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20 ANIVERSARIO

mCRC: Advances in molecularly selected population

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Disclosures

Elena Elez MD PhD:

- Personal speaker honoraria from Organon and Novartis; and personal advisory board honoraria from Amgen, Bayer, Hoffman-La Roche, Merck Serono, Sanofi, Pierre Fabre, MSD, and Servier; and to have received travel and accommodations expenses from Amgen, Array Biopharma, Bristol-Myers Squibb, Merck Serono, Roche, Sanofi and Servier.
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- Non-remunerated roles as Coordinator of the SEOM +MIR Section of Residents and Young Assistants of the Sociedad Española de Oncología Médica (SEOM), Speaker of the ESMO Academy of the European Society for Medical Oncology (ESMO), Volunteer member of the ASCO Annual Meeting Scientific Program Committee and chair of the CRC track at ESMO 2025 annual meeting.

FOCUS ON THE MAPK PATHWAY

BRAFV600E mt mCRC

The BREAKWATER trial

RAS mCRC

Rationale combinations

New drugs

BREAKWATER: Study Design

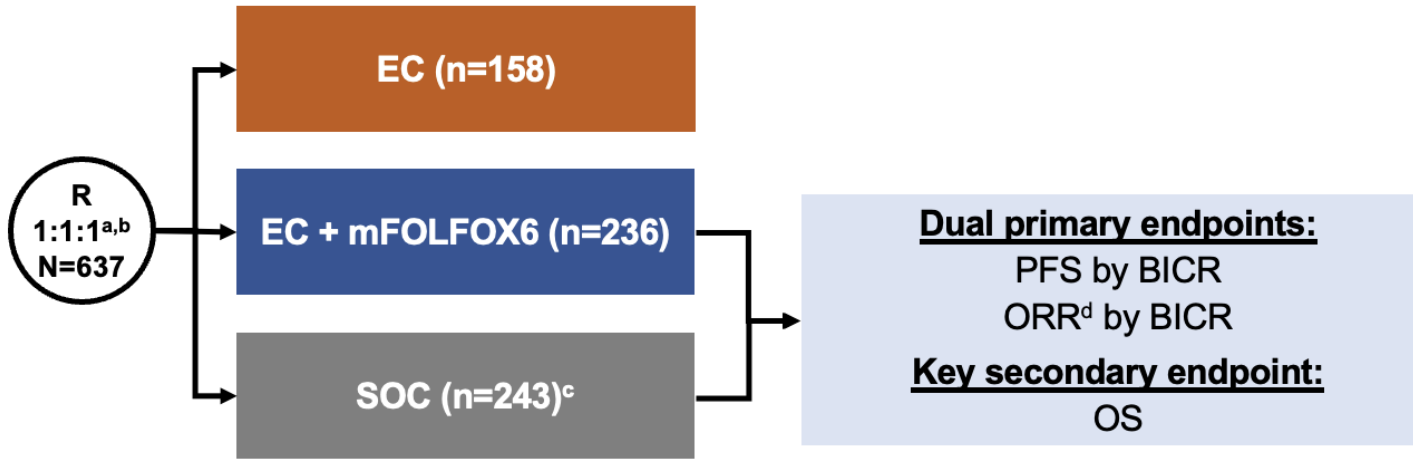
BREAKWATER (NCT04607421) is an open-label, multicenter, phase 3 study in first-line BRAF V600E-mutant mCRC

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 function

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.

Key Demographic and Baseline Disease Characteristics

	EC n=158	EC + mFOLFOX6 n=236	SOC n=243
Age, median (range), years	59 (26-84)	60 (24-81)	62 (28-84)
Sex, n (%)			
Male	79 (50.0)	123 (52.1)	119 (49.0)
Female	79 (50.0)	113 (47.9)	124 (51.0)
ECOG PS, n (%)			
0	79 (50.0)	128 (54.2)	131 (53.9)
1	74 (46.8)	104 (44.1)	98 (40.3)
Side of tumor, n (%)			
Left	69 (43.7)	90 (38.1)	98 (40.3)
Right	89 (56.3)	146 (61.9)	145 (59.7)
No. of organs involved, n (%)[a]			
≤2	86 (54.4)	119 (50.4)	127 (52.3)
≥3	72 (45.6)	117 (49.6)	116 (47.7)
Liver metastases, n (%)[a]			
Yes	94 (59.5)	147 (62.3)	160 (65.8)
No	64 (40.5)	89 (37.7)	83 (34.2)
CEA at baseline, n (%)			
≤5 µg/L	50 (31.6)	64 (27.1)	63 (25.9)
>5 µg/L	102 (64.6)	167 (70.8)	163 (67.1)
CRP at baseline, n (%)			
≤10 mg/L	91 (57.6)	125 (53.0)	118 (48.6)
>10 mg/L	61 (38.6)	105 (44.5)	108 (44.4)

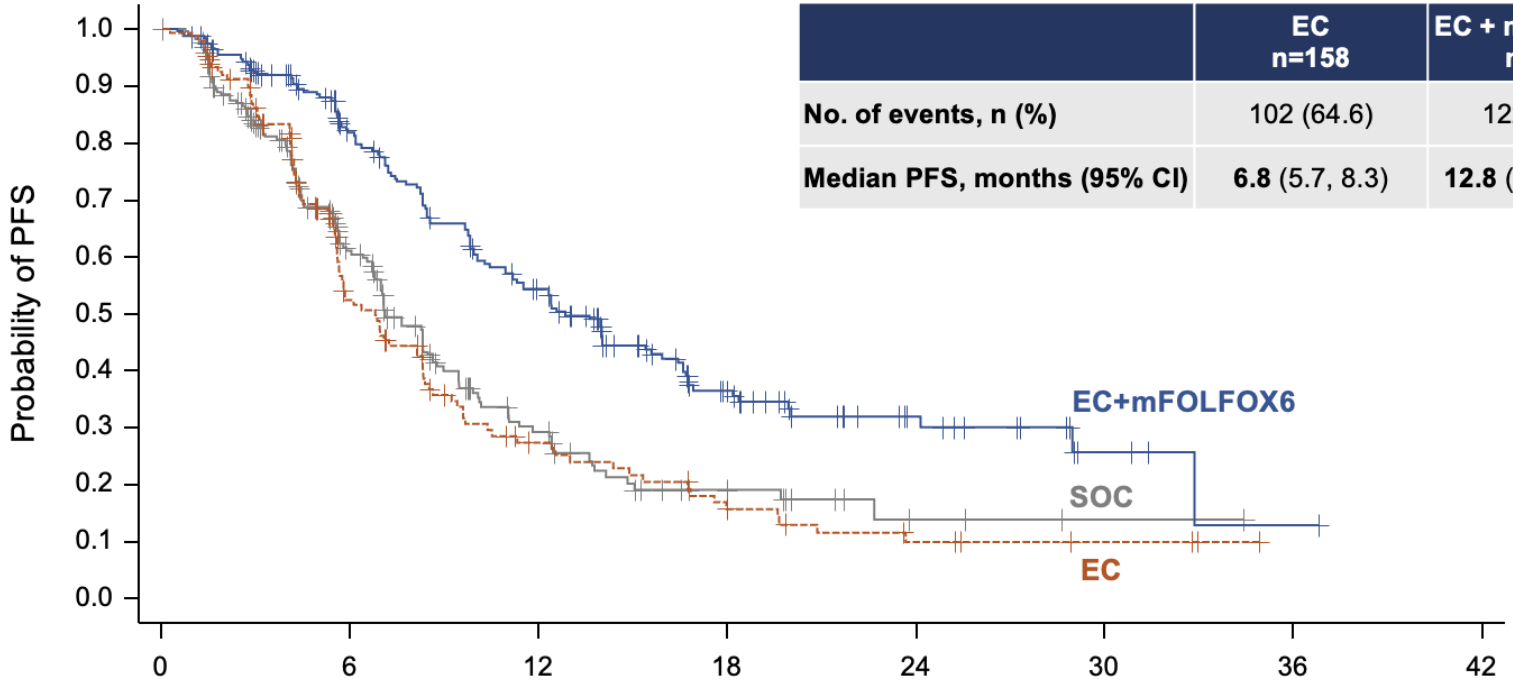
Data cutoff: January 6, 2025.

[a]Based on BICR.

BICR, blinded independent central review; CEA, carcinoembryonic antigen; CRP, C-reactive protein; EC, encorafenib plus cetuximab; ECOG PS, Eastern Cooperative Oncology Group performance status; mFOLFOX6, modified fluorouracil/leucovorin/oxaliplatin; SOC, standard of care.

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)



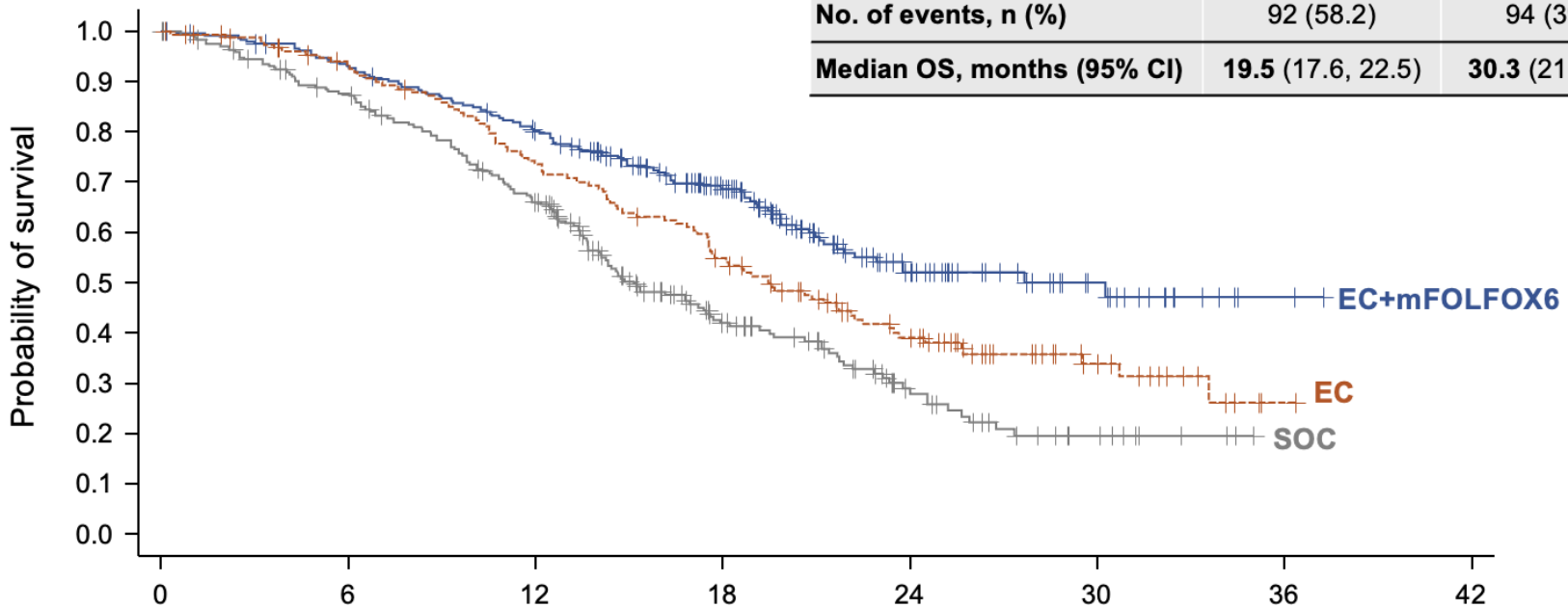
No. at risk							
EC	158	60	24	12	6	3	0
EC+mFOLFOX6	236	156	96	39	16	4	1
SOC	243	100	34	11	3	1	0

Data cutoff: January 6, 2025.

BICR, blinded independent central review; EC, encorafenib plus cetuximab; mFOLFOX6, modified fluorouracil/leucovorin/oxaliplatin; SOC, standard of care.

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)



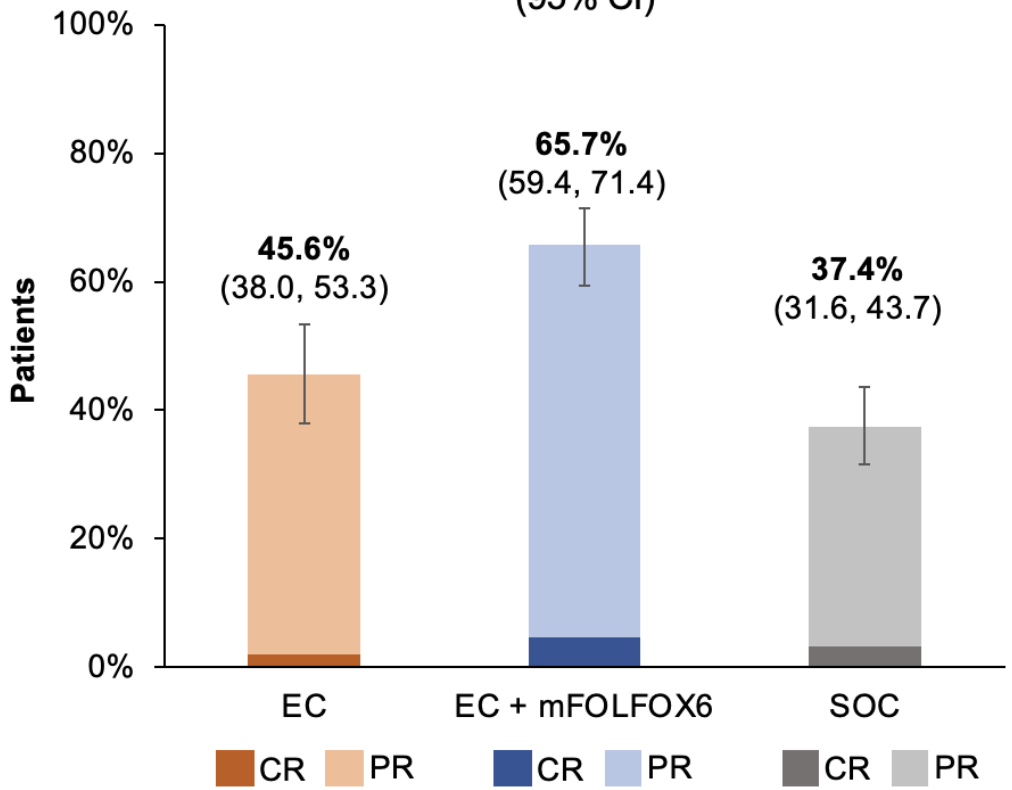
No. at risk								
EC	158	137	107	78	44	16	1	0
EC+mFOLFOX6	236	216	182	121	48	17	2	0
SOC	243	202	147	64	27	9	0	0

Data cutoff: January 6, 2025.

EC, encorafenib plus cetuximab; mFOLFOX6, modified fluorouracil/leucovorin/oxaliplatin; NE, not estimable; SOC, standard of care.

Best Overall Response by BICR (All Randomized Patients)

Confirmed ORR by BICR
(95% CI)



Confirmed Best Overall Response, TTR, and DOR by BICR

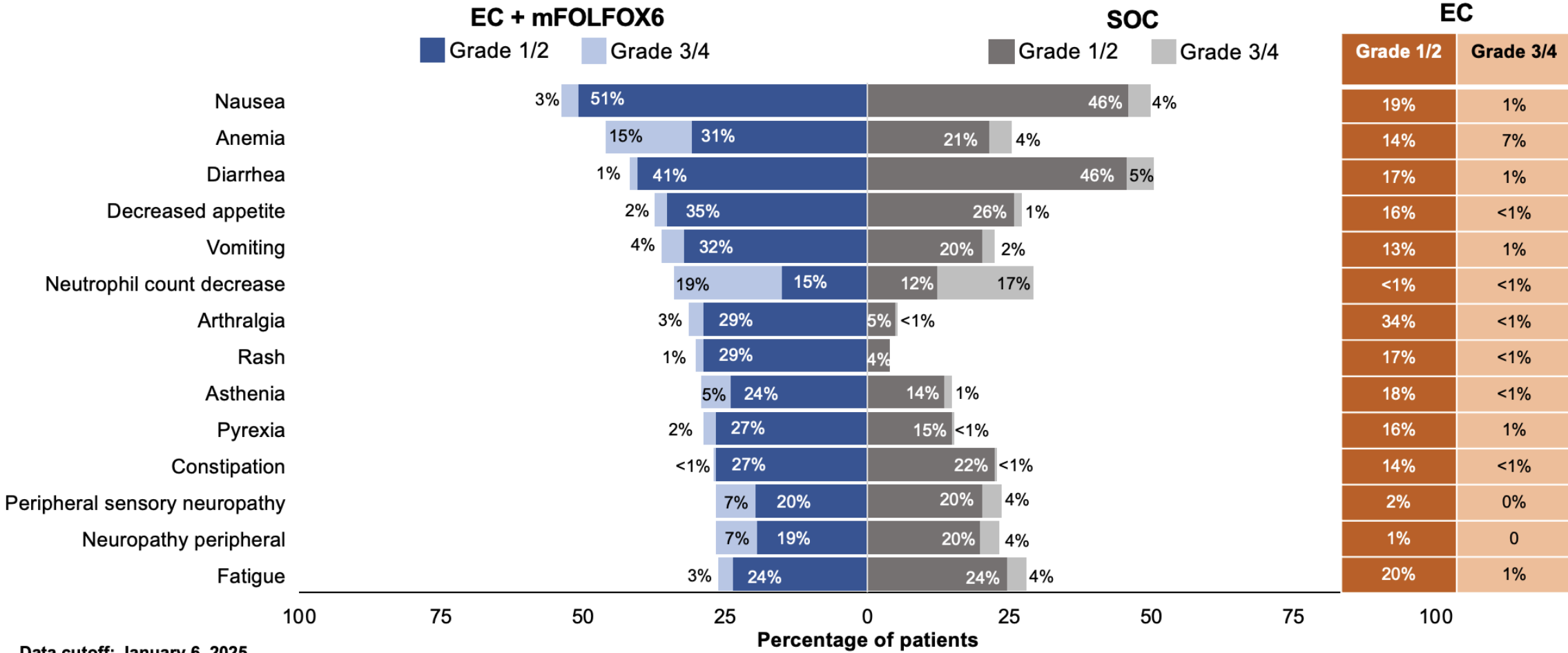
All randomized patients	EC n=158	EC + mFOLFOX6 n=236	SOC n=243
Confirmed best overall response, n (%)[a]			
CR	3 (1.9)	11 (4.7)	8 (3.3)
PR	69 (43.7)	144 (61.0)	83 (34.2)
SD	57 (36.1)	50 (21.2)	85 (35.0)
PD	12 (7.6)	8 (3.4)	21 (8.6)
Responders	**n=72**	**n=155**	**n=91**
TTR, median (range), weeks	6.6 (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.

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



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.

PRESENTED BY: Elena Elez, MD, PhD

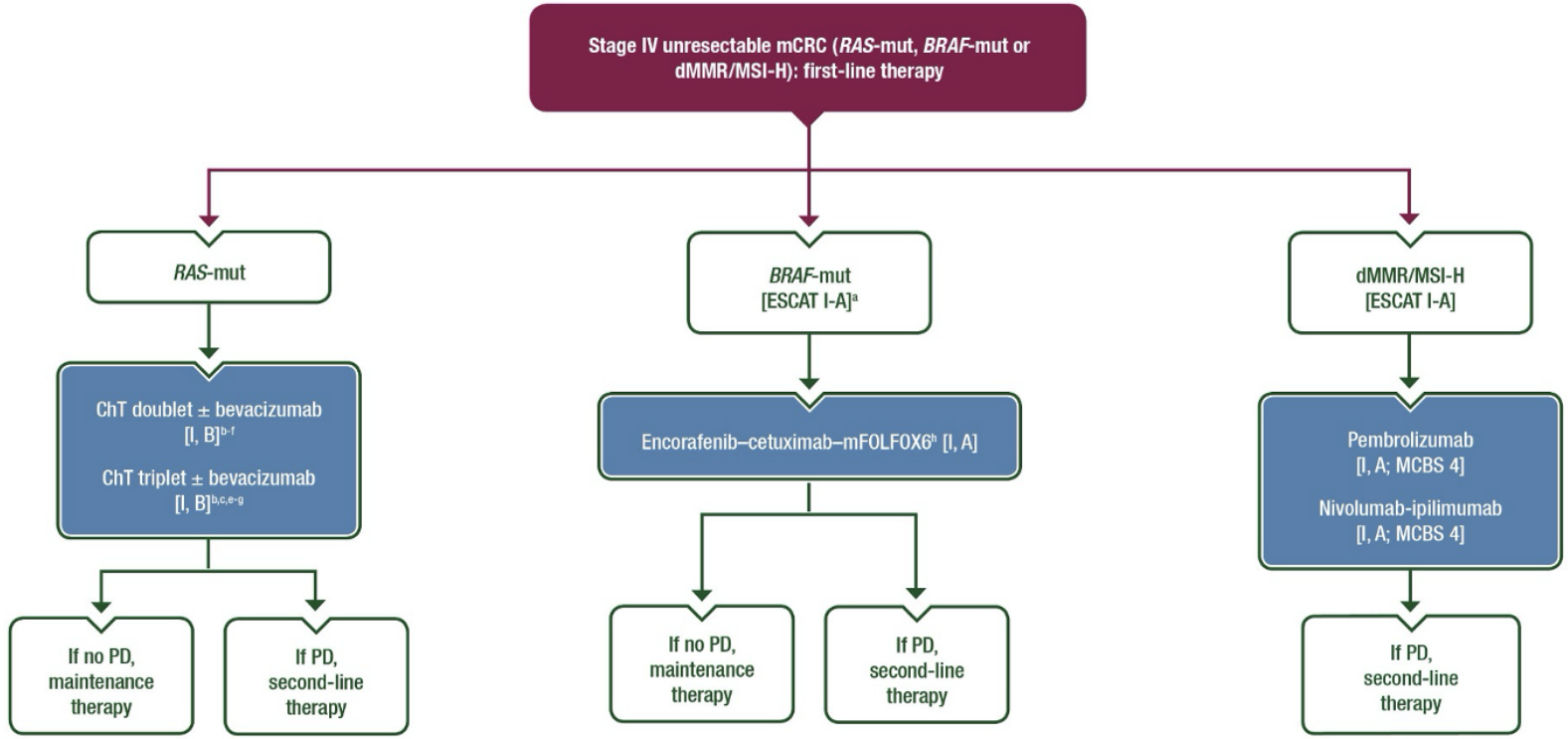
CLINICAL PRACTICE GUIDELINES

ESMO Metastatic Colorectal Cancer Living Guideline
v1.3 July 2025

First-line Therapy

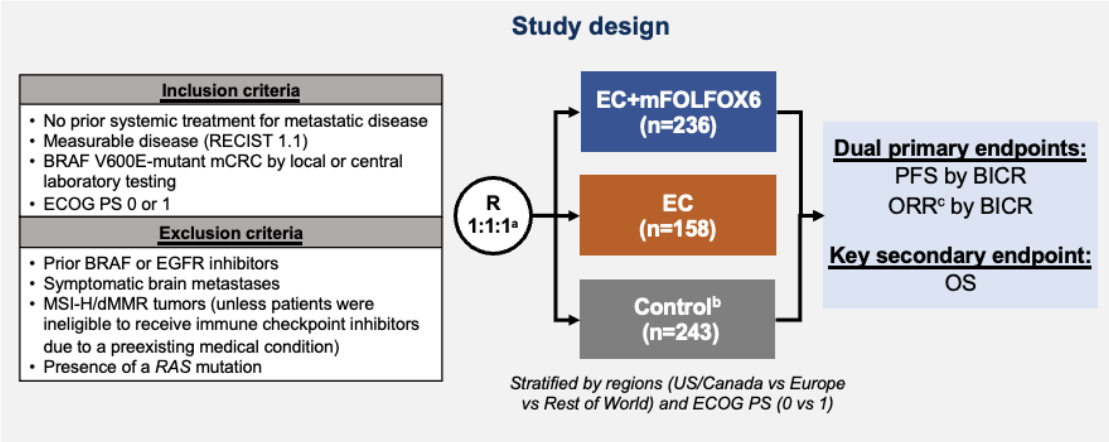
RAS-mut, *BRAF*-mut or dMMR/MSI-H

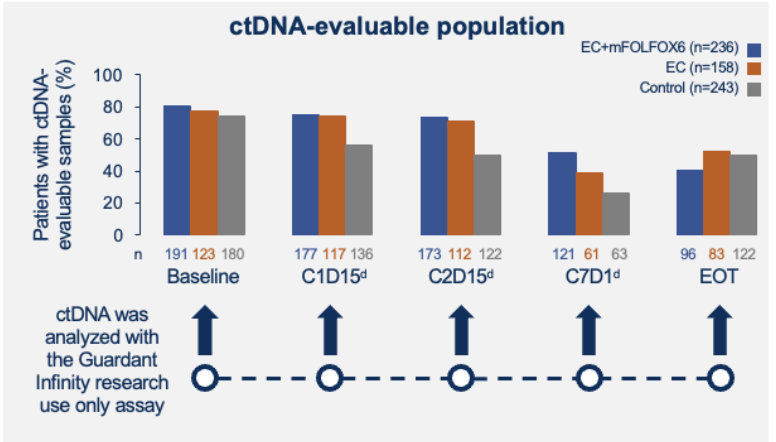
[a]For patients with *BRAF*-mutated tumours who are also dMMR, first-line immunotherapy is recommended [I, A].
[b]In patients presenting with cardiotoxicity and/or hand-foot syndrome on 5-FU or capecitabine-based ChT, S-1 may be used as an alternative [III, B].
[c]Additional details on treatments and drug combinations can be found under the section 'Management of advanced and metastatic disease without potential conversion' (subsections 'First-line treatment' and 'Second-line treatment').
[d]FOLFIRI–cetuximab ESMO-MCBS v2.0 score: 4; FOLFOX4–panitumumab ESMO-MCBS v2.0 score: 4.
[e]In a very selected population.
[f]CAPOX– or FOLFOX4–bevacizumab ESMO-MCBS v2.0 score: 1.
[g]A triplet with FOLFOXIRI plus bevacizumab is an option for selected patients with good PS and without comorbidities [I, B; ESMO-MCBS v2.0 score: 2].
[h]FDA approved, not EMA approved. If FOLFOX–encorafenib–cetuximab is not possible, FOLFOX–bevacizumab [II, B] or FOLFOXIRI–bevacizumab [II, B] could be recommended.



BREAKWATER

- BREAKWATER (NCT04607421) is a phase 3 study evaluating EC with or without mFOLFOX6 vs investigator's choice of chemotherapy ± bevacizumab in patients with previously untreated BRAF V600E-mutant mCRC
  - The Phase 3 portion of BREAKWATER has met both of its dual primary endpoints and its key secondary endpoint, with statistically significant and clinically meaningful improvements in ORR by BICR, PFS by BICR, and OS[1,2]
- EC+mFOLFOX6 was granted accelerated approval by the US FDA as part of Project FrontRunner for patients with BRAF V600E-mutant mCRC, including in the first-line setting[3]; this was followed by several recent full approvals in countries in Latin America and conditional approval in Canada





We present prespecified, exploratory biomarker analysis from the BREAKWATER study, including ctDNA and tumor tissue concordance,[e] baseline *BRAF* V600E VAF status and efficacy, changes in *BRAF* V600E VAF status and efficacy, and the presence of resistance mutations

[a]Following a protocol amendment, enrollment to the EC arm was stopped; patients were randomized 1:1 to the EC+mFOLFOX6 or control arms. [b]mFOLFOX6/FOLFOXIRI/CAPOX ± bevacizumab. [c]In the first 110 patients in each of the EC+mFOLFOX6 and control arms. [d]Cycles are 28 days (4 weeks). [e]ctDNA/tissue concordance was analyzed with the QIAGEN Therascreen® BRAF V600E RGQ PCR Kit. 1. Kopetz S et al, Nat Med. 2025;31:901–908. 2. Élez E, et al. N Engl J Med. 2025; 392:2425-2437. 3. BRAFTOVI Prescribing information 2024. BICR, blinded independent central review; C, Cycle; CAPOX, capecitabine/oxaliplatin; ctDNA, circulating tumor DNA; D, day; EC, encorafenib plus cetuximab; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT, end of treatment; FOLFOXIRI, fluorouracil/leucovorin/oxaliplatin/irinotecan; mFOLFOX6, modified fluorouracil/leucovorin/oxaliplatin; mCRC, metastatic colorectal cancer; MSI-H/dMMR, microsatellite instability-high/deficient mismatch repair; RECIST, Response Evaluation Criteria in Solid Tumors.

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BASELINE *BRAF* V600E ctDNA

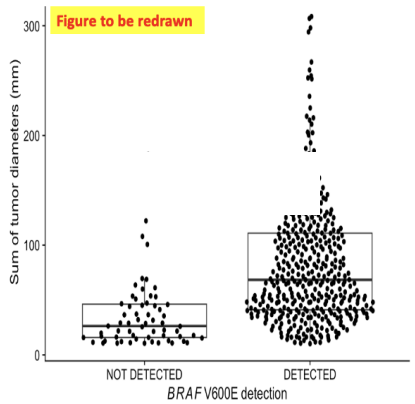
There was high concordance between BRAF V600E ctDNA and tumor tissue testing and there may be a corrolation between high tumor burden and BRAF V600E detection in ctDNA at baseline

ctDNA vs tumor *BRAF* V600E detection

n (%)		Central *BRAF* test (tumor tissue)			
		Detected n=500	Not detected n=6	Indeterminant[b] n=2	Not tested n=6
ctDNA test[a] n=494	Detected n=425	419 (84.8)	0	2 (0.4)	4 (0.8)
	Not detected n=69	61 (12.3)	6 (1.2)	0	2 (0.4)

Overall agreement: 87.4%[c]

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



Data cutoff: Jan 6, 2025.

[a]Guardant Infinity research use only assay. [b]Specimen tested and results cannot be concluded. [c]The number of patients with *BRAF* V600E detected by both assays (n=419) plus the number of patients with *BRAF* V600E not detected by both assays (n=6), divided by the total number of patients with a ctDNA and central testing evaluate sample at baseline (n=486). ctDNA, circulating tumor DNA.

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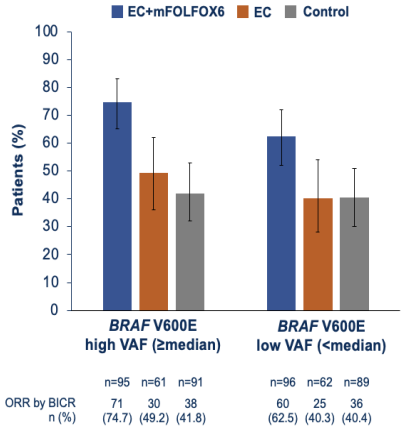
ORR BY BICR AND OS BY BASELINE *BRAF* V600E STATUS

ORR and survival benefit for EC+mFOLFOX6 was independent of baseline BRAF V600E VAF status

ORR by BICR

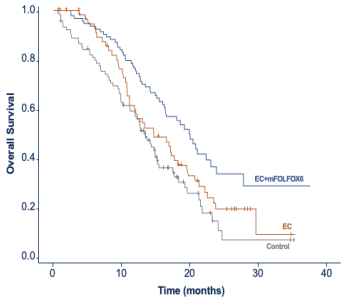


	n=95	n=61	n=91	n=96	n=62	n=89
ORR by BICR n (%)	71 (74.7)	30 (49.2)	38 (41.8)	60 (62.5)	25 (40.3)	36 (40.4)

OS

BRAF V600E high VAF (≥median)

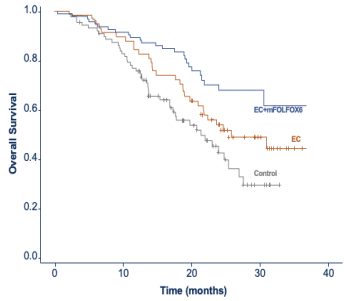
BRAF V600E high VAF (≥median)	EC+mFOLFOX6 n=95	EC n=61	Control n=91
No. of events, n (%)	51 (53.7)	43 (70.5)	65 (71.4)
Median OS (95% CI)	19.9 (16.3, 22.9)	14.6 (11.1, 19.5)	13.5 (11.1, 15.1)
Hazard ratio (95% CI)	0.50 (0.35, 0.73)	0.76 (0.52, 1.13)	–



No. at risk				
EC+mFOLFOX6:	95	80	25	5
EC:	61	42	16	1
Control:	91	56	12	2

BRAF V600E low VAF (<median)

BRAF V600E low VAF (<median)	EC+mFOLFOX6 n=96	EC n=62	Control n=89
No. of events, n (%)	25 (26.0)	29 (46.8)	45 (50.6)
Median OS (95% CI)	NE (30.3, NE)	25.7 (20.9, NE)	21.8 (16.8, 26.8)
Hazard ratio (95% CI)	0.38 (0.24, 0.64)	0.66 (0.41, 1.06)	–



No. at risk				
EC+mFOLFOX6:	96	87	46	11
EC:	62	52	37	13
Control:	89	72	28	5

Data cutoff: Jan 6, 2025.

ORR by BICR error bars show 95% confidence intervals. Median *BRAF* V600E VAF for the entire population was 9.2%.

EC, encorafenib plus cetuximab; mFOLFOX6, modified fluorouracil/leucovorin/oxaliplatin; NE, not estimable; VAF, variant allele frequency.

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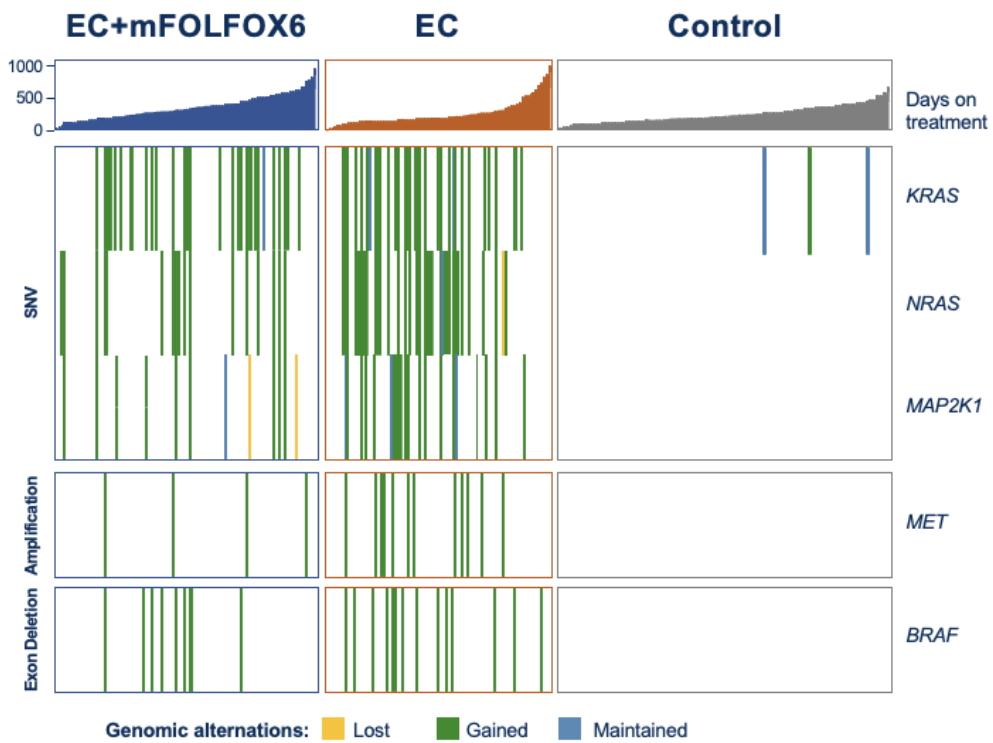
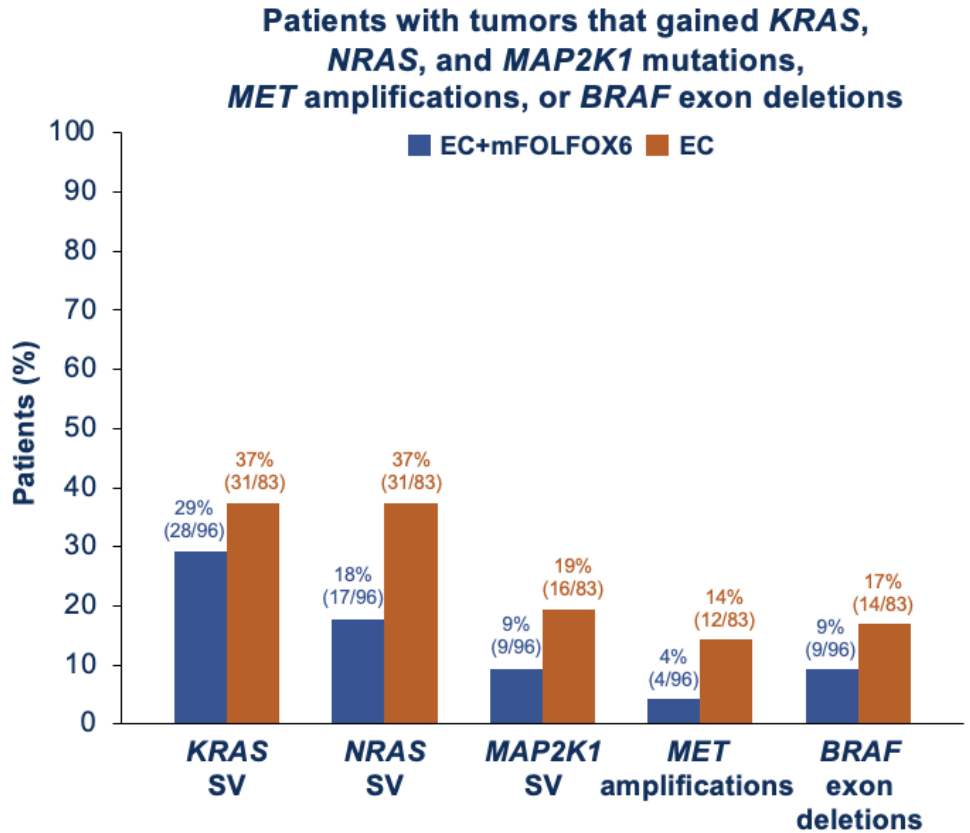
- Additionally, longitudinal modeling indicates fewer patients with detectable BRAF V600E status on treatment, along with a rapid and sustained decline in magnitude of BRAF V600E VAF with EC+mFOLFOX6
- More patients in the EC+mFOLFOX6 arm had undetectable BRAF V600E VAF at C2D15 versus control, and undetectable BRAF V600E ctDNA at C2D15 correlates with longer OS

GENOMIC ALTERATIONS BETWEEN BASELINE AND EOT

Even with longer treatment duration in the EC+mFOLFOX6 arm, fewer patients' tumors gained KRAS, NRAS and MAP2K1 mutations, MET amplifications and BRAF exon deletions at EOT vs EC alone





Response data cutoff: Jan 6, 2025. Biomarker data cutoff: May 1, 2025.
EC, encorafenib plus cetuximab; EOT, end of treatment; mFOLFOX6, modified fluorouracil/leucovorin/oxaliplatin; SV, small variant.

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REMAINNG QUESTIONS AND WHAT TO EXPECT

MSI-H PATIENTS: TREATMENT SEQUENCE

What's Next after ICIs?

SECOND LINE TREATMENT STRATEGIES

EC or FOLFIRI-EC?

IS THERE A ROLE FOR RECHALLENGE?

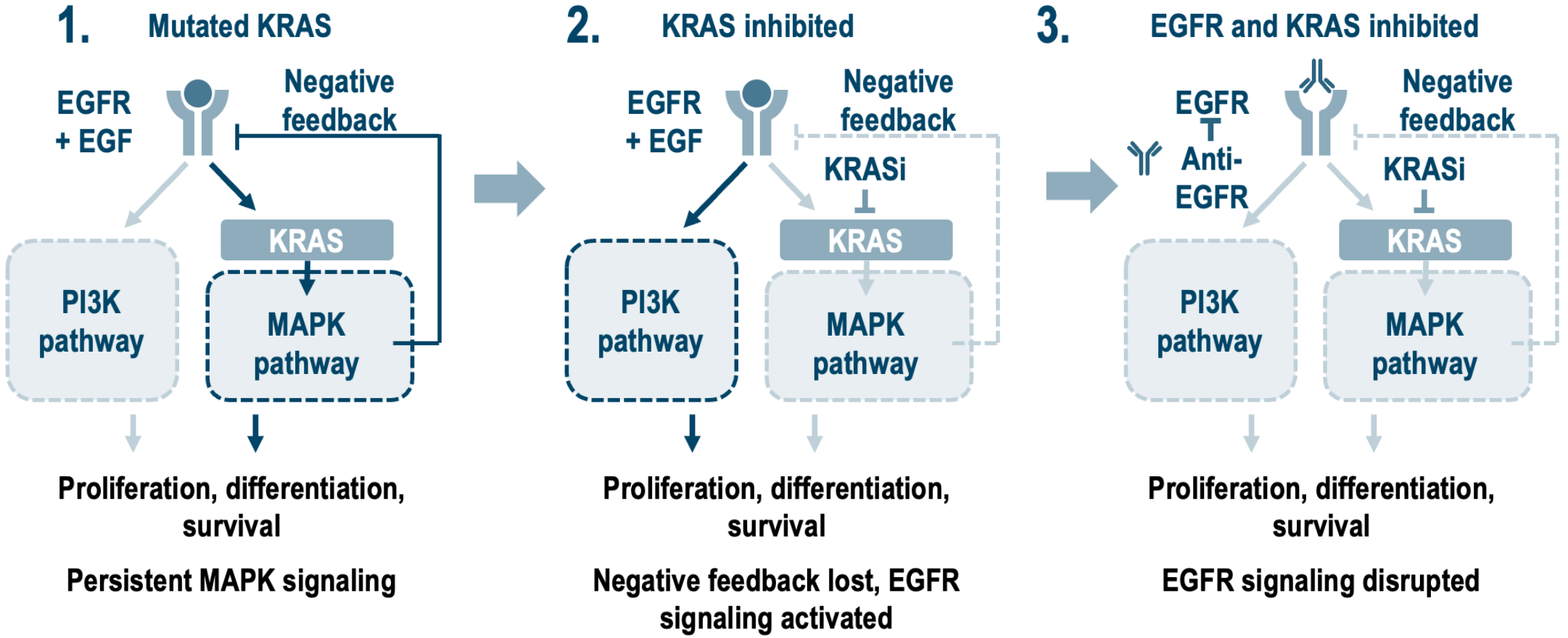
BRICKET REFISH

NEW COMPOUNDS

PD(L)1/VEGF^{I}
ADC
BITES

KRAS MUTATED TUMOURS

The rationale of combining anti-EGFR agents with KRAS inhibitors is to prevent feedback activation



KRAS MUTATED TUMOURS

Trials showing efficacy of ≥2L anti-EGFR agents + KRAS G12C inhibitors for KRAS G12C mCRC

Phase I/II KRYSTAL-1 trial[1]

	Cetuximab + adagrasib* (n=94)
ORR per BICR (primary endpoint), % (95% CI)	34 (25–45)
ORR per investigators assessment, % (95% CI)	43 (32–53)
mPFS per BICR, months (95% CI)	6.9 (5.6–7.4)
mOS, months (95% CI)	16.0 (13.3–18.8)

Phase III CodeBreaK 300 trial[2]

	960 mg sotorasib + panitumumab (n=53)	Trifluridine/ tipiracil or regorafenib (n=54)	HR (95% CI)
ORR, % (95% CI)	30 (18.3–44.3)	2 (0–9.9)	-
mPFS (primary endpoint), months (95% CI)	5.7 (4.2–7.5)	2.0 (1.9–3.9)	0.45 (0.29–0.72)
mOS, months (95% CI)	NE (8.6–NE)	10.3 (7.0–NE)	0.70 (0.41–1.18)

1. Yaeger R, et al. ASCO GI 2025 (Abstract No. 131 – poster); 2. Pietrantonio F, et al. J Clin Oncol 2025;43:2147–2154.

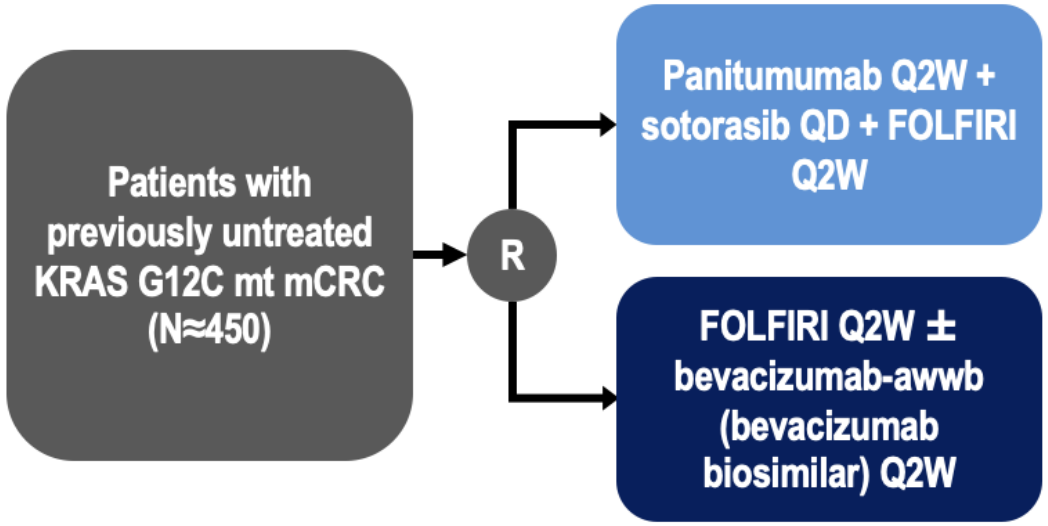
KRAS MUTATED TUMOURS

Ongoing phase III trials in 1L: anti-EGFR agents + KRAS G12C inhibitors in KRAS G12C mt mCRC

CodeBreaK 301

Phase III trial in 1L KRAS G12C mt mCRC

Primary endpoint: PFS per RECIST v1.1

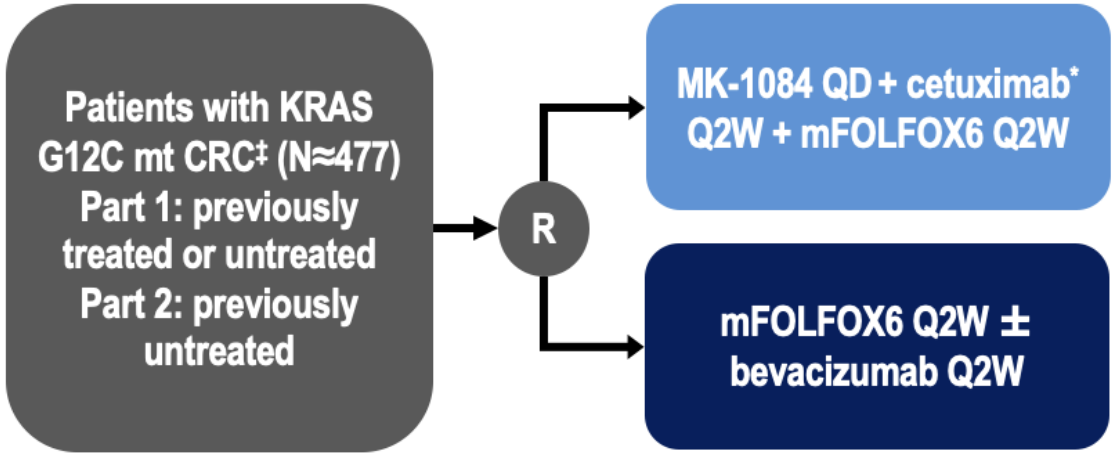


Estimated primary completion: Jan 2028

KANDLELIT-012

Phase III trial in 1L† KRAS G12C mt advanced CRC‡

Primary endpoints: DLTs, AEs,§ and PFS



Estimated primary completion: Aug 2029

1. NCT06252649. 2. NCT06997497.

KRAS MUTATED TUMOURS

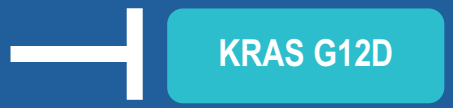
The promising KRAS G12D and pan-RAS inhibitors

Anti-EGFR + KRAS G12D inhibitor*

- KRAS G12Di LY3962673 ± cetuximab (MOONRAY-01)[1]
- KRAS G12Di AZD0022 ± cetuximab (ALAFOSS-01)[2]
- KRAS G12Di INCB161734 ± cetuximab[3]
- KRAS G12D degrader ASP3082 ± cetuximab[4]
- KRAS G12Di GDC-7035 ± panitumumab[5,6]

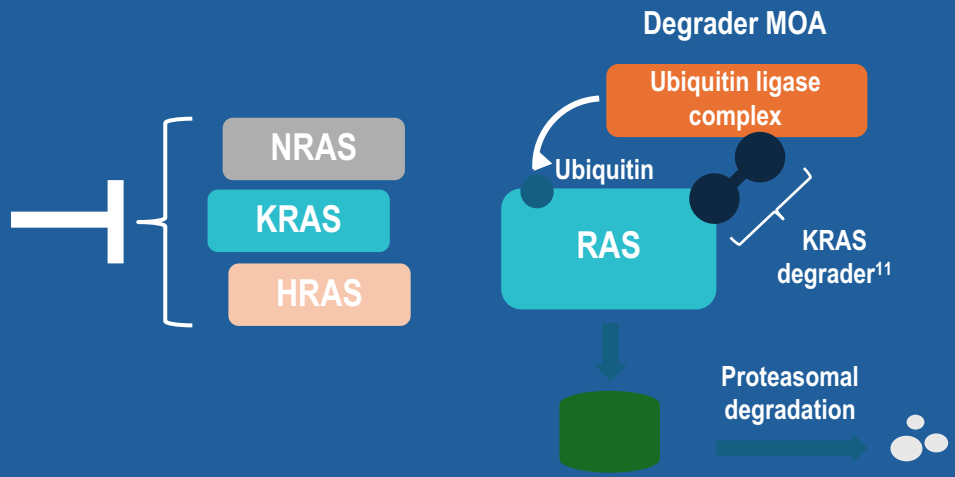
Anti-EGFR + pan-RAS inhibitor + KRAS G12D inhibitor†

- Cetuximab + Pan-RASi ± KRAS G12Di/mFOLFOX6[7]



Anti-EGFR + pan-RAS inhibitor†

- Pan-KRASi LY4066434 ± cetuximab[8]
- Pan-RASi AMG 410 ± panitumumab[9]
- Pan-RAS degrader ASP5834 ± panitumumab[10]



1.https://clinicaltrials.gov/study/NCT06586515;2.https://clinicaltrials.gov/study/NCT06599502;3.https://clinicaltrials.gov/study/NCT06179160;4.https://clinicaltrials.gov/study/NCT05382559;5.https://www.clinicaltrials.gov/study/NCT06619587;6.8.https://www.clinicaltrials.gov/study/NCT06607185;9.https://www.clinicaltrials.gov/study/NCT07094113;10.https://www.clinicaltrials.gov/study/NCT07094204; 11. Tolcher AW, et al. J Clin Oncol 2023;41:TPS764

OTHER PLAYERS IN THE ARENA

HER 2 OVEREXPRESSED

LOW FREQUENCY MOLECULAR ABERRATIONS

NEW COMPOUNDS (ADCs, BITEs)

NEW TARGETS
(DKK1, ATM, revisiting- MET)

THANK YOU!

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