New Strategies in the Management of Patients with Refractory Colorectal Cancer

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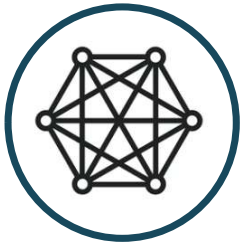
KEY CHALLENGES IN THE MANAGEMENT OF REFRACTORY mCRC

How the clinical context has changed

Old Concept	New Concept
mCRC with **no remaining therapeutic options**.	mCRC with **progression after fluoropyrimidine-, oxaliplatin-, and irinotecan-based regimens** (± targeted therapies).
"Refractory" denoted **treatment exhaustion**.	"Refractory" reflects resistance to these classic cytotoxic backbones, with **active later-line options still available**.



Biological and Clinical Complexity

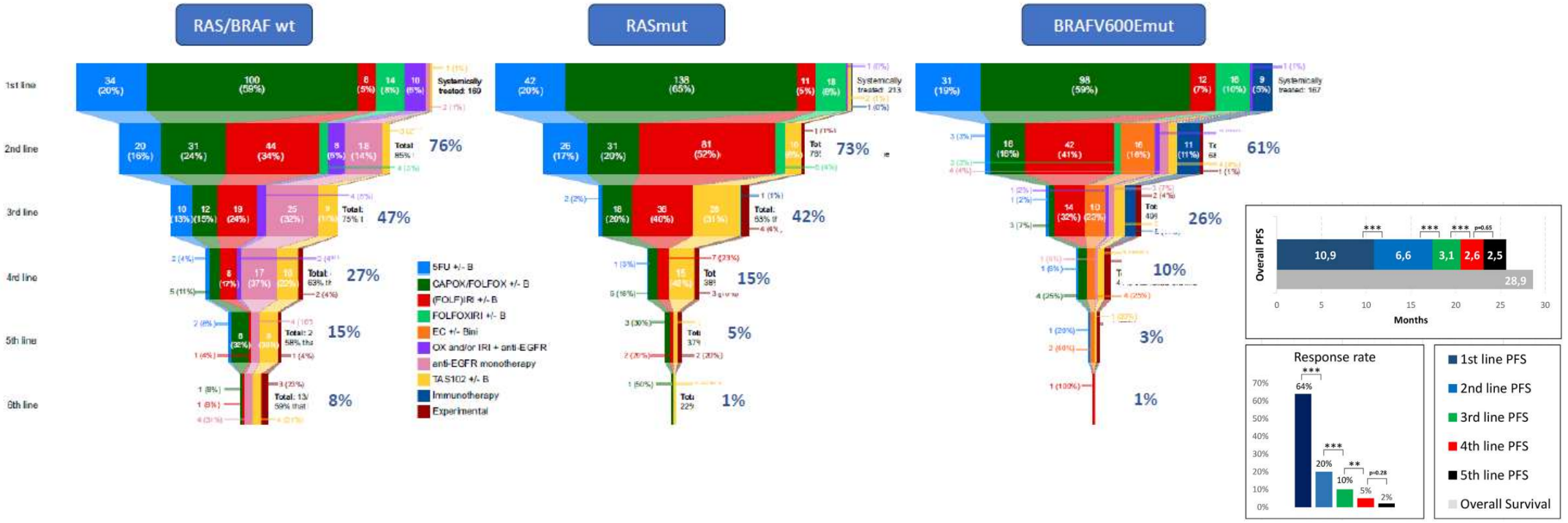
Disease Dynamics and Therapeutic Resistance

Strategic Decision-Making in Limited Therapeutic Landscape

Patient Preferences and Quality-of-Life Priorities

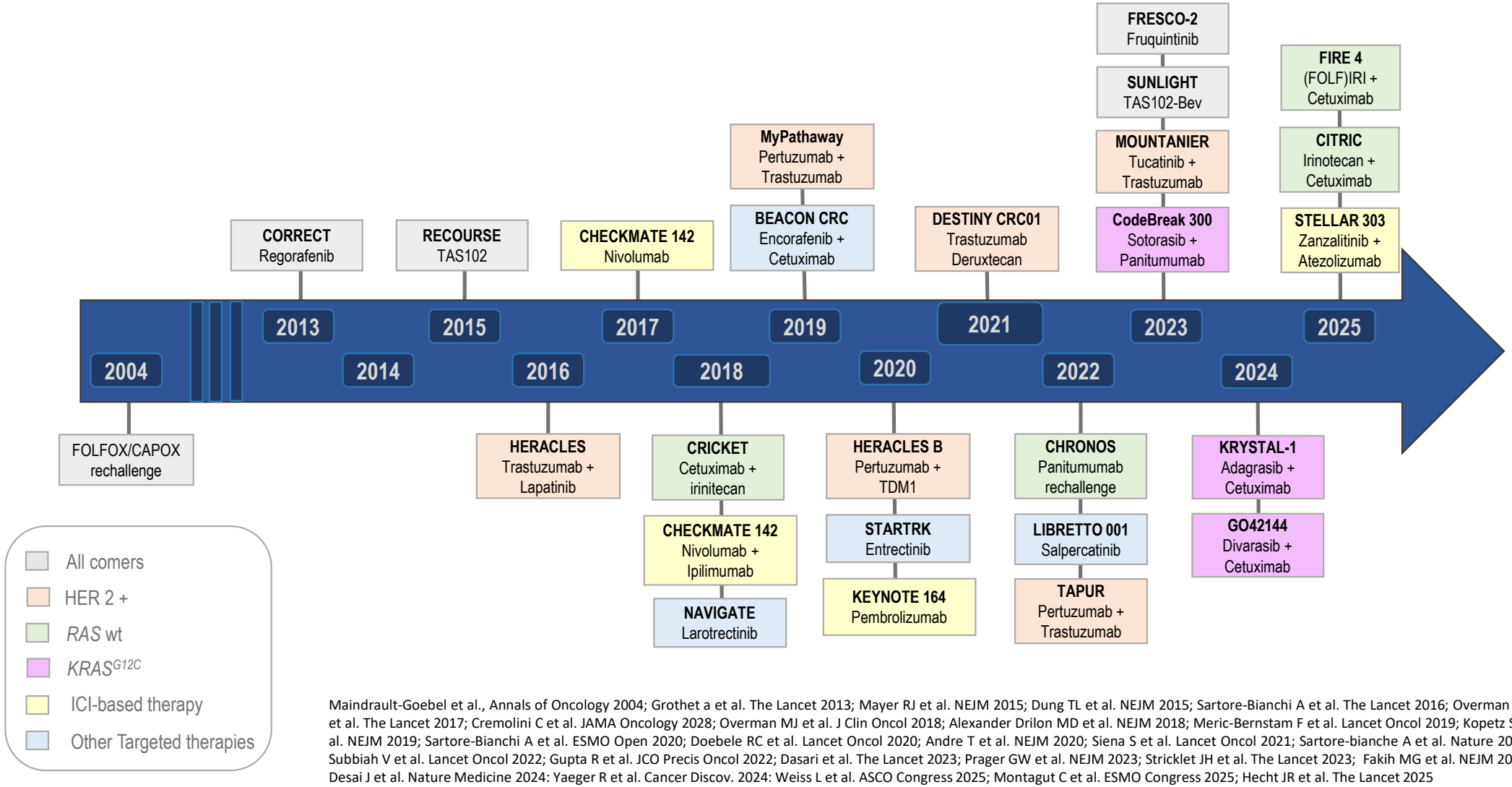
THE FUNNEL EFFECT OF EFFICACY

A notable attrition rate across subsequent lines of therapy is observed, underscoring the **importance of selecting the most effective upfront treatment** and **carefully planning the therapeutic sequence** to optimize outcomes in mCRC management.



Nassau, Int J Cancer 2025
Rossini et al, Eur J Canc 2022

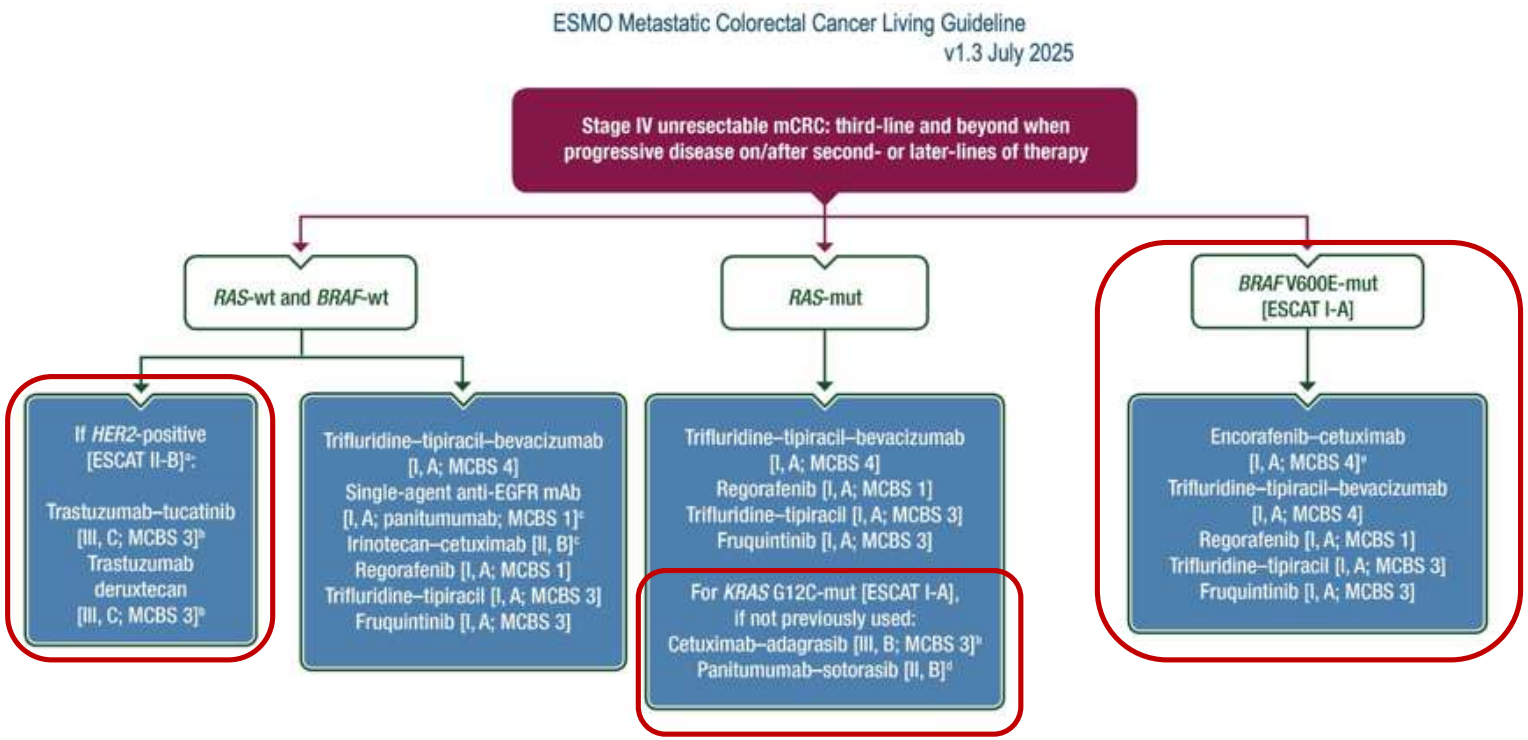
THIRD-LINE TREATMENT AND BEYOND IN mCRC: WHAT WE HAVE?



Maindrault-Goebel et al., Annals of Oncology 2004; Grothet a et al. The Lancet 2013; Mayer RJ et al. NEJM 2015; Dung TL et al. NEJM 2015; Sartore-Bianchi A et al. The Lancet 2016; Overman MJ et al. The Lancet 2017; Cremolini C et al. JAMA Oncology 2028; Overman MJ et al. J Clin Oncol 2018; Alexander Drilon MD et al. NEJM 2018; Meric-Bernstam F et al. Lancet Oncol 2019; Kopetz S et al. NEJM 2019; Sartore-Bianchi A et al. ESMO Open 2020; Doebele RC et al. Lancet Oncol 2020; Andre T et al. NEJM 2020; Siena S et al. Lancet Oncol 2021; Sartore-bianche A et al. Nature 2022; Subbiah V et al. Lancet Oncol 2022; Gupta R et al. JCO Precis Oncol 2022; Dasari et al. The Lancet 2023; Prager GW et al. NEJM 2023; Stricklet JH et al. The Lancet 2023; Fakih MG et al. NEJM 2023; Desai J et al. Nature Medicine 2024: Yaeger R et al. Cancer Discov. 2024: Weiss L et al. ASCO Congress 2025; Montagut C et al. ESMO Congress 2025; Hecht JR et al. The Lancet 2025

CLINICAL PRACTICE ESMO GUIDELINES

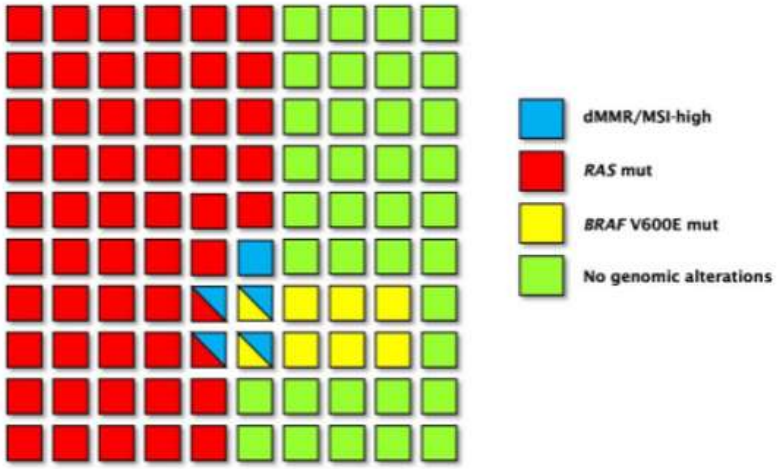
Molecularly guided targeted therapy



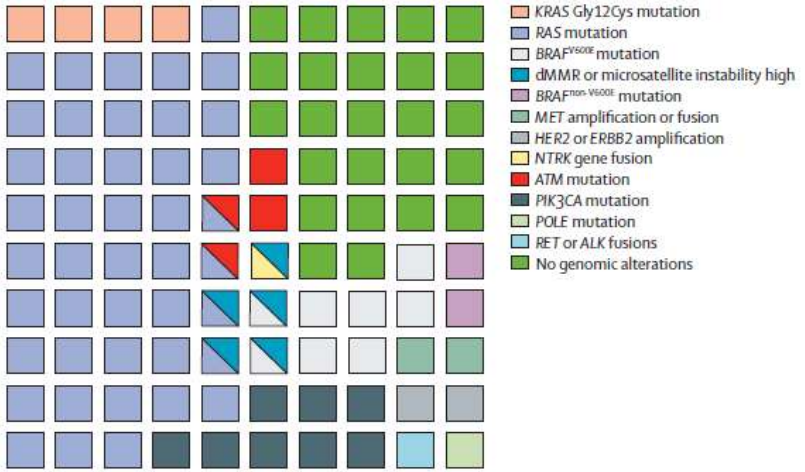
https://www.esmo.org/guidelines/living-guidelines/esmo-living-guideline-metastatic-colorectal-cancer

MOLECULAR LANDSCAPE OF mCRC

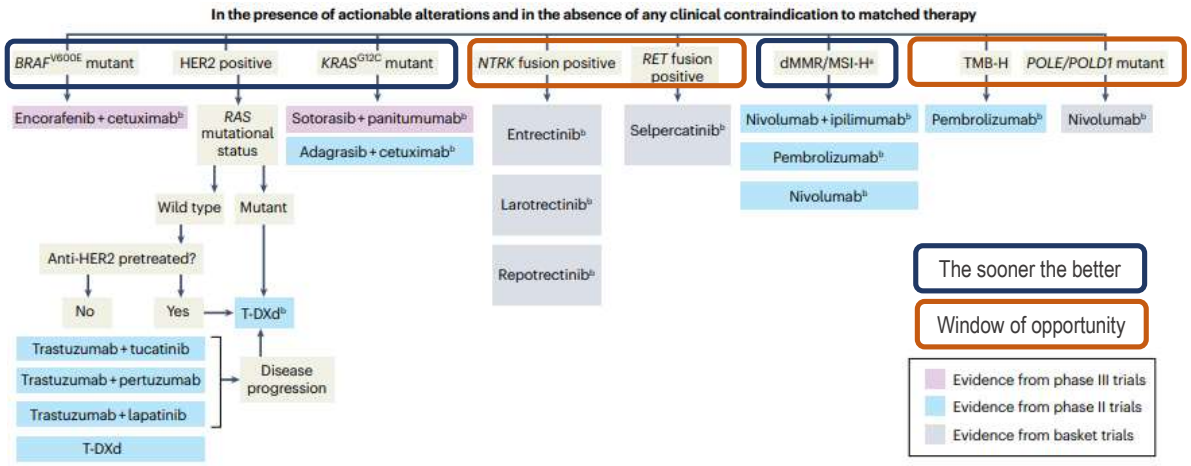
Biomarkers considered in ESMO Guidelines



Molecular biomarkers in mCRC



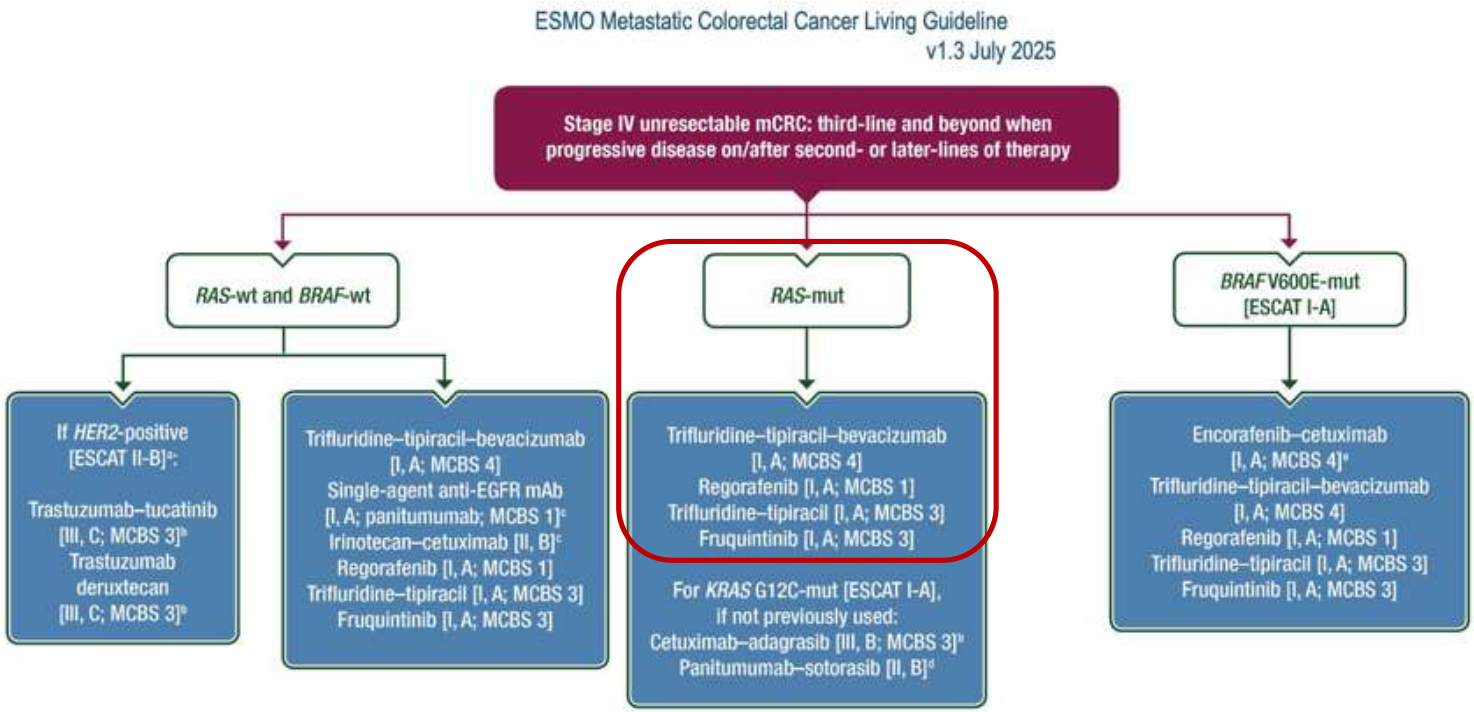
	Matched treatment	ESCAT score[126-128]	OncoKb level
RAS mutation	--	--	--
KRAS Gly12Cys mutation	Adagrasib or sotorasib with or without cetuximab	--	3A
BRAF^{V600E} (ie, Val600Glu) mutation	Encorafenib plus cetuximab	I-A	1
dMMR or microsatellite instability high	Pembrolizumab or dostarlimab (dMMR)	I-A	1
dMMR or microsatellite instability high	Nivolumab plus ipilimumab	I-A	1
BRAF$^{non\text{-}V600E}$ mutation	BRAF blockade (eg, PLX8394)	--	4
MET amplification or fusion	MET blockade	IIIA*	4†
HER2 or *ERBB2* amplification	HER2 blockade‡	II-B	2
NTRK gene fusion	Entrectinib	I-C	1
NTRK gene fusion	Larotrectinib	I-C	1
ATM mutation	Olaparib	IIIA	--
PIK3CA mutation	Alpelisib	IIIA	4
POLE mutation	Anti-PD1 or anti-PD-L1	IIIA	--
RET or ALK fusions	Selpercatinib§	IIIA	1
RET or ALK fusions	ALK blockade¶	IIIA	--
No genomic alterations	--	--	--



Adapted from Cremolini C, ESMO Congress 2023; Ciraci P et al. Nat Rev Clin Oncol 2024; Eng C et al. The Lancet 2024

CLINICAL PRACTICE ESMO GUIDELINES

RAS-Mutant (non-G12C) mCRC



https://www.esmo.org/guidelines/living-guidelines/esmo-living-guideline-metastatic-colorectal-cancer

KEY RESULTS FROM THE MAIN TRIALS IN REFRACTORY mCRC

What are the clinically meaningful outcomes?

Table 3. Phase III trials in mCRC in the third-line setting: summary of efficacy outcomes[a]

	Treatment arm	N	OS Median, months		ASCO[b]	ESMO-MCBS[b]	CCC[b]	PFS Median, months		ASCO[b]	ESMO-MCBS[b]	DCR %	
FTD/TPI + BEV													
SUNLIGHT (NCT04737187)[42]	FTD/TPI + BEV FTD/TPI alone	245 245	10.8 7.5	Δ = 3.3 HR 0.61 $P < 0.001$	✓	✓	✓	5.6 2.4	Δ = 3.2 HR 0.48 $P < 0.001$	✓	✓	77 47	$P < 0.001$
FTD/TPI monotherapy													
RECOURSE (NCT01607957)[43]	FTD/TPI + BSC Placebo + BSC	534 266	7.1 5.3	Δ = 1.8 HR 0.68 $P < 0.0001$	✗	✗	✗	2.0 1.7	Δ = 0.3 HR 0.48 $P < 0.001$	✗	✗	44 16	$P < 0.001$
Regorafenib													
CORRECT (NCT01103323)[44]	Regorafenib + BSC Placebo + BSC	505 255	6.4 5.0	Δ = 1.4 HR 0.77 $P = 0.0052$	✗	✗	✗	1.9 1.7	Δ = 0.2 HR 0.49 $P < 0.0001$	✗	✗	41 15	$P < 0.001$
CONCUR (NCT01584830)[45]	Regorafenib + BSC Placebo + BSC	136 68	8.8 6.3	Δ = 2.5 HR 0.55 $P = 0.00016$	✗	✗	✓	3.2 1.7	Δ = 1.5 HR 0.31 $P < 0.0001$	✗	✓	51 7	$P < 0.0001$
Fruquintinib													
FRESCO-2 (NCT04322539)[46]	Fruquintinib + BSC Placebo + BSC	461 230	7.4 4.8	Δ = 2.6 HR 0.66 $P < 0.0001$	✗	✗	✓	3.7 1.8	Δ = 1.9 HR 0.32 $P < 0.0001$	✗	✓	56 16	$P < 0.0001$
FRESCO (NCT02314819)[47]	Fruquintinib + BSC Placebo + BSC	278 138	9.3 6.6	Δ = 2.7 HR 0.65 $P < 0.001$	✗	✗	✓	3.7 1.8	Δ = 1.9 HR 0.26 $P < 0.001$	✗	✓	62 12	$P < 0.01$

Δ, difference; ASCO, American Society of Clinical Oncology; BEV, bevacizumab; BSC, best supportive care; CCC, Colorectal Cancer Canada; DCR, disease control rate; ESMO-MCBS, European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; FTD/TPI, trifluridine/tipiracil; HR, hazard ratio; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression-free survival.

[a]With the exception of FTD/TPI + BEV versus FTD/TPI monotherapy, no head-to-head studies or comparisons between the treatments have been conducted. Caution should be exercised when making cross-trial comparisons.

[b]Improvements that met recommended thresholds for clinically meaningful outcomes are indicated by a tick (✓) and those that did not meet recommended thresholds are indicated by a cross (✗).

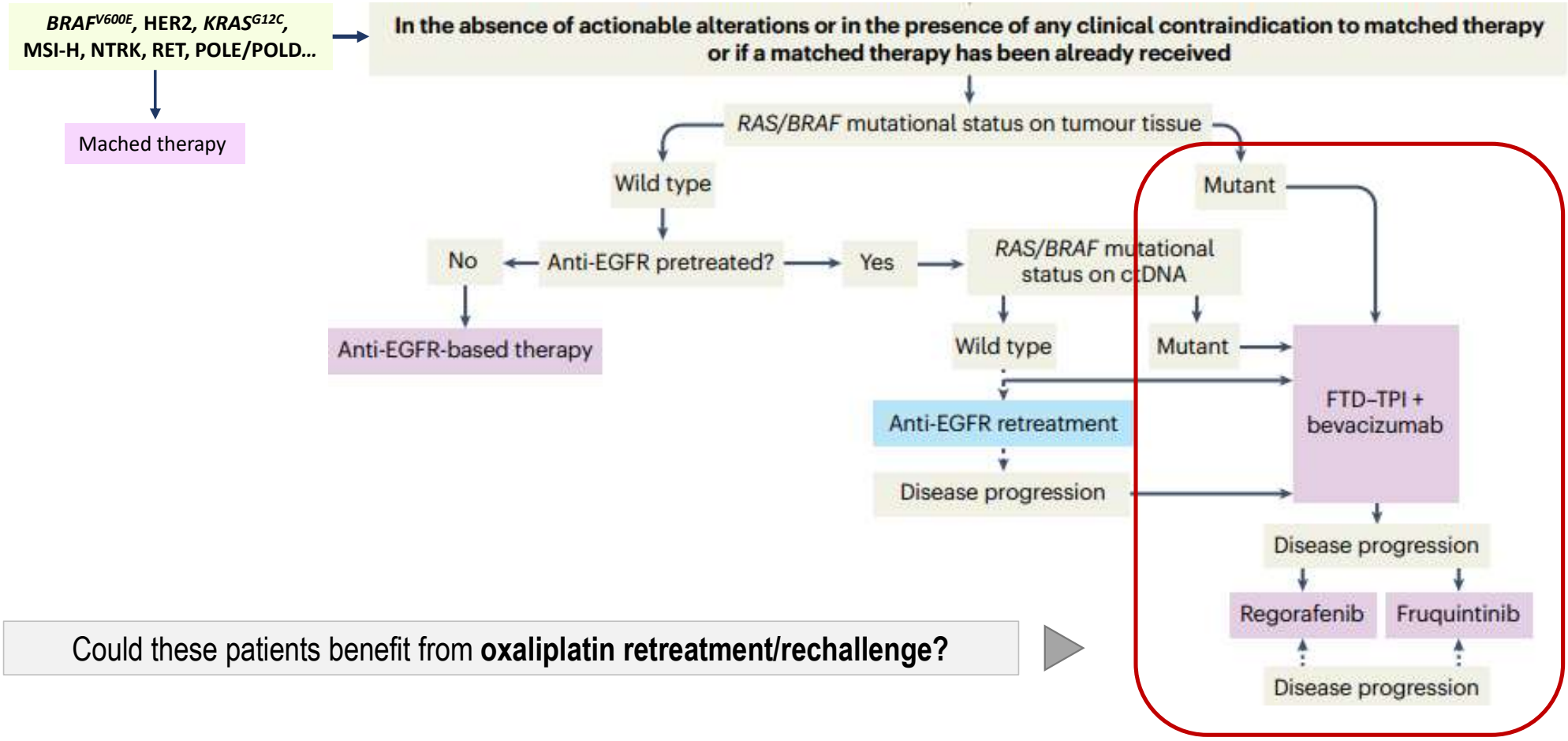
Table 1. Summary of recommended thresholds for clinically meaningful outcomes in refractory mCRC

	Median OS, months	Median PFS, months	QoL assessment
ASCO Clinically Meaningful Outcomes Working Group[3]	Δ: 3-5 HR ≤0.67	Δ: 3-5	—
ESMO-MCBS[2,9]	Δ: ≥3 HR ≤0.65	Δ: ≥1.5 HR ≤0.65	ESMO-MCBS QoL checklist[10]
CCC consensus statements[1]	Δ: ≥2 HR ≤0.75	—	Formal QoL assessment, Q-TWiST, or time to deterioration in ECOG PS

Δ, difference; ASCO, American Society of Clinical Oncology; CCC, Colorectal Cancer Canada; ECOG PS, Eastern Cooperative Oncology Group performance status; ESMO-MCBS, European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; HR, hazard ratio; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression-free survival; Q-TWiST, quality-adjusted time without symptoms or toxicity; QoL, quality of life.

M. Fakih et al. ESMO Open 2024

ALGORITHM FOR SELECTION OF LATE-LINE TREATMENT IN PATIENTS WITH mCRC

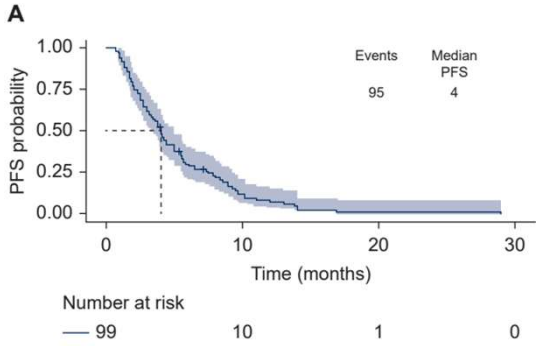


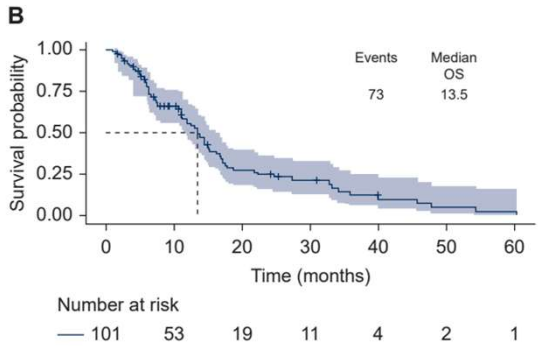
Adapted from Ciraci P et al. Nat Rev Clin Oncol 2024.

RETREATMENT WITH OXALIPLATIN-BASED REGIMENS IN REFRACTORY mCRC

VH Experience

Among 735 patients in 3L/4L, 102 (14%) received oxaliplatin retreatment (69% in 3L; 31% in 4L)





Patients, *n*	DCR (%)	ORR (%)
102	39.4	12

Study	Type	Retreatment strategy	Pts	DCR (%)	ORR (%)	mPFS (m)	mOS (m)
VH	Retr.	Rechallenge Reintroduction	102	39.4	12	4	NA
Re-OPEN	II	Reintroduction	33	39.4	6.1	3.8	9.2
ORION	II	Reintroduction	46	66	NA	4.3	12.9
RETROX	III	Rechallenge Reintroduction	119	57.8	21.6	5.1	NA

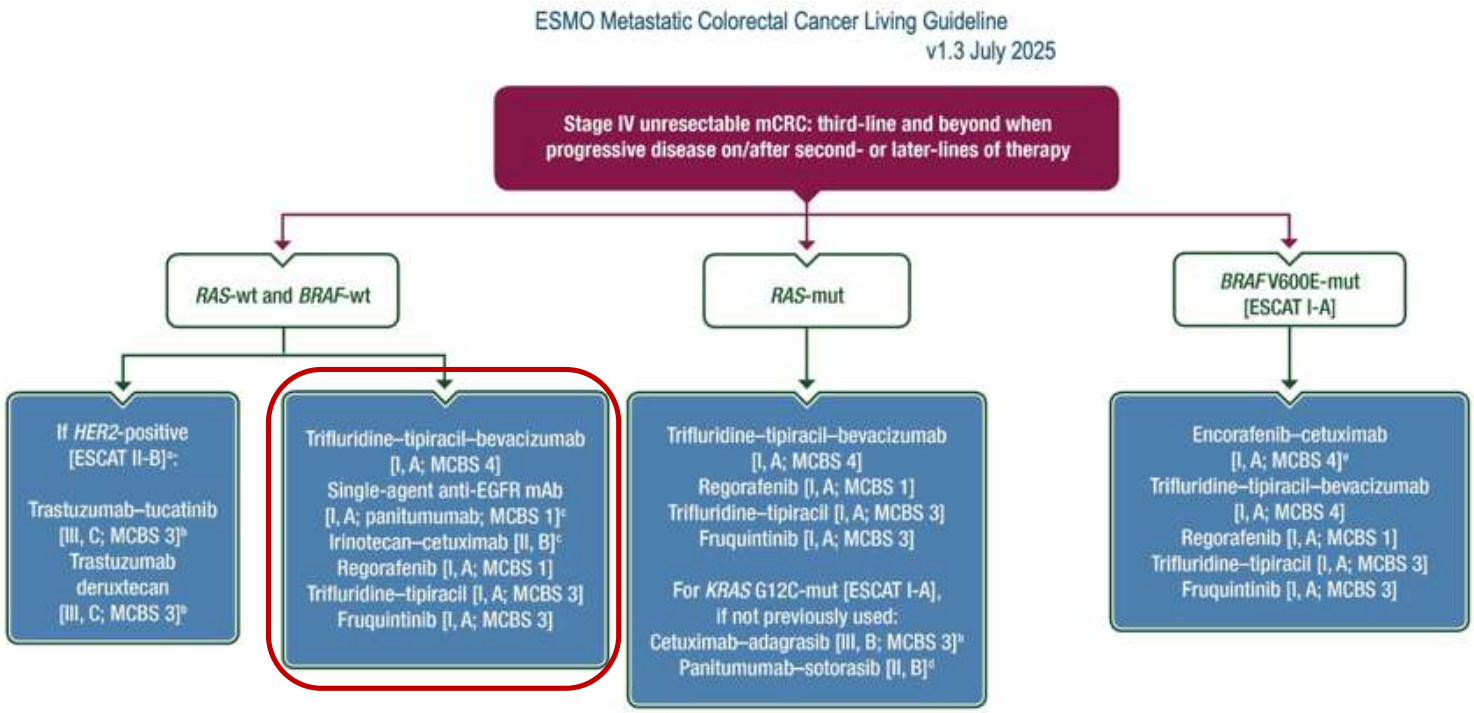
* A subgroup of "best responders" (n=28; 27%) achieved mPFS >6 months.

OXL retreatment may benefit selected patients -> Optimal sequencing remains undefined and influenced by access to alternative agents

Catani G, Salva F et al. ESMO Gastrointestinal Oncology 2025

CLINICAL PRACTICE ESMO GUIDELINES

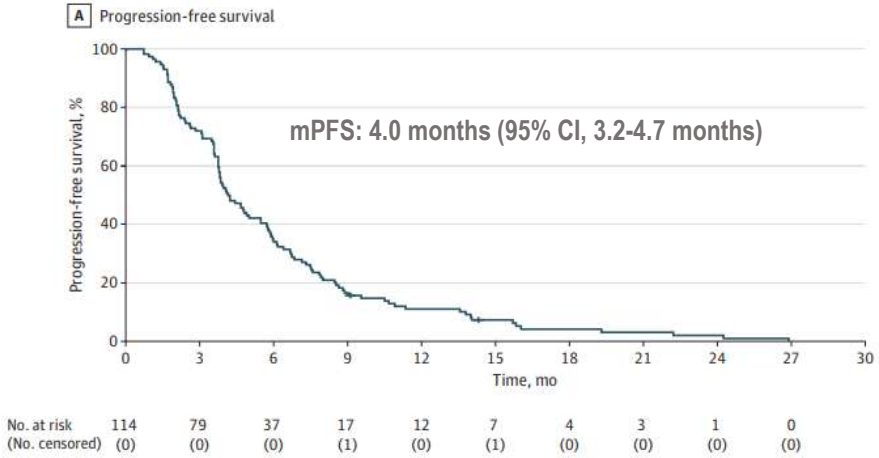
RAS Wild-Type mCRC



https://www.esmo.org/guidelines/living-guidelines/esmo-living-guideline-metastatic-colorectal-cancer

ANTI-EGFR RECHALLENGE EFFICACY IN RAS-WT mCRC BEFORE 2025

Pooled analysis (CAVE, VELO, CRICKET, and CHRONOS)



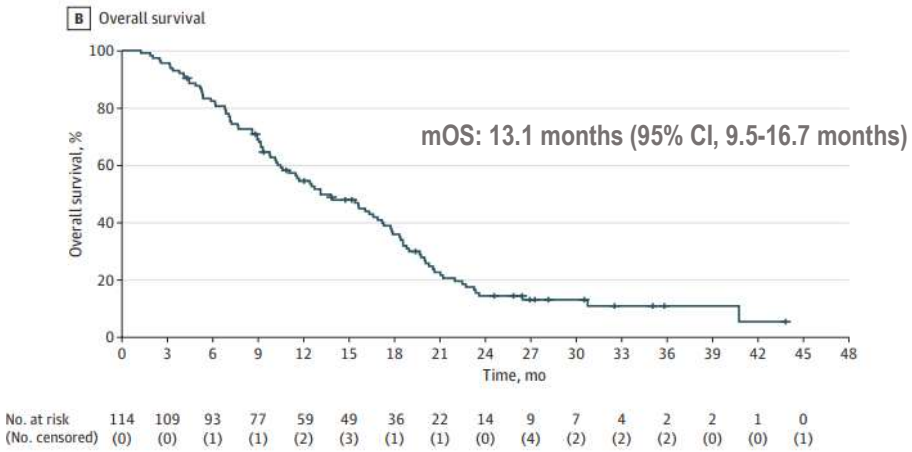


Table 2. Tumor Response of Patients With Metastatic Colorectal Cancer Receiving Anti–Epidermal Growth Factor Receptor Challenge Therapy in 4 Italian Trials

	Patients, No. (%)					
Study	Complete response	Partial response	Stable disease	Progressive disease	Overall response rate	Disease control rate
CAVE (n = 48)	1 (2.1)	3 (6.25)	31 (64.5)	13 (27.1)	4 (8.3)	35 (73.0)
VELO (n = 26)	0	3 (11.5)	18 (69.2)	5 (19.2)	3 (11.5)	21 (81.0)
CRICKET (n = 13)	0	5 (38.5)	5 (38.5)	3 (23.1)	5 (38.5)	10 (77.0)
CHRONOS (n = 27)	0	8 (30.0)	8 (30.0)	11 (41.0)	8 (30.0)	16 (59.3)
Pooled analysis (N = 114)	1 (0.9)	19 (16.7)	65 (57.0)	32 (28.0)	20 (17.5)	82 (72.3)

Abbreviations: CAVE, Avelumab Plus Cetuximab in Pre-treated *RAS* Wild Type Metastatic Colorectal Cancer; CHRONOS, Rechallenge With Panitumumab Driven by *RAS* Dynamic of Resistance; CRICKET, Cetuximab Rechallenge in Irinotecan-pretreated mCRC, *KRAS*, *NRAS* and *BRAF* Wild-type Treated in 1st Line With Anti-EGFR Therapy; VELO, Phase II Randomized Study Evaluating the Efficacy of Panitumumab (Vectibix) and Trifluridine-Tipiracil (Lonsurf) in Pretreated *RAS* Wild Type Metastatic Colorectal Cancer Patients.

Ciardello D, et al. JAMA Network Open 2024

TAS-102 + BEV Vs. ANTI-EGFR RECHALLENGE IN *RAS* WT mCRC

- Previous severe skin toxicity (anti-EGFR therapy).
- Need to extend the anti-EGFR-free interval.
- No need to prioritize objective response rate.
- History of gastrointestinal toxicities.
- Easy administration.

- Previous benefit from anti-EGFR therapy.
- Long anti-EGFR-free interval.
- Need to prioritize objective response rate (ORR).
- History of hematological toxicities.
- Contraindication to anti-VEGF therapy.

It is essential to prioritize and consider the **patient's autonomy and preferences** as a critical aspect of decision-making

KEY RESULTS FROM RANDOMIZED TRIALS IN REFRACTORY *RAS* WT mCRC

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.

Proposed sequence for *RAS wt* refractory mCRC*

- 1st line : FOLFOX/FOLFIRI + targeted agents
- 2nd line: FOLFIRI/FOLFOX + targeted agents

} FOLFOXIRI + targeted agents

- 3rd line: trifluridine tipiracil + bevacizumab
- 4th line: irinotecan cetuximab or cetuximab rechallenge in ctDNA wt patients (> 6 months free-interval)
- 5th line : regorafenib
- 6th line : fruquintinib

1. Grothey A et al. The Lancet 2013; 2. Montagut C et al. ESMO Congress 2025; 3. Germani MM et al. ESMO Congress 2025
*Ducreux M. ESMO Congress 2025

CRITICAL ASPECTS TO CLARIFY IN THE MANAGEMENT OF *RAS* WT REFRACTORY mCRC

How to Hyper-Select Patients

Mutations	CAPRI-GOIM	PARADIGM	CRITIC	PAREIRE
AKT1				+
EGFR-ECD		+	+	+
MAP2K1			+	+
PIK3CA exon 20	+			+
BRAF class I/II non V600E				+
PTEN		+	+	
ERRBB2 amplif.		+	+	
MET		+	+	
ALK fusion		+		
RET fusion		+		
NTRK1 fusion		+		

The Role of Relative MAF

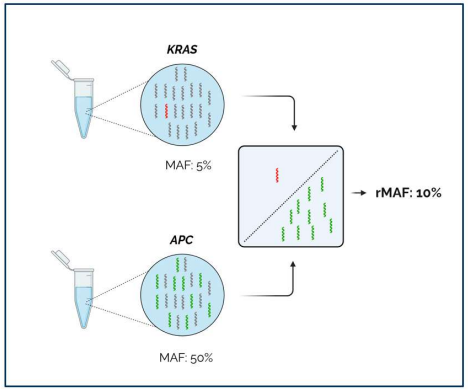
- **Mutational allele frequency (MAF):** proportion of mutated alleles compared to the total number of alleles of a specific gene.
- **Relative MAF:**

$$\frac{\text{MAF of resistance mutation}^{\&} \text{ detected in ctDNA}^{\$}}{\text{MAF of highest pathogenic mutation detected in ctDNA}^{\$}} \times 100\ (\%)$$

Clonal weight of the resistance mutation within the tumor

[&] ***Anti-EGFR resistance mutations:*** *RAS, BRAF, or EGFR-ECD mutations in ctDNA.* [1]

[$] *Analyzed via NGS Guardant360 CDx.* [2]



Example of the relative MAF (rMAF) calculation.

Ducreux M. ESMO Congress 2025
Mascaró P et al. ESMO Congress 2025

TAKE HOME MESSAGES

- Refractory mCRC is now a **biologically stratified, treatment-rich setting** rather than a therapeutic endpoint
- Molecular subgroups (*RASwt, BRAF, HER2, KRAS^{G12C}*) define **divergent therapeutic pathways** with distinct clinical implications
- **Biomarker-driven selection is essential** to optimize benefit, requiring dynamic molecular assessment and precise patient stratification

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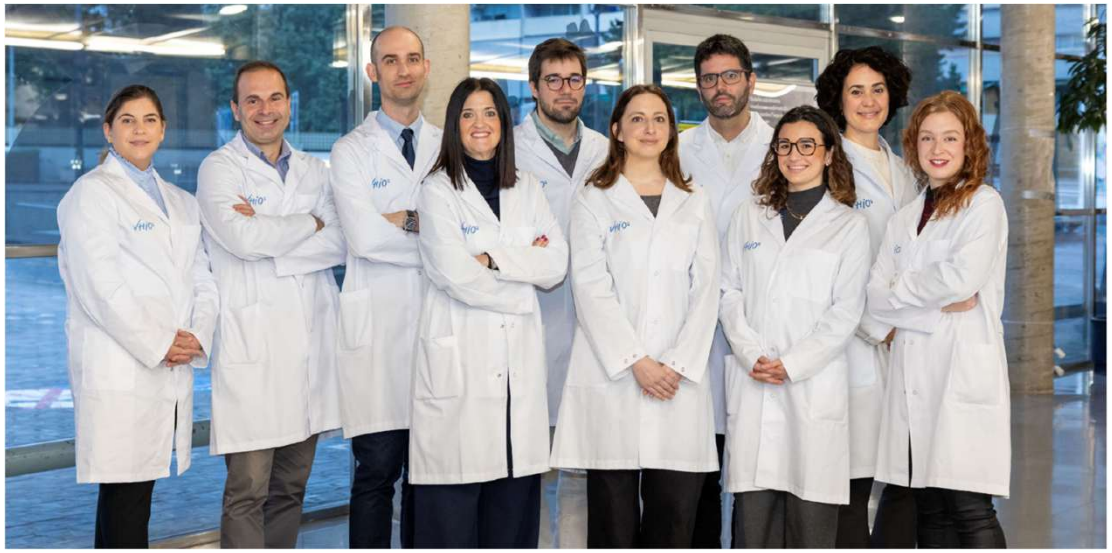

TTD scientific committee

THANK YOU FOR YOUR ATTENTION