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

DESAFÍOS Y AVANCES EN EL TRATAMIENTO DEL CÁNCER COLORRECTAL METASTÁSICO BRAF MUTADO

XXXIII SIMPOSIO INTERNACIONAL TTD
OVIEDO. 10, 11 y 12 DE DICIEMBRE DE 2025

Eduardo Polo Marqués

Hospital Universitario Miguel Servet. Zaragoza.

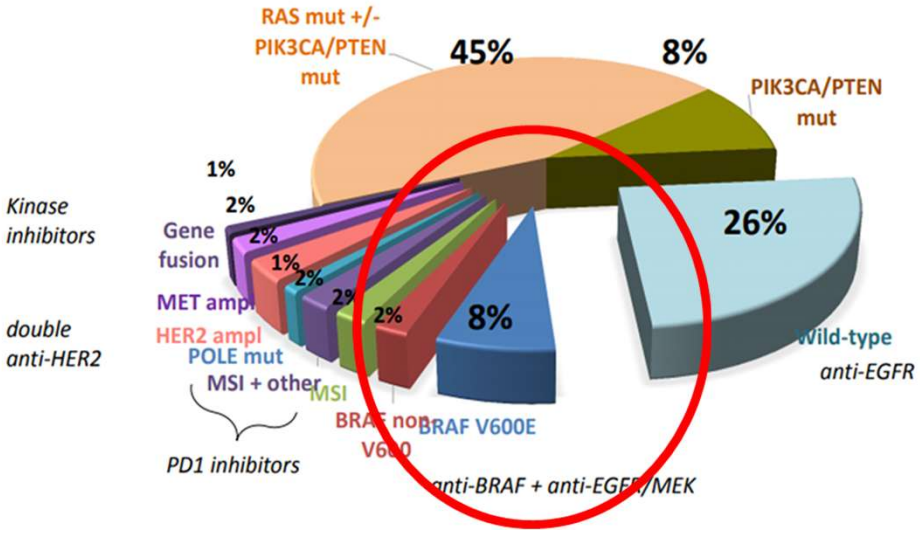
TTD

Disclosure information

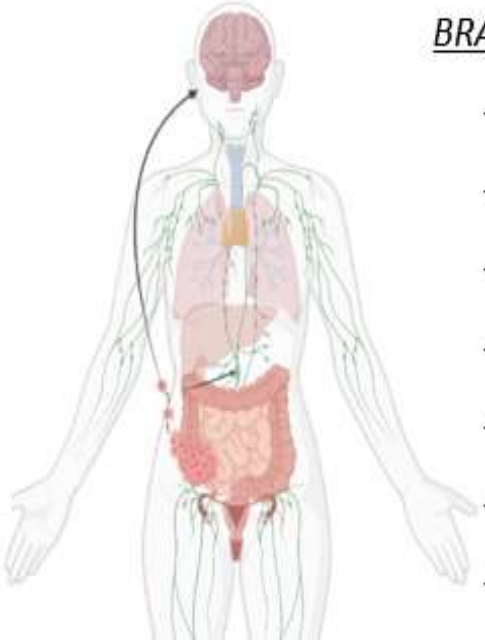
- Employment: SALUD ARAGON, Hospital Universitario Miguel Servet. Zaragoza. Spain
- Consultant or Advisory Role or speaking: Merck, Incyte, Amgem, Takeda, Pierre Fabre, Servier.
- Accommodation expenses from: Servier, Amgem,Merck.

ESCENARIO CLINICO

Genomic markers in metastatic CRC



Clinical and molecular features:



BRAF-V600E mutation clinical picture:

- Low prevalent mutation (≃12%)
- Old females
- Right-sided
- High-grade, mucinous tumors
- Co-occurrence with MSI (30%),
- CpG island methylator phenotype
- Nodal, brain and peritoneal spread

Frequency of *BRAF* mutations in human cancers

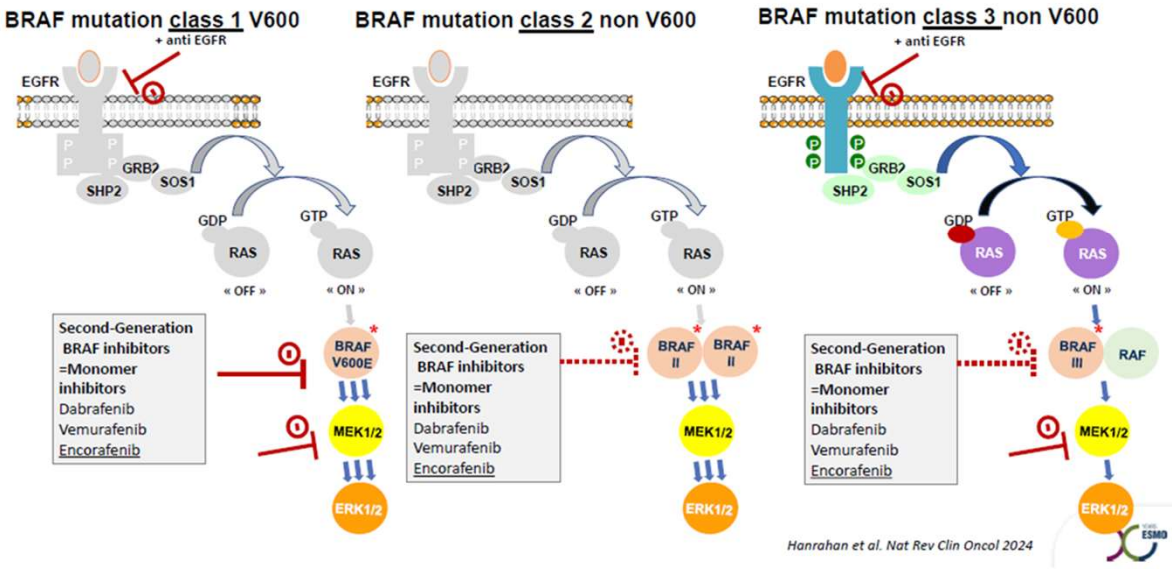
Relative prevalence of BRAF mutation by type and by cancer type.

		BRAF/ total N	Class 1, 2 , 3 / ALL BRAF		
Cancer types	**N of tumors sequenced**	**BRAF (ALL)**	**CLASS 1**	**CLASS 2**	**CLASS 3**
Melanoma	3203	1271 **39,7%**	985 **77,5%**	160 **12,5%**	101 **7,9%**
Thyroid carcinoma	496	165	161	4	0
Multiple myeloma	39	6	3	1	2
Small intestinal malignancies	742	66	11	18	33
Colorectal adenocarcinoma	14,680	1280 **8,7%**	1012 **79,06%**	80 **6,25%**	171 **13,35%**
Cancer of unknown primary	2894	120	68	22	25
Non-small cell lung cancer	18,944	772 **4,07%**	237 **30,7%**	264 **34,2%**	237 **30,7%**

Owsley J et al., Prevalence of class I-III BRAF mutations among 114,662 cancer patients in a large genomic database Med (Maywood). 2021 Jan;246(1):31-39.

BRAF inhibitors

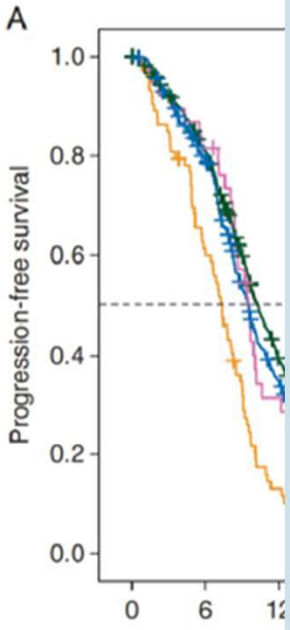
3 classes of BRAF mutations



FACTOR PRONOSTICO DESFAVORABLE

Prognostic Im

- Pooled analysis of 5

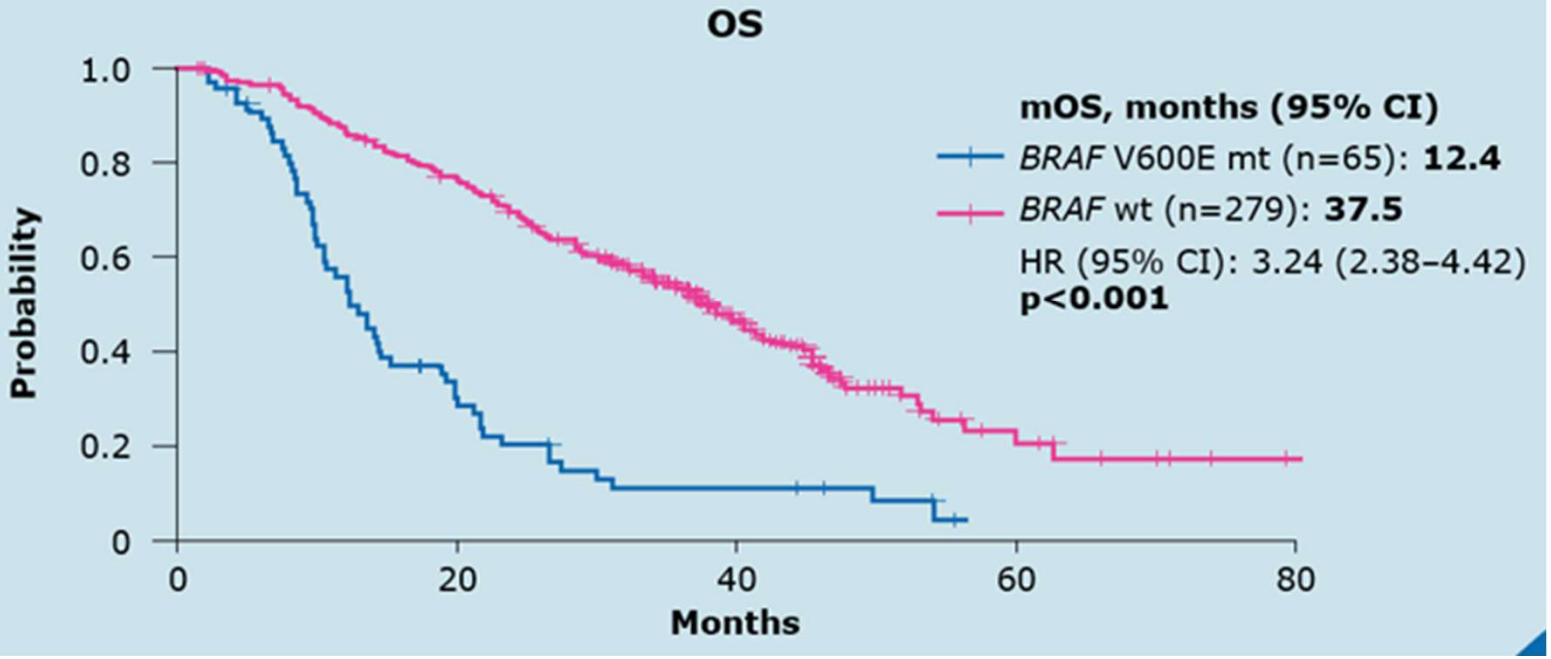


Modest DP, *et al. Ann Oncol* 2016:27 (

BRAF mt mCRC is associated with poor survival[1]

Multicenter, prospective, observational J-BROS study

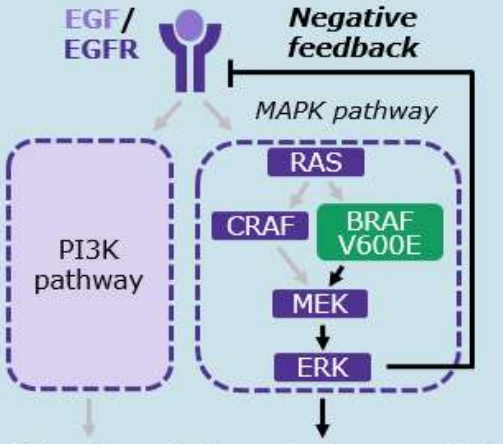
Patients underwent 1L systemic CT-based therapy according to investigator's choice (the majority received CT + anti-EGFR agent or bevacizumab)[1]



The rationale of combining anti-EGFR agents with BRAF inhibitors is to prevent feedback activation[1,2]

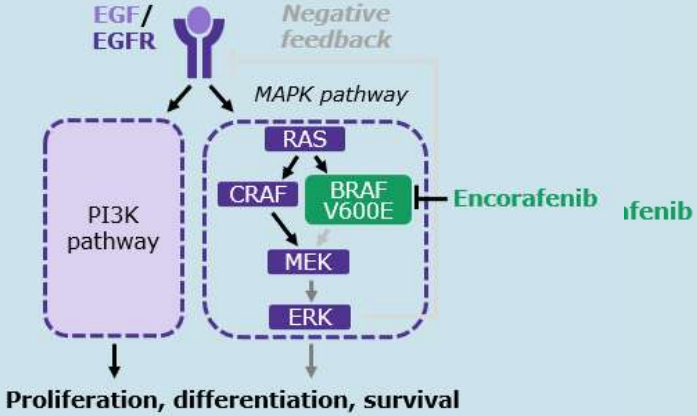
BRAF inhibition alone has limited activity in *BRAF* mt mCRC because of pathway reactivation though EGFR signaling[2]

1. Mutated *BRAF*



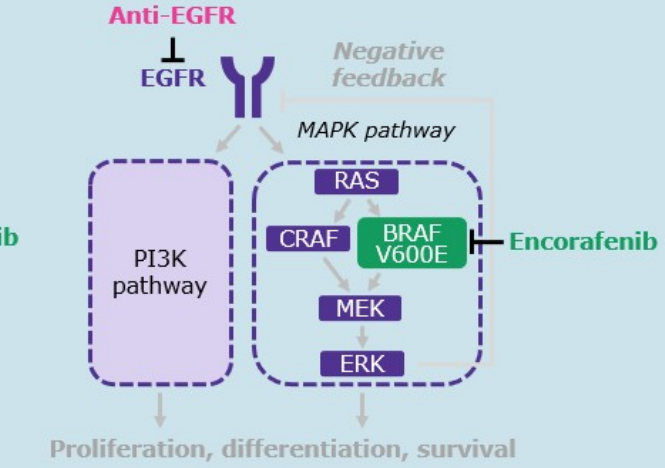
Persistent MAPK signaling

2. BRAF V600E mt inhibited



Negative feedback lost, EGFR signaling activated

3. EGFR and BRAF V600E mt inhibited



EGFR signaling disrupted

BEACON CRC: Study design

Phase III, randomised, international open-label study of encorafenib + cetuximab ± binimetinib vs investigator's choice of FOLFIRI + cetuximab or irinotecan + cetuximab in patients with *BRAF*^{V600E}-mutant mCRC[1–3]

Phase III (N=665)[2,3]

Safety lead-in (N=30)[1]

Encorafenib
300 mg PO daily

Binimetinib
45 mg PO BID

Cetuximab
Standard weekly dose*

R
1:1:1†

- **Encorafenib + binimetinib + cetuximab**‡ (n=224)
- **Encorafenib + cetuximab** (n=220)
- **Control**¶ (Investigator's choice; n=221)

Primary endpoints[2,3]

Triplet vs control
OS
ORR per RECIST v1.1 by BICR§

Key secondary endpoints[2,3]

Doublet vs control
OS
All randomised patients
PFS
DoR
Safety

BEACON CCR

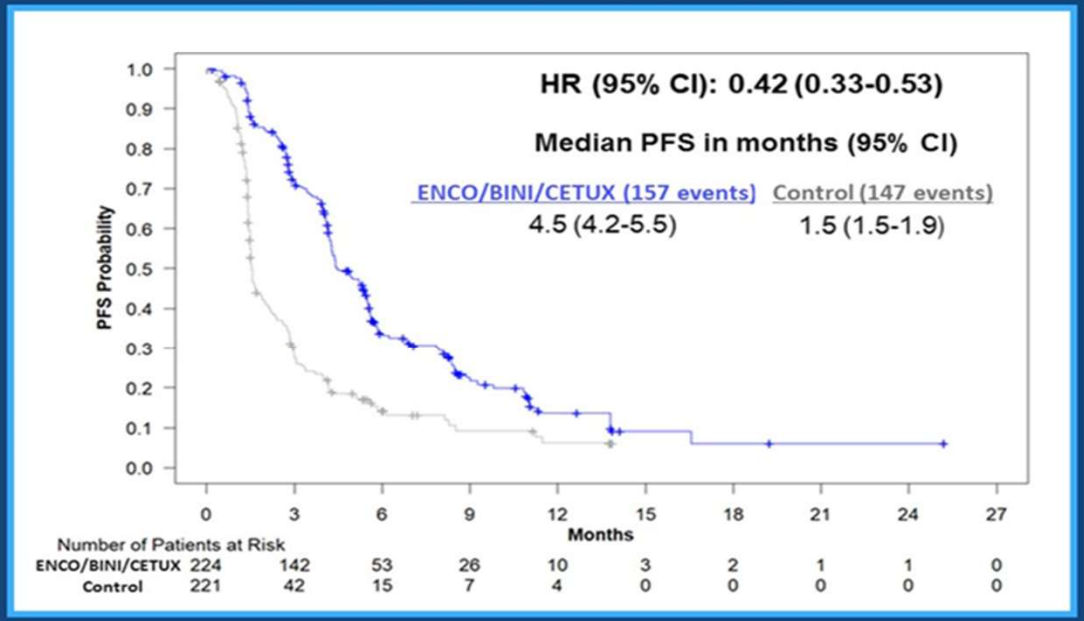
XXXIII SIMPOSIO INTERNACIONAL / INTERNATIONAL SYMPOSIUM
11 - 12 DE DICIEMBRE DE 2025
OVIEDO

Objective Response Rate (First 331 Randomized Patients)

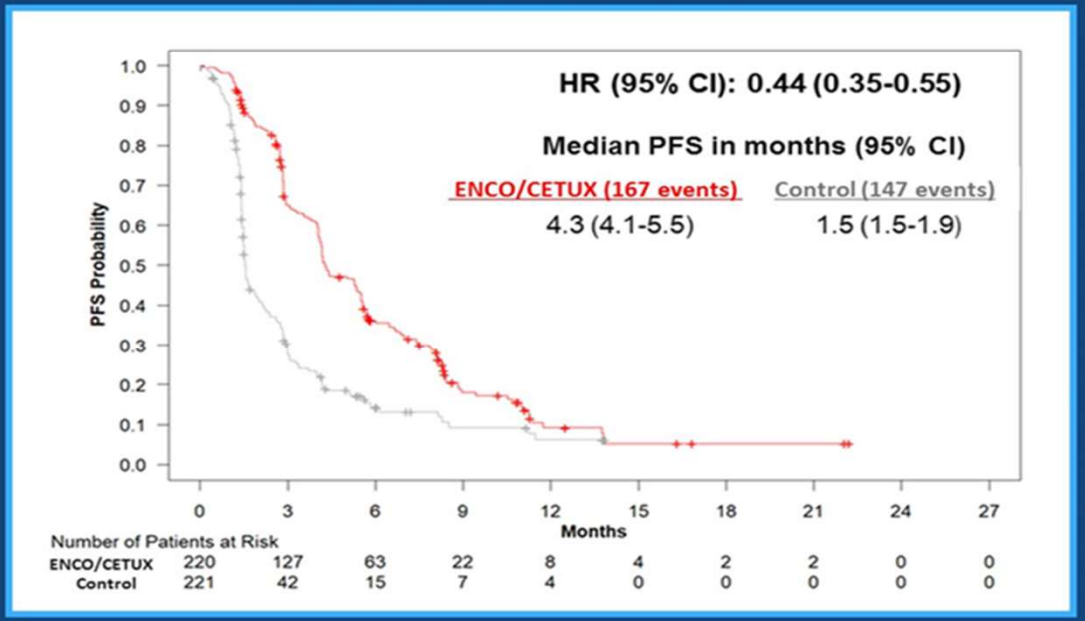
Confirmed Response by blinded central review	ENCO/BINI/CETUX N=111	ENCO/CETUX N=113	Control N=107
Objective Response Rate	**26%**	**20%**	**2%**
95% (CI)	(18%, 35%)	(13%, 29%)	(<1%, 7%)
p-value vs. Control	<0.0001	<0.0001	

Updated Progression Free Survival*

ENCO/BINI/CETUX vs Control



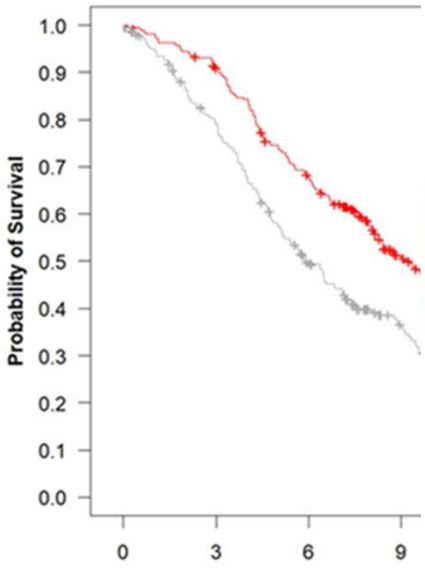
ENCO/CETUX vs Control



BEACON CCR

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

Updated Overall Survival: ENCO/CETUX vs Control



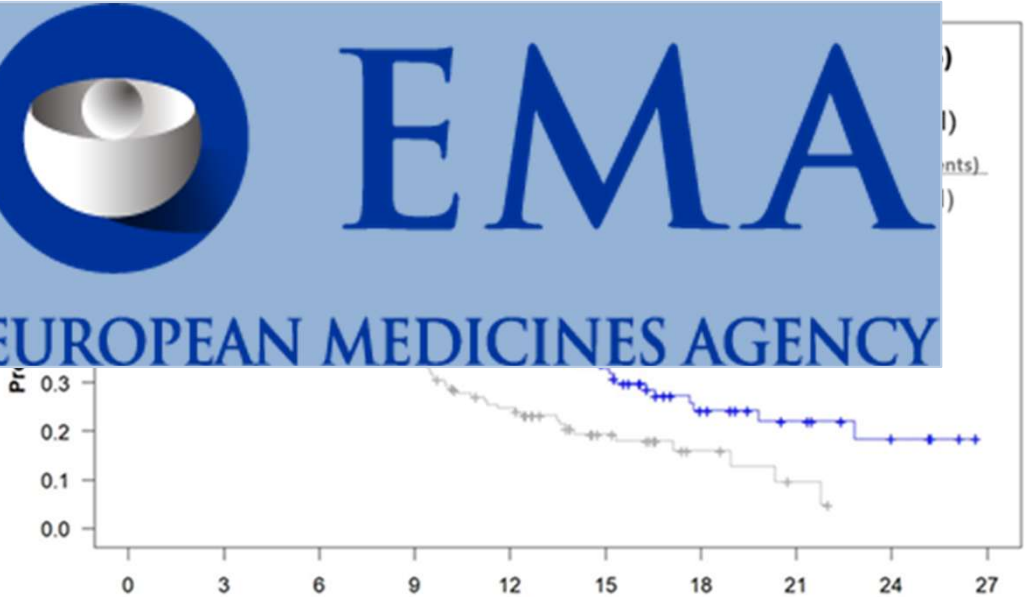
FDA APPROVED

Months

Number of Patients at Risk										
ENCO/CETUX	220	197	143	83	47	28	13	7	2	0
Control	221	166	98	54	33	15	6	2	0	0

Updated Overall Survival: ENCO/BINI/CETUX vs Control

EMA
EUROPEAN MEDICINES AGENCY

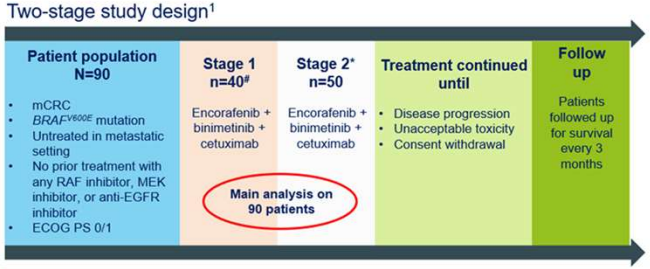


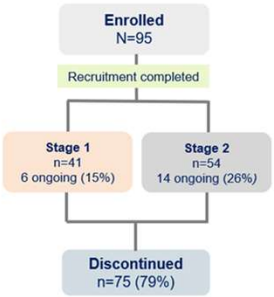
Number of Patients at Risk										
ENCO/BINI/CETUX	224	198	157	89	56	33	15	9	4	0
Control	221	166	98	54	33	15	6	2	0	0

Moving targeted therapy to the first line:

ANCHOR CRC: Phase II study in 1L *BRAF*^{V600E}-mutant mCRC

Two-stage study design[1]





Primary objective and endpoint: cORR (investigator-assessed)
H0 rejection if lower limit of the 95% CI for cORR ≥30% (≥37 confirmed responses in 90 patients)
Secondary endpoints: PFS, OS, safety, QoL, PK

TRIBE trial: FOLFIRI-BVZ vs FOLFOXIRI-BVZ

	Overall survival			Progression-free survival			Best response		
	Median (months)	Hazard ratio	p value	Median (months)	Hazard ratio	p value	Overall response	Odds ratio	p value
Intention-to-treat population									
FOLFIRI plus bevacizumab (n=256)	25·8 (22·5–29·1)	0·80 (0·65–0·98)	0·03	9·7 (9·2–10·9)	0·77 (0·65–0·93)	0·006	139 (54%)	1·59 (1·10–2·28)	0·013
FOLFOXIRI plus bevacizumab (n=252)	29·8 (26·0–34·3)	–	–	12·3 (11·0–13·3)	–	–	164 (65%)	–	–
Extended RAS and BRAF subgroup population									
FOLFIRI plus bevacizumab (n=176)	24·9 (21·1–29·1)	0·84 (0·66–1·07)	0·16	9·8 (9·2–11·2)	0·80 (0·64–0·99)	0·042	98 (56%)	1·46 (0·94–2·26)	0·089
FOLFOXIRI plus bevacizumab (n=181)	28·6 (25·4–33·6)	–	–	12·1 (10·5–13·2)	–	–	117 (65%)	–	–
RAS and BRAF wild-type subgroup									
FOLFIRI plus bevacizumab (n=45)	33·5 (22·3–39·7)	0·77 (0·46–1·27)	0·52*	12·2 (9·5–14·4)	0·85 (0·55–1·30)	0·68*	27 (60%)	1·17 (0·50–2·75)	0·63*
FOLFOXIRI plus bevacizumab (n=48)	41·7 (30·1–53·1)	–	–	13·7 (10·1–18·1)	–	–	31 (65%)	–	–
BRAF-mutation-positive subgroup									
FOLFIRI plus bevacizumab (n=12)	10·7 (3·1–24·8)	0·54 (0·24–1·20)	–	5·5 (1·6–11·2)	0·57 (0·27–1·23)	–	5 (42%)	1·82 (0·38–8·78)	–
FOLFOXIRI plus bevacizumab (n=16)	19·0 (8·2–28·6)	–	–	7·5 (5·1–15·0)	–	–	9 (56%)	–	–
RAS-mutation-positive subgroup									
FOLFIRI plus bevacizumab (n=119)	23·9 (20·5–27·9)	0·88 (0·65–1·18)	–	9·5 (8·8–11·1)	0·78 (0·60–1·02)	–	66 (55%)	1·55 (0·91–2·62)	–
FOLFOXIRI plus bevacizumab (n=117)	27·3 (22·0–31·3)	–	–	12·0 (10·3–13·2)	–	–	77 (66%)	–	–
RAS wild-type subgroup									
FOLFIRI plus bevacizumab (n=57)	26·8 (20·5–35·9)	0·78 (0·51–1·20)	0·66†	11·0 (9·0–12·4)	0·84 (0·58–1·21)	0·77†	32 (56%)	1·28 (0·61–2·69)	0·66†
FOLFOXIRI plus bevacizumab (n=64)	37·1 (24·1–42·7)	–	–	12·8 (9·6–16·0)	–	–	40 (63%)	–	–

Targeted therapy 1st line:

ORR: 47%

mPFS: 5,8 months

mOS: 18,3 months

¿?

BRAF mutated subgroup:

ORR: 56%

mPFS: 7,5 months

mOS: 19 months

How can we optimize outcomes of targeted therapy?

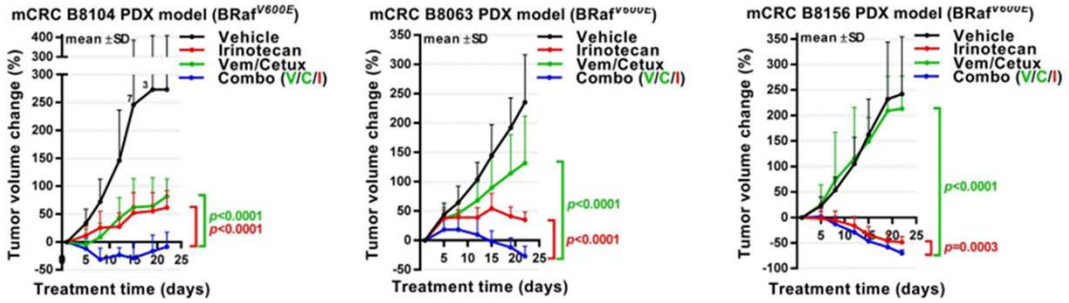
The sooner the better

Overcoming resistance

- **Combination with other agents?**
  - other targeted therapy?
  - **chemotherapy?**
  - ICI?
- Other mechanisms of targeting?

Concurrent chemotherapy may improve responses to BRAF + EGFR

PDX models from on-study biopsies from responding patients on S1406



Benefit from BRAF/EGFR	Modest benefit from BRAF/EGFR	No benefit from BRAF/EGFR
Regression with the triplet	Regression with the triplet	Regression with the triplet

Randomized Trial of Irinotecan and Cetuximab With or Without Vemurafenib in BRAF-Mutant Metastatic Colorectal Cancer (SWOG S1406) Scott Kopetz *et al. J Clin Oncol. 2020 Dec 23;39(4):285–294*

BREAKWATER TRIAL

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

BARCELONA 2024 ESMO congress

Study Design and Methods

Safety lead-in
Participants who have received ≤1 prior treatment for mCRC

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

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

Primary endpoint
- Safety (frequency of DLTs)

Secondary endpoints
- Safety (AEs, dose interruptions/ modifications/discontinuations)
- PKs
- Antitumor activity (ORR, DOR, TTR, PFS, and OS)

Inclusion criteria
- BRAF V600E-mutant mCRC (blood or tumor tissue)
- ≤1 prior systemic treatment for mCRC
- ECOG PS of 0 or 1
- No prior treatment with BRAF or EGFR inhibitors or both oxaliplatin and irinotecan
- No MSI-H or dMMR mCRC[a]

Phase 3[b]
Participants who have not received prior systemic treatment for mCRC

R 1:1:1

Arm A
EC
(n≈150)

Arm B
EC + mFOLFOX6
(n≈235)

Arm C (Control)
mFOLFOX6/FOLFOXIRI/CAPOX ± bevacizumab
(n≈235)

Primary endpoints
- PFS and ORR by BICR

Key secondary endpoint
- OS

Secondary endpoints
- ORR and PFS by investigator
- DOR and TTR by BICR and investigator
- Safety
- PROs
- Biomarkers (correlation with clinical outcomes)

Cohort 3[c]
Participants who have not received prior systemic treatment for mCRC

R 1:1

Arm D
EC + FOLFIRI
(n=68)

Arm E
FOLFIRI ± bevacizumab
(n=68)

Primary endpoint
- ORR by BICR

Key secondary endpoint
- PFS by BICR

Secondary endpoints
- OS
- PFS and ORR by investigator
- DOR and TTR by BICR and by investigator
- Safety
- PROs
- Biomarkers (correlation with clinical outcomes)

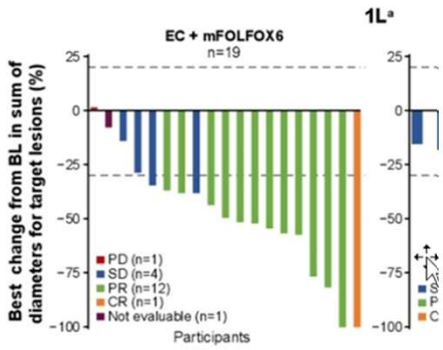
BREAKWATER ASCO 2023

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

SLI BREAKWATE

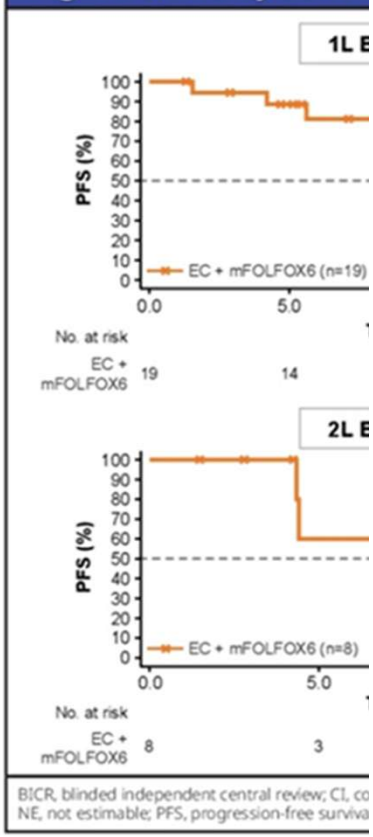
SLI BREAKWATER

Figure 2: Best Percentage Cha



[a]Only includes participants with target lesions at baseline and ≥1
BICR, blinded independent central review; BL, baseline; BOR, bes
modified fluorouracil/leucovorin/oxaliplatin; PD, progressive dise

Figure 3: PFS by BICR

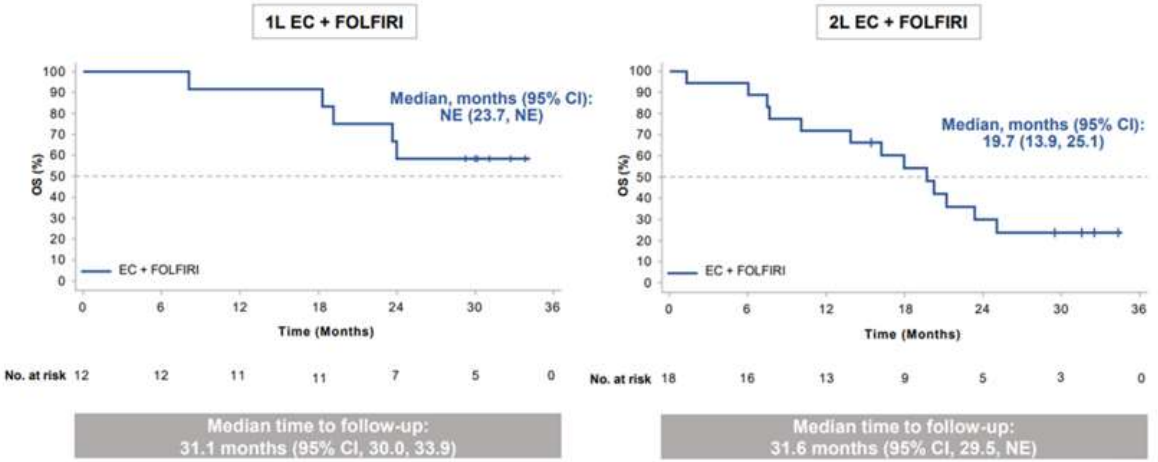


BICR, blinded independent central review; CI, co
NE, not estimable; PFS, progression-free surviva

	EC + FOLFIRI	
	1L (n=12)	2L (n=18)
Best overall response, n (%)[a,b]		
CR	2 (16.7)	1 (5.6)
PR	8 (66.7)	7 (38.9)
SD	1 (8.3)	7 (38.9)
Non-CR/non-PD	1 (8.3)	2 (11.1)
PD	0	0
Not evaluable	0	1 (5.6)[c]
ORR (CR + PR), n (%)[b]	10 (83.3)	8 (44.4)
95% CI[d]	55.2, 95.3	24.6, 66.3
Median DOR, months[b,e]	NE	12.5
95% CI[f]	12.4, NE	5.5, NE
Median PFS, months[b]	NE	12.6
95% CI[f]	13.8, NE	6.9, 18.0

Overall Survival by Line of Therapy

BARCELONA 2024 ESMO congress



Median time to follow-up:
31.1 months (95% CI, 30.0, 33.9)

Median time to follow-up:
31.6 months (95% CI, 29.5, NE)

BREAKWATER- ASCO GI 2025

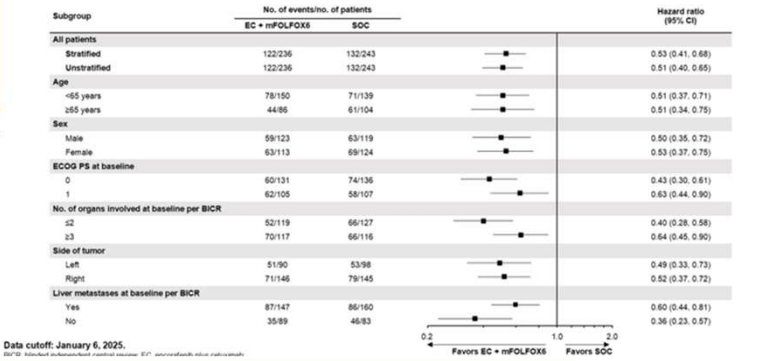
XXXIII SIMPOSIO INTERNACIONAL / INTERNATIONAL SYMPOSIUM
11 - 12 DE DICIEMBRE DE 2025

FDA U.S. FOOD & DRUG ADMINISTRATION

FDA grants accelerated approval to encorafenib with cetuximab and mFOLFOX6 for metastatic colorectal cancer with a BRAF V600E mutation

BREAKWATER ASCO 2025

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



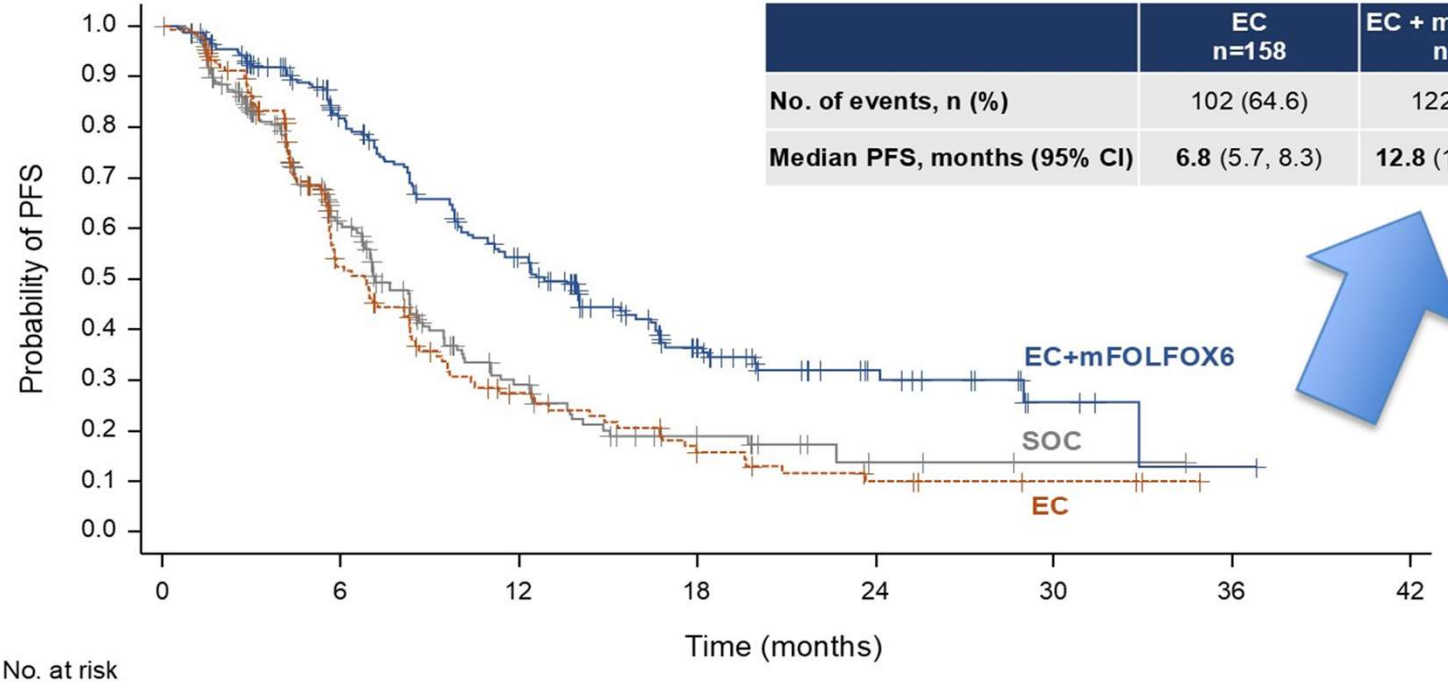
Subgroup	No. of events/no. of patients: EC + mFOLFOX6	No. of events/no. of patients: SOC	Hazard ratio (95% CI)
All patients			
Stratified	122/236	132/243	0.53 (0.41, 0.68)
Unstratified	122/236	132/243	0.51 (0.40, 0.65)
Age			
<65 years	78/150	71/139	0.51 (0.37, 0.71)
≥65 years	44/86	61/104	0.51 (0.34, 0.75)
Sex			
Male	59/123	63/119	0.50 (0.35, 0.72)
Female	63/113	69/124	0.53 (0.37, 0.75)
ECOG PS at baseline			
0	60/131	74/136	0.43 (0.30, 0.61)
1	62/105	58/107	0.63 (0.44, 0.90)
No. of organs involved at baseline per BICR			
≤2	52/119	66/127	0.40 (0.28, 0.58)
≥3	70/117	66/116	0.64 (0.45, 0.90)
Side of tumor			
Left	51/90	53/98	0.49 (0.33, 0.73)
Right	71/146	79/145	0.52 (0.37, 0.72)
Liver metastases at baseline per BICR			
Yes	87/147	86/160	0.60 (0.44, 0.81)
No	35/89	46/83	0.36 (0.23, 0.57)

Data cutoff: January 6, 2025.

Favors EC + mFOLFOX6 | Favors SOC

PFS by BICR (All Arms)

	EC n=158	EC + mFOLFOX6 n=236	SOC n=243
No. of events, n (%)	102 (64.6)	122 (51.7)	132 (54.3)
Median PFS, months (95% CI)	**6.8** (5.7, 8.3)	**12.8** (11.2, 15.9)	**7.1** (6.8, 8.5)



No. at risk							
EC	158	60	24	12	6	3	0
EC+mFOLFOX6	236	156	96	39	16	4	1
SOC	243	100	34	11	3	1	0

Data cutoff: January 6, 2025.

BREAKWATER ASCO 2025

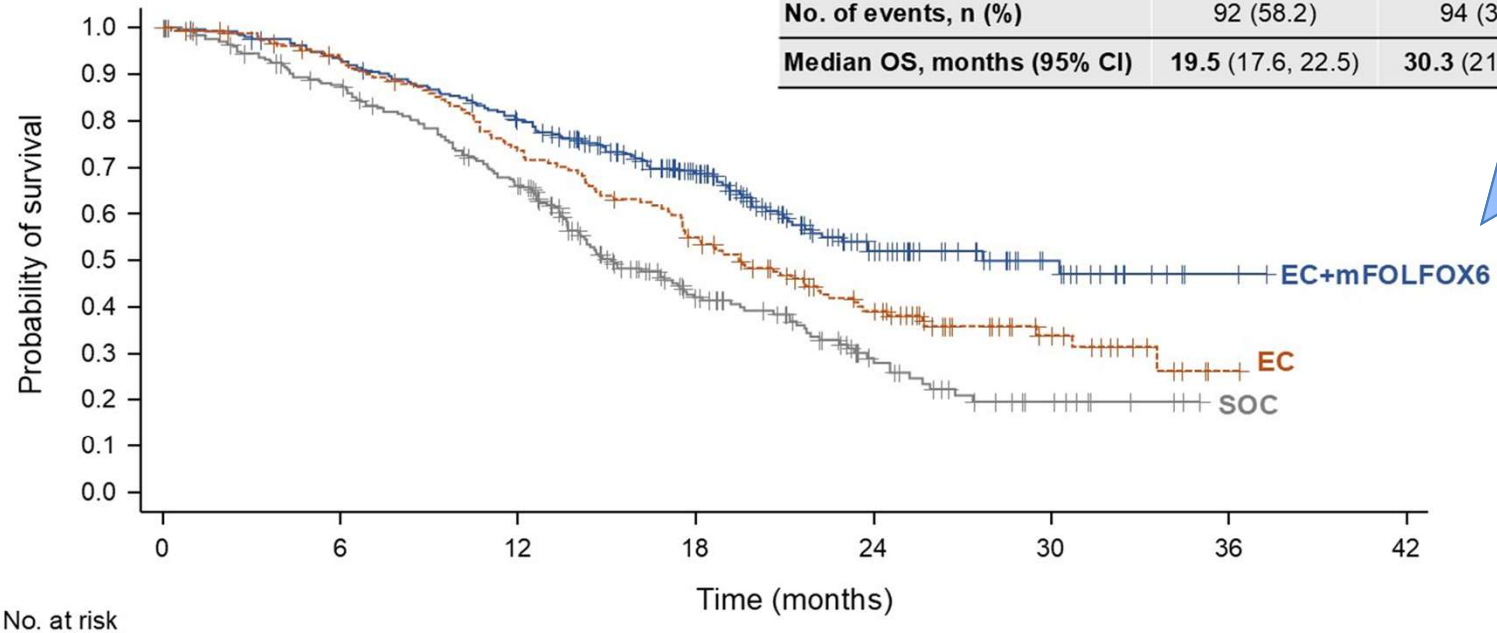
Subgroup Analysis of OS (EC + mFOLFOX6 and SOC)

Subgroup	No. of events/no. of patients: EC + mFOLFOX6	No. of events/no. of patients: SOC	Hazard ratio (95% CI)
All patients			
Stratified	94/236	148/243	0.49 (0.38, 0.63)
Unstratified	94/236	148/243	0.48 (0.37, 0.62)
Age			
<65 years	56/150	85/139	0.44 (0.31, 0.62)
≥65 years	38/86	63/104	0.54 (0.36, 0.82)
Sex			
Male	54/123	71/119	0.59 (0.42, 0.85)
Female	40/113	77/124	0.38 (0.26, 0.56)
ECOG PS at baseline			
0	42/131	76/136	0.42 (0.29, 0.62)
1	52/105	72/107	0.54 (0.38, 0.77)
No. of organs involved at baseline per BICR			
≤2	32/119	66/127	0.39 (0.25, 0.59)
≥3	62/117	82/116	0.52 (0.38, 0.73)
Side of tumor			
Left	38/90	62/98	0.48 (0.32, 0.72)
Right	56/146	86/145	0.49 (0.35, 0.68)
Liver metastases at baseline per BICR			
Yes	73/147	104/160	0.58 (0.43, 0.78)
No	21/89	44/83	0.31 (0.18, 0.52)

Data cutoff: January 6, 2025.
BICR, blinded independent central review; EC, encorafenib plus cetuximab;

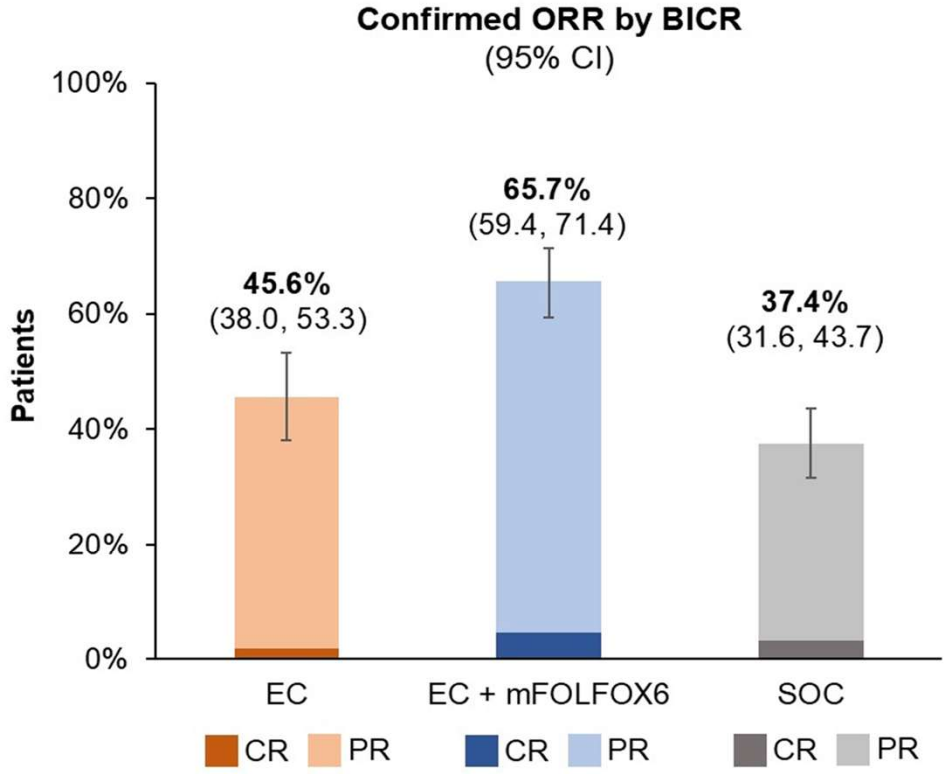
OS (All Arms)

	EC n=158	EC + mFOLFOX6 n=236	SOC n=243
No. of events, n (%)	92 (58.2)	94 (39.8)	148 (60.9)
Median OS, months (95% CI)	**19.5** (17.6, 22.5)	**30.3** (21.7, NE)	**15.1** (13.7, 17.7)

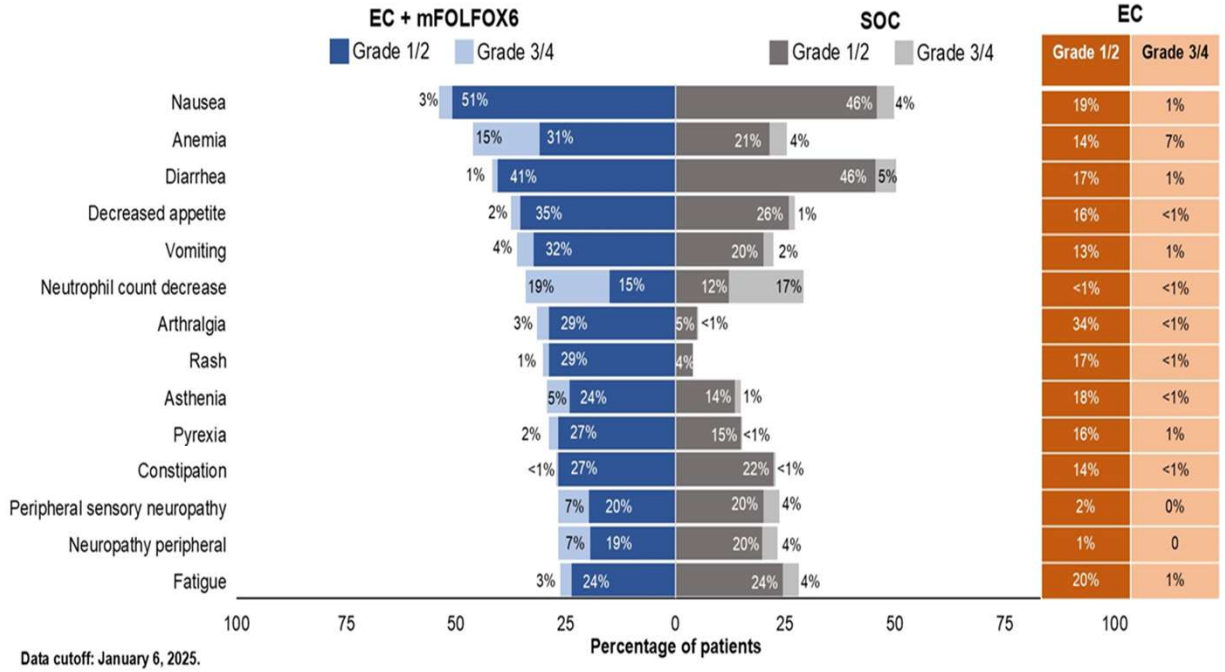


No. at risk								
EC	158	137	107	78	44	16	1	0
EC+mFOLFOX6	236	216	182	121	48	17	2	0
SOC	243	202	147	64	27	9	0	0

Best Overall Response by BICR



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



Data cutoff: January 6, 2025.

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.

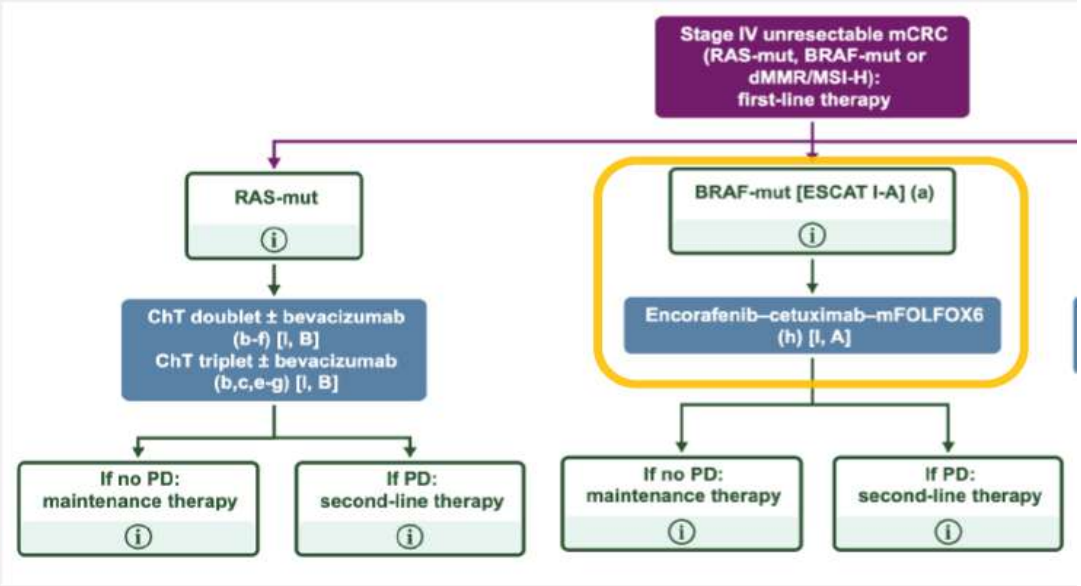
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

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

ESMO mCRC Living Guidelines



www.esmo.org/guideline
V 1.3-July 2025

Sharlene Gill, MD

BREAKWATER-ESMO 2025

XXXIII SIMPOSIO INTERNACIONAL / INTERNATIONAL SYMPOSIUM

BASELINE *BRAF* V600E ctDNA

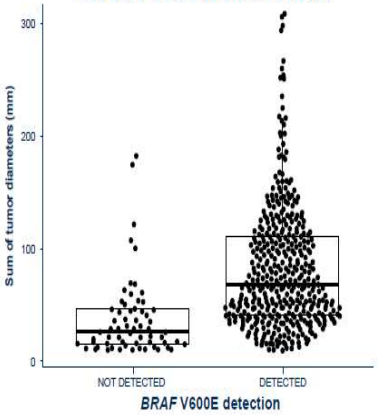
There was high concordance between BRAF V600E ctDNA and tumor tissue testing and there may be a correlation between high tumor burden and BRAF V600E detection in ctDNA at baseline

ctDNA vs tumor *BRAF* V600E detection

n (%)		Central *BRAF V600E* test (tumor tissue)[b]	
		Detected n=480	Not detected n=6
BRAF V600E ctDNA test[a] n=494	Detected n=425[b]	419 (84.8)	0
	Not detected n=69[b]	61 (12.3)	6 (1.2)

Overall agreement: 87.4%[c]

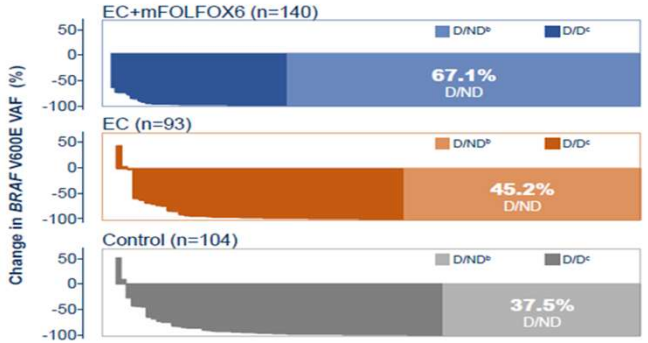
Correlation of baseline tumor burden and *BRAF* V600E detection in ctDNA



CHANGE IN *BRAF* V600E VAF STATUS AT C2D15[a]

More patients in the EC+mFOLFOX6 arm had undetectable BRAF V600E VAF at C2D15 versus control, and undetectable BRAF V600E ctDNA at C2D15 correlates with longer OS

Waterfall plot of change in *BRAF* V600E VAF status



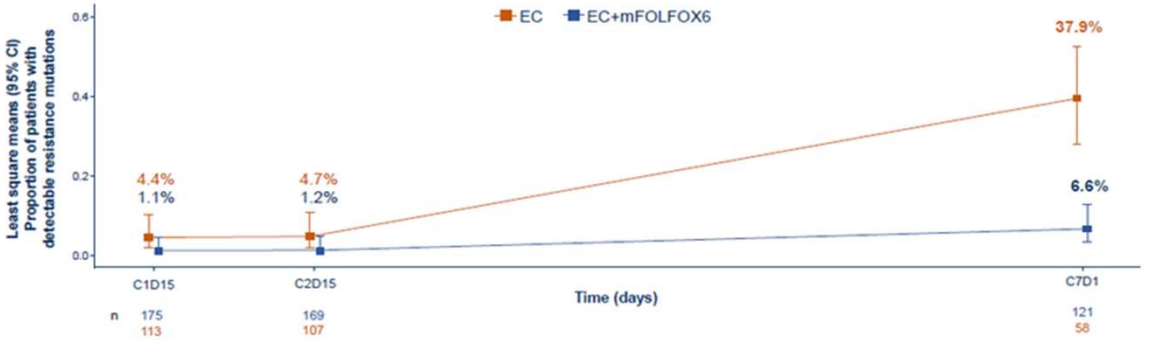
OS by change in *BRAF* V600E VAF status

	D/ND[b]	D/D[c]
EC+mFOLFOX6	n=94	n=46
Median OS (95% CI)	NE (21.1, NE)	16.2 (11.3, 19.1)
Hazard ratio	0.30	–
EC	n=42	n=51
Median OS (95% CI)	25.7 (17.6, NE)	14.6 (10.7, 18.2)
Hazard ratio	0.36	–
Control	n=39	n=65
Median OS (95% CI)	21.4 (16.8, NE)	14.3 (12.7, 17.6)
Hazard ratio	0.50	–

EMERGENCE OF GENOMIC RESISTANCE MECHANISMS

EC in combination with mFOLFOX6 vs EC alone results in fewer patients acquiring known genomics resistance alterations at C7D1

Proportion of patients with detectable acquired genomic resistance alterations by visit
Resistance mutations included: *KRAS*, *NRAS*, *MAP2K1*, *MET* amplification, *BRAF* exon deletion



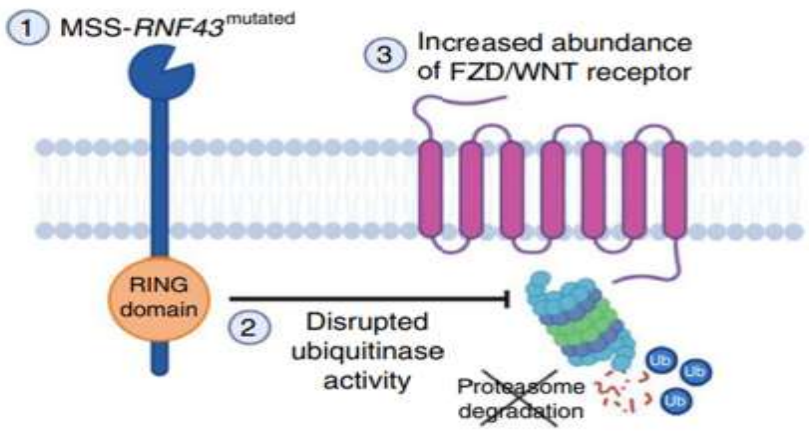

¿ hay algo más allá de
BREAKWATER?

FACTORES PREDICTIVOS DE RESPUESTA a iBRAF: RNF43

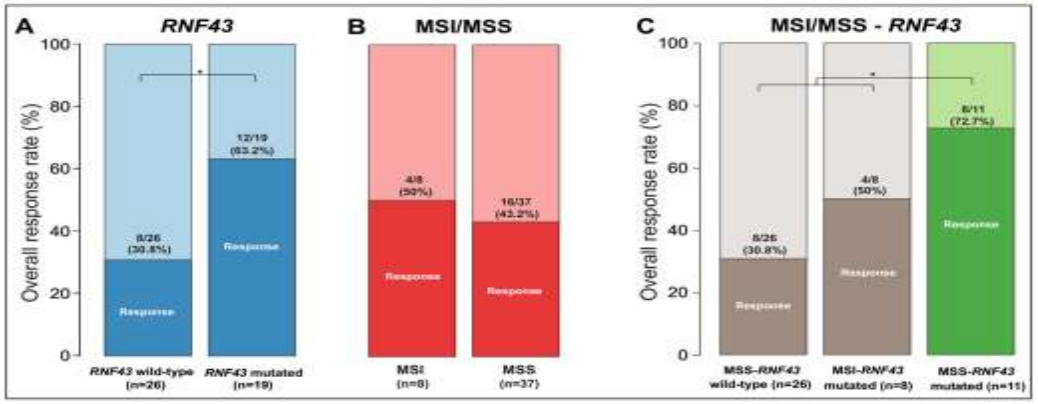
XXXIII SIMPOSIO INTERNACIONAL INTERNATIONAL SYMPOSIUM
11 - 12 DE DICIEMBRE DE 2025
OVIEDO

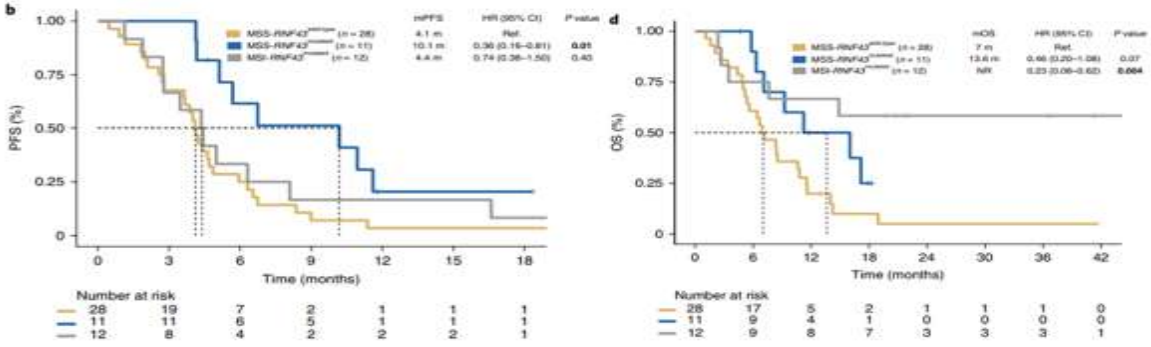
- **RNF43 is a ubiquitin ligase that regulates negatively Wnt pathway.**
- **When RNF43 is inactivated or mutated, Wnt/β-catenin signaling is potentiated, activating the MAPK pathway.**
- **RNF43 mutations result in increased sensitivity to BRAF inhibitors + anti-EGFR antibodies.**

Development of predictive biomarkers:



RNF43 is a tumor suppressor gene, involved in suppression of the WNT–β-catenin pathway through promoting the degradation of FZD/WNT receptors

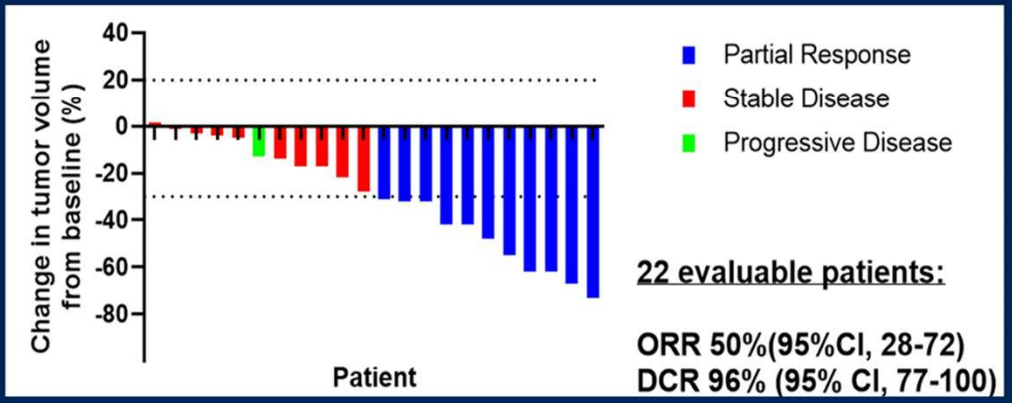




NOVEDADES EN EL ESCENARIO REFRACTARIO CON TERAPIA DIRIGIDA EN BRAF MUTADO

Phase I/II trial of encorafenib, cetuximab, and nivolumab in patients with microsatellite stable, *BRAF*^{V600E} metastatic colorectal cancer

Overall response: encorafenib + cetuximab + nivolumab

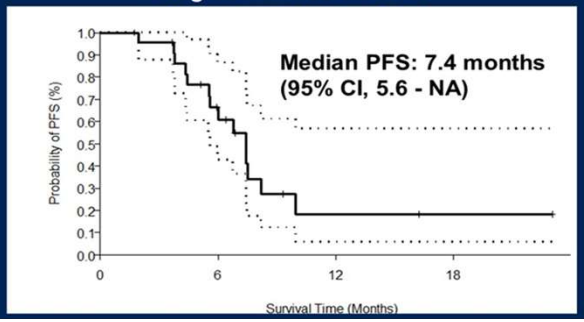


22 evaluable patients:

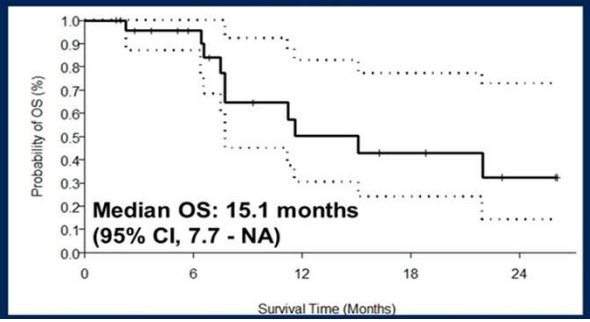
ORR 50%(95%CI, 28-72)
DCR 96% (95% CI, 77-100)

Survival outcomes: encorafenib + cetuximab + nivolumab

Progression-free survival



Overall survival



SWOG 2107

Pts with MSS, *BRAF*^{V600E} metastatic CRC, AND
- 1-2 prior lines of systemic therapy
- ECOG PS 0-1
- No prior (1) BRAF, MEK, ERK; (2) anti-EGFR; or (3) immune checkpoint therapy

R

2:1

N=75

Encorafenib + cetuximab + nivolumab

Encorafenib + cetuximab

SWOG
Leading cancer research. Together.

Accrual completed across US NCTN; read-out expected 2026.

NOVEDADES EN EL ESCENARIO REFRACTARIO CON TERAPIA DIRIGIDA EN BRAF MUTADO

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

BRAVE, phase Ib/II trial

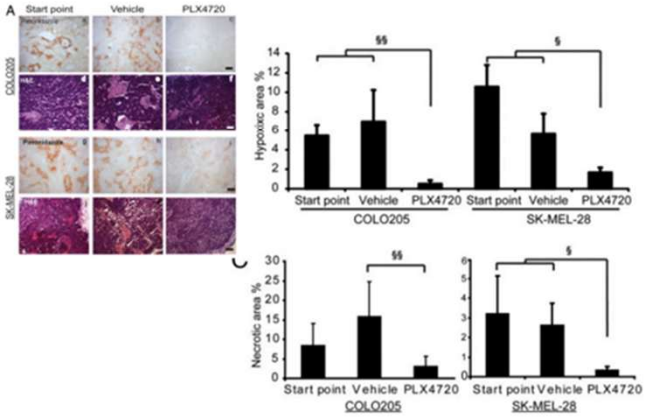
mCRC
MSS, BRAF V600E
1 or 2 previous lines

Encorafenib-
cetuximab-
bevacizumab

cerrado reclutamiento
recientemente N=50

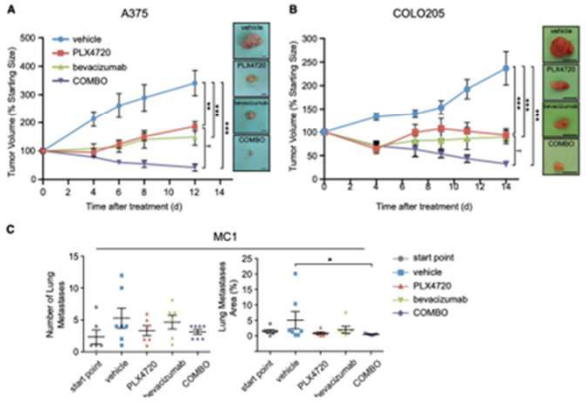
ANGIOGENESIS AND BRAF INHIBITION

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

BRAF mutado V600E-MSI-H- SEAMARK

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

TPS3634

SEAMARK: Randomized Phase 2 Study of Pembrolizumab + Encorafenib + Cetuximab vs Pembrolizumab Alone for First-Line Treatment of *BRAF* V600E–Mutant Microsatellite Instability–High (MSI-H)/Mismatch Repair–Deficient (dMMR) Metastatic Colorectal Cancer (mCRC)

Scott Kopetz,[1] Tanios Bekaii-Saab,[2] Takayuki Yoshino,[3] Chin-Hee Chung,[4] Xiaosong Zhang,[4] Josep Tabernero[5]

[1]MD Anderson Cancer Center, Houston, TX, USA; [2]Mayo Clinic, Phoenix, AZ, USA; [3]National Cancer Center Hospital East, Kashiwa, Japan; [4]Pfizer, New York, NY, USA; [5]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, UVic-UCC, Barcelona, Spain

Patient Population

Open-Label, Multicenter, Randomized, Phase 2 (N=104)

- Previously untreated stage IV mCRC
- Locally confirmed MSI-H/dMMR
- Locally confirmed *BRAF* V600E mutation in tumor tissue or blood
- Measurable disease per RECIST 1.1
- ECOG PS ≤1
- Adequate organ function

Randomization 1:1 (stratified by ECOG PS: 0 vs 1)

Triplet arm (arm A)
Encorafenib
+ cetuximab
+ pembrolizumab
(n=52)

Control arm (arm B)
Pembrolizumab
(n=52)

Primary Endpoint	PFS per investigator according to RECIST 1.1
Secondary Endpoints	Safety and tolerability, OS, OR, DOR, and QOL

CERRADO. PENDIENTE DE RESULTADOS

Phase II ECLYPse trial[1,2]

Patients with *BRAF* V600E mt mCRC, ECOG PS ≤1 → **2L encorafenib + cetuximab***

PD

Recruitment into trial (estimated N=25)

→ **Encorafenib + cetuximab + FOLFIRI***

Primary endpoint: 6-month PFS rate
Secondary endpoints: PFS, OS, DoR, ORR, DCR, toxicity

Phase II BAYONET trial[3]

Patients with *BRAF* V600E mt mCRC → **Encorafenib + cetuximab***

CR, PR, or ≥4 months SD

PD

Recruitment into trial (N=30)

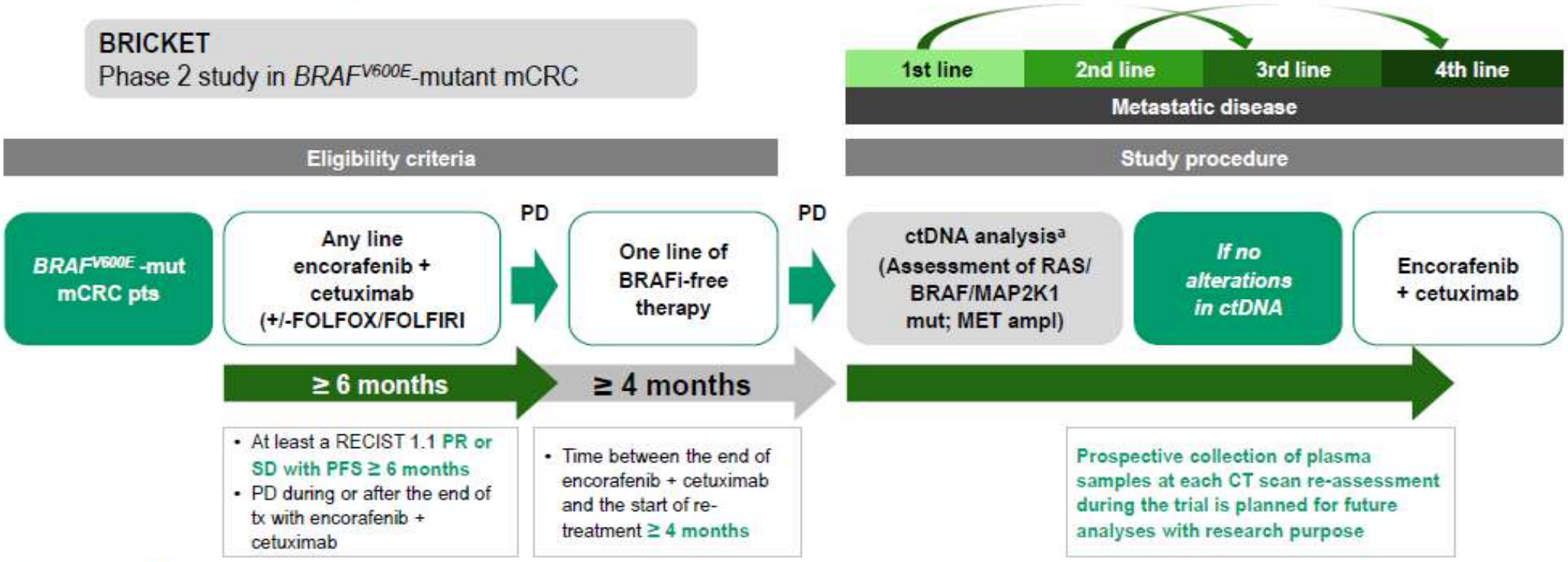
→ **Encorafenib + cetuximab + binimetinib†**

Primary endpoint: 12-week PFS rate
Secondary endpoints: PFS, OS, ORR, DCR, TTF, incidence of AEs

1. EU Clinical Trials. Available at: https://euclinicaltrials.eu/ctis-public/view/2023-508615-24-00 (last accessed October 2025); 2. NCT06640166. Available at:

Future Perspectives: ctDNA-informed Re-treatment

BRICKET
Phase 2 study in *BRAF*^{V600E}-mutant mCRC



[a]By G360 CDx (CE-IVD).
CT, Computed tomography; ctDNA, circulating tumour DNA.

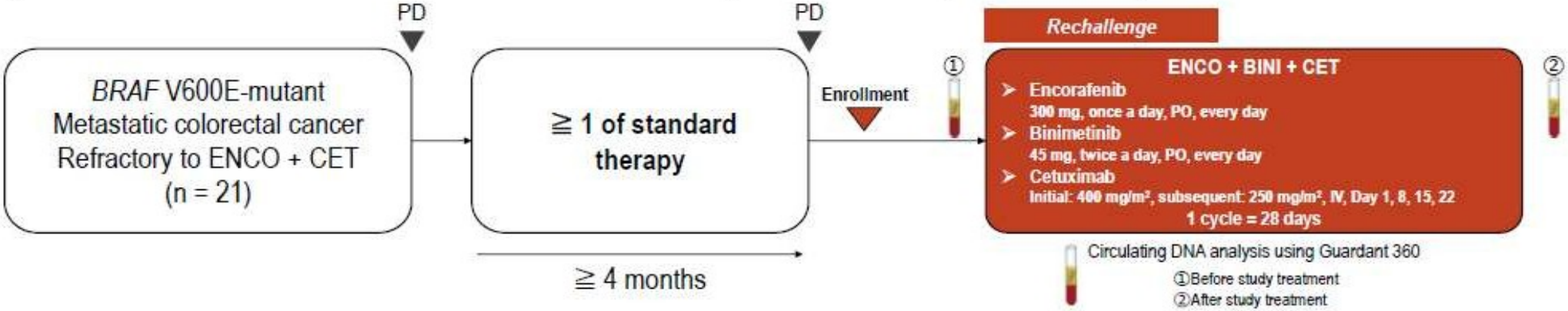
Takayuki YOSHINO, M.D. PhD.

Slide adapted from Prof. C Cremolini's presentation at the 2024 ESMO Satellite Symposium

ESMO

TRIDENTE trial; Rechallenge Strategy on BRAF Inhibitor

A single-arm, multicenter phase II trial designed to evaluate the efficacy and safety of the rechallenge with ENCO+BINI+CET for patients with *BRAF* V600E-mutant mCRC who were refractory to ENCO + CET (jRCTs031210511)



Key inclusion criteria

- *RAS* (*KRAS/NRAS*) wild-type and *BRAF* V600E-mutant mCRC
- Best response in the previous ENCO + CET was CR or PR
- ≧ 4 months of interval between the previous ENCO
- Confirmed disease progression within 4 weeks after last administration of previous ENCO
- ECOG PS 0 or 1

The primary endpoint

- **ORR by investigator's assessment**

Sample size : 21 (*Complete*)

Period

Registration : Jan/2022～Mar/2025 (39 months)

Total : Jan/2022～Mar/2026 (51 months)

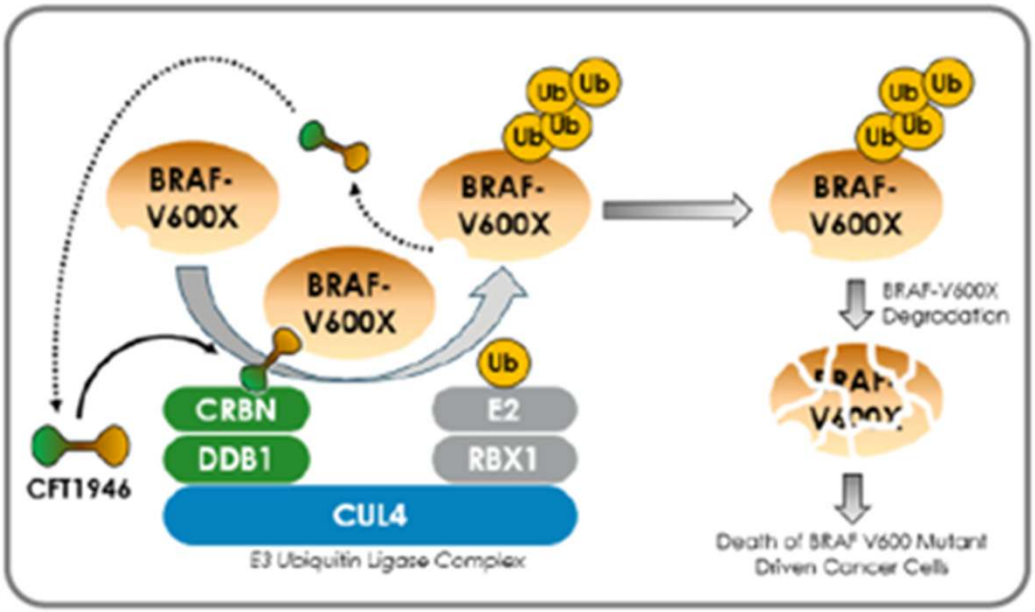
Takayuki YOSHINO, M.D. PhD.

Kotani D, Yoshino T, et al. ASCO-GI 2023.

ESMO

PROTACs (protein degraders)

Degradation of BRAF V600X with CFT1946



CFT1946 exploits cells' own proteosome machinery for targeted degradation of oncogenic BRAF V600X

CFT1946-1101: Study Design and Study Status

Phase 1 trial in BRAF V600 Mutant Solid Tumors

KEY INCLUSION CRITERIA[1]

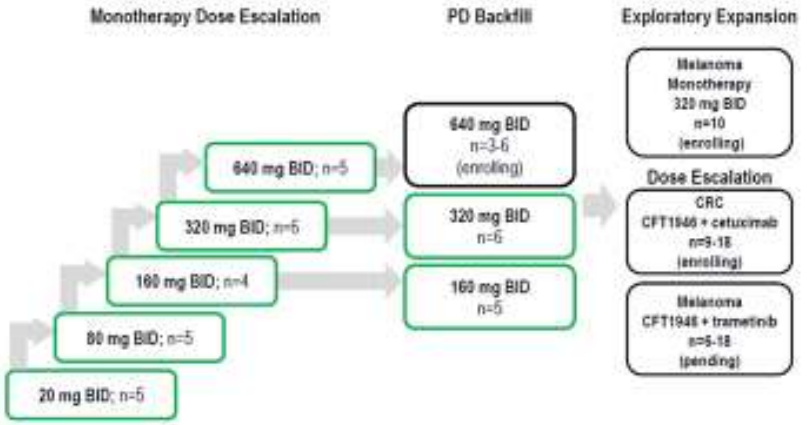
- BRAF V600 mutant measurable solid tumors with ≥1 prior line of SoC therapy for unresectable locally advanced or metastatic disease
- Melanoma patients must have received prior BRAFi therapy
- CRC, ATC, NSCLC or other non-CNS solid tumors: prior BRAFi therapy unless not available per SoC
- No CNS involvement (primary tumor or metastatic disease), except if clinically stable

Study Endpoints

PRIMARY
- Safety and tolerability
- Determine RP2D

SECONDARY
- Estimate anti-tumor activity
- Assess PK and PD

[1]EU CT No. 2022-501696-30, NCT05668585

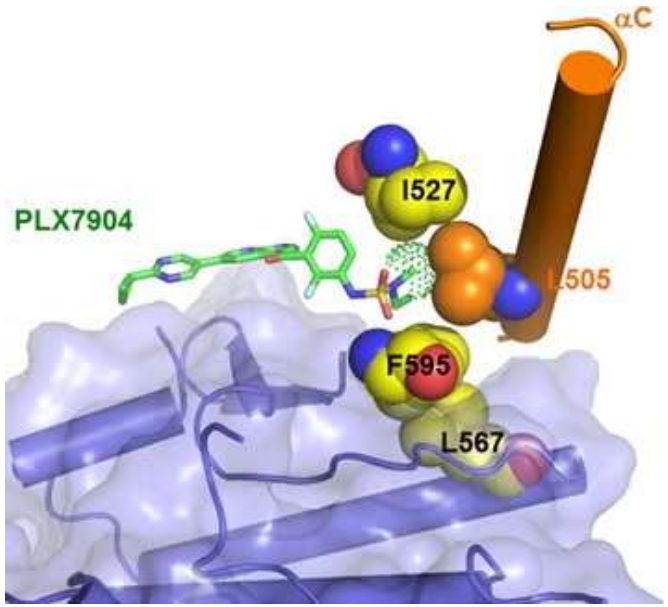


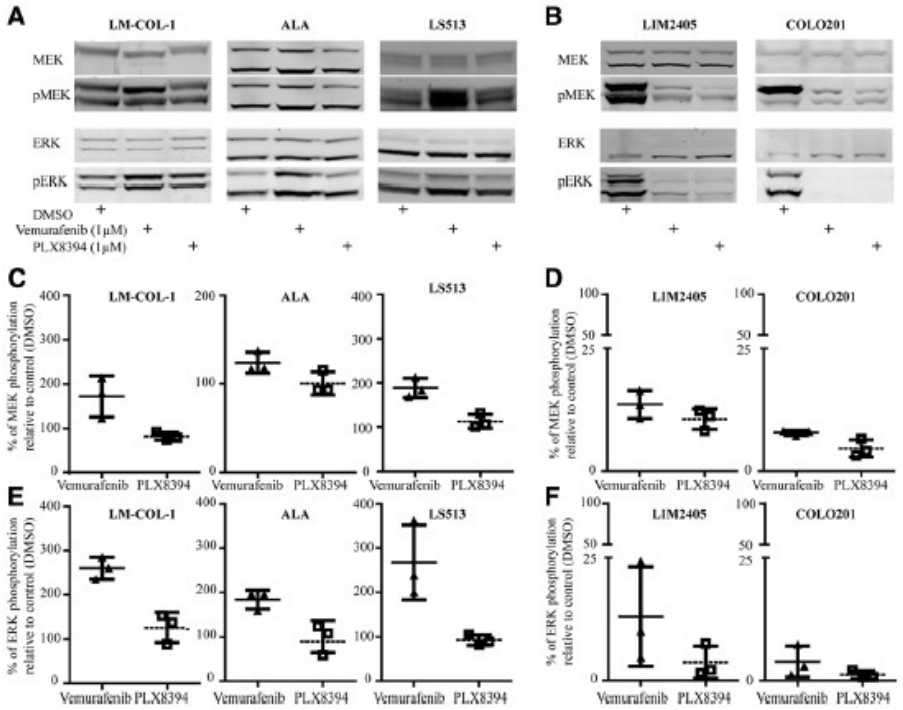
CFT1946 binds to the mutant form of BRAF, to be destroyed by the proteasome, which slows down intracellular kinase activity, reducing tumor proliferation

NOVEL BRAF INHIBITORS: PLX8394 o paradox

NOVEL BRAF INHIBITORS
(PLX8394 AND PLX7904), DUBBED AS "PARADOX BREAKERS", were developed to inhibit V600 mutated oncogenic BRAF without causing paradoxical MAPK pathway activation.

Fase preclinica





CONCLUSIONES-*take home message*

- FOLFOX + EC es el nuevo estándar de 1L en cáncer colorrectal avanzado BRAF mutado V600E MSS. (Breakwater, FDA, ESMO living CCR guidelines)
- Pendiente de establecer el tratamiento de 1L en BRAF mutado V600E MSI (Seamark)
- Necesidad de aclarar el “continium of care” en pacientes que van a recibir la terapia dirigida en primera línea
  - Quimioterapia más anti VEGF ?
  - Mantenimiento a la progresión con EC+ quimioterapia ó inh MEK ?
  - Estrategias de “rechallenge” ?
  - iBRAF de nueva generación ? PROTACS?


GRACIAS