XXXIII SIMPOSIO INTERNACIONAL
INTERNATIONAL SYMPOSIUM
11 - 12 DE DICIEMBRE DE 2025
OVIEDO

Innovación y estudios traslacionales: pilares para la generación de evidencia científica en el tratamiento médico del cáncer

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Barcelona

11-Diciembre-2025

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DECLARATION OF INTERESTS

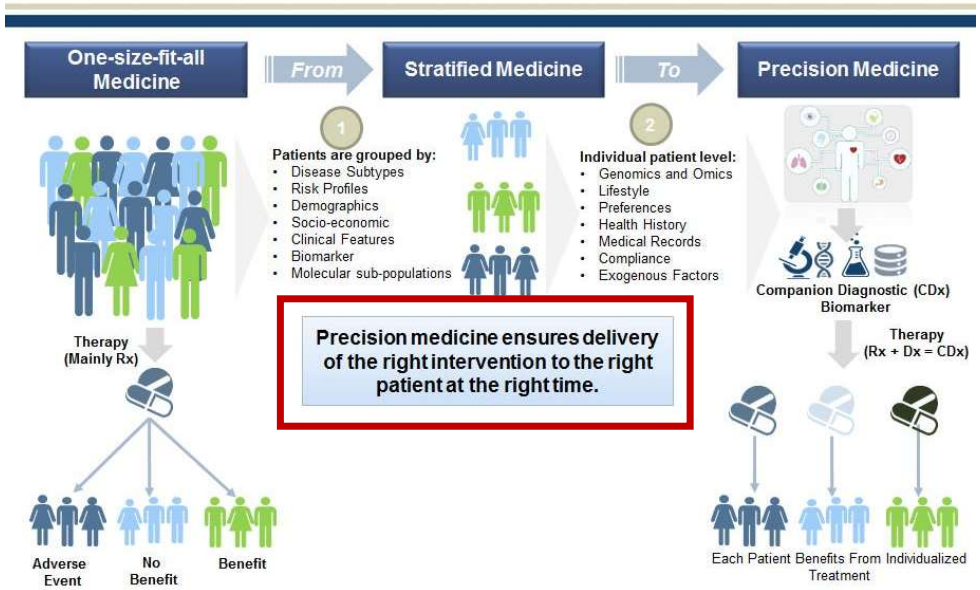
- Scientific consultancy role for Alentis Therapeutics, Amgen, AstraZeneca, Aveo Oncology, Boehringer Ingelheim, Cardiff Oncology, CARSgen Therapeutics, Chugai, Daiichi Sankyo, F. Hoffmann-La Roche Ltd, Genentech Inc, hC Bioscience, Immodulon Therapeutics, Inspirna Inc, Lilly, Marengo, Menarini, Merck Serono, Merus, MSD, Mirati, Neophore, Novartis, Ona Therapeutics, Orion Biotechnology, Peptomyc, Pfizer, Pierre Fabre, Sanofi, Scandion Oncology, Scorpion Therapeutics, Seattle Genetics, Servier, Sotio Biotech, Taiho, Takeda Oncology and Tolremo Therapeutics.
- Stocks: Oniria Therapeutics, Alentis Therapeutics, Pangaea Oncology and 1TRIALSP.
- Educational collaboration with Medscape Education, PeerView Institute for Medical Education and Physicians Education Resource (PER).
- Employed by the Vall d'Hebron Hospital Campus and Institute of Oncology (VHIO).
- Chair of Cancer Core Europe (CCE) and member of the Executive Board of OECI.

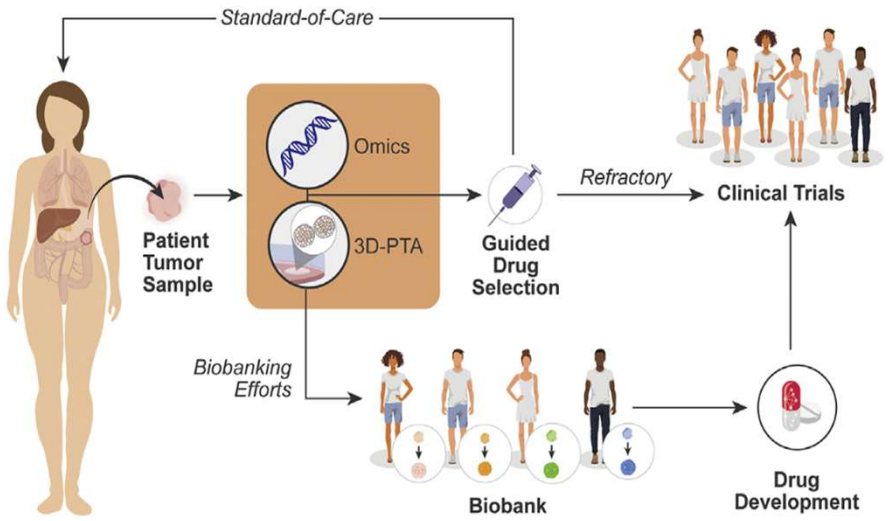
OUTLINE

- Precision Oncology & Translational Research
- Successful stories of the contribution of translational research:
  - Treatment in BRAFV600E mCRC
  - Anti-EGFR therapies in mCRC
- A glimpse into the future

PRECISION ONCOLOGY

"Precision medicine (analogous to personalized medicine) is an innovative approach that uses information about an individual's genomic, environmental, and lifestyle information to guide decisions related to their medical management" [1]

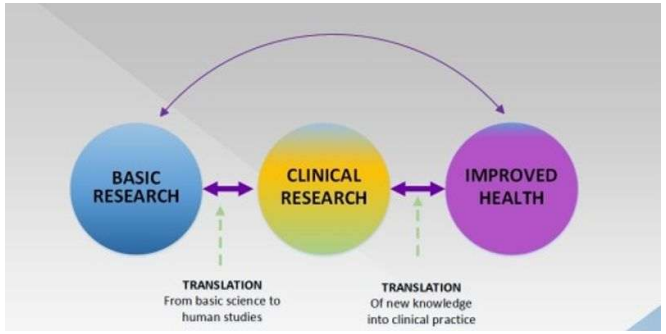


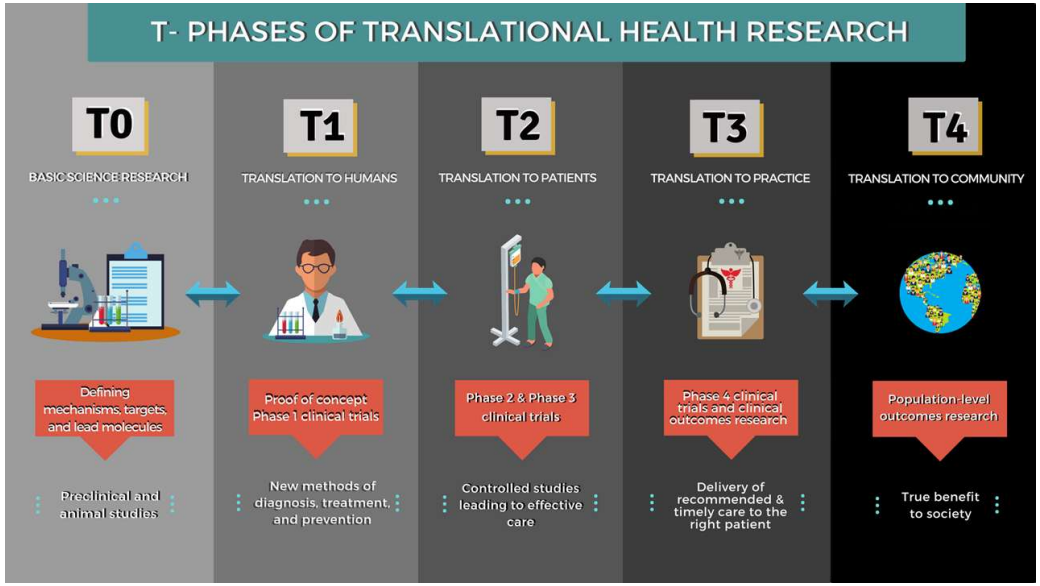


Shree B et al. Cancer Cell 2022

TRANSLATIONAL RESEARCH

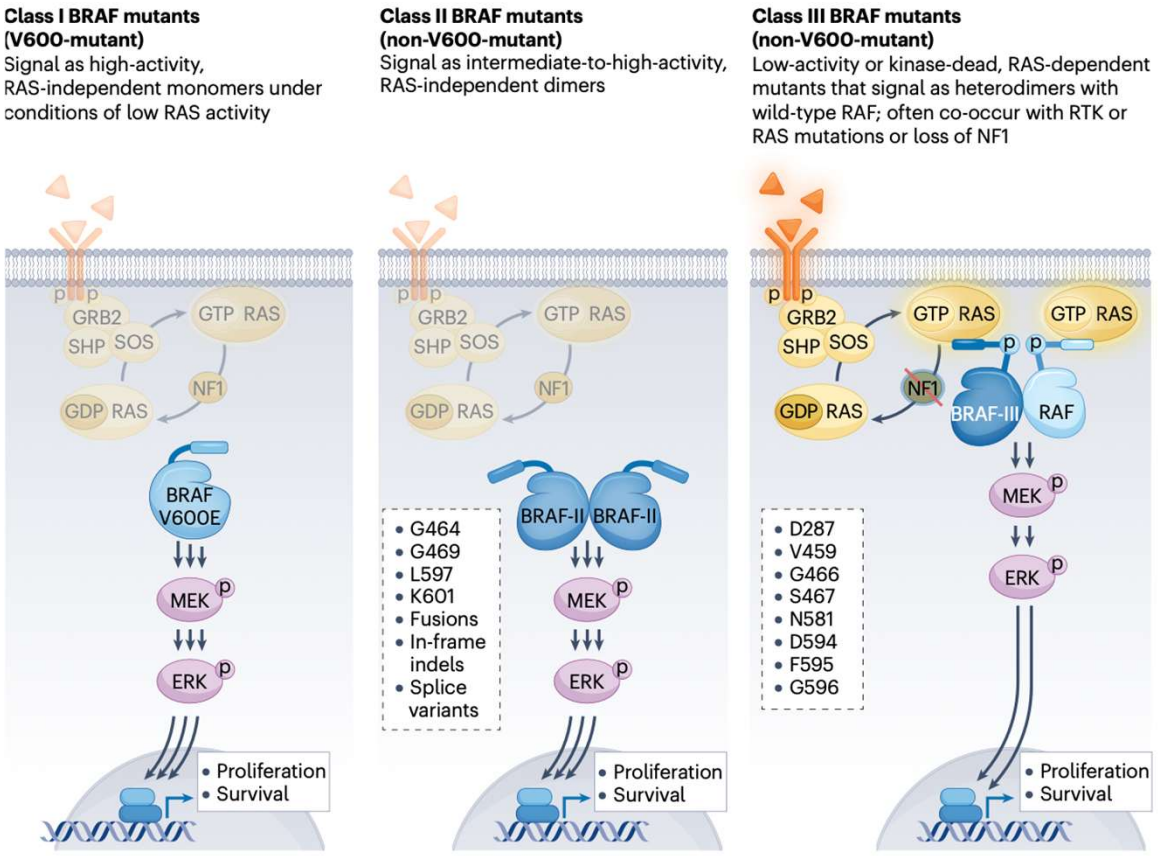
- Translational research, also known as translational medicine or translational science, is the process of applying scientific discoveries from basic research to develop new ways to diagnose, treat, and prevent disease in humans.
- It focuses on bridging the gap between laboratory findings and practical applications in clinical and community settings. Essentially, it's about moving research "from the bench to the bedside" and then into the community.
- The purpose of translational research is to test, in humans, novel therapeutics strategies developed through basic research and experimentation.





TREATMENT IN *BRAFV600E* MCRC

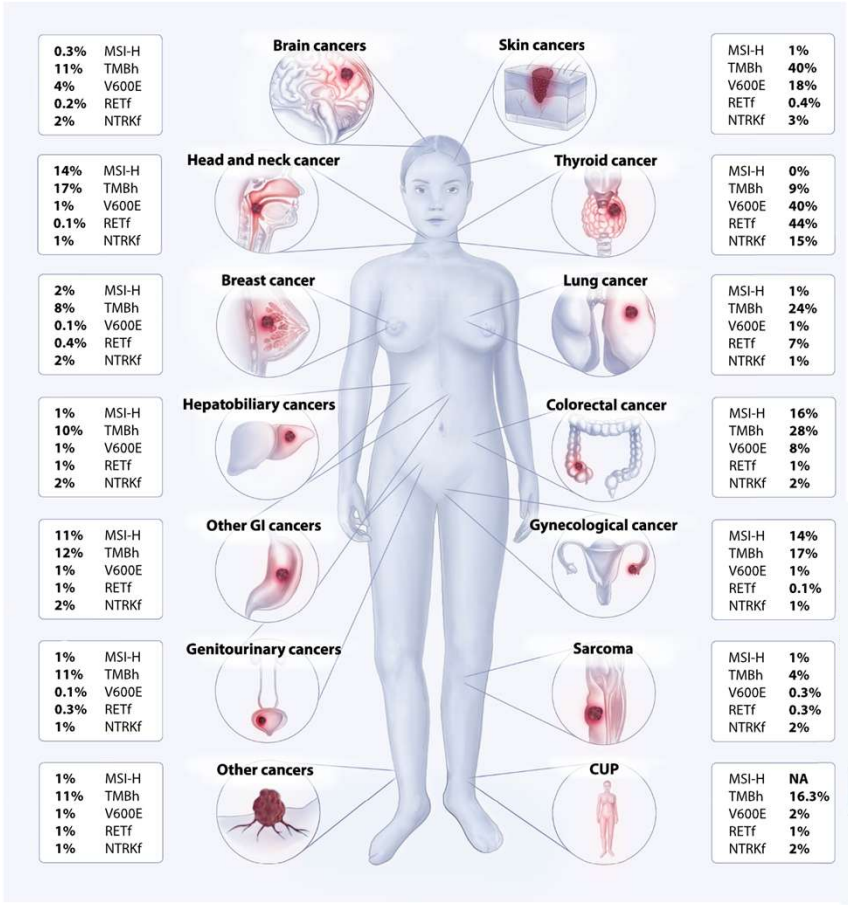
DEFINING *BRAF* MUTATIONS

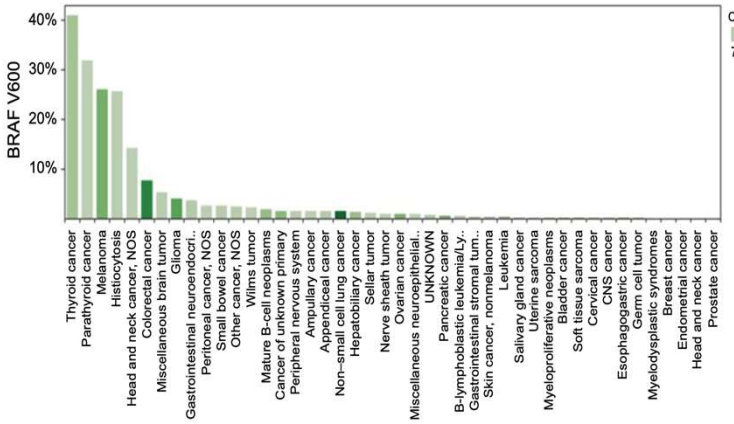


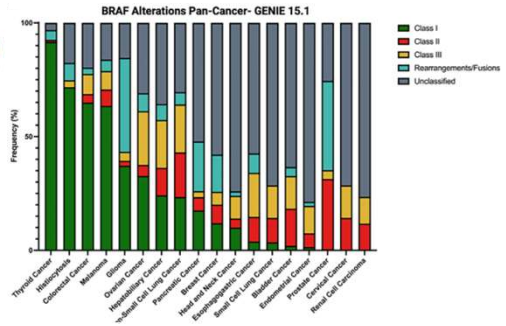
- *BRAF* mutations can be classified based on their function and their effects on BRAF dimerization.
  - **Class I** mutations have BRAF activity as monomers.
  - **Class II** mutations are constitutively active only as dimers.
  - **Class I and II** mutations are both RAS-independent and activate the MAPK pathway.
  - **Class III** mutations require coexisting RAS activation.
- *BRAF*-V600E constitutes the 95% of *BRAF* mutations in CRC.

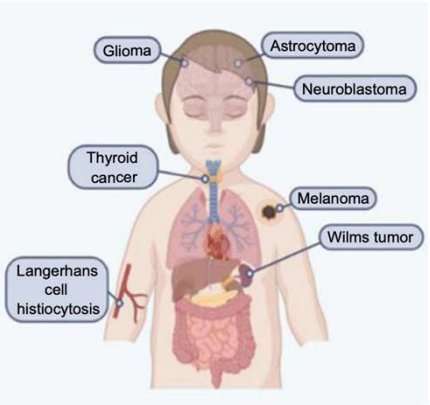
Hanrahan AJ. Nat Rev Clin Oncol 2024

BRAFV600 IN HUMAN CANCERS





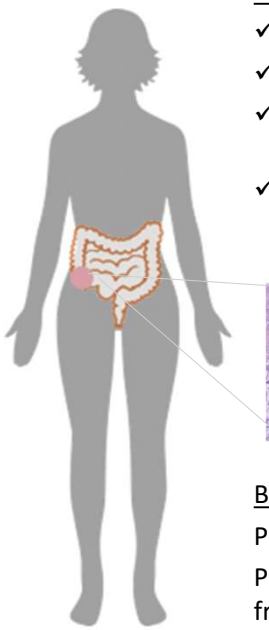


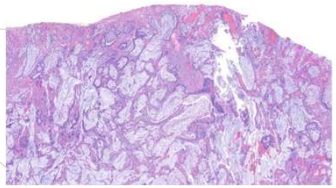


- *BRAF* mutations are ubiquitous in both solid and haematological cancers, adults and children.
- Thyroid cancer, melanoma, colorectal cancer, and gliomas are the solid tumours with the highest prevalence of the *BRAF*V600 mutation.

Subbiah V, et al. *CA Cancer J Clin* 2024; Adashek JJ, et al. Mol Cancer Ther 2022; Frequency of BRAFV600 mutations in 43 different tumour types across 2963 simples in the AACR GENIE database

BRAFV600E Mutations in mCRC





BRAFV600E: 8 to 12% mCRC[1]

Phenotype[2]:

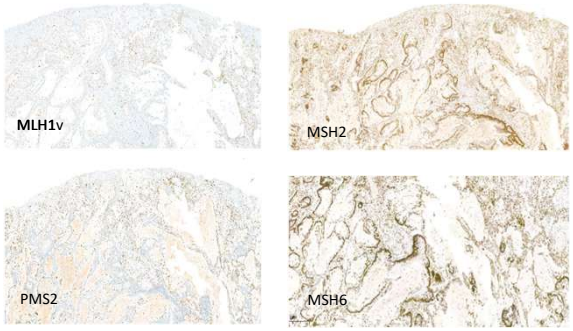
- ✓ Female sex
- ✓ Mucinous right-sided tumors
- ✓ High tumor burden: Peritoneal, lymph node M1
- ✓ <5% M1 achieve liver surgery

Biomarker role:

Prognostic[4]: mOS 8-24m

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

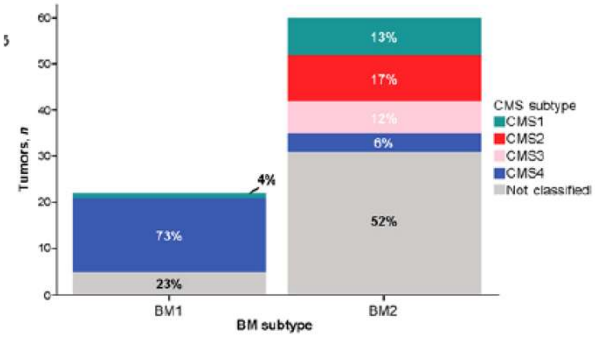
20-30% of BRAFV600E tumors present microsatellite instability (dMMR/MSI-H)[3]



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

BRAFV600E mCRC is a molecularly complex and heterogeneous disease[7-9]:

- ✓ Enrichment CMS1 and CMS4 subtypes
- ✓ BM1: 30%, KRAS/AKT pathway activation, strong immune profile
- ✓ BM2: 70%, cell cycle and cycle checkpoint–related deregulation



1.Sorbye H et al. PLoS One 2015; 2.Tran B et al. Cancer 2011; 3. Venderbosch S et al. Clin Cancer Res 2014; 4. Seligmann JF et al. Ann Oncol 2017; 5. Rowland A et al. Br J Cancer 2015; 6. Weisenberger DJ et al. Nat Genet 2006; 7. Barras D et al. Clin Cancer Res 2017; 8. Kopetz S et al. J Clin Oncol 39, 2021; 9. Middleton G et al. Clin Cancer Res 2020

FROM TUMOUR-AGNOSTIC TO TISSUE-SPECIFIC

Tissue is the issue

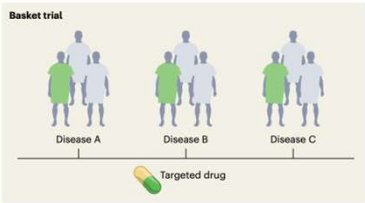
VE-BASKET

First-in-kind histology-independent Vemurafenib

BRAF V600–positive (testing per local methods)
Vemurafenib, 960 mg twice daily orally
Primary end point
- Response rate at wk 8

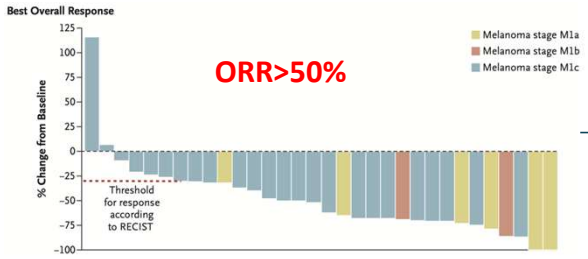
Secondary end points
- Progression-free survival
- Time to progression
- Best overall response
- Time to response
- Duration of response
- Clinical benefit rate
- Overall survival
- Safety

- NSCLC
- Cholangiocarcinoma
- All others
- ECD/LCH
- Anaplastic thyroid cancer
- Breast cancer
- Ovarian cancer
- Multiple myeloma
- Colorectal cancer



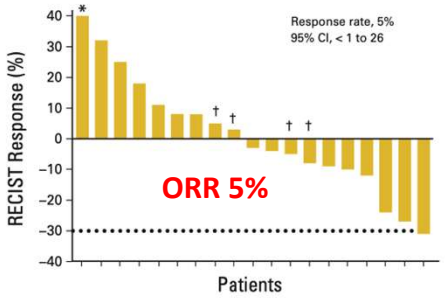
Metastatic melanoma

Vemurafenib



Metastatic colon cancer

Vemurafenib



Hyman D; et al. N Engl J Med. 2015;Sosman JA, et al. N Engl J Med. 2012; Flaherty Kt et al. N Engl J Med. 2010; Kopetz S, et al. J Clin Oncol 2010; Falchook GS, et al. Lancet. 2012; Delord JP, et al. Clin Cancer Res. 2017

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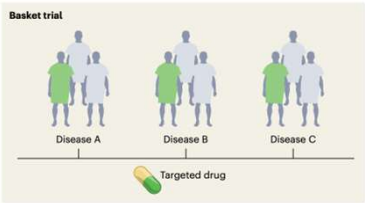
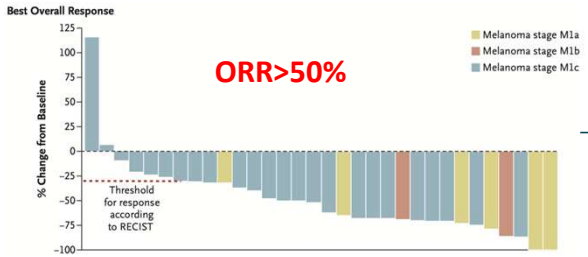
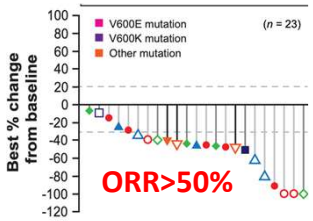


Metastatic melanoma

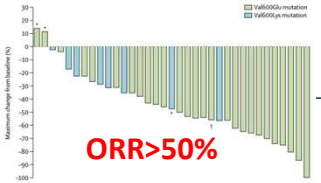
Vemurafenib



Encorafenib

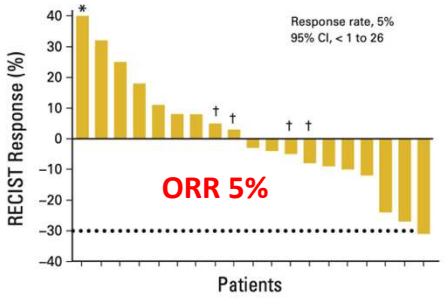


Dabrafenib



Metastatic colon cancer

Vemurafenib

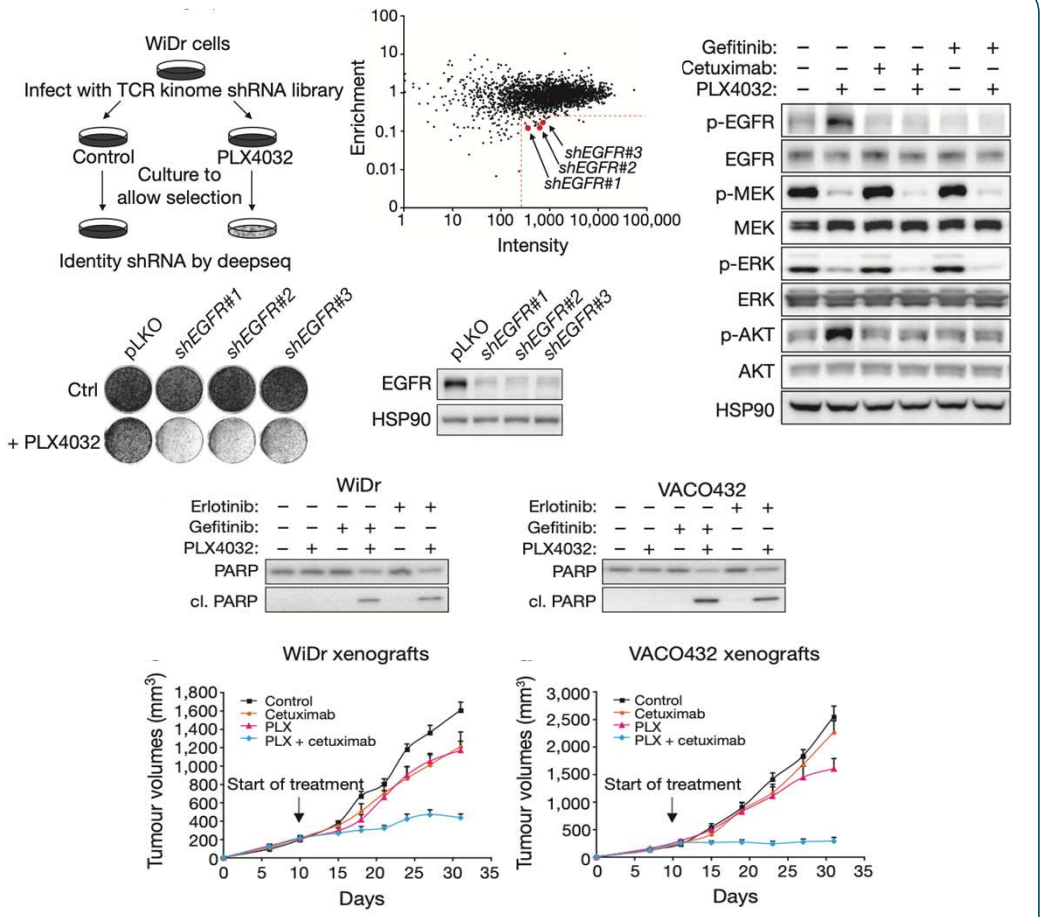


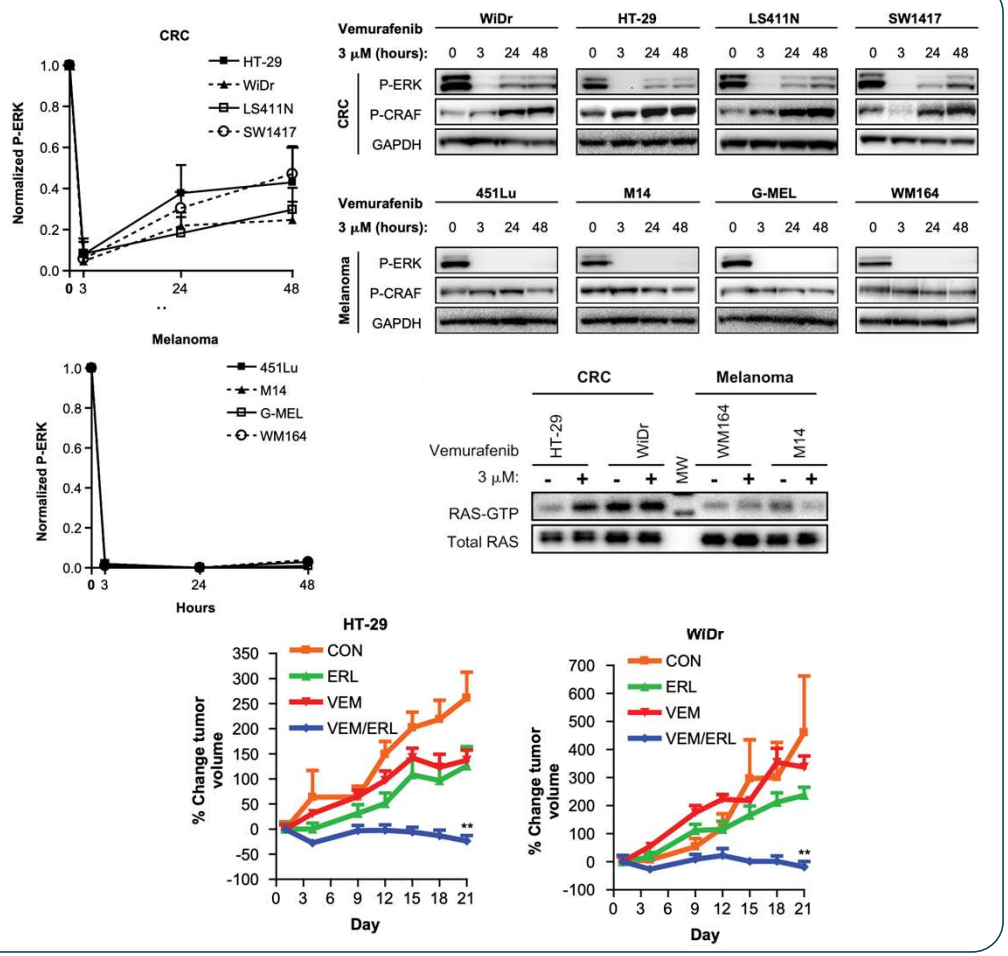
Drug	ORR	NCT
Dabrafenib	11%	NCT00880321
Encorafenib	0%	NCT017509188

Hyman D; et al. N Engl J Med. 2015;Sosman JA, et al. N Engl J Med. 2012; Flaherty Kt et al. N Engl J Med. 2010; Kopetz S, et al. J Clin Oncol 2010; Falchook GS, et al. Lancet. 2012; Delord JP, et al. Clin Cancer Res. 2017

FROM TUMOUR-AGNOSTIC TO TISSUE-SPECIFIC

Tissue is the issue





Prahallad A et al. Nature. 2012; Corcoran RB et al. Cancer Discov. 2012

BEACON STUDY

Patients with BRAFV600E mCRC with disease progression after 1 or 2 prior regimens; ECOG PS 0-1; and no prior treatment with any RAF inhibitor, MEK inhibitor, or EGFR inhibitor

Safety lead-in (N = 30)

Encorafenib
300 mg PO daily

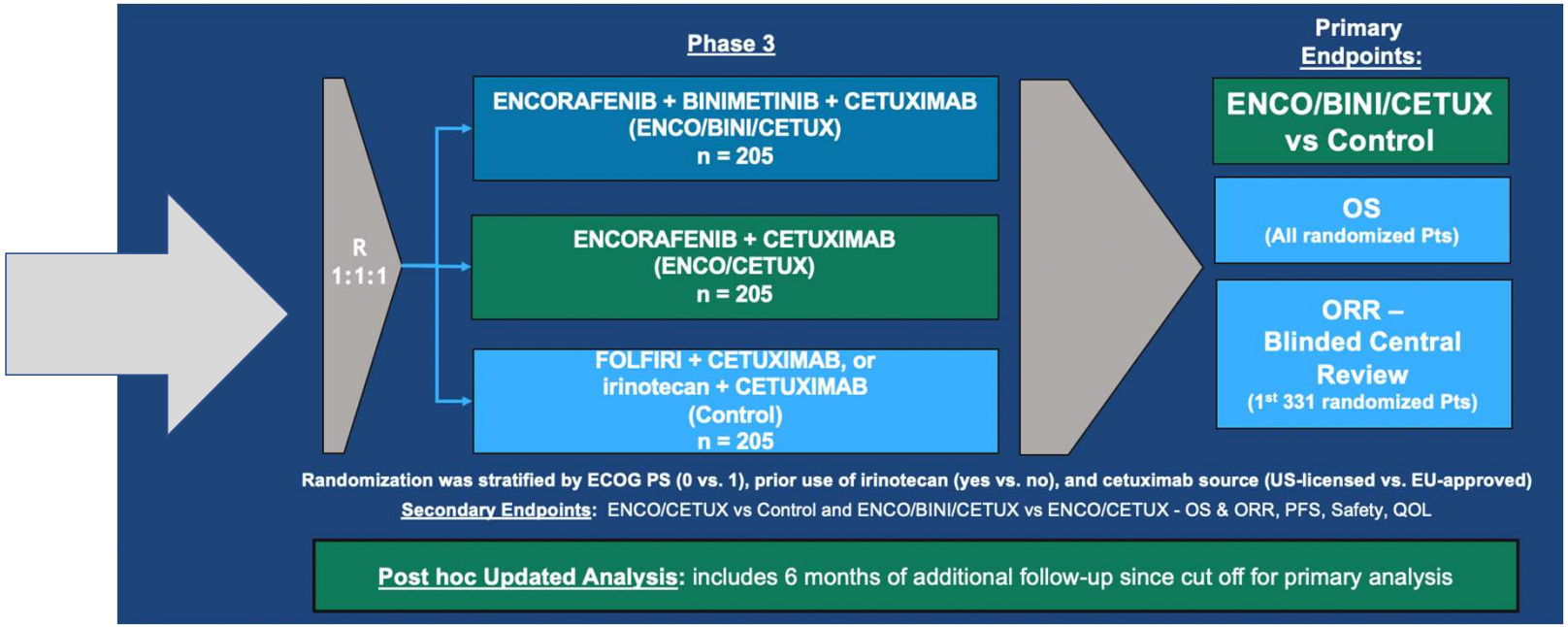
+

Binimetinib
45 mg PO BID

+

Cetuximab
Standard weekly dosing*

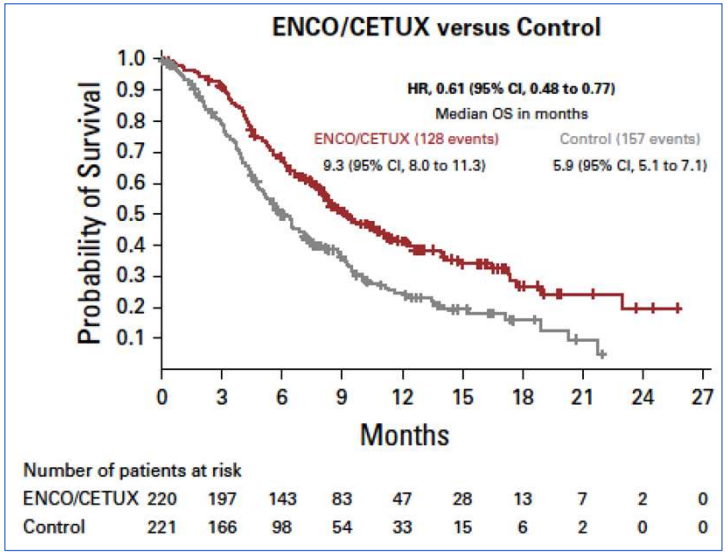
*Initial dose of 400 mg/m^2 of body surface area as an initial dose, then 250 mg/m^2 weekly

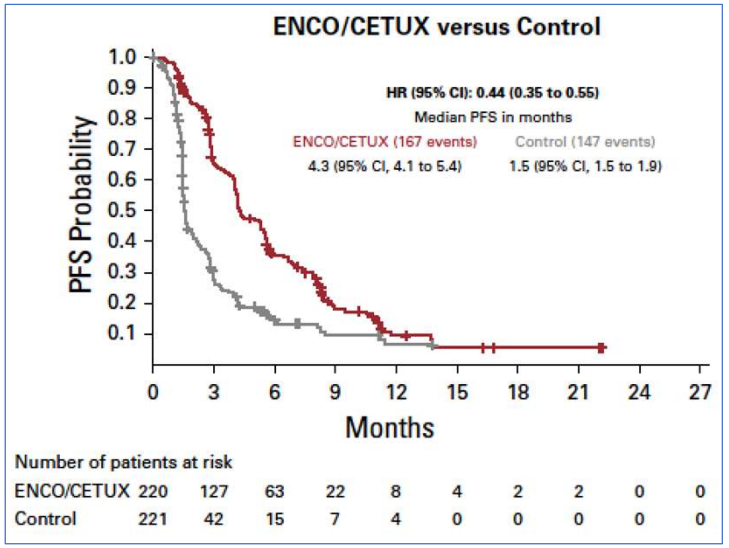


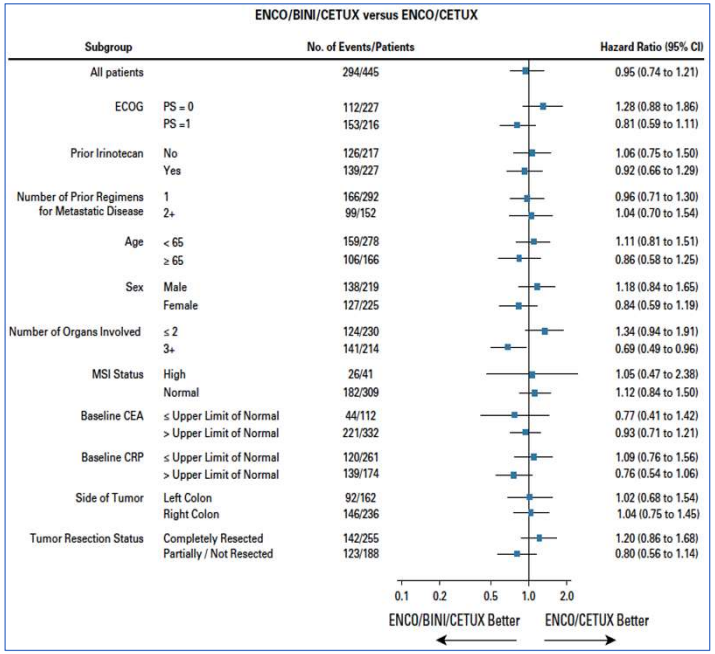
1. Kopetz S et al. N Engl J Med 2019; 2. Tabernero J et al J Clin Oncol 2021

BEACON STUDY

- The Beacon Study met its primary endpoint showing significant benefit in terms of OS, PFS and ORR favoring the investigational arms[1]
- No meaningful differences were observed between the doublet and the triplet combinations[1]
- The investigational combinations showed a favorable safety profile with longer maintenance of quality of life over the control arm[1,2]





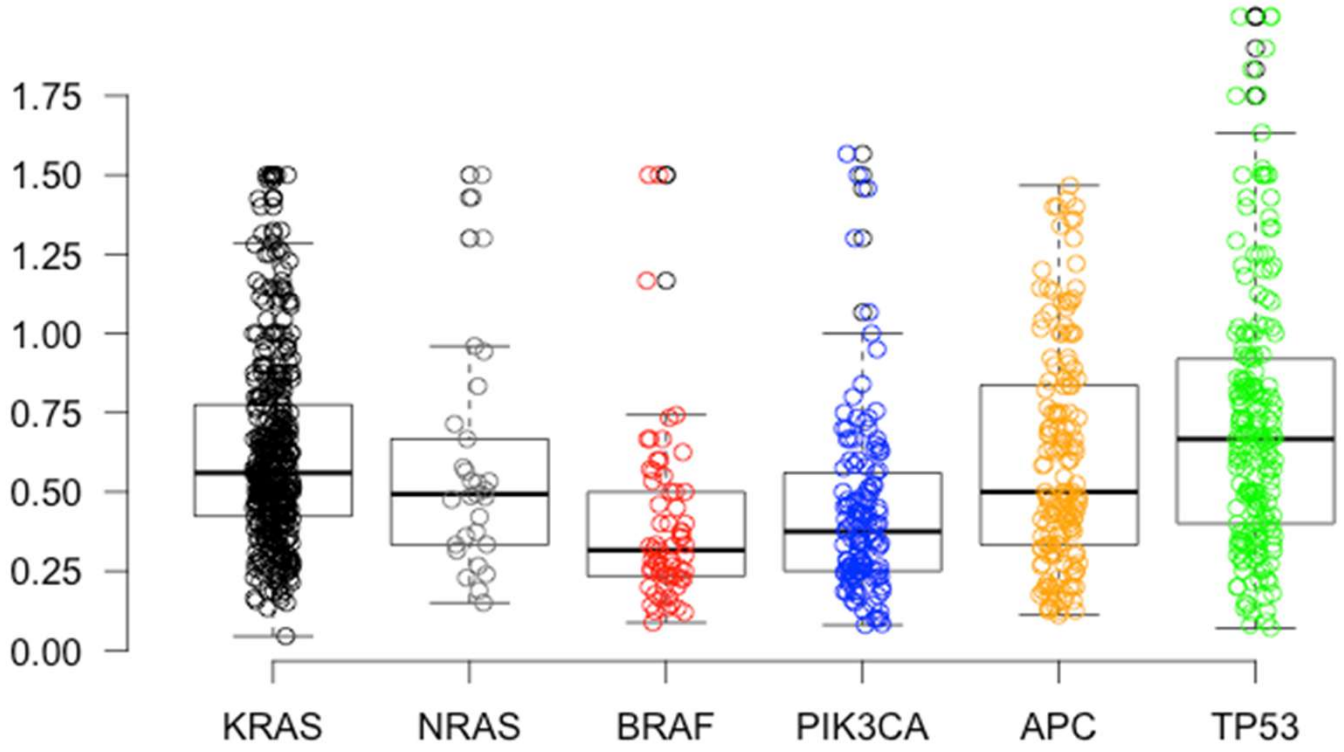


1. Kopetz S et al. N Engl J Med 2019; 2. Tabernero J et al J Clin Oncol 2021

DETERMINANTS OF LIMITED ACTIVITY

adjMAFs (adjusted MAFs) =

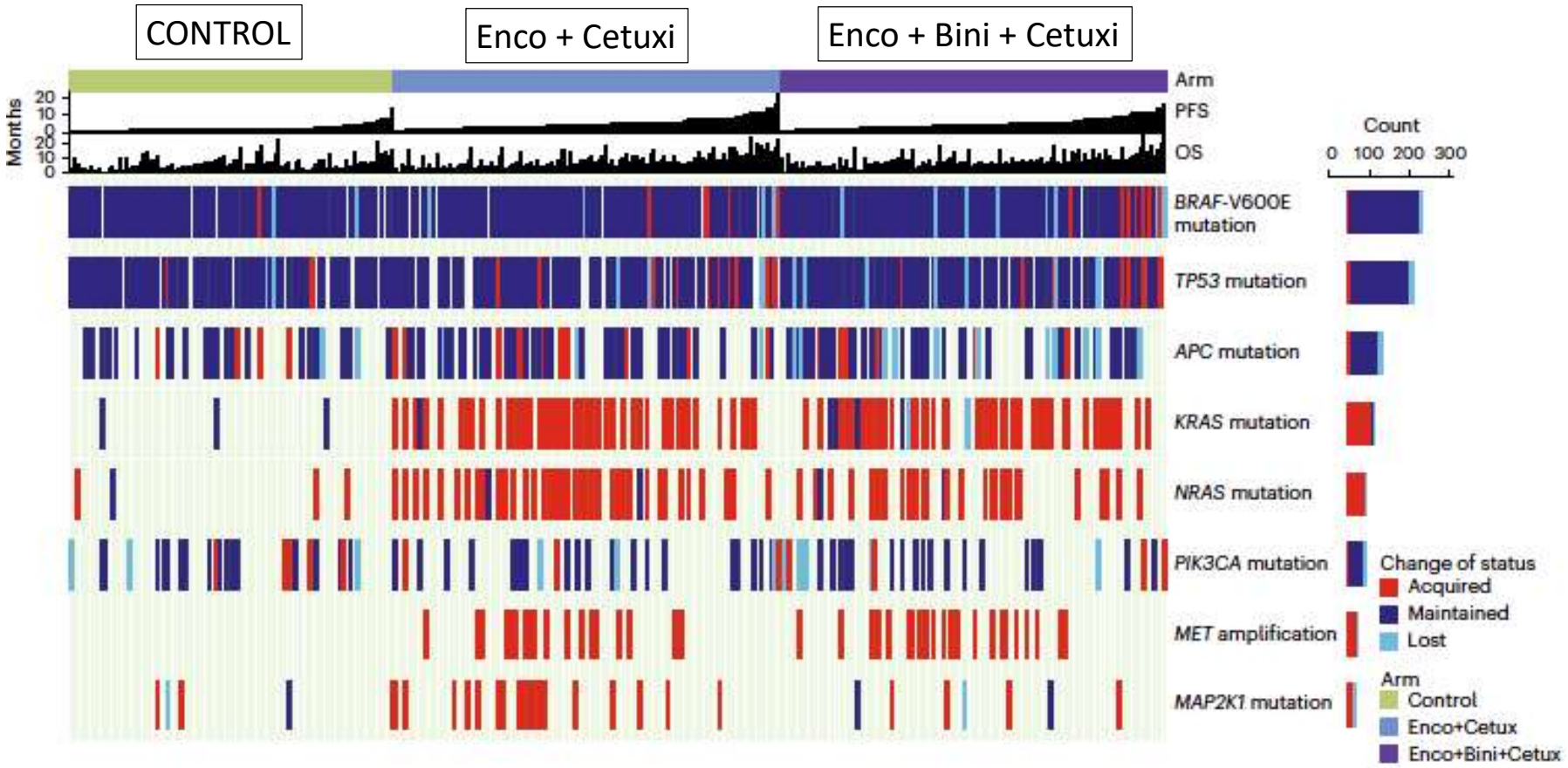
MAF/tumor purity



	KRAS	NRAS	BRAF	PIK3CA	APC	TP53
MEDIAN =	0.56	0.49	0.31	0.37	0.50	0.67

Dienstmann et al, Mol Oncol 2017

DETERMINANTS OF RESISTANCE BY LIQUID BIOPSY



Kopetz S et al, Nat Med 2024

BREAKWATER: STUDY DESIGN

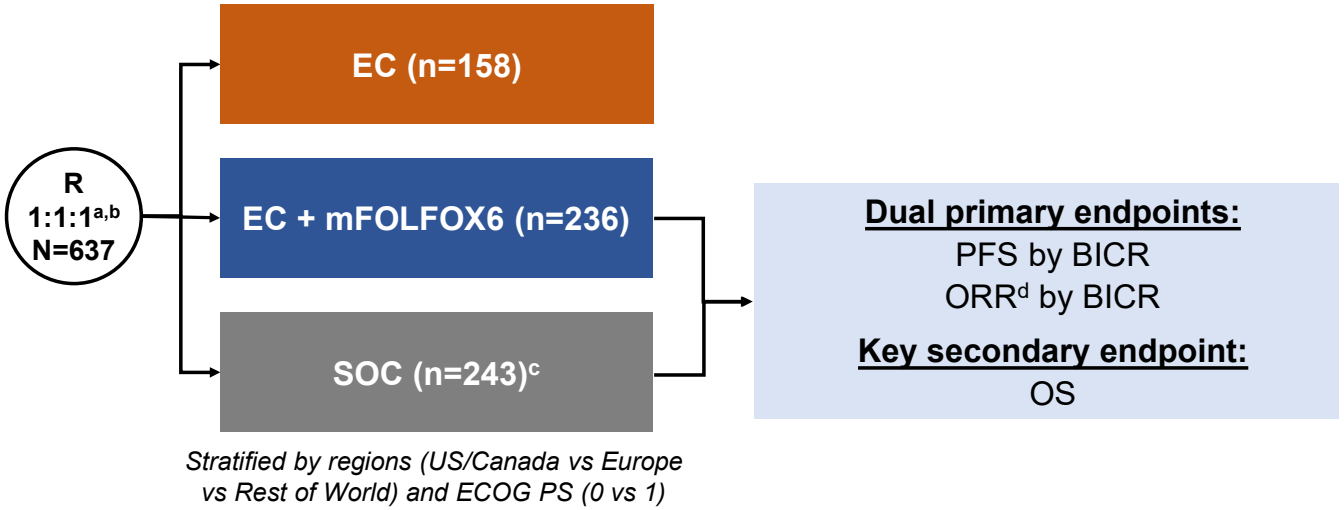
BREAKWATER (NCT04607421) is an open-label, multicenter, phase 3 study in first-line BRAF V600E-mutant mCRC

Inclusion criteria

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

Exclusion criteria

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



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

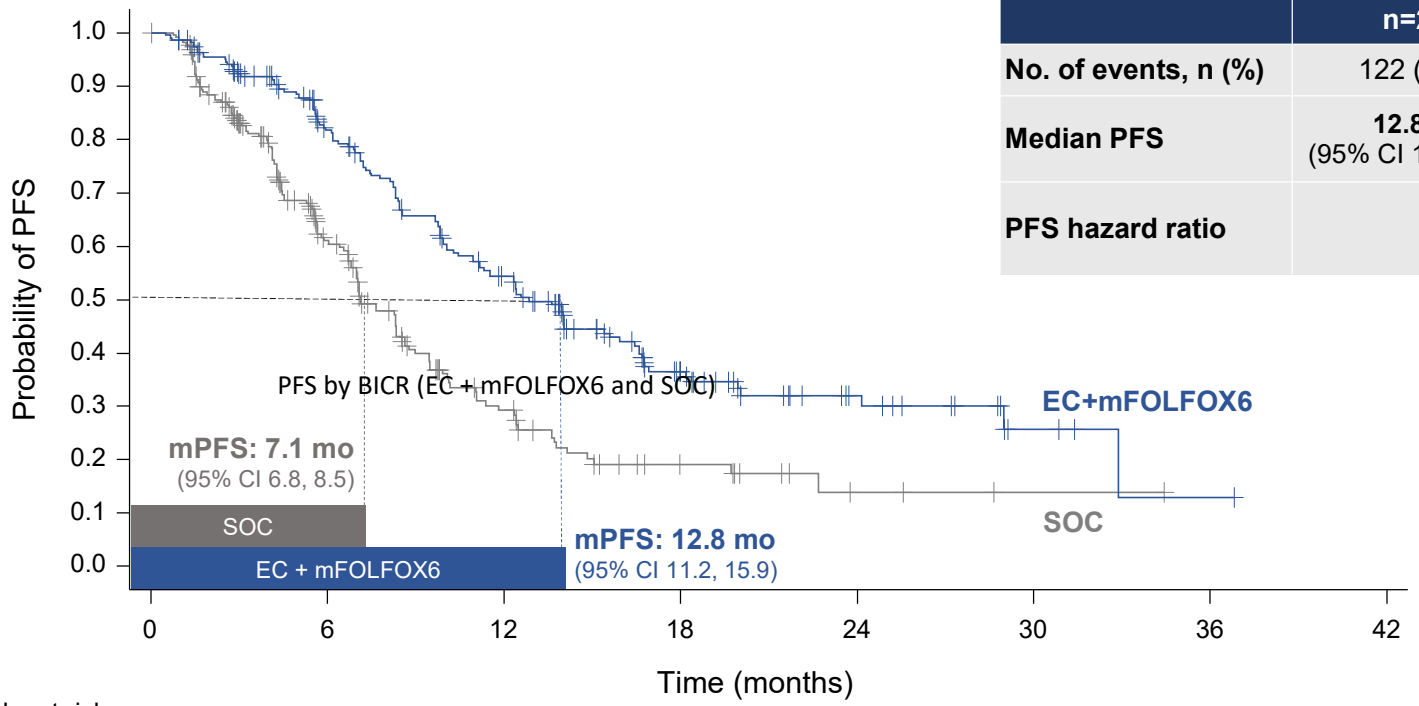
We present the primary analysis of PFS by BICR and a second interim analysis of OS in the EC + mFOLFOX6 and SOC arms, the efficacy data in the EC arm, and safety data in all arms

[a]Following a protocol amendment, enrollment to the EC arm was stopped and patients were randomized 1:1 to the EC + mFOLFOX6 or SOC arms. [b]Patients were enrolled between November 16, 2021, and December 22, 2023. [c]mFOLFOX6/FOLFOXIRI/CAPOX ± bevacizumab. [d]In the first 110 patients in each of the EC + mFOLFOX6 and SOC arms.

BICR, blinded independent central review; CAPOX, capecitabine/oxaliplatin; dMMR, deficient mismatch repair; EC, encorafenib plus cetuximab; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; FOLFOXIRI, fluorouracil/leucovorin/oxaliplatin/irinotecan; mFOLFOX6, modified fluorouracil/leucovorin/oxaliplatin; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high; RECIST, Response Evaluation Criteria in Solid Tumors.

BREAKWATER: PFS BY BICR (EC + mFOLFOX6 AND SOC)

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



No. at risk							
EC+mFOLFOX6	236	156	96	39	16	4	1
SOC	243	100	34	11	3	1	0

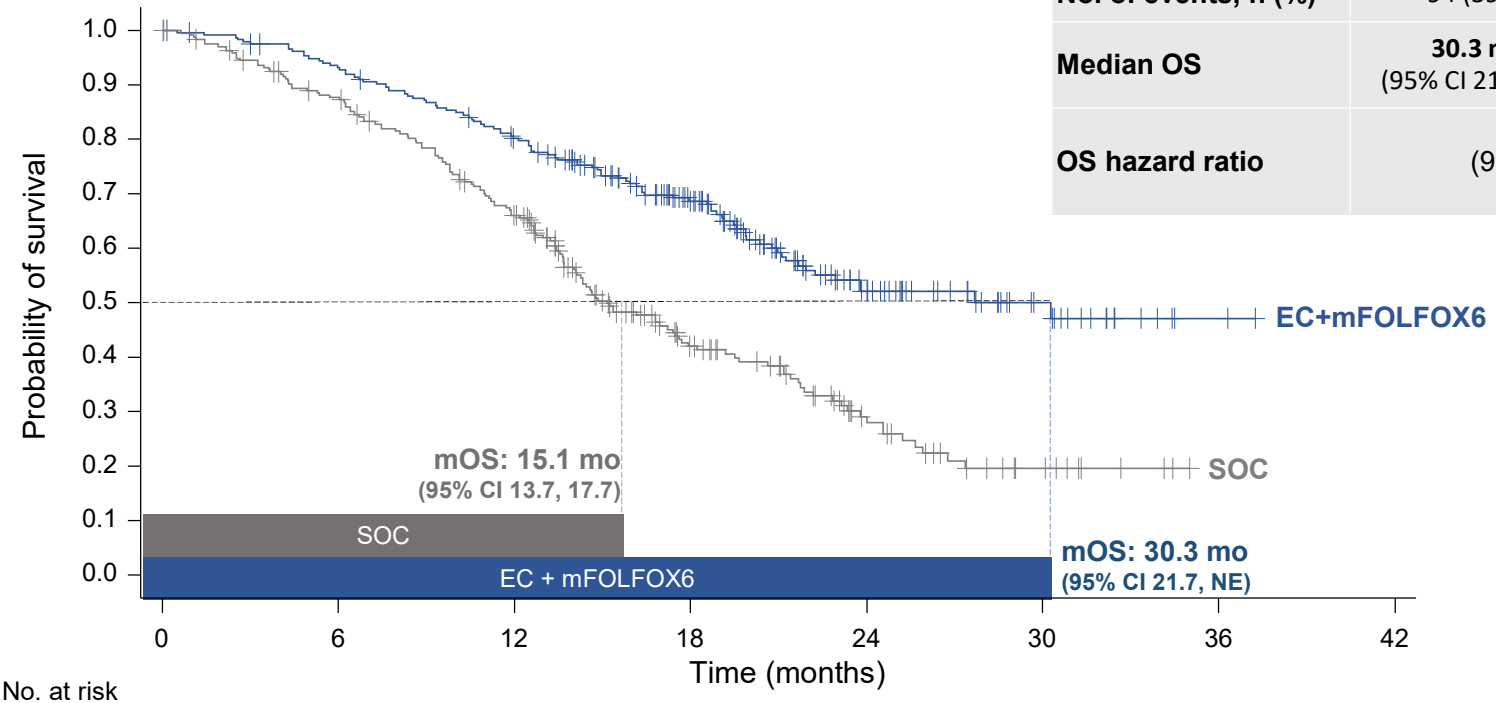
Data cutoff: January 6, 2025.

BICR, blinded independent central review; EC, encorafenib plus cetuximab; mFOLFOX6, modified fluorouracil/leucovorin/oxaliplatin; SOC, standard of care; mPFS, median progression-free survival

Elez E et al, Proc ASCO 2025, NEJM 2025

BREAKWATER: OS (EC + mFOLFOX6 AND SOC)

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



No. at risk								
EC+mFOLFOX6	236	216	182	121	48	17	2	0
SOC	243	202	147	64	27	9	0	0

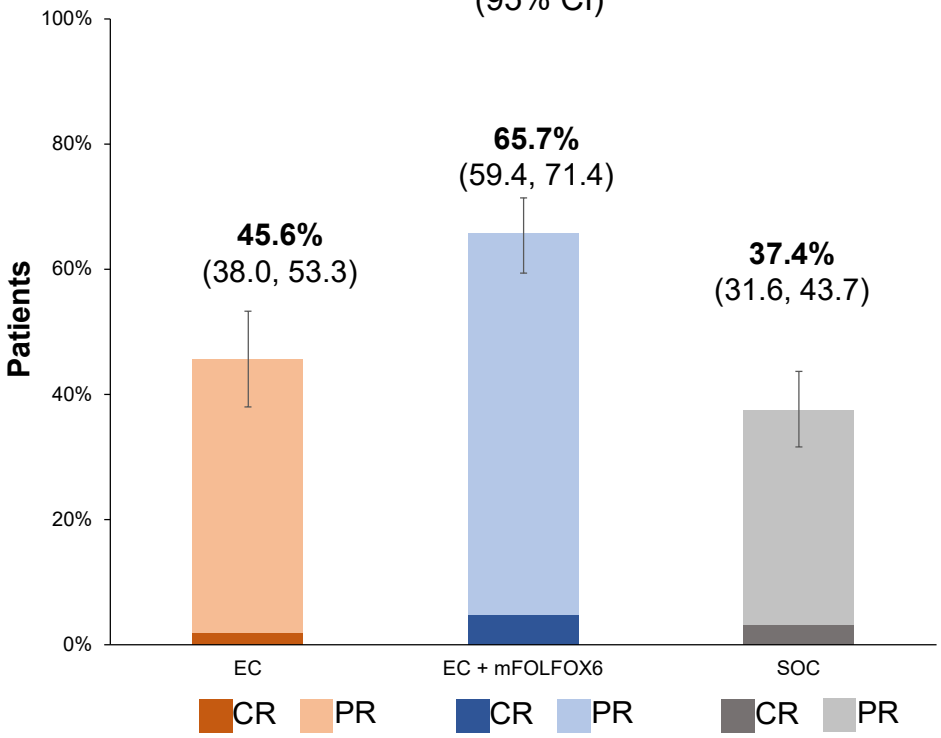
Data cutoff: January 6, 2025. [a]Exceeding the threshold for statistical significance in this interim analysis.

EC, encorafenib plus cetuximab; mFOLFOX6, modified fluorouracil/leucovorin/oxaliplatin; NE, not estimable; SOC, standard of care; mOS, median overall survival

Elez E et al, Proc ASCO 2025, NEJM 2025

BREAKWATER: BEST ORR BY BICR

Confirmed ORR by BICR
(95% CI)



Confirmed Best Overall Response, TTR, and DOR by BICR

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

Data cutoff: January 6, 2025.

[a]Non-CR/PD: 7 (4.4%), 5 (2.1%), and 9 (3.7%), respectively; not evaluable: 10 (6.3%), 18 (7.6%), and 37 (15.2%), respectively.

BICR, blinded independent central review; CR, complete response; DOR, duration of response; EC, encorafenib plus cetuximab; mFOLFOX6, modified fluorouracil/leucovorin/oxaliplatin; PD, progressive disease; PR, partial response; SD, stable disease; SOC, standard of care; TTR, time to response.

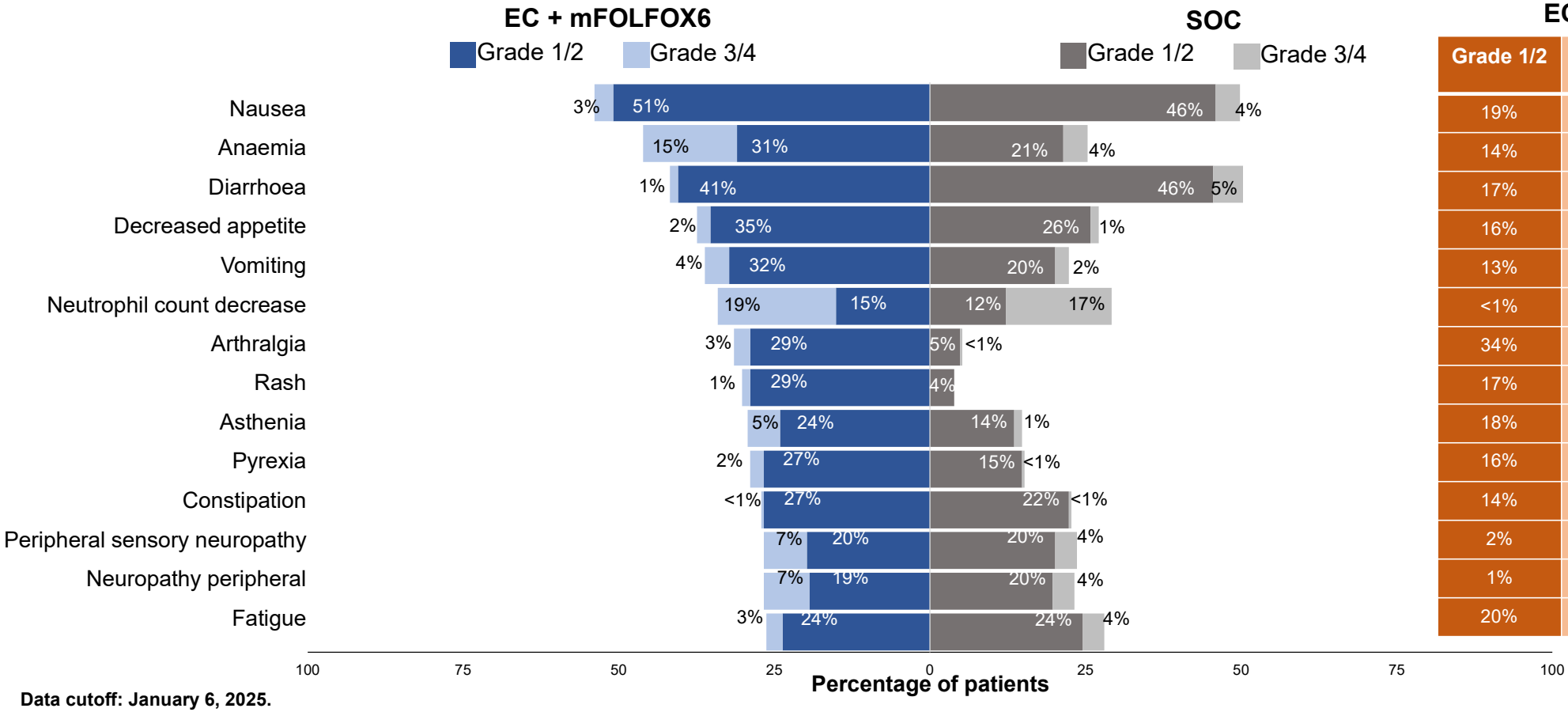
BREAKWATER: SAFETY SUMMARY

Patients, n (%)	EC n=153	EC + mFOLFOX6 n=232	SOC n=229
Duration of treatment, median (range), weeks	27.0 (2.0-153.6)	49.8 (1.3-161.9)	25.9 (2.0-150.0)
All causality			
TEAE	149 (97.4)	232 (100)	227 (99.1)
Grade 3 or 4 TEAE	65 (42.5)	189 (81.5)	153 (66.8)
Grade 5 TEAE	4 (2.6)	10 (4.3)	10 (4.4)
Serious TEAE	46 (30.1)	107 (46.1)	89 (38.9)
TEAE leading to permanent discontinuation of any study treatment	20 (13.1)	62 (26.7)	40 (17.5)
TEAE leading to dose reduction of any study treatment	16 (10.5)	152 (65.5)	124 (54.1)
TEAE leading to dose interruption of any study treatment	63 (41.2)	212 (91.4)	168 (73.4)
Treatment-related			
AE related to any drug	136 (88.9)	232 (100)	217 (94.8)
Grade 3 or 4 TRAE	24 (15.7)	177 (76.3)	134 (58.5)
Grade 5 TRAE	0	0	1 (0.4)[a]
Serious AE related to any drug	10 (6.5)	45 (19.4)	50 (21.8)

Data cutoff: January 6, 2025.
[a]Sepsis (preferred term).
AE, adverse event; EC, encorafenib plus cetuximab; mFOLFOX6, modified fluorouracil/leucovorin/oxaliplatin; SOC, standard of care; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Elez E et al, Proc ASCO 2025, NEJM 2025

BREAKWATER: Most Frequent (≥25%) TEAEs



EC		
	Grade 1/2	Grade 3/4
Nausea	19%	1%
Anaemia	14%	7%
Diarrhoea	17%	1%
Decreased appetite	16%	<1%
Vomiting	13%	1%
Neutrophil count decrease	<1%	<1%
Arthralgia	34%	<1%
Rash	17%	<1%
Asthenia	18%	<1%
Pyrexia	16%	1%
Constipation	14%	<1%
Peripheral sensory neuropathy	2%	0%
Neuropathy peripheral	1%	0
Fatigue	20%	1%

Data cutoff: January 6, 2025.

[a]Frequency is based on the EC + mFOLFOX6 arm.

EC, encorafenib plus cetuximab; mFOLFOX6, modified fluorouracil/leucovorin/oxaliplatin; SOC, standard of care; TEAE, treatment-emergent adverse event.

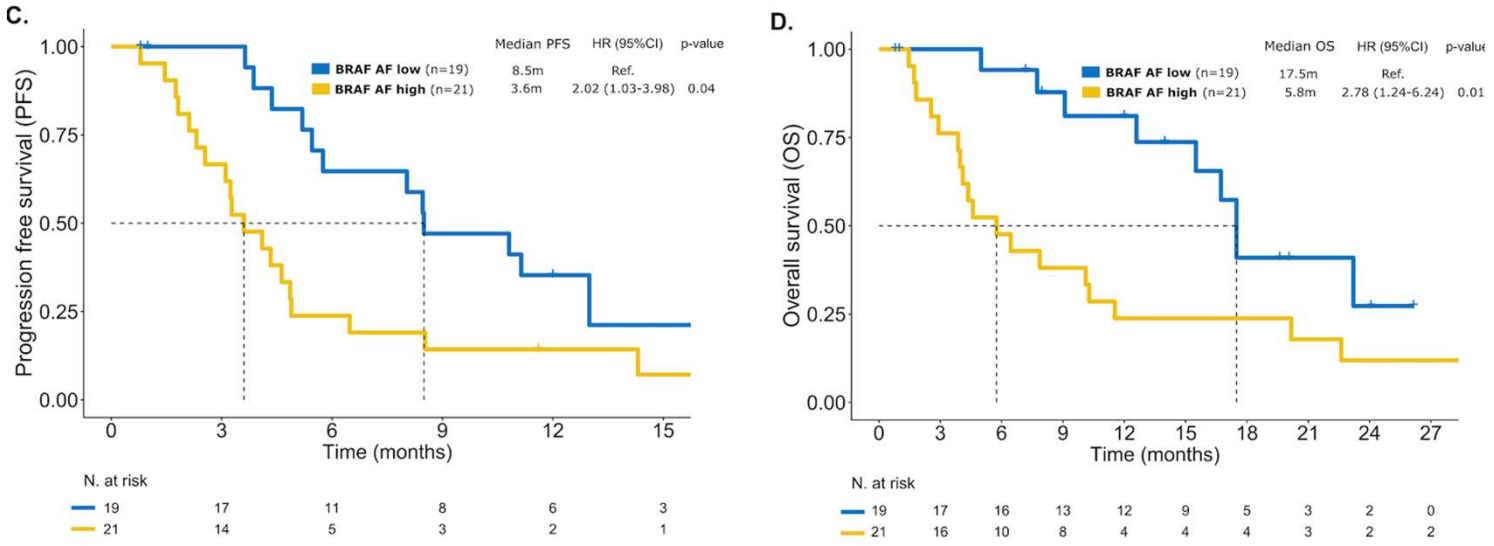
Elez E et al, Proc ASCO 2025, NEJM 2025

CAN WE SQUEEZE THE BEACON REGIMEN OUTCOMES?

Strategy 1: Optimize patient Selection

STRATEGY 1: OPTIMIZE PATIENT SELECTION

Role of plasmatic BRAF-V600E allele fraction as prognostic factor in metastatic colorectal cancer treated with encorafenib-cetuximab +/- binimetinib



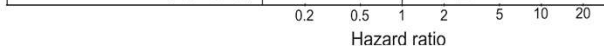
Ros J et al. Ann Oncol 2023

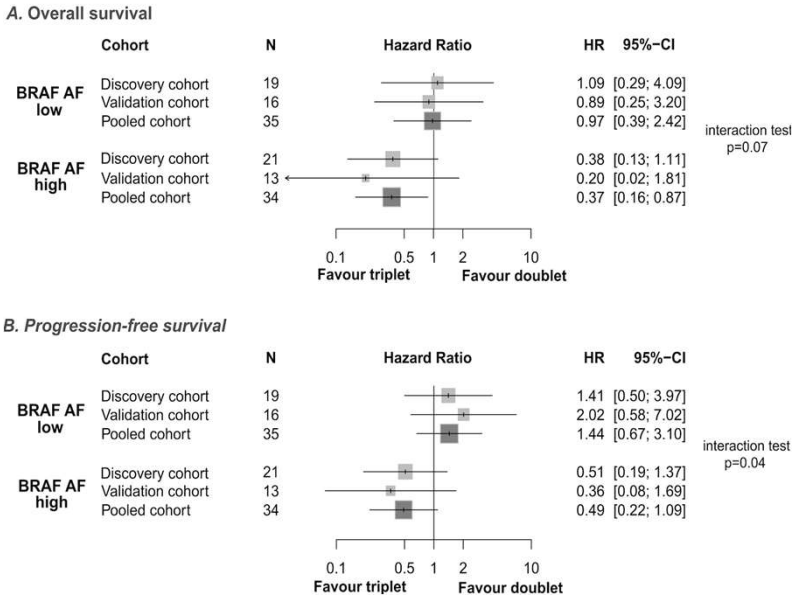
STRATEGY 1: OPTIMIZE PATIENT SELECTION

Role of plasmatic BRAF-V600E allele fraction as prognostic factor in metastatic colorectal cancer treated with encorafenib-cetuximab +/- binimetinib

Overall survival

Variable		N	Univariate analysis HR (95%CI)	p-value	Multivariate analysis HR (95%CI)	p-value
Age	<60 years	20	Reference		Reference	
	>60 years	20	0.76 (0.36, 1.64)	0.488	0.48 (0.19, 1.20)	0.12
Sex	Female	26	Reference			
	Male	14	1.15 (0.53, 2.49)	0.720		
ECOG	0	22	Reference		Reference	
	1+	18	8.67 (2.98, 25.22)	<0.001	9.86 (2.61, 37.2)	**<0.001**
Primary tumor	Left	16	Reference			
	Right	24	1.14 (0.52, 2.50)	0.748		
Metastatic sites	1−2	27	Reference		Reference	
	3−4	13	3.11 (1.41, 6.86)	0.005	2.03 (0.77, 5.38)	0.15
Liver metastasis	No	24	Reference		Reference	
	Yes	16	4.05 (1.73, 9.47)	0.001	1.14 (0.33, 3.94)	0.83
Prior lines	0-1	21	Reference			
	2+	19	0.89 (0.41, 1.89)	0.752		
MSS/MSI	MSI	6	Reference			
	MSS	31	1.75 (0.52, 5.93)	0.370		
Treatment	Doublet	26	Reference			
	Triplet	14	0.59 (0.26, 1.31)	0.192		
CEA levels	Low (<10)	28	Reference		Reference	
	High (>10)	12	2.78 (1.24, 6.25)	0.013	2.60 (0.72, 9.30)	0.14
NLR levels	Low (<3)	18	Reference			
	High (>3)	22	1.17 (0.55,2.52)	0.68		
Albumin levels	Low (<3.5)	7	Reference		Reference	
	High (>3.5)	33	0.30 (0.12, 0.72)	0.008	1.39 (0.30, 6.37)	0.67
BRAF AF	Low (<1%)	19	Reference		Reference	
	High (>1%)	21	2.78 (1.24, 6.24)	0.013	3.22 (1.17, 8.83)	**0.02**



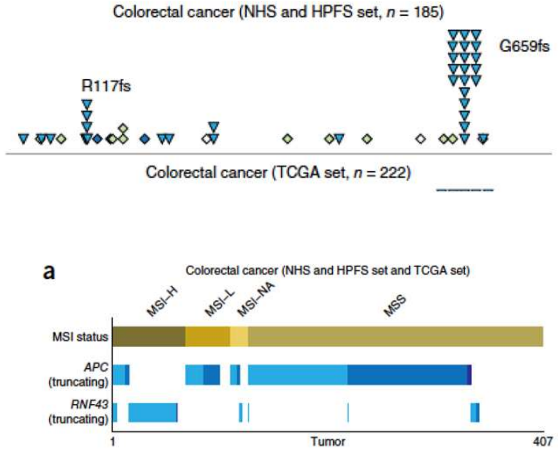


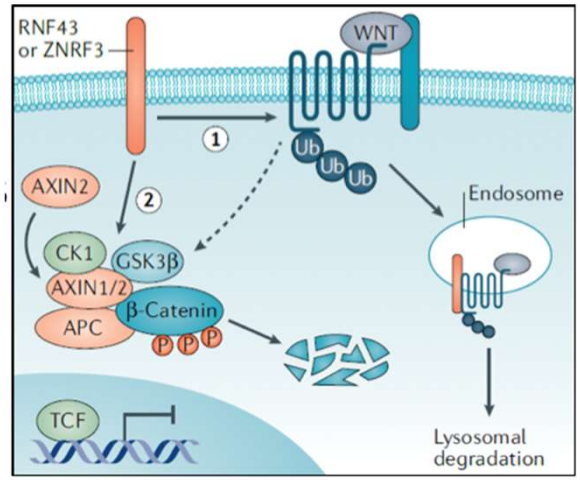
Ros J et al. Ann Oncol 2023

STRATEGY 1: OPTIMIZE PATIENT SELECTION

RNF43 encodes an E3 ubiquitin ligase that negatively regulates Wnt signaling

- Truncating mutations of RNF43 are more prevalent in MSI/dMMR tumors and show mutual exclusivity with inactivating APC^{MT} in CRC[1]
- These mutations would activate the WNT/B-cat pathway less efficiently than APC^{MT}
- The real interplay between RNF43 and BRAF pathways has not been established yet



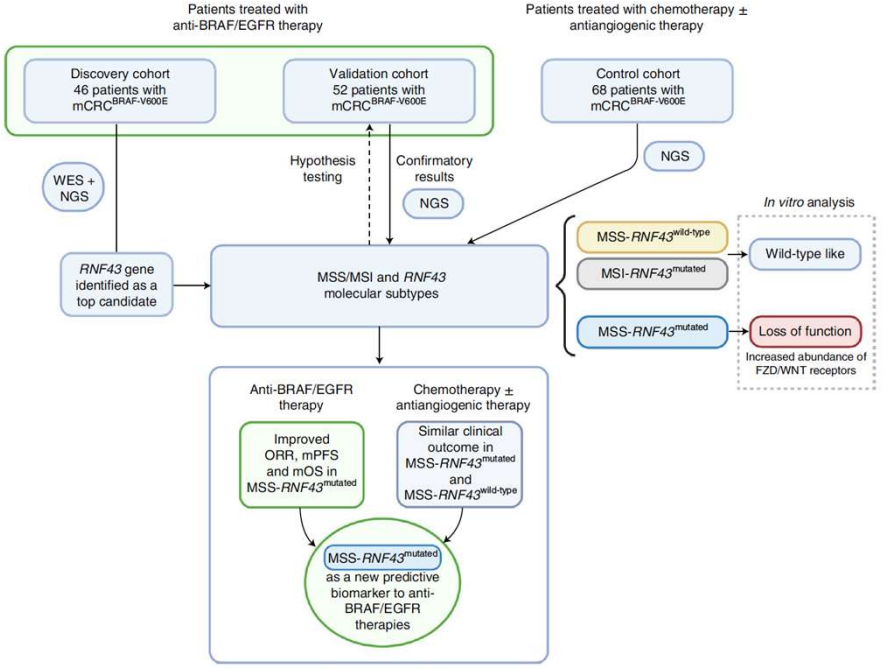


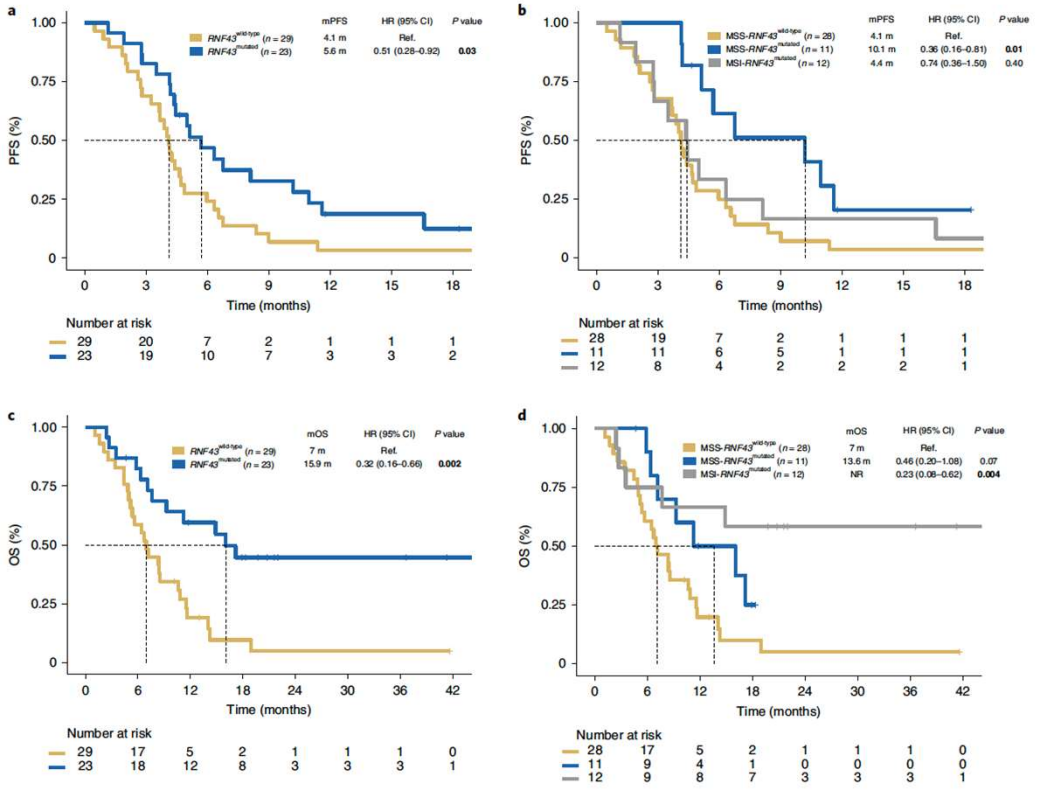
1. Giannakis M et al. Nat Gen 2014

2. Bugter JM et al. Nat Rev Cancer 2021

STRATEGY 1: OPTIMIZE PATIENT SELECTION

RNF43 mutations predict response to anti-BRAF/EGFR combinatory therapies in BRAFV600E mCRC





Elez E et al. Nat Med 2022

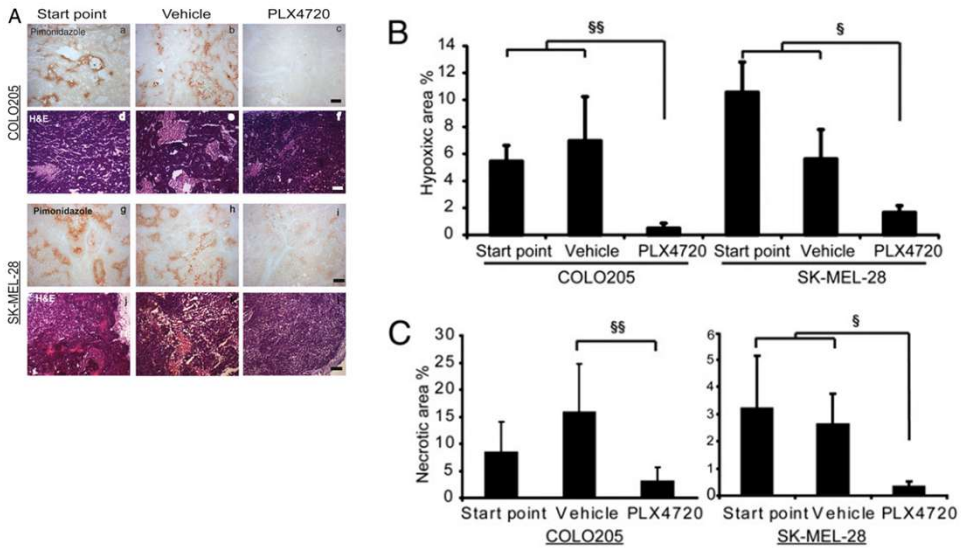
CAN WE SQUEEZE THE BEACON REGIMEN OUTCOMES?

Strategy 2: Preventing resistance

STRATEGY 2: PREVENTING RESISTANCE

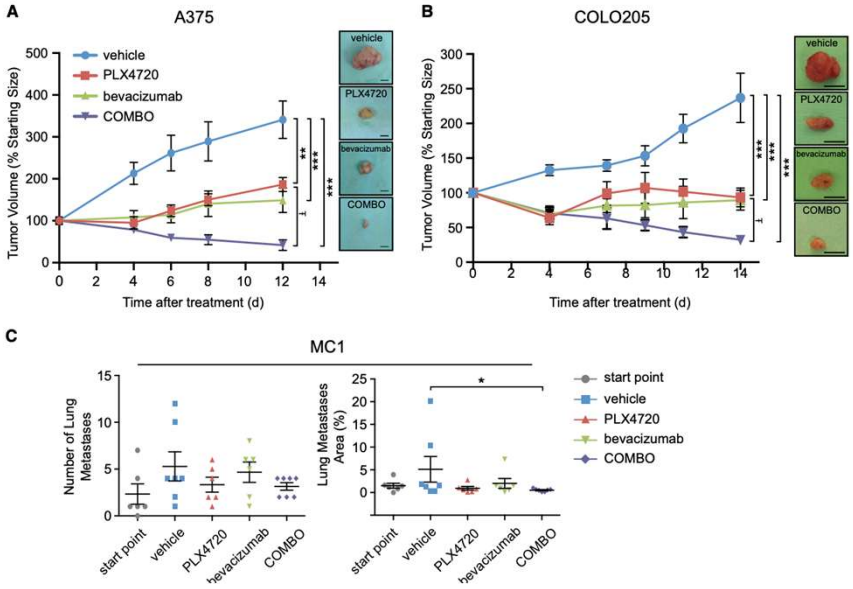
Angiogenesis and BRAF inhibition

Targeting oncogenic serine/threonine-protein kinase BRAF in cancer cells inhibits angiogenesis and abrogates hypoxia



Bottos A et al. PNAS 2012

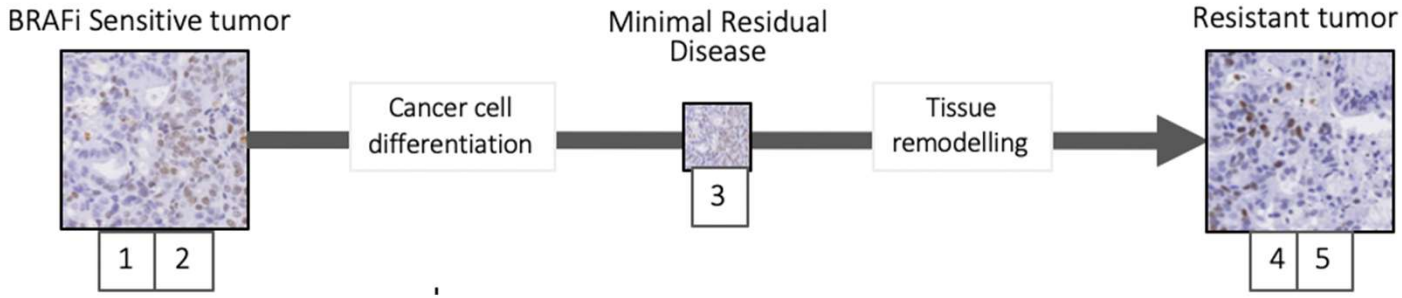
VEGF blockade enhances the antitumor effect of BRAFV600E inhibition

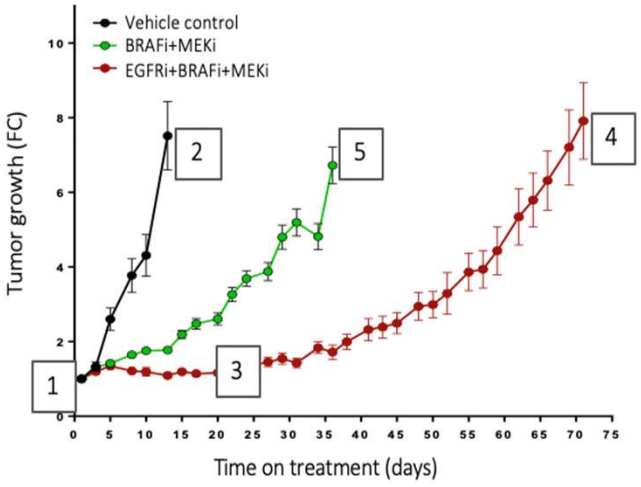


Comunanza V et al. PNAS 2017

STRATEGY 2: PREVENTING RESISTANCE

Angiogenesis and BRAF inhibition





WES, sWGS, Methylome, IHC;
Radiomics, Single Cell RNA seq

Identification of Druggable Targets Responsible for Tumor Resistance

New Drug Combinations

TARGETING ANGIOGENESIS TO OVERCOME TREATMENT RESISTANCE IN BRAF MUTANT METASTATIC COLORECTAL SETTING.

Clinical Trials Information System (CTIS) code: 2023-503643-34-00

Protocol Number: VHIO23001

Phase: 1b/2

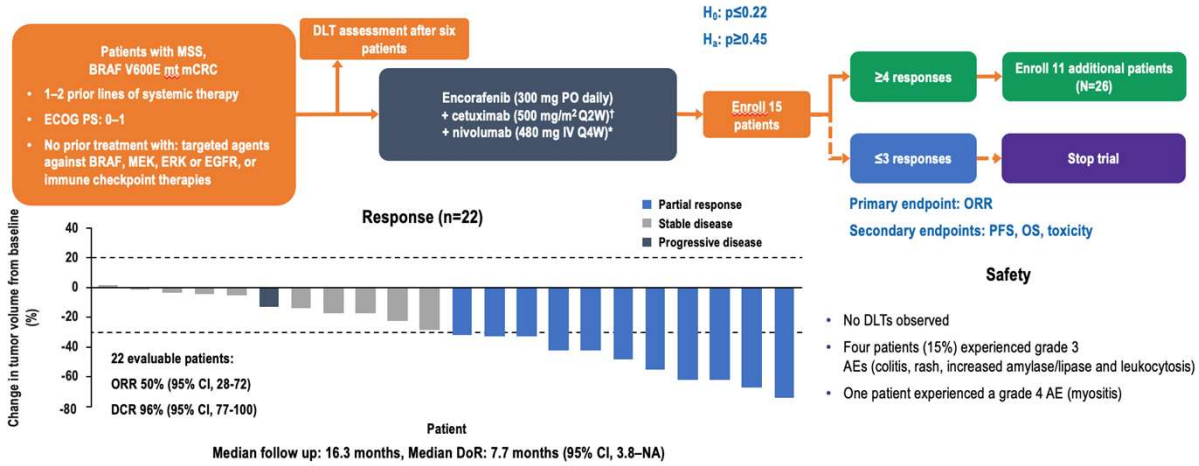
GRUPO DE TRATAMIENTO DE LOS TUMORES DIGESTIVOS

CAN WE SQUEEZE THE BEACON REGIMEN OUTCOMES?

Strategy 3: Immune modulation

STRATEGY 3: IMMUNE MODULATION

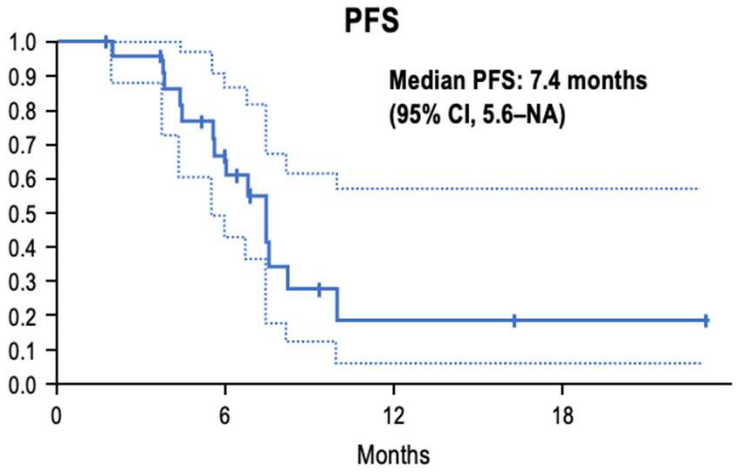
- 43% of BRAFV600E CRC can be classified as CMS1[1].
- It has been described the potential of an increased T-cell infiltration after BRAF targeted therapy in paired patient tumor biopsies and promising activity of PD-1/BRAF/MEK inhibition strategies[2].
- Furthermore, EGFR/BRAF inhibition has demonstrated to induce DNA damage, increased mutability and triggered microsatellite instability[3]. Encouraging data has been presented combining PD1-inh + BRAF/EGFR inhibitors in BRAFV600E MSS mCRC.

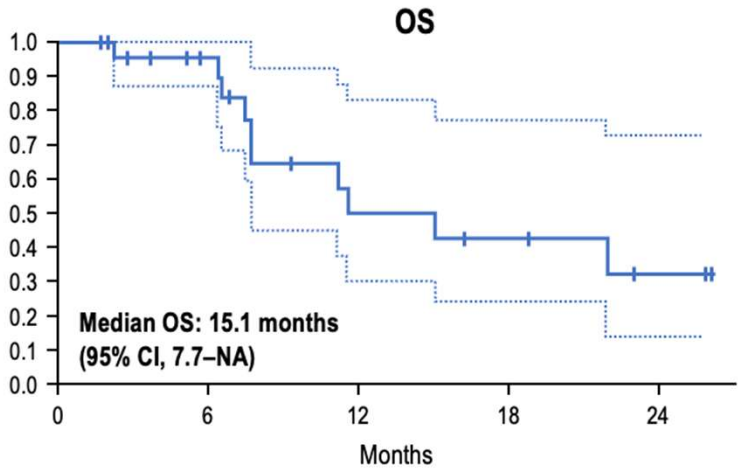


1. Guinney J et al. Nat Med 2015; 2. Corcoran R et al. Ann Oncol 2020; 3. Russo M et al. Science 2019; 3. Morris V et al. J Clin Oncol 2022

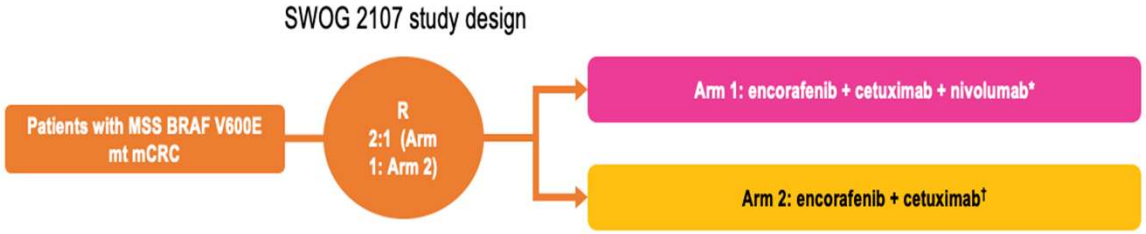
STRATEGY 3: IMMUNE MODULATION

Encorafenib + cetuximab + nivolumab* is safe/well tolerated and active for patients with MSS BRAFV600E mCRC





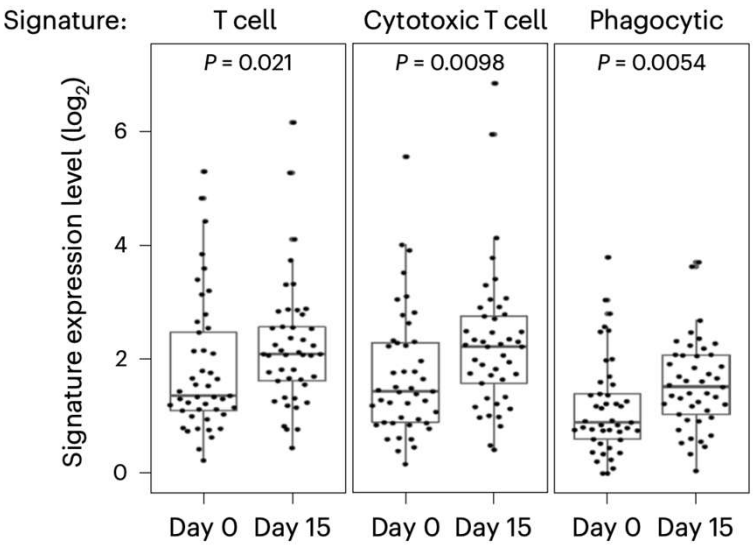
SWOG 2107 test the benefit of addition of nivolumab to encorafenib + cetuximab in patients with MSS BRAF V600E mCRC



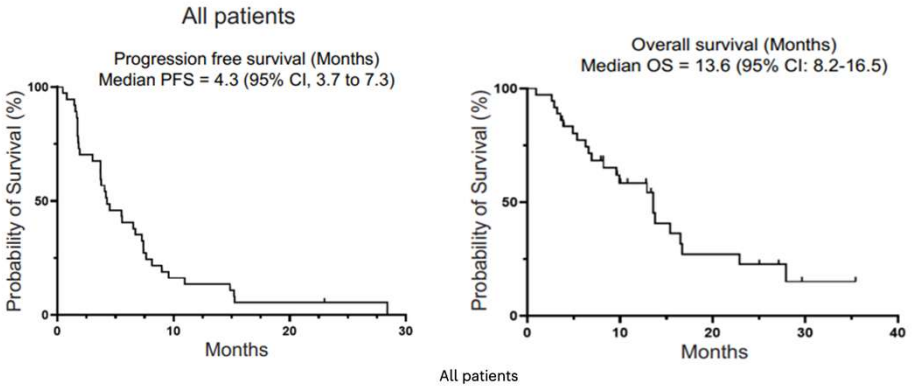
Morris V et al. ASCO GI 2022

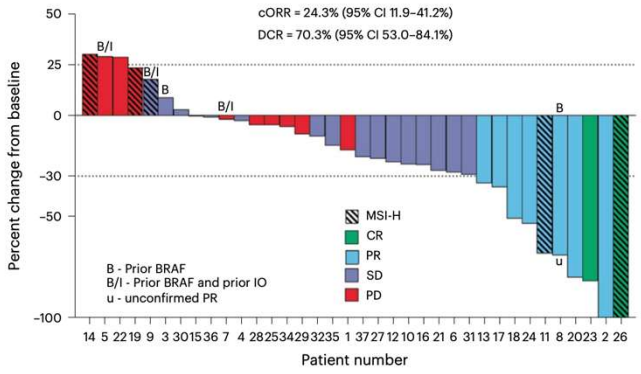
STRATEGY 3: IMMUNE MODULATION

Combined PD-1, BRAF and MEK inhibition in BRAFV600E CRC, regardless of MSS/MSI status



Potential tumour cell-intrinsic mechanism of cooperativity between MAPK inhibition and immune response



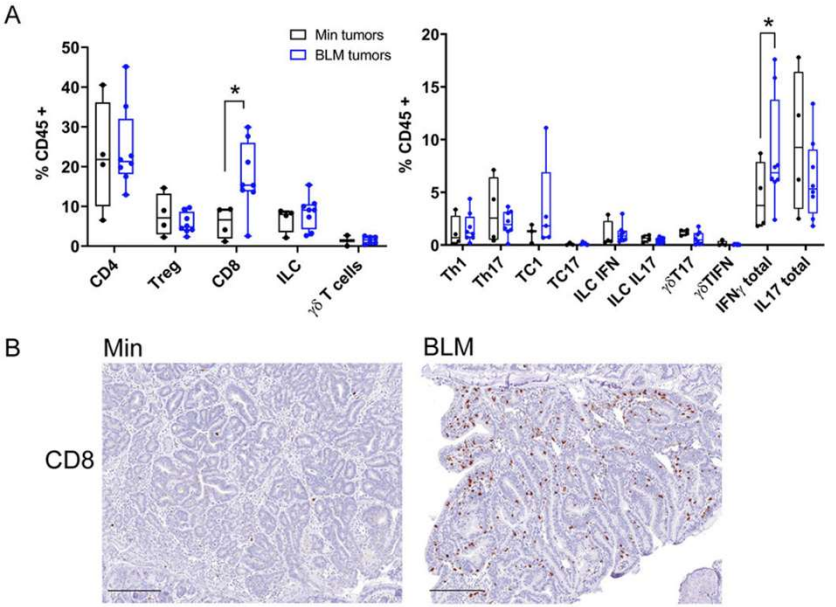


Tian J et al, Nat Med 2023

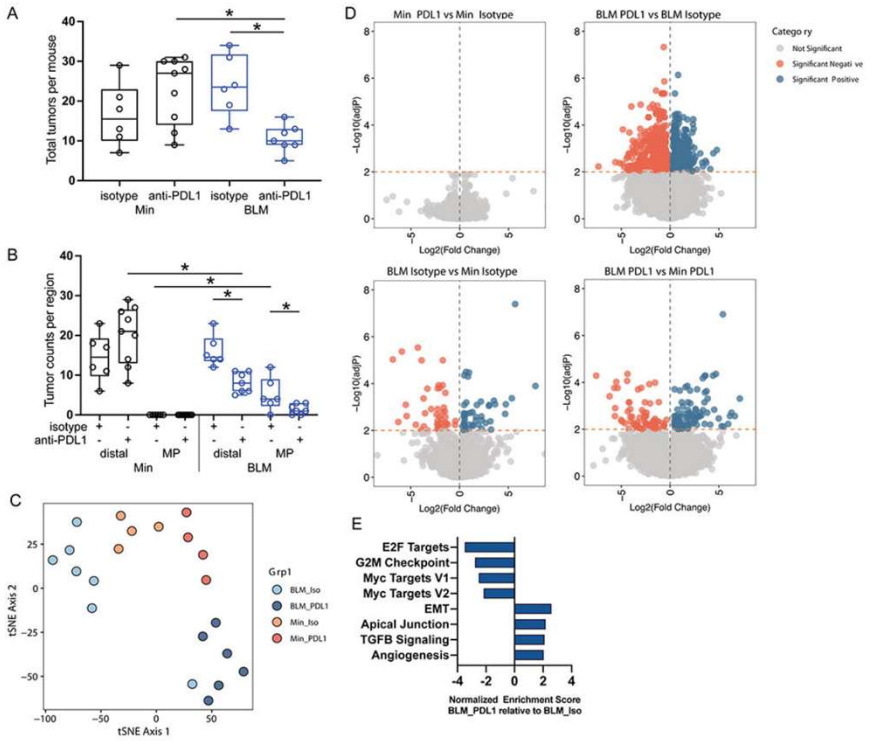
STRATEGY 3: IMMUNE MODULATION

Targeting the bacterial microbiota

Bacterial-driven inflammation and mutant BRAF expression combine to promote murine colon tumorigenesis that is sensitive to immune checkpoint therapy



Wnt-driven multiple intestinal neoplasia (MinApcΔ716/+) enterotoxigenic Bacteroides fragilis (ETBF) murine model
ETBF-colonized BRAF V600E Lgr5 CreMin (BLM) mice

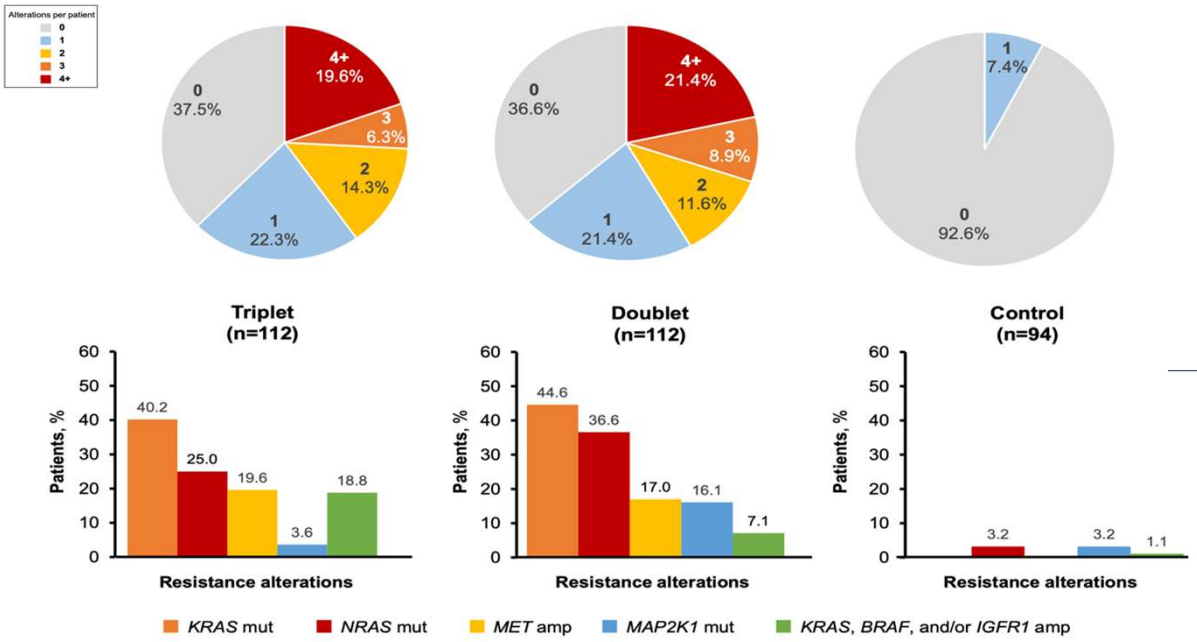


DeStefano C et al. Cancer Discov 2021

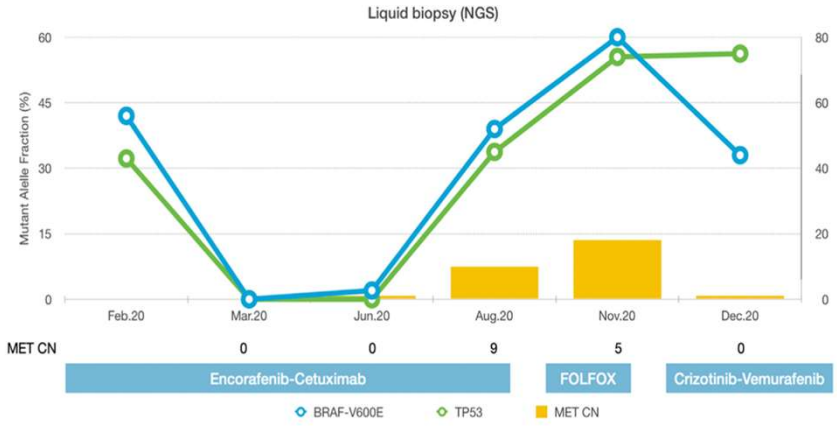
CAN WE OVERCOME RESISTANCE?

CAN WE OVERCOME RESISTANCE?

BEACON study: Key Acquired Resistance Alterations in ctDNA



Almost 60% of the patients treated with BRAF inhibitor presented a genomic acquired mechanism of resistance

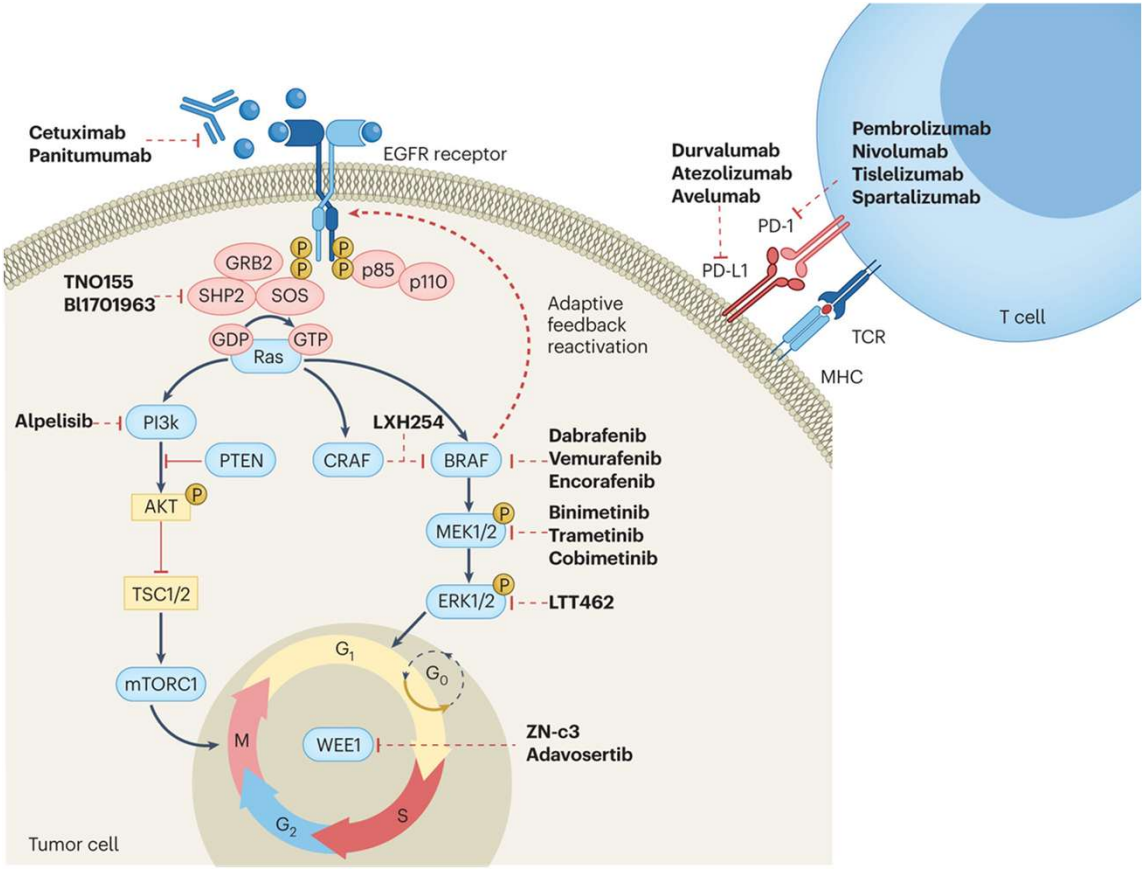


There is a window-of-opportunity to target specific molecular subtypes upon progression

Kopetz S et al, ESMO 2022, Nat Med 2024; Ros J et al. Eur J Cancer 2022

CAN WE OVERCOME RESISTANCE?

New targets and drugs



Elez E et al. Nat Med 2023

ANTI-EGFR THERAPIES IN mCRC

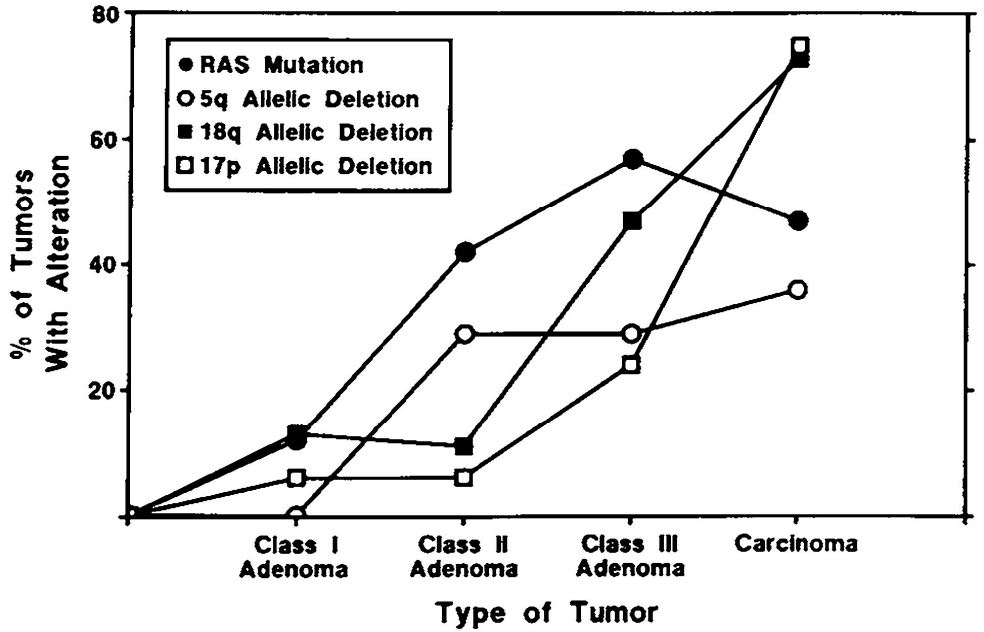
LESSONS THAT SHOULD HAVE BEEN LEARNED IN CRC

Genetic alterations during colorectal-tumour development

Table 1. *Ras*-Gene Mutations in Colorectal Tumors.

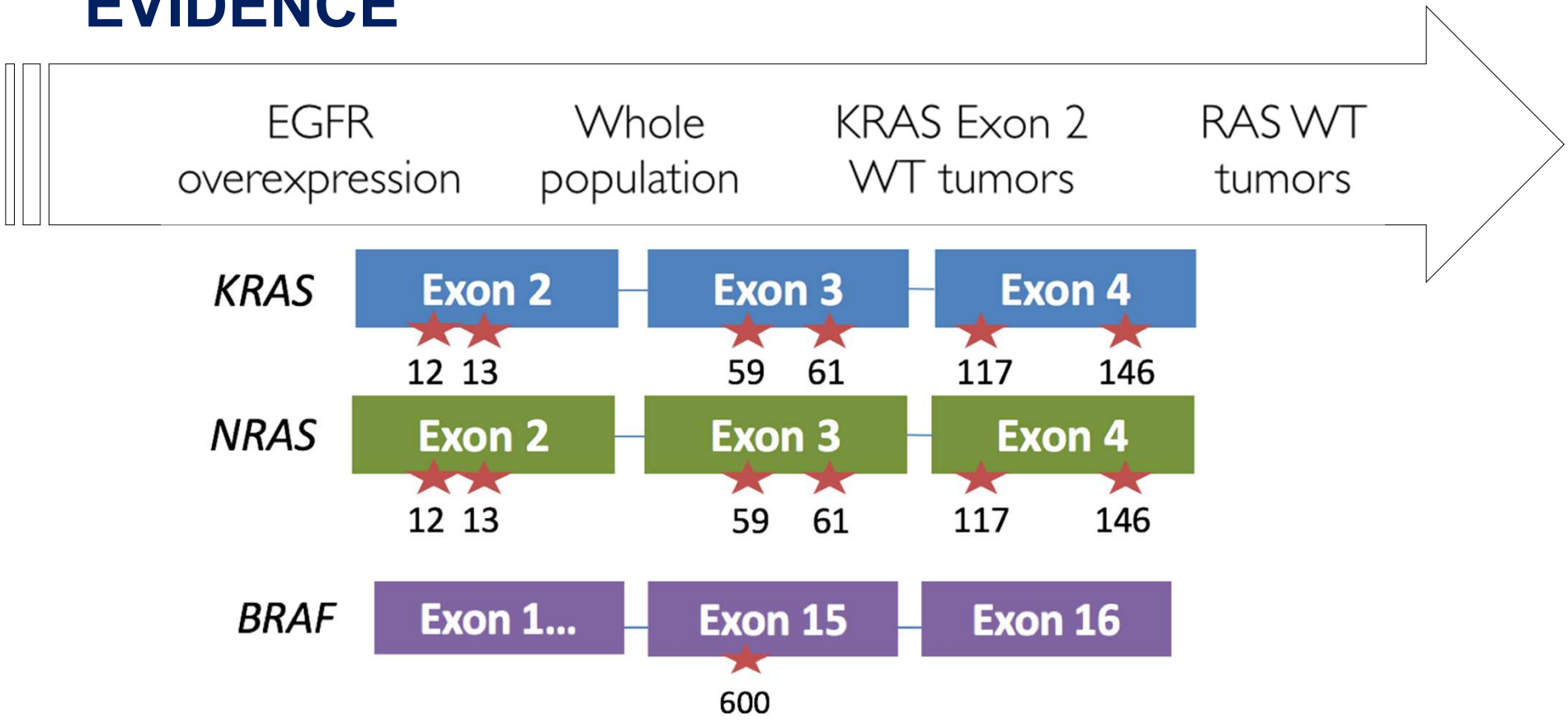
Gene	Codon	Mutation*	Class I Adenomas	Class II Adenomas	Class III Adenomas	Carcinomas
			number of tumors with mutation			
K-*ras*	12	GGT–GAT GLY–ASP	2	3	3	11
K-*ras*	12	GGT–AGT GLY–SER	1	0	1	5
K-*ras*	12	GGT–TGT GLY–CYS	0	0	1	6
K-*ras*	12	GGT–GCT GLY–ALA	0	0	2	2
K-*ras*	12	GGT–GTT GLY–VAL	1	0	3	6
K-*ras*	13	GGC–GAC GLY–ASP	1	4	1	7
K-*ras*	61	CAA–CAC GLN–HIS	0	0	1	1
N-*ras*	12	GGT–TGT GLY–CYS	0	1	0	1
N-*ras*	13	GGT–GAT GLY–ASP	0	0	0	1
N-*ras*	13	GGT–CGT GLY–ARG	0	0	0	1
N-*ras*	61	CAA–CGA GLN–ARG	0	0	0	2
Total no. of tumors with mutation			5	8	12	43
Tumors without mutation			35	11	9	49
Percent of tumors with mutation			12	42	57	47

*For each mutation, the nucleotide (top line) and amino acid (bottom line) sequence of the codon present in the corresponding proto-oncogene is listed on the left, and the sequence present in the tumor is listed on the right.



Volgestein B et al. New Engl J Med 1988

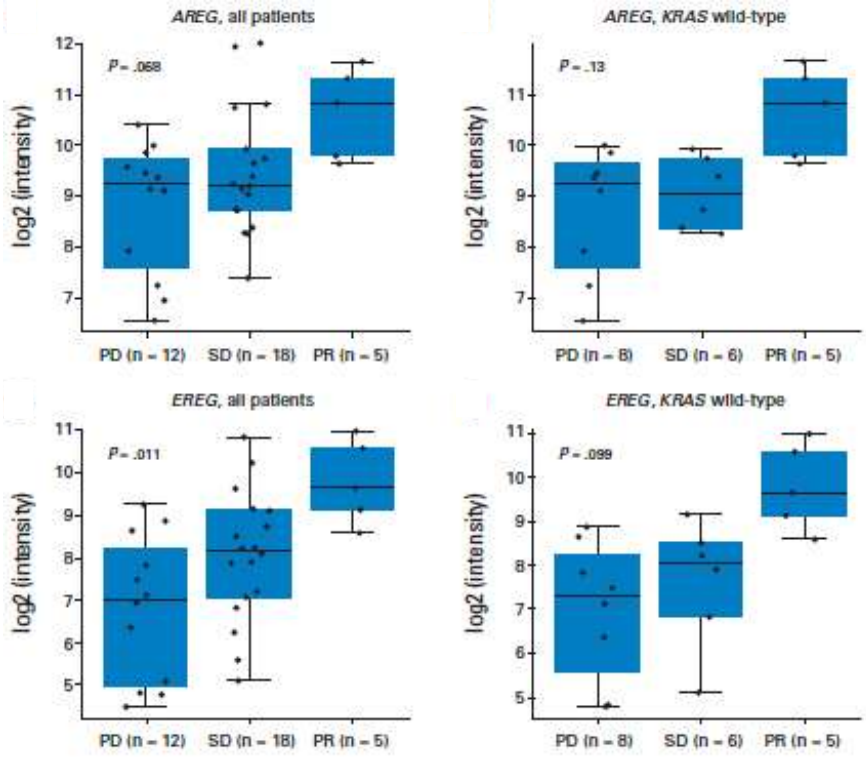
THE RETROSPECTIVE STORY OF ANTI-EGFR ACTIVITY EVIDENCE

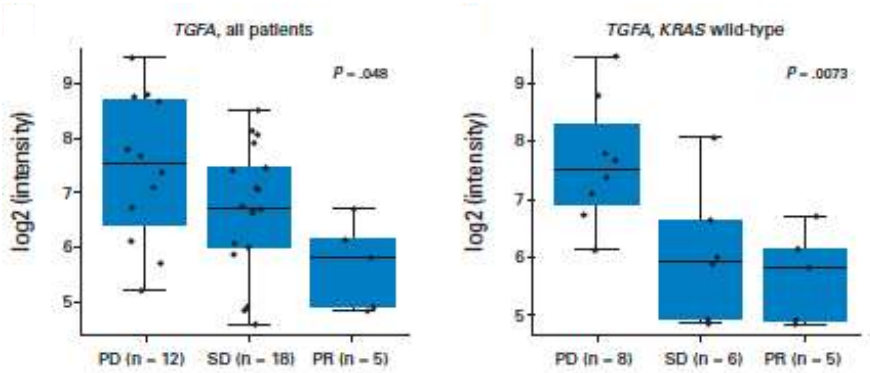


Khambata-Ford S et al J Clin Oncol 2007; Benvenuti S et al. Cancer Res 2007; Tabernero J et al. J Clin Oncol 2010; Van Cutsem E et al. J Clin Oncol 2015; Douillard JY, et al. N Engl J Med 2013

CETUXIMAB: BIOMARKERS OF RESPONSE BEYOND RAS

Pharmacodynamic evaluation: RNA expresión profiling in tumours

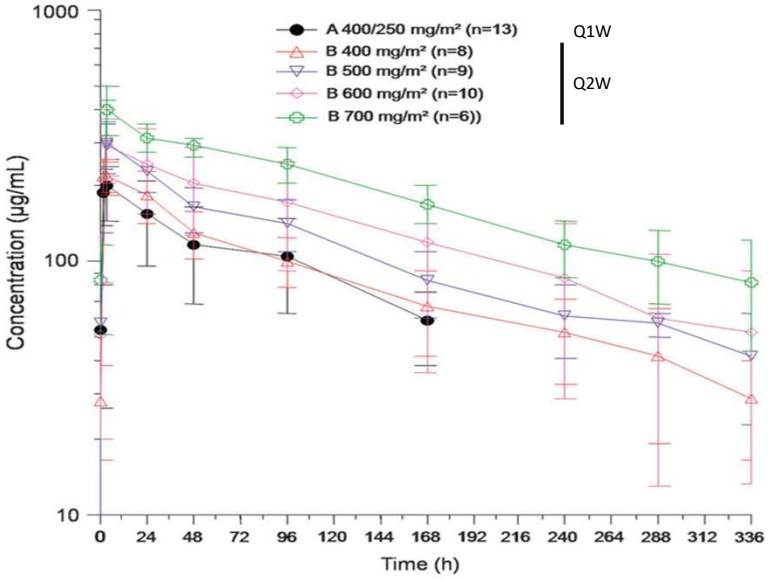




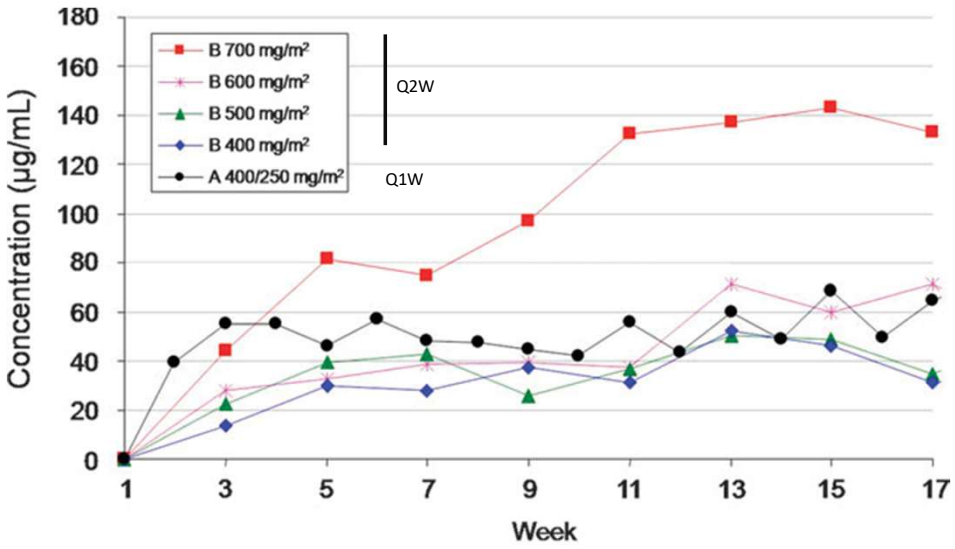
Tabernero J et al. J Clin Oncol 2010

CETUXIMAB: Q1W VS Q2W

Pharmacokinetic evaluation



Mean (+/- standard deviation) serum cetuximab concentrations at W5



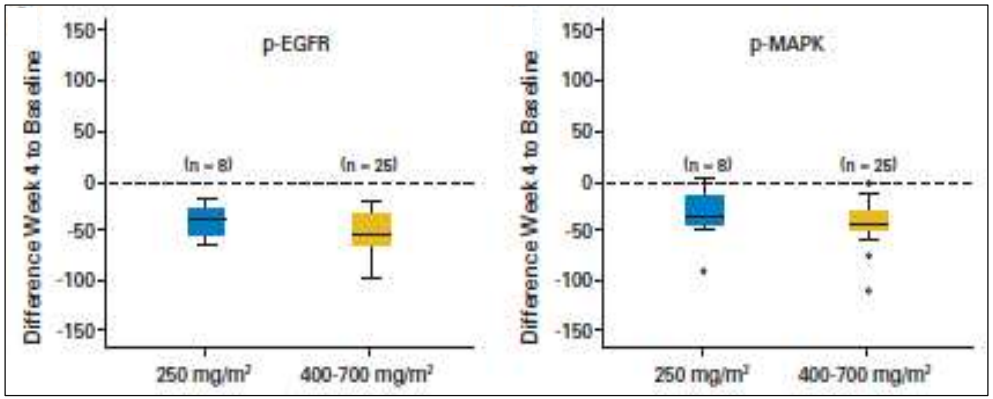
Median serum cetuximab trough concentrations

Tabernero J et al. Ann Oncol 2010

CETUXIMAB: Q1W VS Q2W

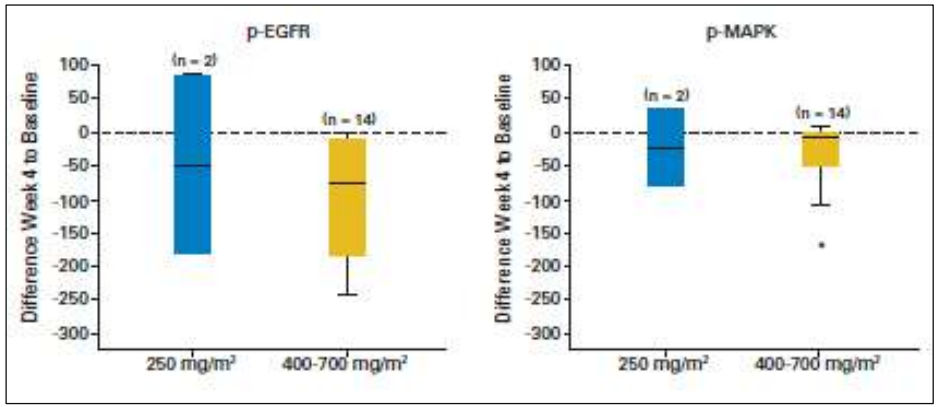
Pharmacodynamic evaluation

SKIN



Q1W Q2W Q1W Q2W

TUMOUR



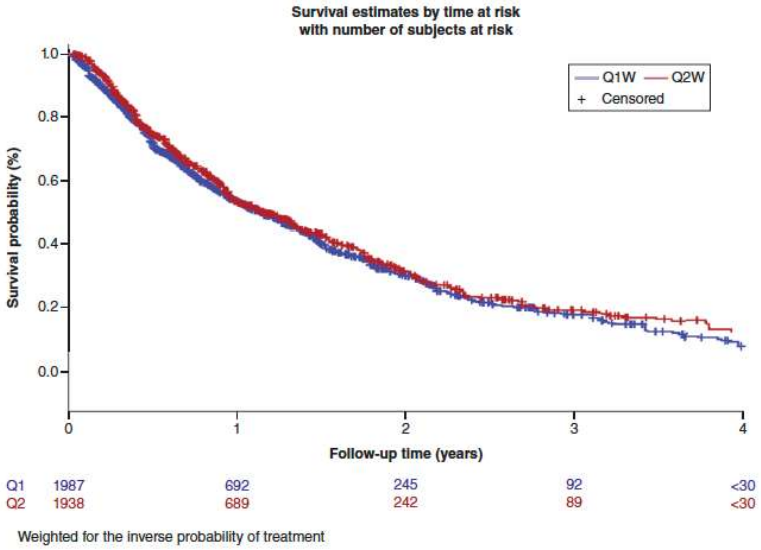
Q1W Q2W Q1W Q2W

Tabernero J et al. J Clin Oncol 2010

CETUXIMAB: Q1W VS Q2W

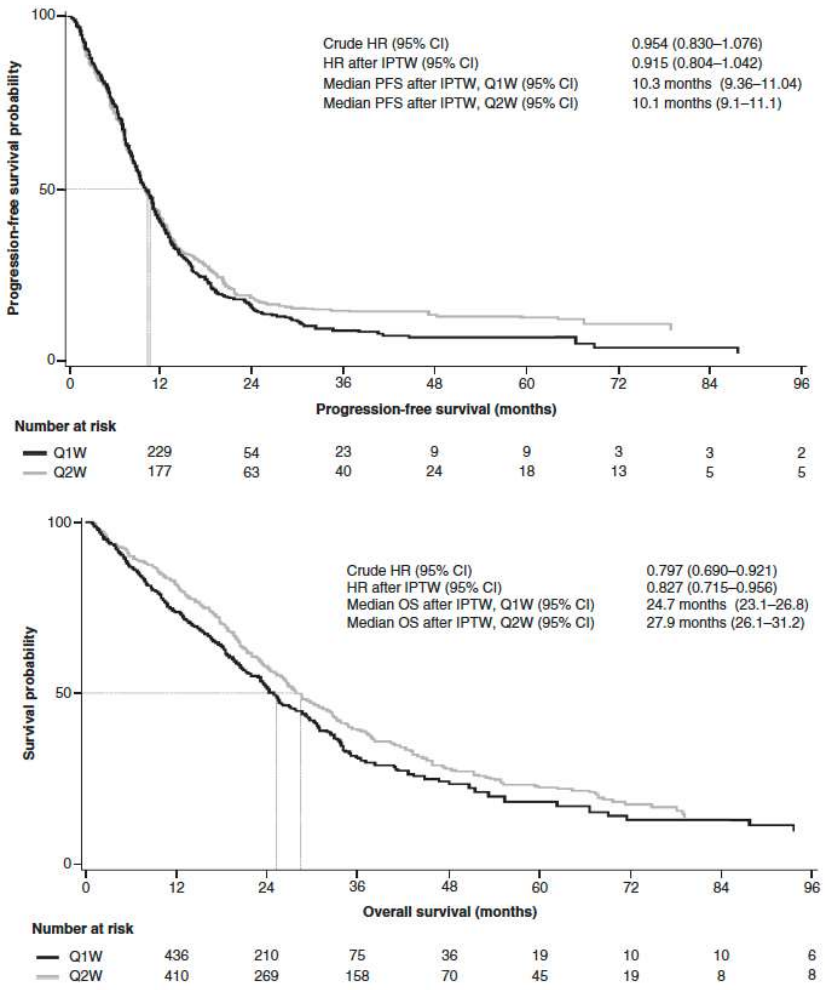
RWD

QUICK study



Weighted for the inverse probability of treatment

PADIS study



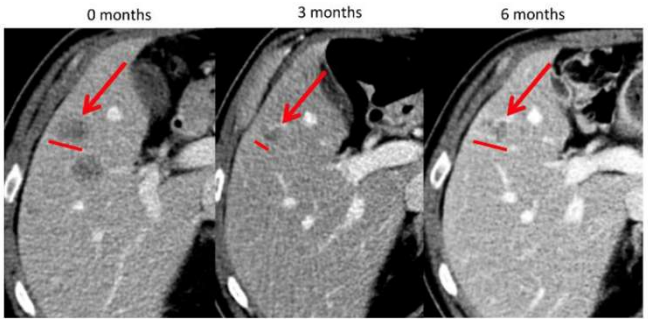
Kasper S et al. Eur J Cancer 2021; Lamy FX et al. J Comp Eff Res 2020; Bokemeyer K et al. Future Oncol 2023

A GLIMPSE INTO THE FUTURE

THE POTENTIAL OF RADIOMICS

Delta-radiomics predicts CRC liver metastases response to FOLFOX

LESION	BASELINE (mm)	3 months (mm)	6 months (mm)	10 months (mm)	Real class	Predicted class
1	18	5	5	0	R+ (CR)	R+
2	17	5	6	14	R+	R+
3	15	5	16	21	R-	R-
4	23	10	10	19	R+	R+
5	16	7	10	18	R+	R+
6	17	8	10	14	R+	R+



The algorithm correctly classified liver metastases that responded to therapy for 10 mo and classified a liver lesion (lesion 3) that showed a PD after 6 mo

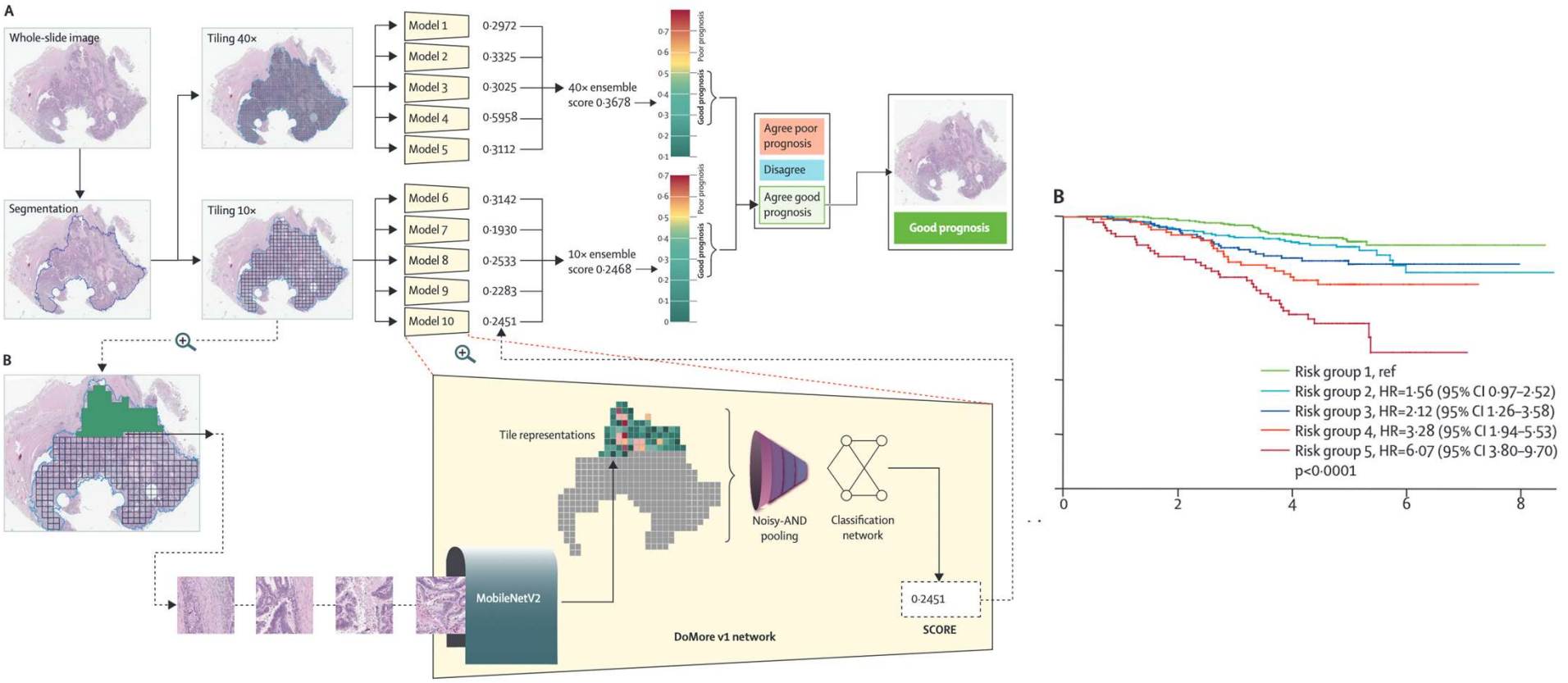
Radiomics and molecular biomarker identify 99% responders, 100% non-responders in mCRC

Study Included, Signature and Regimens		Performance Estimates	References
Training sets	*n*	*AUC, 95% C.I.*	
Giannini (2022), radiomics signature and chemotherapy	172	0.99, 95% C.I. 0.97–1.00	[75]
Nakanishi (2021), radiomics signature and chemotherapy	94	0.851, 95% C.I. 0.771–0.93	[79]
Wei (2021), radiomics signature and chemotherapy	144	0.935, 95% C.I. 0.897–0.973	[80]
Dercle (2020), radiomics signature and chemotherapy	78	0.75, 95% C.I. 0.63–0.85	[87]
Dercle (2020), radiomics signature and targeted therapy	78	0.83, 95% C.I. 0.75–0.92	[87]
Maaref (2020), radiomics signature and targeted therapy	162	0.83, 95% C.I. 0.78–0.87	[86]
Validation sets		*AUC, 95% C.I.*	
Giannini (2022), radiomics signature and chemotherapy	70	0.93, 95% C.I. 0.87–0.96	[75]
Nakanishi (2022), radiomics signature and chemotherapy	32	0.779, 95% C.I. 0.617–0.94	[79]
Wei (2021), radiomics signature and chemotherapy	48	0.830, 95% C.I. 0.688–0.973	[80]
Lu (2020), 18-gene signature and chemotherapy (FOLFOX)	29	0.877, 95% C.I. 0.747–1.00	[101]
Lu (2020) 18-gene signature and chemotherapy (FOLFIRI)	21	0.778, 95% C.I. 0.575–0.979	[101]
Dercle (2020), radiomics signature and chemotherapy	51	0.59, 95% C.I. 0.44–0.72	[87]
Dercle (2020), radiomics signature and targeted therapy	38	0.80, 95% C.I. 0.69–0.94	[87]
Zhu (2020), radiomics signature and targeted therapy	79	0.849, 95% C.I. 0.737–0.926	[98]
Zhu (2020), radiomics signature and targeted therapy	73	0.833, 95% C.I. 0.695–1.00	[98]
Maaref (2020), radiomics signature and targeted therapy	40	0.88, 95% C.I. 0.85–0.94	[86]
Validation sets		*HR, 95% C.I.*	
Lu (2020), *MLK1*-gene signature and chemotherapy (FOLFOX)	29	0.358, 95% C.I. 0.178–0.717	[101]
Lu (2020), *CCDC124*-gene signature and chemotherapy (FOLFOX)	29	0.563, 95% C.I. 336–0.943	[101]
Lu (2021), radiomics learning models and targeted therapy	526	0.49, 95% C.I. 0.4–0.61	[85]
Abraham (2021), 67-gene signature and targeted therapy	103	0.483, 95% C.I. 0.270–0.864	[99]
Abraham (2021), 67-gene signature and targeted therapy	545	0.629, 95% C.I. 0.404–0.981	[99]

AI models reporting AUC and/or HR for evaluating predictive response or OS included in the metanalysis

Giannini V et al, Cancers 2022, Russo V et al, Cancers 2022

THE POTENTIAL OF PATHOMICS



Skrede OJ et al. Lancet 2020

THE GOAL: TRANSLATIONAL MEDICINE TO ACHIEVE P4 MEDICINE (PREDICTIVE, PERSONALIZED, PREVENTIVE, PARTICIPATIVE)

To develop extremely sensitive & robust prognostic/predictive biomarkers at a single patient level

TECHNICAL VALIDATION

CLINICAL UTILITY

FEASIBILITY

Precision Medicine ensures delivery of the right intervention to the right patient at the right time

Auffray C, Hood L, Biotechnol J 2012

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