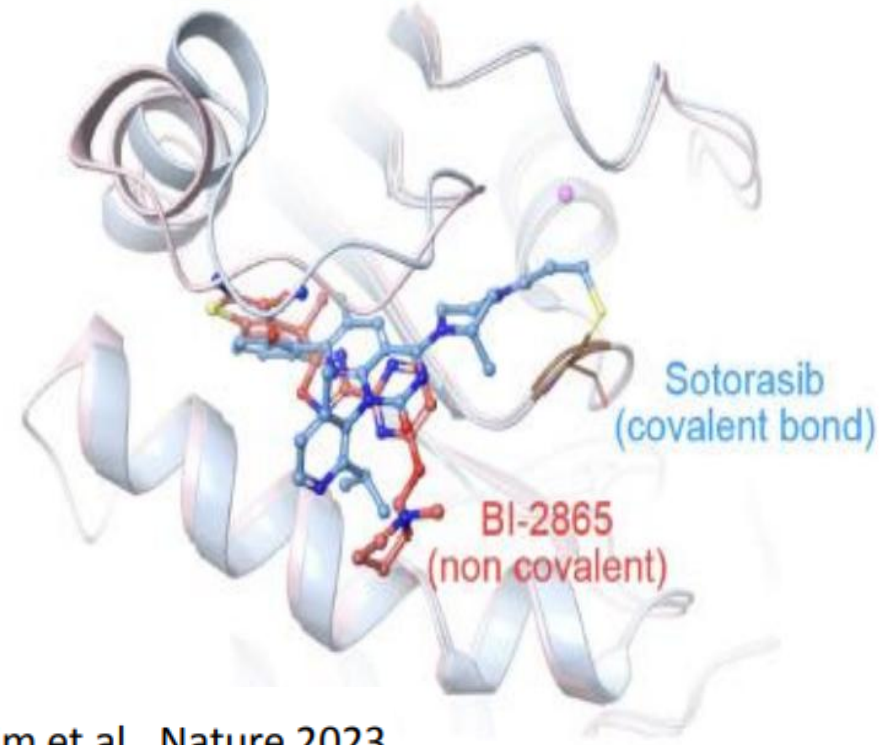
KRAS G12X NSCLC (N=40) [1, 2]	
ORR	**38%**
DCR	**85%**
SOC Benchmark, Docetaxel[3]	
ORR	13%
DCR	60%

KRAS G12X PDAC (N=46) [1, 2]	
ORR	**20%**
DCR	**87%**
SOC Benchmark, GnP[3]	
ORR	11%
DCR	56%

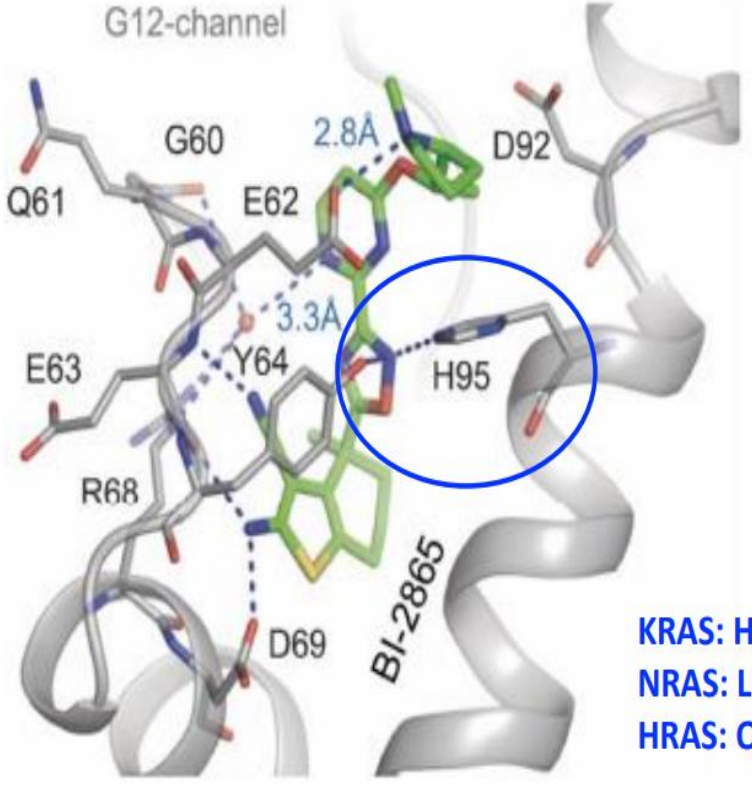
(1) Patients who received first dose of RMC-6236 at least 8 weeks prior to data extract date.
(2) Tumor response per RECIST 1.1.
(3) Docetaxel efficacy from CodeBreaK 200, Lancet (2023) 401: 733-746.
GnP=Gemcitabine plus nab-paclitaxel; GnP efficacy from Br J Cancer (2022) 126:1394-1400.

KRAS-selective (panKRAS) inhibitors

BI-2865



Kim et al., Nature 2023

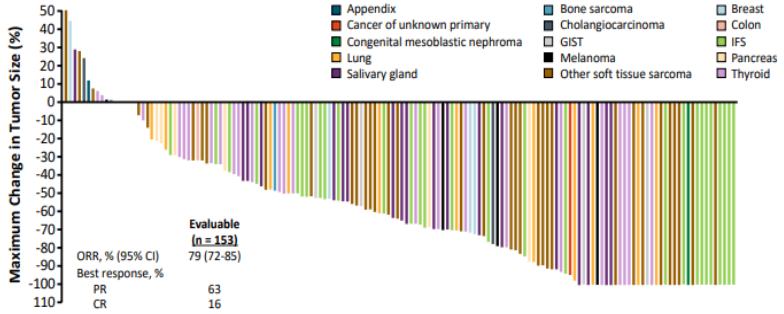


KRAS: H95
NRAS: L95
HRAS: Q95

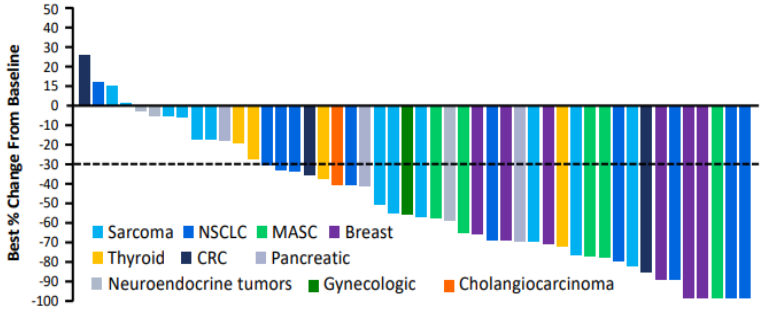
Alteraciones infrecuentes

NTRK fusion: Clinical results across tumour types

Larotrectinib



Entrectinib



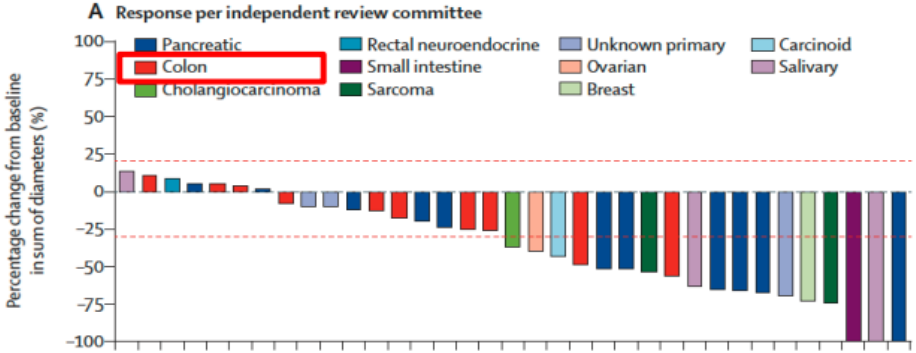
Hong DS, Lancet Oncol. 2020; Doebele et al., Lancet Oncol 2020

Shen L, et al. ASCO GI 2024

RET fusion - Selpercatinib

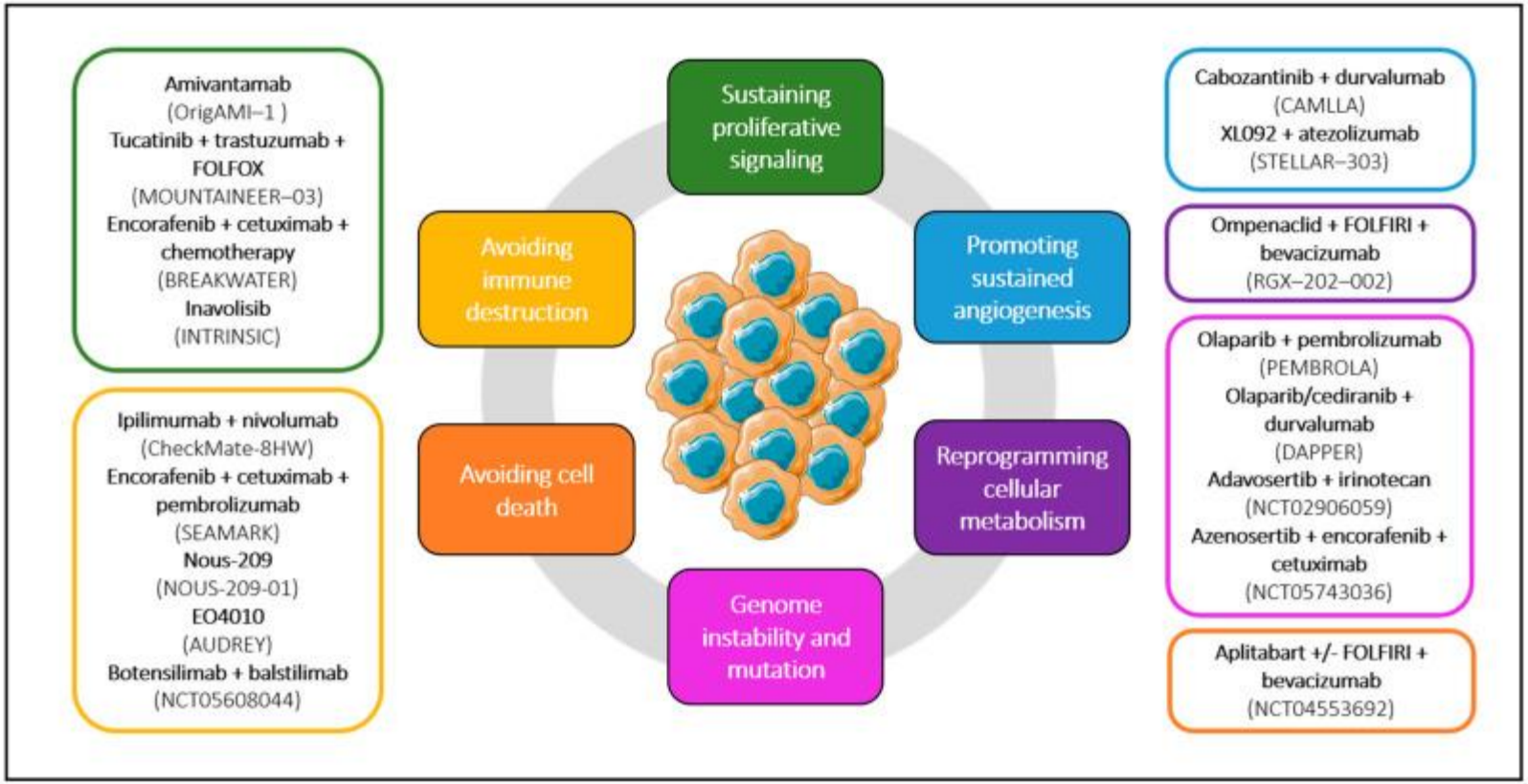
LIBRETTO-001

Phase 1/2, open label, basket trial
RET fusion-positive solid tumours
other than lung or thyroid tumours

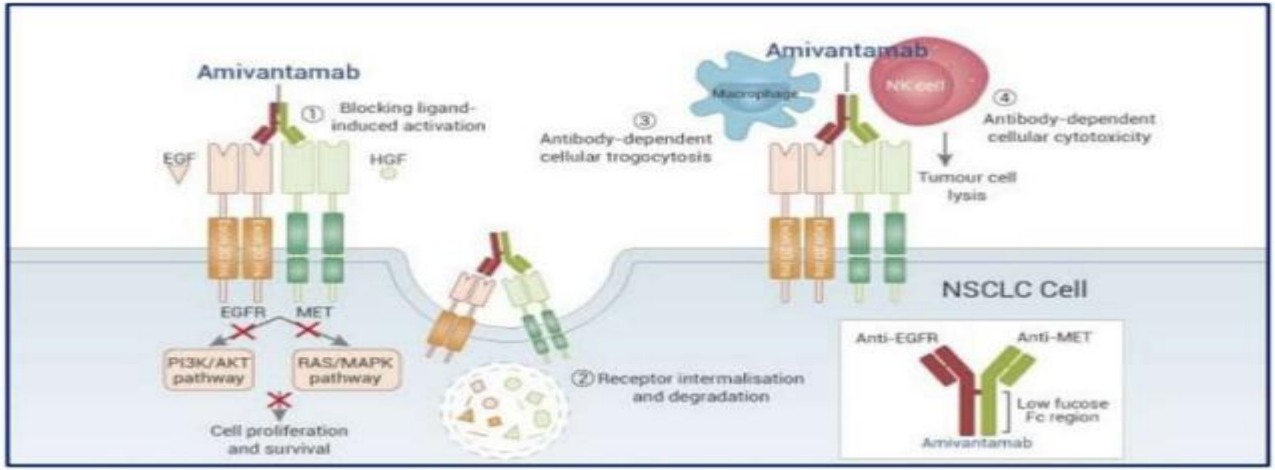


	Number of patients per primary diagnosis	Independent review committee assessment	
		Objective response rate (95% CI)	Median duration of response, months (IQR)
All *RET* fusion-positive solid tumour types	41	43·9% (28·5–60·3)	24·5 (9·2–NR)
Colon	10	20·0% (2·5–55·6)	9·4 (5·6–13·3)

Subbiah V et al. Lancet Oncol. 2022 Oct;23(10):1261-1273.


Amivantamab
(OrigAMI–1)
Tucatinib + trastuzumab + FOLFOX
(MOUNTAINEER–03)
Encorafenib + cetuximab + chemotherapy
(BREAKWATER)
Inavolisib
(INTRINSIC)
Ipilimumab + nivolumab
(CheckMate-8HW)
Encorafenib + cetuximab + pembrolizumab
(SEAMARK)
Nous-209
(NOUS-209-01)
EO4010
(AUDREY)
Botensilimab + balstilimab
(NCT05608044)
Sustaining proliferative signaling
Avoiding immune destruction
Promoting sustained angiogenesis
Avoiding cell death
Reprogramming cellular metabolism
Genome instability and mutation
Cabozantinib + durvalumab
(CAMLLA)
XL092 + atezolizumab
(STELLAR–303)
Ompenaclid + FOLFIRI + bevacizumab
(RGX–202–002)
Olaparib + pembrolizumab
(PEMBROLA)
Olaparib/cediranib + durvalumab
(DAPPER)
Adavosertib + irinotecan
(NCT02906059)
Azenosertib + encorafenib + cetuximab
(NCT05743036)
Aplitabart +/- FOLFIRI + bevacizumab
(NCT04553692)

- **MET** puede encontrarse sobreexpresado o amplificado en el CCRm, lo que deriva en la mediación de la resistencia a las terapias antiEGFR
- **Amivantamab** es un anticuerpo biespecífico EGFR-MET totalmente humano con actividad inmunodirigida
- **Origami:** Estudio de fase 1b/2, abierto, de amivantamab en monoterapia y junto a quimioterapia en pacientes con CCRm



(image) https://www.medchemexpress.com/literature

Origami[1-3]: A Phase 1b/2, Open-Label Study of Amivantamab Monotherapy and in Addition to SOC Chemotherapy in patients with Advanced or mCRC

Key Eligibility Criteria

- ECOG PS score of 0–1
- Eligible for 1L or 2L therapy
- No prior EGFRi

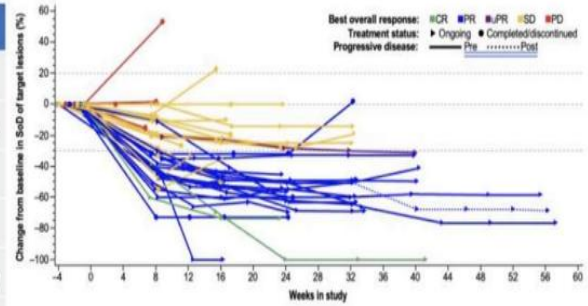
Cohort D: Amivantamab + mFOLFOX6 (n=20)

Cohort E: Amivantamab + FOLFIRI (n=23)

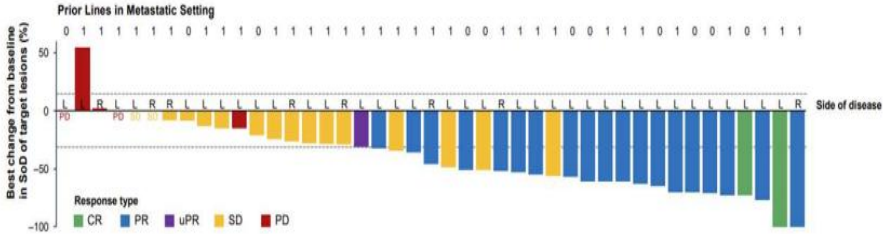
Durable anti-tumor activity with amivantamab + FOLFOX or FOLFIRI

Investigator-assessed	Total (N=43)
ORR[a,b]	49% (95% CI, 33–65)
Median DoR[c]	7.4 months (95% CI, 5.6–NE)
Time to response[c]	8.3 weeks
DCR	88% (95% CI, 75–96)
Median PFS	7.5 months (95% CI, 7.4–NE)
Received curative intent surgery, n	5 completed (2 more scheduled)

Patients could undergo curative intent surgery and were censored upon procedure completion.



- Median (range) follow-up was 7.3 months (1.1–14.4)
- 67% (29/43) of patients remain on treatment[d]
- ORR was 64% among patients on 1L therapy and 44% among patients on 2L therapy



ORIGAMI-2

KRAS/NRAS and *BRAF* wild-type, **first-line,** left-sided, metastatic colorectal cancer

R 1:1

- Amivantamab + FOLFOX or FOLFIRI (n~500)
- Cetuximab + FOLFOX or FOLFIRI (n~500)

ORIGAMI-3

KRAS/NRAS and *BRAF* wild-type, EGFR inhibitor–naïve, recurrent or metastatic colorectal cancer post-chemo **(2L)**

R 1:1

- Amivantamab + FOLFIRI (n~350)
- Cetuximab or bevacizumab + FOLFIRI (n~350)

1. 61186372GIC2002 (ORIGAMI) NCT05379595, 2. Oberstein PE, et al. J Clin Oncol 42, 2024 (suppl 3; abstr 135), 3. Pietrantonio F et al. ESMO 2024

Conclusiones

1. **CCRm mediado por alteraciones moleculares son un subgrupo relevante**
2. **Las terapias dirigidas poseen alta eficacia clínica**
3. **Existe un número creciente de opciones terapéuticas**
(en el horizonte: KRAS G12D e inhibidores pan-RAS, nuevas combinaciones,amivantanab, etc.)
4. **Las pruebas moleculares son clave**
5. **El desarrollo de las pruebas moleculares permitirán identificar más alteraciones moleculares**
(por ejemplo, biopsia líquida en primera línea; WES/WGS del tumor para pruebas basadas en ctDNA, etc.)

!Muchas Gracias!