XVII SIMPOSIUM
BASES BIOLÓGICAS DEL CÁNCER
E INNOVACIÓN TERAPÉUTICA

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

SALAMANCA, 22 Y 23 DE MAYO DE 2025

Opciones de tratamiento en cáncer colorectal metastásico refractario (CCRm)

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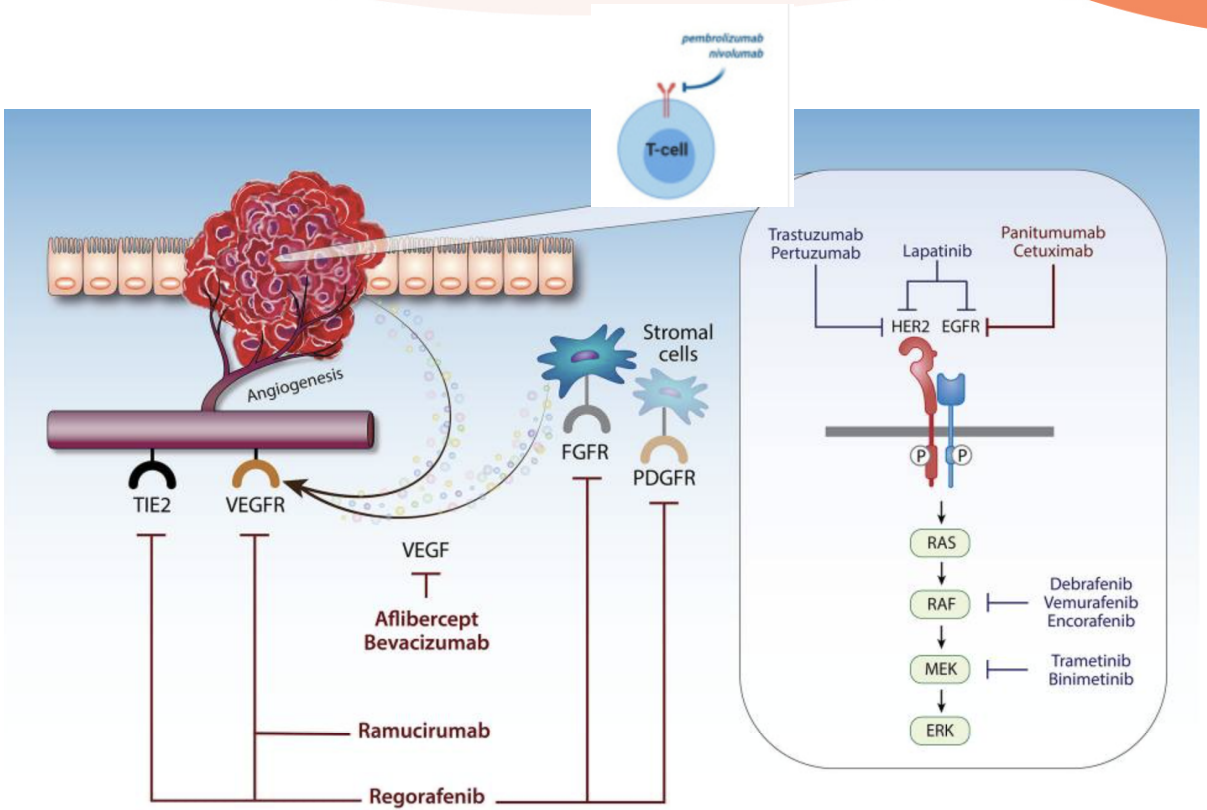
- Introducción
    - Refractariedad y objetivos
- Opciones de tratamiento
    - Sin selección molecular
    - Con selección molecular (guiadas por biomarcador)
- Líneas futuras
- Conclusiones

Es importante conocer los complejos mecanismos por los que cuales las células del CCR metastatizan

- Heterogeneidad tumoral
- Alteraciones genéticas y epigenéticas
- Transición mesénquima-epitelio
- Micro ambiente tumoral

… identificar biomarcadores predictores de respuesta a terapias dirigidas
... desarrollo de nuevas terapias

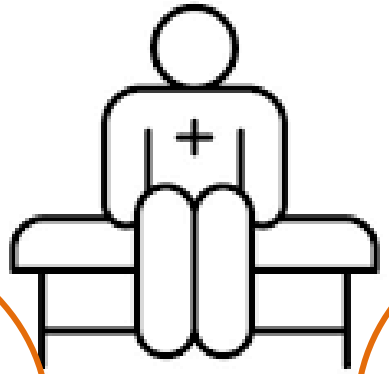


Alice E Shin. Metastatic colorectal cancer: mechanisms and emerging therapeutics. Trends pharmac Science 2023

localización
tumor
síntomas

Objetivo
terapeútico

Evidencia
científica



Preferencias
del paciente

Características
del **paciente**

Características
moleculares

Summary of recommendations	LoE, GoR
Testing for **MMR status** [ESCAT: I-A, if detection by NGS] and *KRAS*, *NRAS* exon 2, 3 and 4 and ***BRAF* mutations** [ESCAT: I-A] is recommended in all patients at the time of metastatic colorectal cancer diagnosis	I, A
RAS testing is mandatory before treatment with anti-EGFR monoclonal antibodies and can be carried out on either the primary tumour or other metastatic sites	III, A
***BRAF* V600E mutations** [ESCAT: I-A] status should be assessed simultaneously with the evaluation of *RAS*, for prognostic assessment and for the option of treatment with targeted therapy	I, B
DMMR/MSI-H [ESCAT: I-A, if detection by NGS] testing in metastatic colorectal cancer: • Can assist in genetic counselling for Lynch syndrome • Is recommended as the initial molecular work-up in metastatic disease for its predictive value for the use of immune checkpoint inhibitors	II, B I, A
Identification of HER2 overexpression (by IHC) and/or ***HER2* amplification** [ESCAT: II-B] is recommended in patients with *RAS*-wt to detect those who may benefit from targeted therapy	-
When multigene tumour NGS is available and applicable, testing is advised for: • ***KRAS* G12C** [ESCAT: I-A] • ***POLE* mutations** [ESCAT: II-B] • Genomic aberrations for which targeted therapeutics are approved in tumour-agnostic indications [***NTRK* fusions, *RET* fusions, TMB-H**; ESCAT: I-C]	 I, A III, C III, C
Testing of other biomarkers including ***ALK* and *ROS1* gene fusions** [ESCAT: III-A], mutations of *PIK3CA* and HER2-activating mutations is not recommended outside clinical trials	IV, D

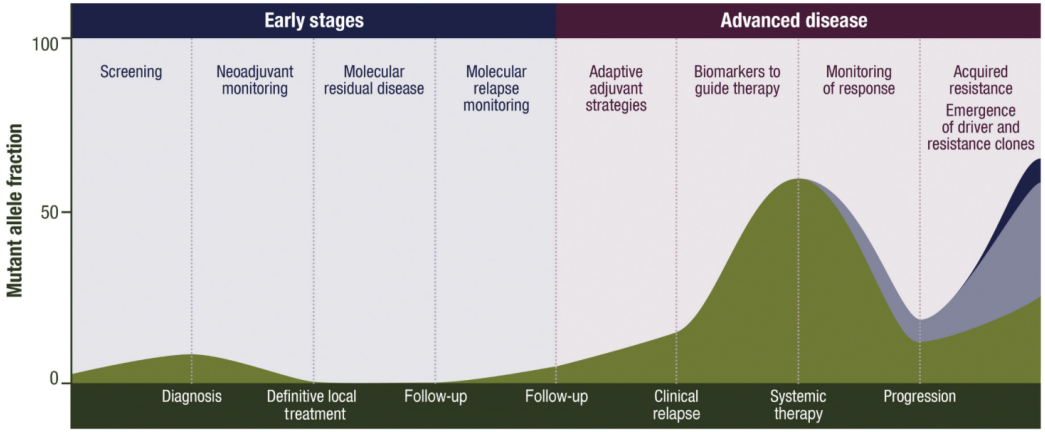
ESMO

CLINICAL PRACTICE GUIDELINES

ESMO living guidelines 2025

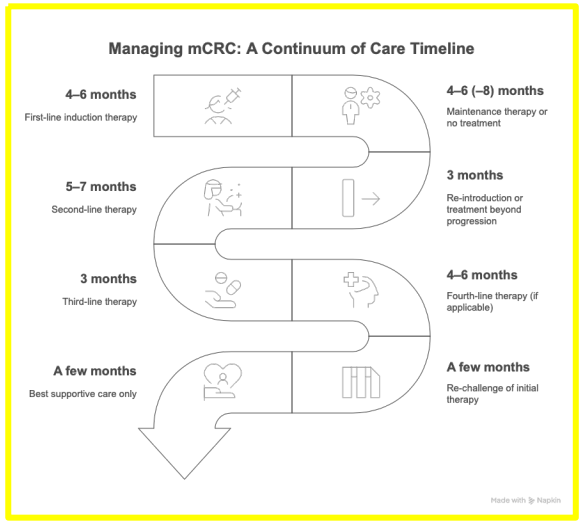
ESMO recommendations on the use of circulating tumour DNA assays for patients with cancer: a report from the ESMO Precision Medicine Working Group

Pascual et al. Annals of Oncol 2022



Tumour type	Indications	ESCAT tier and level of evidence	Recommendation
Colorectal cancer	*BRAF* (for V600E mutation) MSI-H *NTRK* 1/2/3 fusions *KRAS/NRAS* mutations (exon 2,3,4) *ERBB2* amplification *EGFR-ECD* (for mutations in the extracellular domain S492, G465, S464, V441)	IA[151] IA[147,152] IC[134] N/A (resistance biomarker) IB[57,153,154] IB[73]	*KRAS/NRAS/BRAF*^{V600E}/MSI for chemotherapy-naive metastatic colorectal cancer is recommended when tissue testing is not feasible or urgent therapeutic decision making. *KRAS/NRAS/BRAF/EGFR*-ECD for pretreated patients if EGFR rechallenge is planned.

- La **refractariedad** en el cáncer colorrectal metastásico (mCRC) se define como la progresión de la enfermedad después de recibir tratamientos de primera y segunda línea, que generalmente incluyen quimioterapia basada en fluorouracilo con oxaliplatino e irinotecán, terapias dirigidas contra VEGF (principalmente bevacizumab) y terapias dirigidas contra EGFR en tumores RAS wild-type
- Los **objetivos** del tratamiento son **prolongar supervivencia** y mantener la **calidad** de vida



The European Society for Medical Oncology (ESMO) has communicated a treatment objective wherein 50% of 'fit' first-line patients should be eligible for third-line therapy[1]

[2] RWD-ACROSS	Line of Therapy		
	First	Second	Third
	Overall		
Number of patients	(n = 2002)	(n = 1428)	(n = 725)

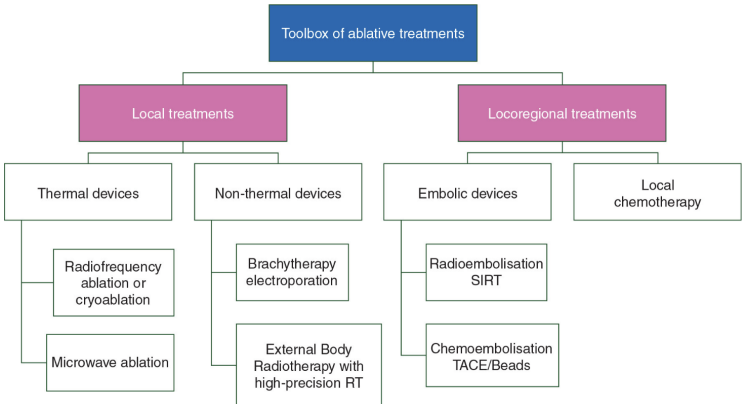
[1] Abraham Ann Oncol 2016

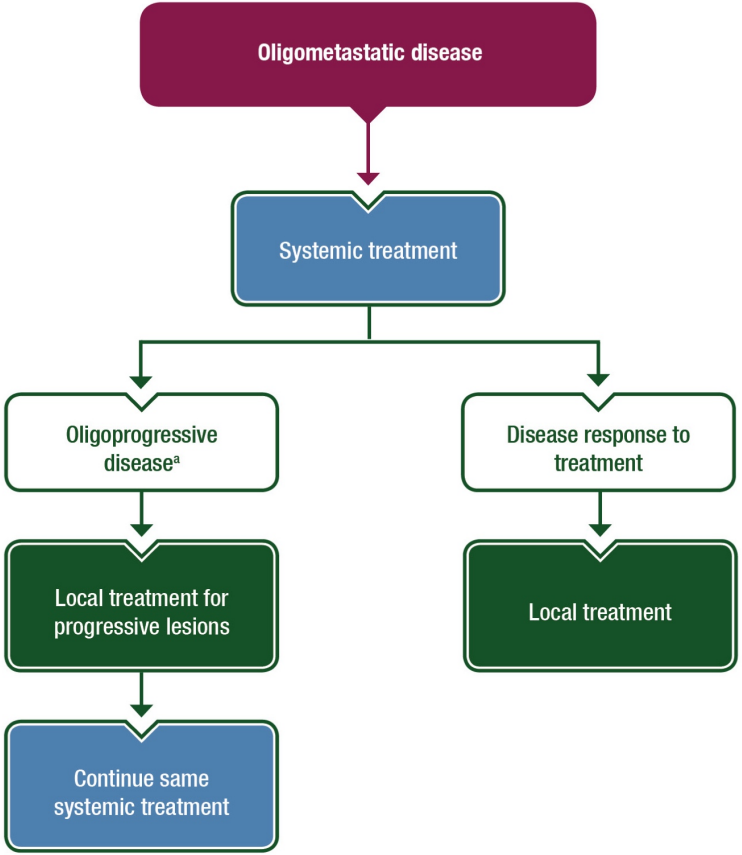
[2] Pericay C. Real-World Outcomes in Patients with Metastatic Colorectal Cancer in Spain: The RWD-ACROSS Study. Cancers Sept 2023

CLINICAL PRACTICE GUIDELINES

Oligometastatic Disease

[a]Very limited recurrence in a metastatic lesion in a patient receiving systemic treatment.



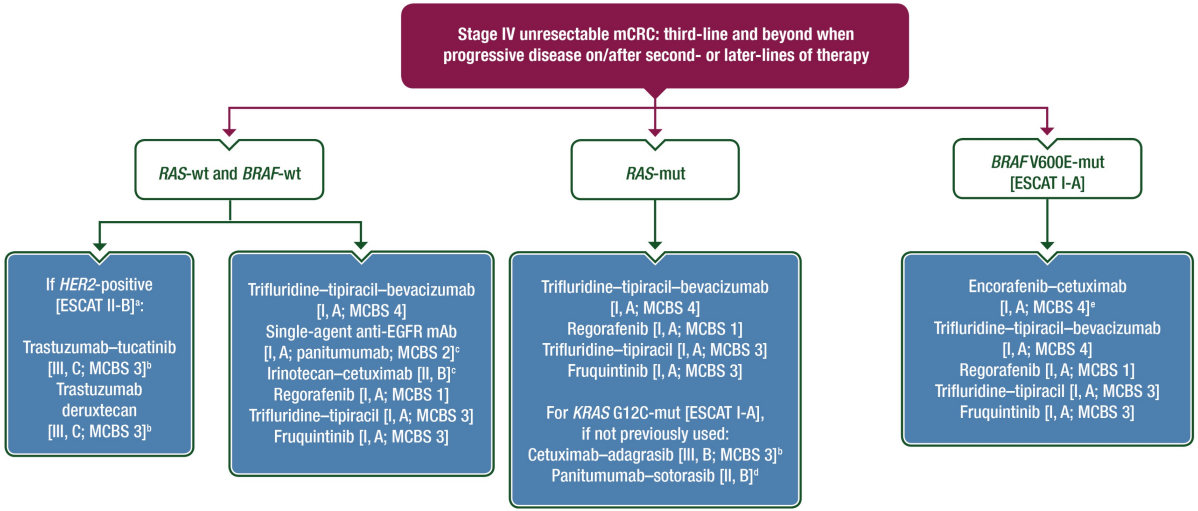


ESMO

CLINICAL PRACTICE GUIDELINES

Stage IV Unresectable mCRC

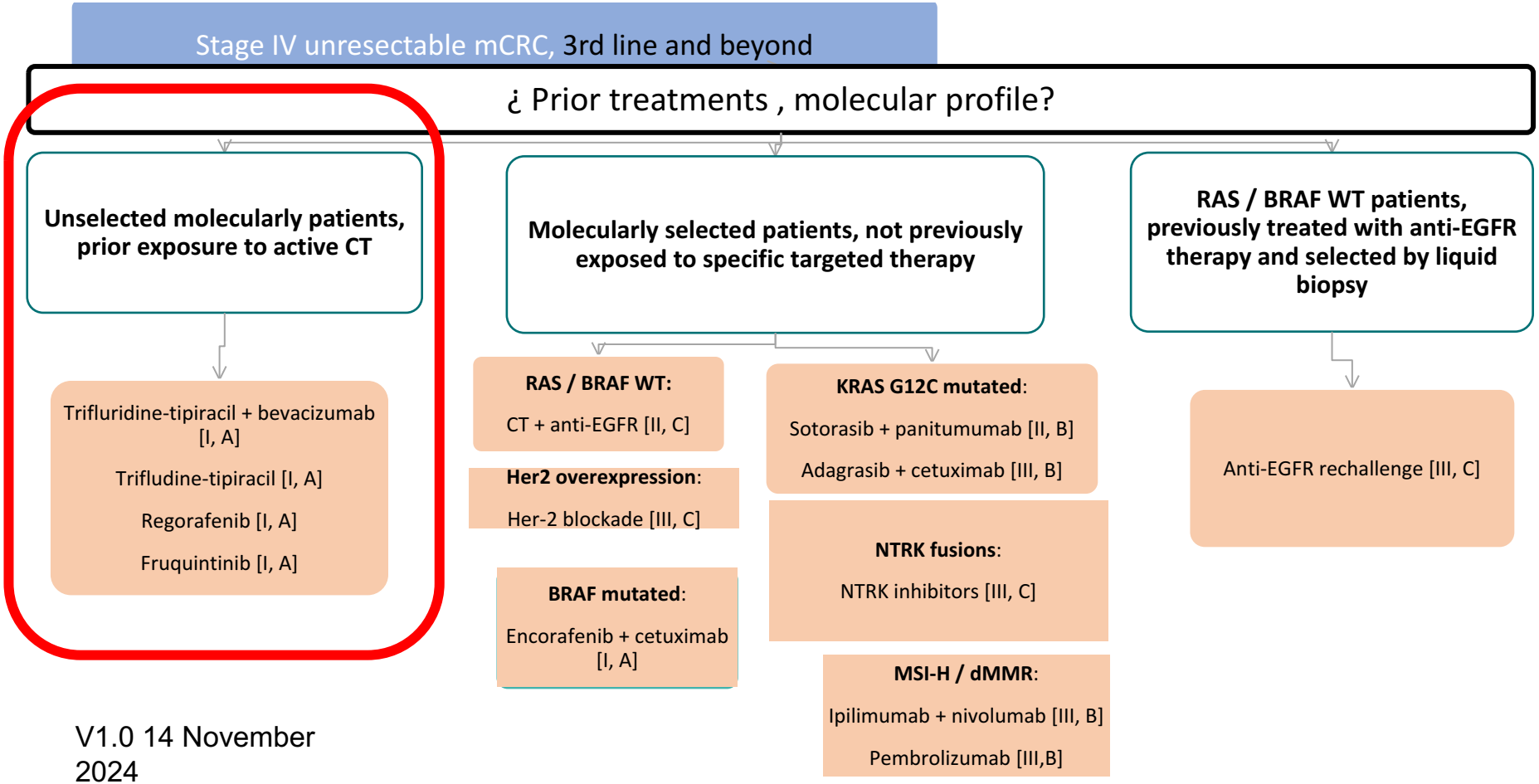
Third-line and Beyond



[a]For a summary of recommended anti-HER2 regimens for mCRC, see Supplementary Table S6 available at https://doi.org/10.1016/j.annonc.2022.10.003.
[b]FDA approved, not EMA approved.
[c]In patients with *RAS*-wt who were not previously treated with anti-EGFR monoclonal antibodies.
[d]FDA approved, not EMA approved.
[e]Treatment for *BRAF*-mut patients if not used in the second line.

ESMO

2025 Updated version V1.0 SEOM-GEMCAD-TTD clinical guidelines for the systemic treatment of metastatic colorectal cancer (2022)



V1.0 14 November 2024

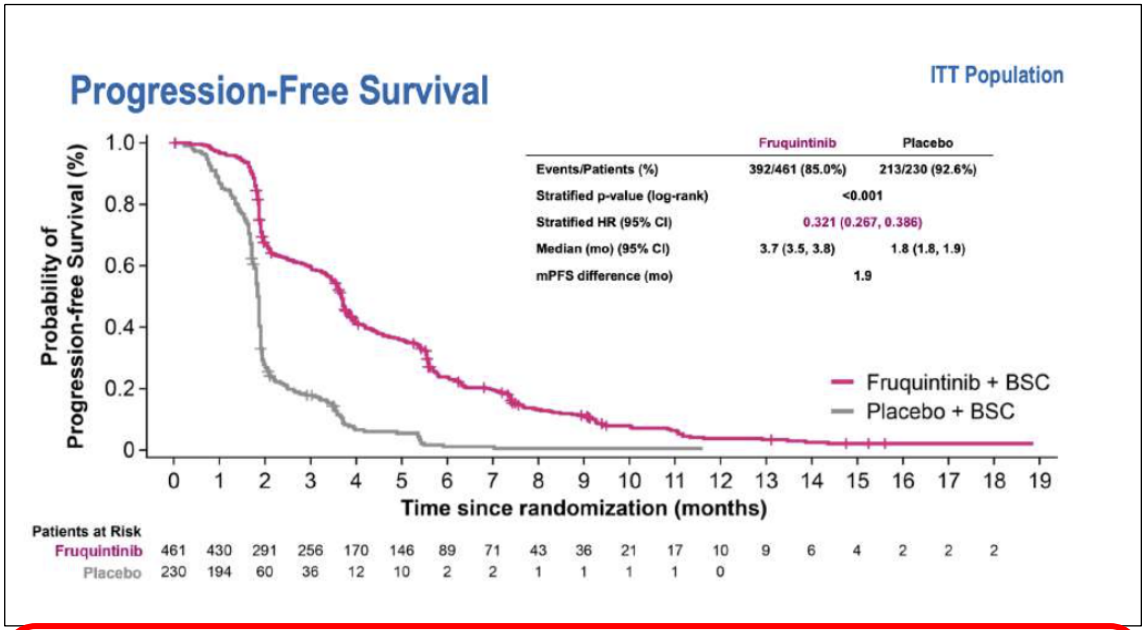
Opciones sin selección molecular

Tratamiento	Ensayo	Aleatorización	n	m SLP (meses)	m SG (meses)	ORR	DCR	Efectos Secundarios Principales
Regorafenib	CORRECT[1] (2013)	vs Placebo	760	2.0 vs 1.9	6.4 vs 5.0	1.0% vs 0.0%	40% vs 33%	Fatiga, hipertensión, diarrea, dolor abdominal, erupción cutánea.
TAS-102	RECOURSE [2] (2015)	vs Placebo	800	2.0 vs 1.7	7.1 vs 5.3	3.2% vs 0.0%	41% vs 27%	Neutropenia, fatiga, náuseas, anorexia, diarrea.
TAS-102 + Bevacizumab	SUNLIGHT[3] (2023)	vs TAS-102	473	5.7 vs 3.8	9.2 vs 7.3	7.5% vs 3.1%	62% vs 47%	Hipertensión, hemorragias, trombocitopenia, diarrea, fatiga.
Fruquintinib	FRESCO-2[4] (2023)	vs Placebo	692	3.7 vs 1.8	9.3 vs 6.6	4.5% vs 0.0%	58% vs 37%	Fatiga, hipertensión, diarrea, disminución del apetito.

Elaboración propia, no comparación directa

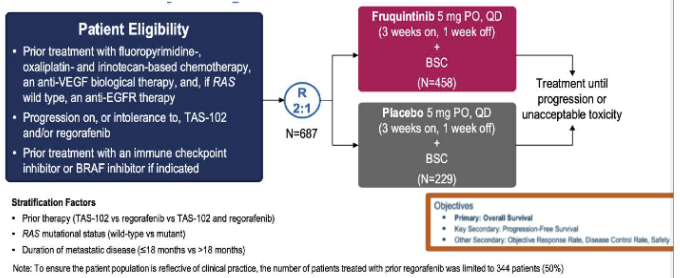
[1]O'Neil BH, et al.. Lancet. 2015 Dec 12;386(10002):2383-91
[2]Grothey A, et al. Lancet. 2013 Jan 12;381(9863):303-1
[3]Prager GW, Taieb J, Fakih M, et al. *N Engl J Med*. 2023;388(18):1657–1667
[4]Dasari A, Lonardi S, García-Carbonero R, et al. *The Lancet*. 2023;402(10395):41-53. doi:10.1016/S0140-6736(23)00772-9

Opciones **SIN** selección molecular



Variable	**Fruquintinib**	Placebo	HR (IC 95%)	p-valor
SG	7.4 meses (6.7–8.2)	4.8 meses (4.0–5.8)	0.66 (0.55–0.80)	**<0.0001**

THE LANCET



73% >3L

Beneficio en todos los subgrupos
- TAS-102 previo 47%
- Regorafenib 12%
- Ambos , un 41 %
- Bevacizumab 96%

Buen perfil toxicidad:
- 63% Aes >3: HTA 14%, astenia 7%

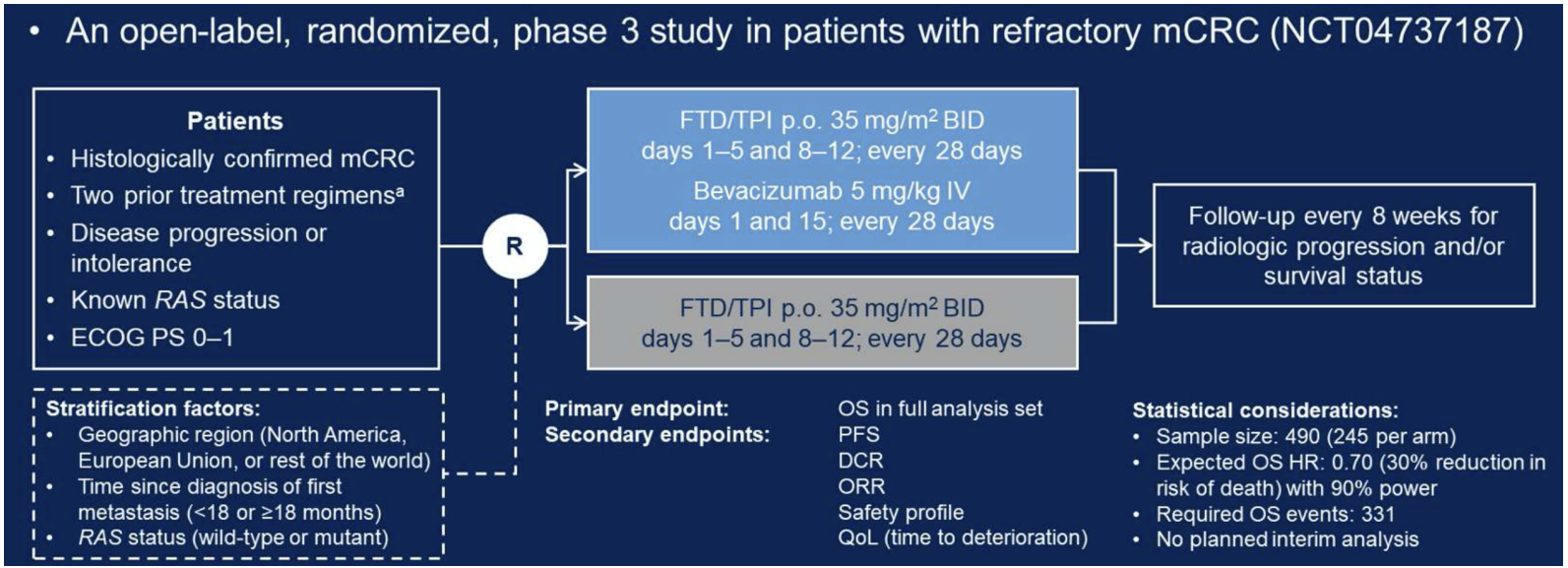
Dasari A, et al. ESMO 2022 (LBA25). Dasari A, et al. Lancet 2023.

Opciones **SIN** selección molecular

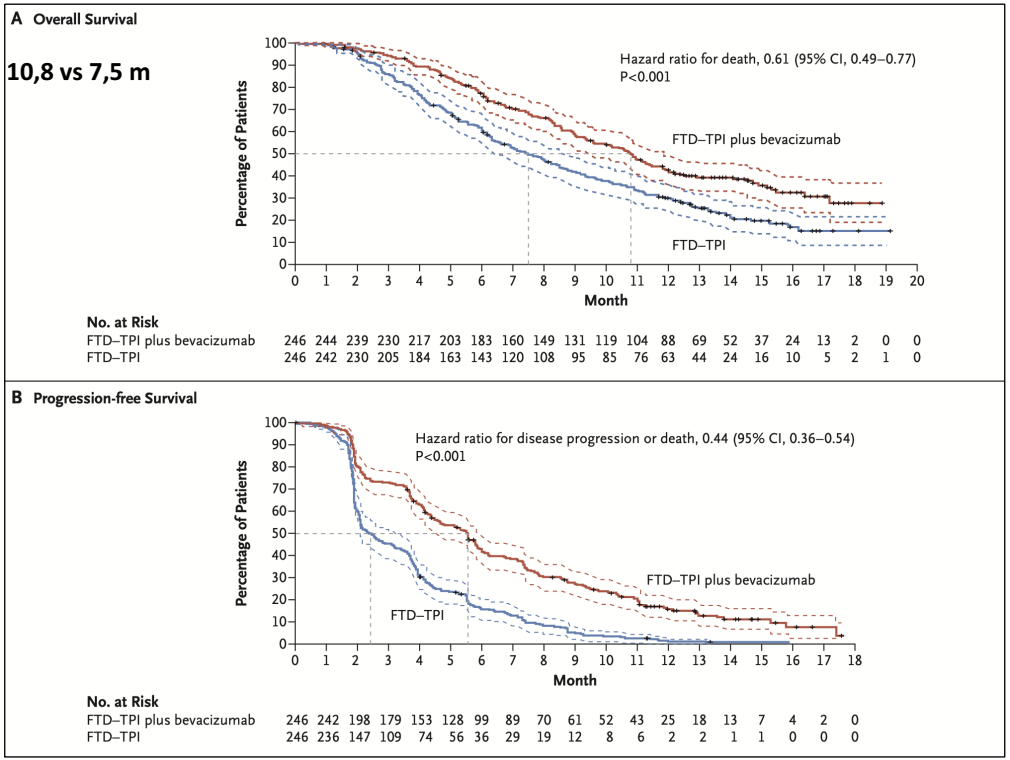
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trifluridine–Tipiracil and Bevacizumab in Refractory Metastatic Colorectal Cancer



Tabernero J et al. ASCO GI 2023 (#4 oral presentation). Prager GW et al. N Engl J Med 2023



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trifluridine–Tipiracil and Bevacizumab in Refractory Metastatic Colorectal Cancer

Estudio 3L **casi puro** (>90% pacientes) que muestra **beneficio de la combinación frente a tratamiento efectivo**

Demuestra beneficio de mantener iVEGF

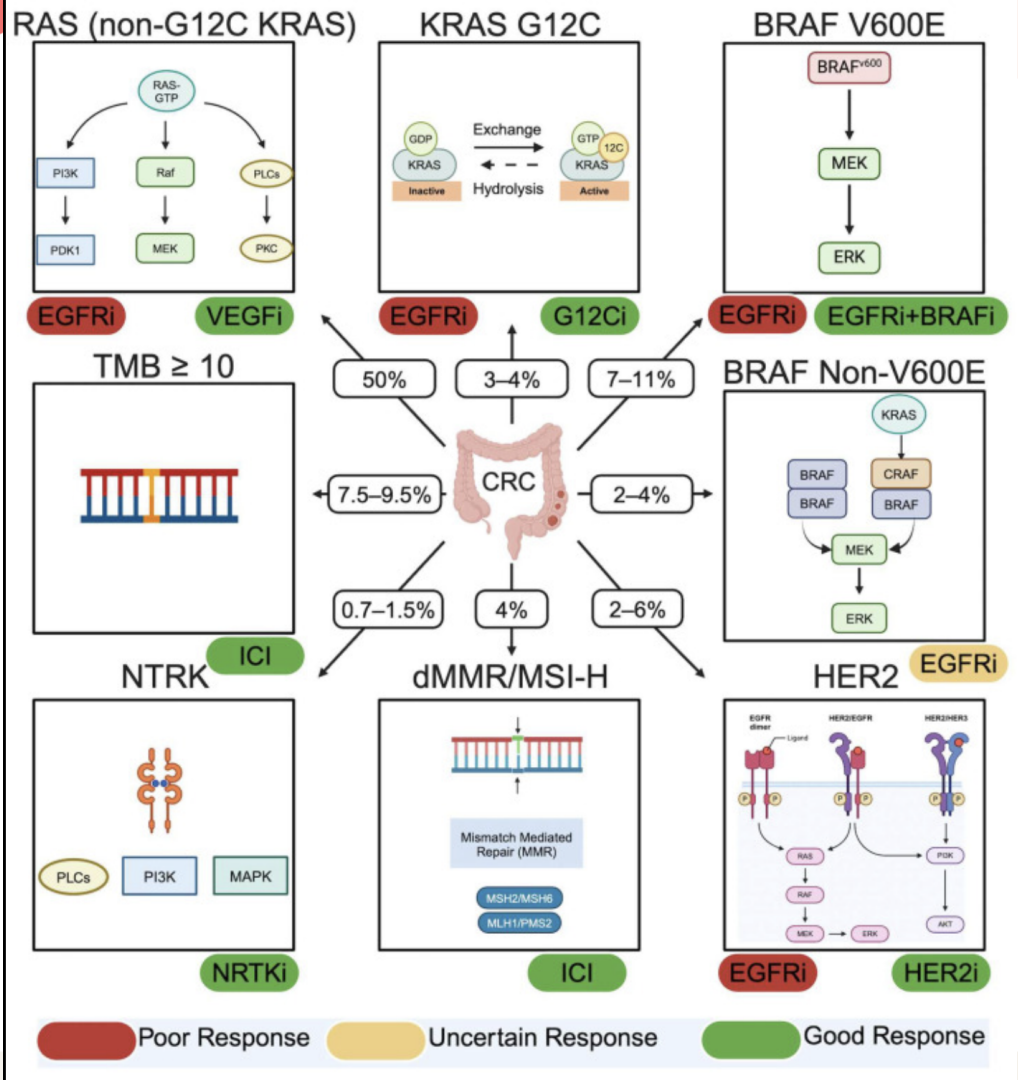
Beneficio **todos los subgrupos**

- Edad
- Sexo
- Localización
- Estatus RAS (**69% RASm**)
- antiVEGF previo (100%)

Tabernero J et al. ASCO GI 2023 (#4 oral presentation). Prager GW et al. N Engl J Med 2023

- Introducción
  - Refractariedad y objetivos
- Opciones de tratamiento
  - Sin selección molecular
  - Con selección molecular
    (dirigidas por biomarcador)
- Líneas futuras
- Conclusiones

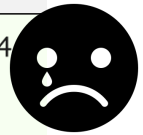
- **dMMR/MSI-H:** inmunoterapia (si no previa)
- **RAS/BRAF wt:** Rechallenge
- **BRAF mV600E**
- **Her2**
- **NTRK**
- **KRAS G12C**
- Otros: RET, ALK, FGR2-3



Ashouri K. Cancers (Basel) 2024 Aug.

Tratamiento guiado por biomarcador (selección molecular)

Trial Name [Ref.]	% of mCRC	Phase	Treatment Options	N	ORR %	PFS Months	OS Months
Selected patients, data mainly from phase 2							
BRAFmut	8–12%	3	Encorafenib + cetuximab (2nd line)	220	20	4.2	8.4
HER2+ and RASwt	3–5%	2	Anti-HER2 treatment	19–53	10–55	2.9–6.9	10.6–24.1
RASwt and BRAFwt	30%	2	Anti-EGFR rechallenge	28–39	3–54	2.4–6.6	8.2–9.8
$KRAS_{G12C}$	3%	1/2	Adagrasib and cetuximab	28	46	6.9	13.4
$KRAS_{G12C}$	3%	3	Sotorasib and panitumumab	53	26	5.6	NR
NTRK gene fusions	<1%	2	Entrectinib, larotrectinib	10–19	20–47	3.0–5.5	12–16



Line Schmidt. Cancers (Basel) Dec 2023

dMMR/MSI-H (4%)

The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE

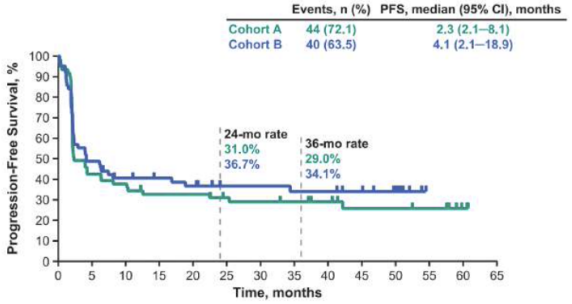
PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

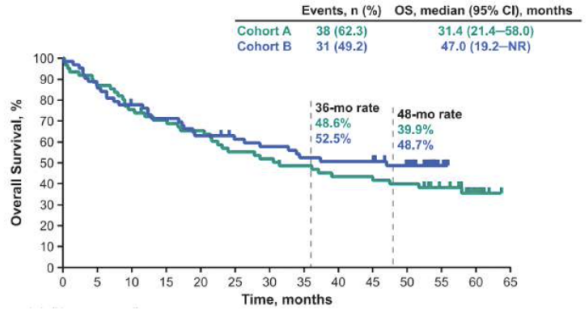
D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring,

Pembrolizumab for previously treated, microsatellite instability–high/mismatch repair–deficient advanced colorectal cancer: final analysis of KEYNOTE-164

Unresectable or metastatic MSI-H/dMMR CRC
≥2 prior systemic therapies (cohort A) or ≥1 prior systemic therapy (cohort B).

	Cohort A n = 61		Cohort B n = 63	
	n	% (95% CI)[a]	n	% (95% CI)[a]
ORR	20	32.8 (21.3–46.0)	22	34.9 (23.3–48.0)
Best overall response				
CR	3	4.9 (1.0–13.7)	9	14.3 (6.7–25.4)
PR	17	27.9 (17.1–40.8)	13	20.6 (11.5–32.7)
SD	11	18.0 (9.4–30.0)	13	20.6 (11.5–32.7)
PD	28	45.9 (33.1–59.2)	25	39.7 (27.6–52.8)
Non-evaluable	2	3.3 (0.4–11.3)	3	4.8 (1.0–13.3)
DCR[b]	31	50.8 (37.7–63.9)	35	55.6 (42.5–68.1)
DOR median (range),[c] months		NR (6.2–58.5+)		NR (4.4–52.4+)
Estimated DOR[c] ≥ 36 months, %		89.7		95.5





Le DT et al. NEJM. 2015 LeDT et al Eur J Cancer 2023

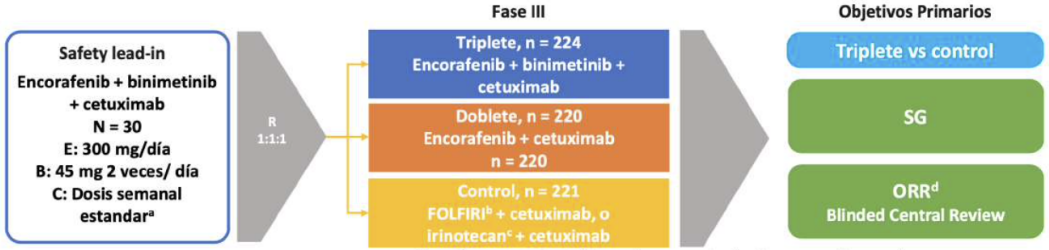
mBRAF V600E (8-10%)

ORIGINAL ARTICLE

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

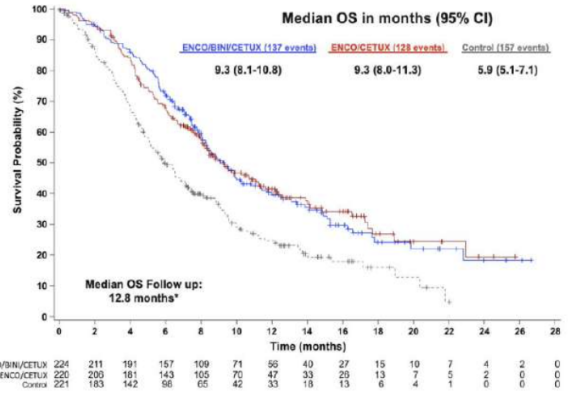
Encorafenib Plus Cetuximab as a New Standard of Care for Previously Treated *BRAF* V600E–Mutant Metastatic Colorectal Cancer: Updated Survival Results and Subgroup Analyses from the BEACON Study

BEACON CRC : Fase III, Pacientes con CCRm BRAFV600E con progresión de la enfermedad tras 1 o 2 líneas previas; ECOG PS de 0 o 1; y sin tratamiento previo con ningún inhibidor de RAF, inhibidor de MEK o inhibidor de EGFR



Estratificación por ECOG PS (0 vs. 1), uso previo de irinotecan (si vs. no), y origen de cetuximab (licencia-USA vs. Aprobado-UE).

Principales Objetivos secundarios:
- SG doblete vs control
- SLP
- DoR en todos los grupos
- Seguridad en todos los grupos
- QoL en todos los grupos



Confirmed Response by BICR	ENCO/BINI/CETUX N=224	ENCO/CETUX N=220	Control N=221
Objective Response Rate[a]	**27%**	**20%**	**2%**
95% (CI)	(21, 33)	(15, 25)	(<1, 5)

Kopetz S et al. NEJM 2019. Tabernero J, et al. J Clin Oncol 2021.

- ✓ Aprobado FDA
- ✓ Aprobado EMA
- X No financiación AEMPS

*In the EU, encorafenib is approved in combination with cetuximab for the ≥2L treatment of BRAF mt mCRC, while the combination treatment of encorafenib + cetuximab + binimetinib is not approved for these patients; the combination encorafenib and cetuximab is not reimbursed in Spain. Cetuximab is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)- expressing, RAS wild-type metastatic colorectal cancer in combination with irinotecan-based chemotherapy, in first-line in combination with FOLFOX, as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan. †Patients received Q2W cetuximab, while the Erbitux EU SmPC states that cetuximab should be administered QW.

HER2 (5%)

Trial	Biomarker	Description	Outcomes
HERACLES-A (phase II)[22,125,127]	HER2 positivity (HERACLES pathological criteria[a])	Trastuzumab plus lapatinib in patients with chemorefractory *KRAS*-WT disease ($n=27$)	ORR 28%; mPFS 4.7 months in patients with *ERBB2* GCN >9.5 and 3.7 months in patients with *ERBB2* GCN <9.5; mOS 10.0 months
My Pathway (phase II)[134]	HER2 positivity assigned based on IHC (3+ staining), FISH (*ERBB2*:*CEP17* >2.0) and/or NGS (*ERBB2* copy number gain)	Trastuzumab plus pertuzumab in patients with *KRAS*-unselected chemorefractory disease ($n=56$)	All patients ($n=56$): ORR 32%; mPFS 2.9 months; mOS 11.5 months *KRAS*-WT ($n=43$): ORR 40%; mPFS 5.3 months; mOS 14.0 months
TRIUMPH (phase II)[135]	*ERBB2* amplifications determined using tissue and/or ctDNA analysis	Trastuzumab plus pertuzumab in patients with chemorefractory *RAS*-WT disease ($n=18$)	ORR 35% (tissue-positive), 33% (ctDNA-positive); mPFS 4 months
MOUNTAINEER (phase II)[137]	HER2 positivity determined using IHC (3+ or 2+ staining and FISH-positive), FISH and/or NGS	Trastuzumab plus tucatinib in patients with chemorefractory *RAS*-WT disease ($n=26$)	ORR 55%; mPFS 6.2 months; mOS 17.3 months
HERACLES-B (phase II)[128]	HER2 positivity (HERACLES pathological criteria[a])	T-DM1 plus pertuzumab in patients with chemorefractory *RAS*-/*BRAF*-WT disease ($n=31$)	ORR 10%, DCR 80%, mPFS 4.8 months
DESTINY-CRC01 (phase II)[133]	HER2 positivity Cohort A: HER2 IHC 3+ or IHC 2+ staining and ISH-positive ($n=53$) Cohort B: IHC 2+ staining and ISH-negative ($n=7$) Cohort C: IHC 1+ staining ($n=18$)	T-DXd in patients with disease progression on two or more prior regimens ($n=78$)	Cohort A: ORR 45.3% (43.8% in patients who had previously received HER2-targeted therapy); DCR 83%; mPFS and mOS not reached No responses observed in cohorts B and C

Di Nicolantonio F, et al. Nat Rev Clin Oncol 2021.

Fu et al. [34] (18 patients)	Trastuzumab + Pyrotinib	22.2% CI 6.4–47.69 (4/18)	61.11% CI 35.8–82.7 (11/18)	3.4 (1.8–4.3)
Cumulative weighted Meta-analysis	Pooled: a. ORR with 95% CI b. DCR with 95% CI c. PFS	a. 31.33% (95% CI 24.27–38.39)	b.74.37% (95% CI 64.57–84.17)	c. 6.2 months

Akshit Chitkara A Meta-Analisis . Sep 2023

mKRAS G12C (3% CCRm)

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

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

Yaeger R et al. DOI: 10.1056/NEJMoa2212419

CLINICAL PROBLEM

KRAS G12C mutations occur in 3 to 4% of patients with metastatic colorectal cancer. Adagrasib — an oral, small-molecule inhibitor of mutant KRAS G12C protein — has shown promising clinical activity in patients with *KRAS* G12C-mutated tumors, including colorectal cancer. Whether combining adagrasib with an epidermal growth factor receptor (EGFR) antibody could be an effective treatment strategy is unknown.

CLINICAL TRIAL

Design: A phase 1–2, open-label, nonrandomized clinical trial assessed the safety and efficacy of adagrasib, either as monotherapy or combined with the EGFR inhibitor cetuximab, in heavily pretreated patients with metastatic colorectal cancer with a *KRAS* G12C mutation.

Intervention: 44 patients with measurable disease according to RECIST, version 1.1, received oral adagrasib alone twice daily, and 32 patients with measurable or evaluable disease according to the same criteria received adagrasib twice daily plus intravenous cetuximab either once weekly or once every 2 weeks. The primary outcome in the monotherapy group was objective response (complete or partial response). The primary outcome in the combination-therapy group was safety.

RESULTS

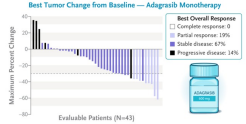
Efficacy: Among evaluable patients, 19% (95% CI, 8 to 33) in the monotherapy group had an objective response, with a median response duration of 4.3 months. In the combination-therapy group, 46% (95% CI, 28 to 66) had a response, with a median response duration of 7.6 months.

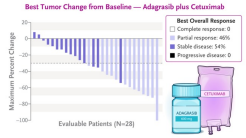
Safety: Treatment-related adverse events were common and generally reversible. Grade 3 or 4 treatment-related adverse events occurred in 34% of the patients in the monotherapy group and 16% of the patients in the combination-therapy group.

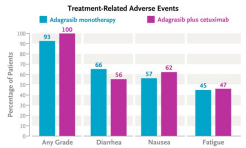
LIMITATIONS AND REMAINING QUESTIONS

- The nonrandomized trial design precluded comparisons between treatment groups.
- The activity and safety of adagrasib plus cetuximab as compared with standard chemotherapy are unknown and are currently under investigation.

Links: Full Article | NEJM Quick Take







CONCLUSIONS

Among previously treated patients with metastatic colorectal cancer with a *KRAS* G12C mutation, adagrasib — used alone or in combination with cetuximab — showed promising antitumor activity and resulted in no new safety concerns.

Adagrasib	mPFS:5.6 months mOS: 19.8 months ORR: 19% (8/43)
Adagrasib + Cetuximab	mPFS: 6.9 months mOS: 13.4 months ORR: 46% (13/28)

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Sotorasib plus Panitumumab in Refractory Colorectal Cancer with Mutated *KRAS* G12C

Fakih MG et al. DOI: 10.1056/NEJMoa2308795

CLINICAL PROBLEM

The *KRAS* G12C mutation occurs in 3% to 4% of patients with metastatic colorectal cancer and may be associated with a poor prognosis. KRAS G12C inhibition alone has shown limited efficacy in colorectal cancer. Combining the KRAS G12C inhibitor sotorasib with the epidermal growth factor receptor (EGFR) inhibitor panitumumab showed promise in an early trial involving patients with chemorefractory colorectal cancer with mutated *KRAS* G12C, but additional data are needed.

CLINICAL TRIAL

Design: A phase 3, multicenter, open-label, randomized trial examined the efficacy and safety of sotorasib in combination with panitumumab as compared with the investigator's choice of trifluridine–tipiracil or regorafenib (standard care) in adults with chemorefractory metastatic colorectal cancer with mutated *KRAS* G12C.

Intervention: 160 patients who had not previously received a KRAS G12C inhibitor received sotorasib at one of two doses (960 or 240 mg orally once daily) plus panitumumab or standard care. The primary end point was progression-free survival.

RESULTS

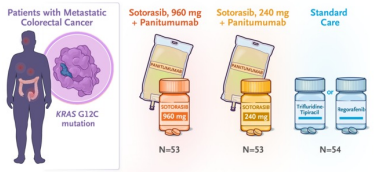
Efficacy: After a median follow-up of 7.8 months, progression-free survival was significantly longer with the 960-mg dose of sotorasib plus panitumumab than with standard care.

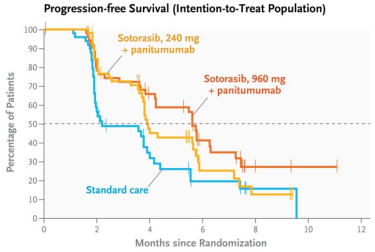
Safety: The most common grade ≥3 treatment-related adverse events were dermatitis acneiform, hypomagnesemia, and rash in the 960-mg sotorasib–panitumumab group; hypomagnesemia and diarrhea in the 240-mg sotorasib–panitumumab group; and neutropenia, anemia, and hypertension in the standard-care group.

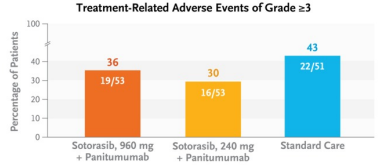
LIMITATIONS AND REMAINING QUESTIONS

- The trial was not powered to detect a difference in overall survival among the groups; longer follow-up is needed.
- Most patients were White or Asian; only one Black patient was enrolled.

Links: Full Article | NEJM Quick Take | Editorial





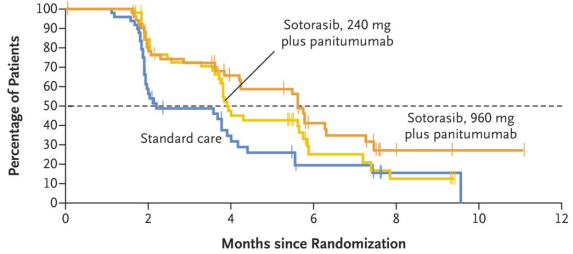


CONCLUSIONS

In adults with chemorefractory metastatic colorectal cancer with mutated *KRAS* G12C, combining the KRAS G12C inhibitor sotorasib at a dose of 960 mg with the EGFR inhibitor panitumumab resulted in longer progression-free survival than standard care.

This Research Summary was updated on January 17, 2025, at NEJM.org.

A Progression-free Survival (Intention-to-Treat Population)



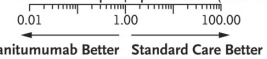
	Median Progression-free Survival	Hazard Ratio for Disease Progression or Death (95% CI)	Two-Sided P Value
	mo		
Sotorasib, 960 mg plus Panitumumab	5.62	0.48 (0.30–0.78)	0.005
Sotorasib, 240 mg plus Panitumumab	3.91	0.59 (0.37–0.95)	0.036
Standard Care	2.04		

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	

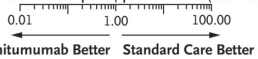
B Subgroup Analysis for Progression-free Survival — Sotorasib, 960 mg plus Panitumumab

Subgroup	Sotorasib, 960 mg plus Panitumumab	Standard Care	Hazard Ratio for Disease Progression or Death (95% CI)
	no. of patients		
All patients	53	54	0.48 (0.30–0.78)
Age			
<65 yr	32	27	0.52 (0.26–1.04)
≥65 yr	21	27	0.43 (0.20–0.92)
Sex			
Male	29	24	0.59 (0.30–1.15)
Female	24	30	0.35 (0.17–0.73)
Time from initial diagnosis of metastatic disease to randomization			
≥18 mo	29	31	0.42 (0.20–0.84)
<18 mo	24	23	0.51 (0.24–1.07)
Location of tumor			
Right side	24	16	0.41 (0.19–0.90)
Left side	28	37	0.62 (0.32–1.20)
Body site at initial diagnosis			
Colon	37	37	0.45 (0.25–0.80)
Rectum	16	17	0.57 (0.24–1.31)
No. of lines of previous therapy for metastatic disease			
1 or 2	37	28	0.39 (0.21–0.72)
≥3	16	26	0.58 (0.22–1.47)
Liver metastasis			
Yes	38	38	0.35 (0.20–0.61)
No	15	16	0.82 (0.30–2.21)



C Subgroup Analysis for Progression-free Survival — Sotorasib, 240 mg plus Panitumumab

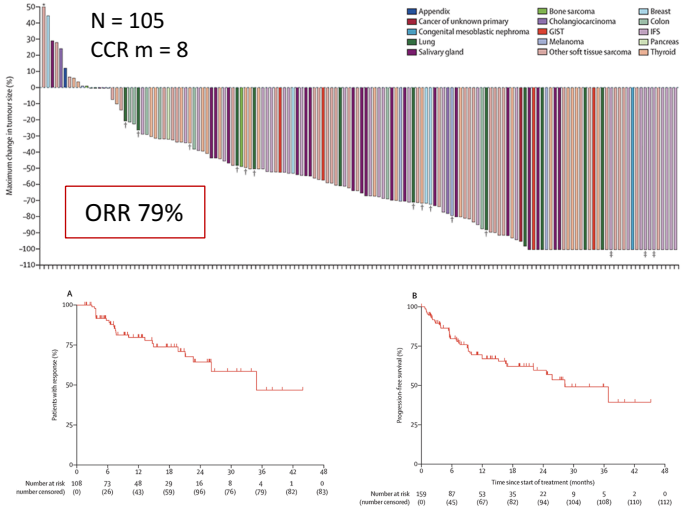
Subgroup	Sotorasib, 240 mg plus Panitumumab	Standard Care	Hazard Ratio for Disease Progression or Death (95% CI)
	no. of patients		
All patients	53	54	0.59 (0.37–0.95)
Age			
<65 yr	39	27	0.63 (0.32–1.23)
≥65 yr	14	27	0.36 (0.14–0.91)
Sex			
Male	26	24	0.71 (0.37–1.37)
Female	27	30	0.63 (0.31–1.27)
Time from initial diagnosis of metastatic disease to randomization			
≥18 mo	29	31	0.49 (0.25–0.97)
<18 mo	22	23	0.78 (0.40–1.52)
Location of tumor			
Right side	17	16	0.59 (0.27–1.32)
Left side	36	37	0.58 (0.33–1.03)
Body site at initial diagnosis			
Colon	32	37	0.53 (0.30–0.95)
Rectum	21	17	0.47 (0.21–1.02)
No. of lines of previous therapy for metastatic disease			
1 or 2	29	28	0.56 (0.31–1.02)
≥3	24	26	0.58 (0.27–1.26)
Liver metastasis			
Yes	36	38	0.47 (0.28–0.80)
No	17	16	0.56 (0.20–1.51)

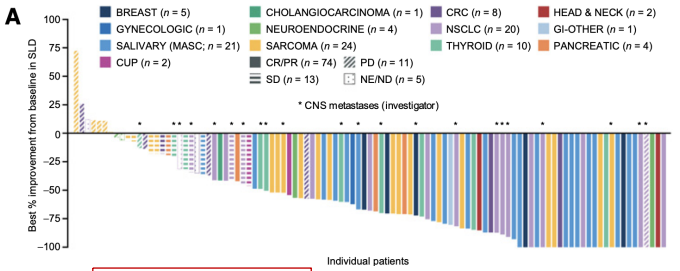


Fusiones NTRK (<1 % CCRm)

- **0.5% de CCRm MSS/pMMR**
- 5% de MSI-H/dMMR
  - 15% MSI-H/dMMR + RAS/BRAF WT
  - **40% pérdida expresión MLH1 + RAS/BRAF WT**

Larotrectinib[1] y Entrectinib[2]
FINANCIADOS POR SNS



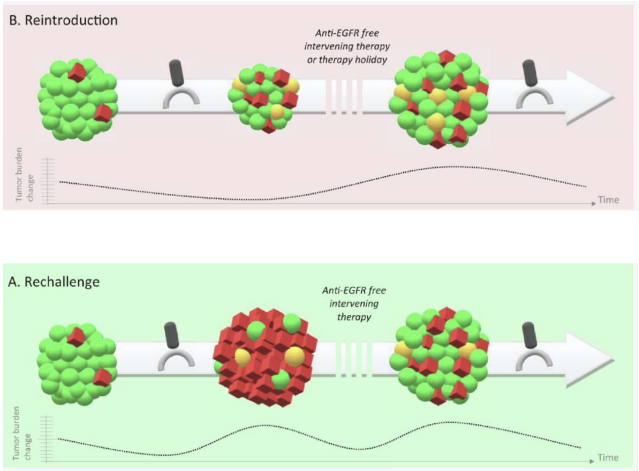


N = 121
CCR m = 10
- ORR 20%
- mPFS 2.8 m
- **mOS 16 m**

[1]Drilon A. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. Lancet Oncol 2020

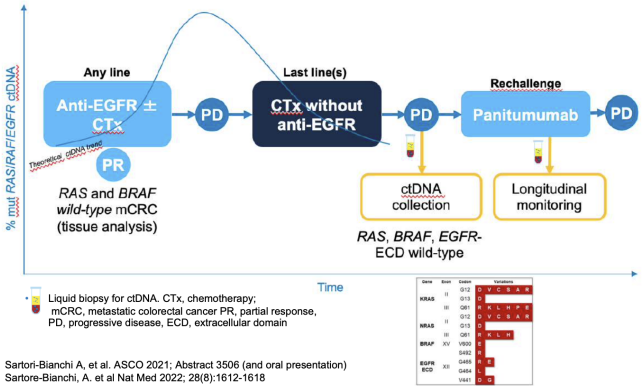
[2]Demetri GD. Updated Integrated Analysis of the Efficacy and Safety of Entrectinib in Patients With NTRK Fusion-Positive Solid Tumors. Clin Cancer Res 2022

RAS/BRAF WT (30%) : RECHALLENGE CON iEGFRE

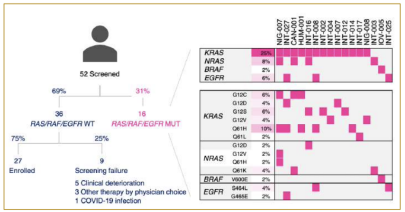


Circulating tumor DNA to guide rechallenge with panitumumab in metastatic colorectal cancer: the phase 2 CHRONOS trial

Anti-EGFR rechallenge therapy with panitumumab driven by circulating tumor DNA molecular selection



Sartori-Bianchi A, et al. ASCO 2021; Abstract 3506 (and oral presentation)
Sartore-Bianchi, A. et al Nat Med 2022; 28(8):1612-1618



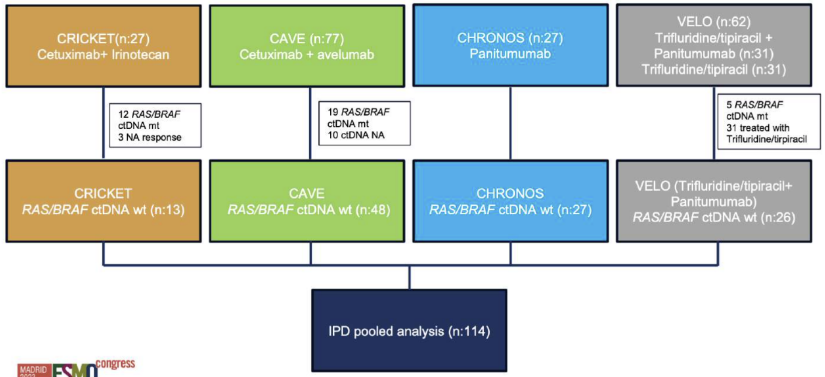
Liquid biopsy avoids ineffective treatment in 30% of clinically eligible cases

- La presencia de mutaciones de resistencia en ctDNA
  - se asocia a no respuesta
  - fue independiente del intervalo libre de iEGFRE
- Eficacia de rechallenge independiente de nº líneas previas/lateralidad

Sartori-Bianchi A, et al. ASCO 2021; Abstract 3506 (and oral presentation)
Sartore-Bianchi, A. et al Nat Med 2022; 28(8):1612-1618

RAS/BRAF WT: RECHALLENGE CON iEGFRE (30%)

Rechallenge with EGFR inhibitors in ctDNA *RAS/BRAF* wild type refractory metastatic colorectal cancer: an individual patients' data pooled analysis from 4 phase II trials



Annals of Oncology (2023) 34(suppl_2):S410-S457. 10.1016/annonc/annonc1323

Original Investigation | Oncology

Anti-EGFR Rechallenge in Patients With Refractory ctDNA *RAS/BRAF* wt Metastatic Colorectal Cancer
A Nonrandomized Controlled Trial

SLP	4 m
SG	13,1 m
	~33% de pacientes vivos a los 18 meses
ORR	17.5%
DCR	72.3%

No se observó diferencia en SG según nº de líneas previas
Mejores resultados si no hay Mts hepáticas

JAMA Network Open. 2024;7(4):

Limitaciones del análisis conjunto de estudios de rechallenge anti-EGFR

Heterogeneidad de los tratamientos:

- pacientes de 4 estudios fase II con esquemas distintos (cetuximab + irinotecán, cetuximab + avelumab, panitumumab, etc.).
- No hay consenso actual sobre el mejor régimen de *rechallenge* anti-EGFR.

Diferencias en las plataformas de ctDNA:

CHRONOS utilizó **ddPCR de alta sensibilidad**, incluyendo sólo pacientes sin alteraciones en RAS, BRAF ni dominio extracelular de EGFR.

CAVE y VELO usaron la plataforma **Idylla™ Biocartis**, con diferente umbral de sensibilidad.

Se desconoce aún el impacto clínico de alelos mutados en **baja frecuencia**.

Otros mecanismos de resistencia no evaluados:

Mutaciones o amplificaciones en **EGFR ECD**, **MAP2K1**, **ERBB2**, entre otras, podrían influir en la resistencia a EGFR.

Se sugiere usar paneles de **NGS más amplios** para una mejor selección futura de pacientes

Ensayo CAVE-2 : cetuximab + avelumab vs. cetuximab monoterapia

Ensayo PARERE : Secuencia: panitumumab as third-line treatment followed by regorafenib at disease progression or the reverse sequence

- Introducción
  - Refractariedad y objetivos
- Opciones de tratamiento
  - Sin selección molecular
  - Con selección molecular (guiadas por biomarcador)
- Líneas futuras
- Conclusiones

1. Terapias dirigidas en nuevos subgrupos moleculares

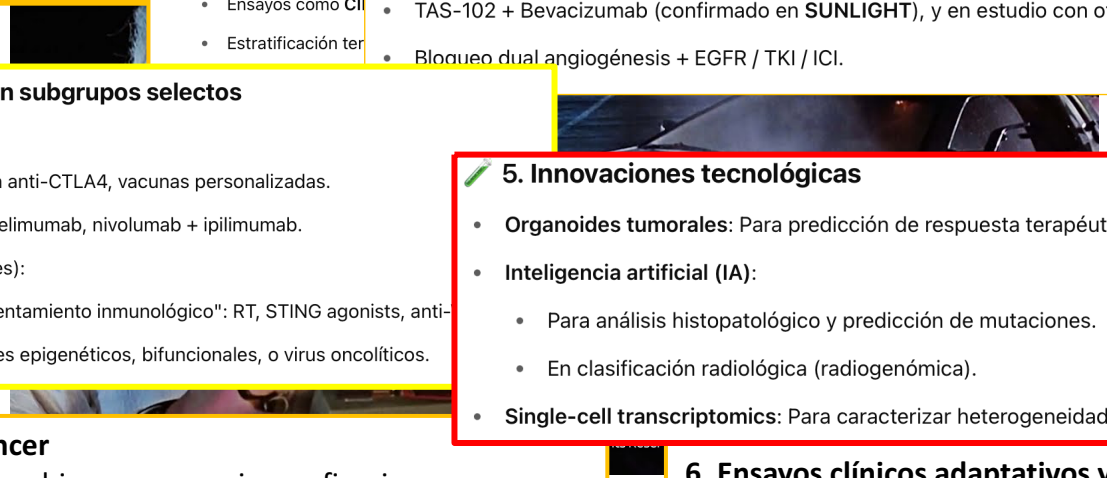
- **KRAS G12C**: Combinaciones con inhibido
- **BRAF no V600E**: Desarrollo de estrategia
- **HER2**: Nuevos conjugados (trastuzumab
- **Fusiones NTRK, RET, ALK, ROS1**: Uso de
- **FGFR, MET, CLDN18.2**: Nuevas dianas en

2. Oncología de precisión basada en ctDNA

- **Biopsia líquida dinámica**:
  - Monitorización de respuesta
  - Detección de resi
  - Selección para re
- **MRD y seguimiento l**
  - Ensayos como **CI**
  - Estratificación ter

3. Nuevas combinaciones terapéuticas

- Anti-EGFR + inmunoterapia (ej. **CAVE-2**).
- Fruquintinib + inmunoterapia.
- TAS-102 + Bevacizumab (confirmado en **SUNLIGHT**), y en estudio con otros agentes.
- Bloqueo dual angiogénesis + EGFR / TKI / ICI.



🧠 4. Inmunoterapia en subgrupos selectos

- **MSI-H/dMMR**:
  - Combinaciones con anti-CTLA4, vacunas personalizadas.
  - Durvalumab + tremelimumab, nivolumab + ipilimumab.
- **MSS** (inmunorresistentes):
  - Estrategias de "calentamiento inmunológico": RT, STING agonists, anti-
  - Ensayos con agentes epigenéticos, bifuncionales, o virus oncolíticos.

🧪 5. Innovaciones tecnológicas

- **Organoides tumorales**: Para predicción de respuesta terapéutica.
- **Inteligencia artificial (IA)**:
  - Para análisis histopatológico y predicción de mutaciones.
  - En clasificación radiológica (radiogenómica).
- **Single-cell transcriptomics**: Para caracterizar heterogeneidad intratumoral.

6. Microbiota y cáncer

•Modulación de microbioma para mejorar eficacia inmunoterapia y QT.
•biomarcador de respuesta o toxicidad.
•Ensayos de modulación con prebióticos, antibióticos selectivos o FMT.

6. Ensayos clínicos adaptativos y plataformas moleculares

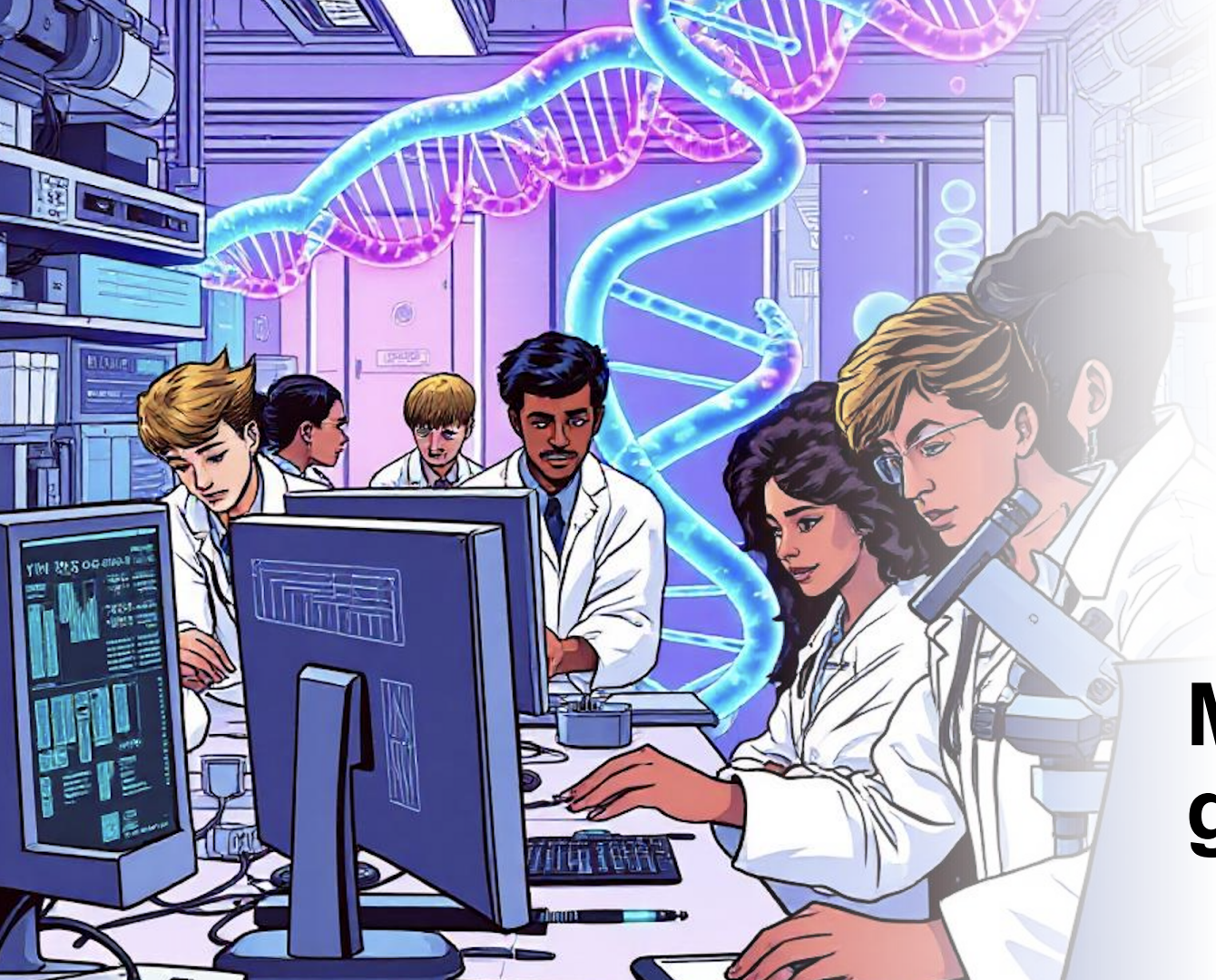
•**PLATFORM trials**: COLOMBUS, MODUL, ACCORD, NCTN-MATCH.
•Adaptación terapéutica en función de biomarcadores dinámicos.

Conclusiones/reflexiones

- 3 línea actual*:*
  - *Trifluridina-tipiracilo + Bevacizumab :* beneficio frente a tratamiento activo
  - *Fruquintinib : otra nueva opción de tratamiento*
  - *En CCRM RAS/BRAF WT el Rechallenge con iEGFRE :* 3L y/o sucesivas PERO siempre en población seleccionada (biopsia líquida) y con peso si queremos ORR

- Debemos seguir buscando poblaciones con alteraciones molecularmente potencialmente tratables con terapia dirigida = tratamiento personalizado ➔ ¿NGS para todos?

- CONTINUUM OF CARE: seleccionar, buscar y cuidar para que cada vez más pacientes se beneficien de líneas sucesivas y con ello ir sumando



Muchas gracias