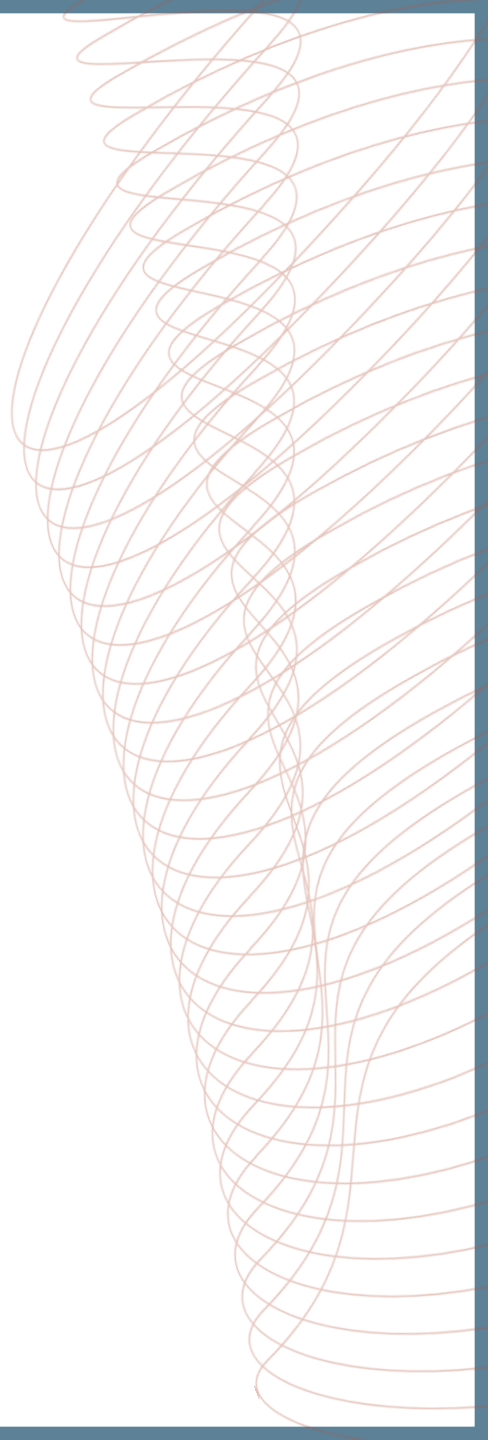




COR2ED

THE HEART OF MEDICAL EDUCATION

CLINICAL TOPIC NEWSLETTER

**THE LATEST DEVELOPMENTS IN
BRAF-MUTATED AND MSI-H CRC**

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July 2025

DEVELOPED BY GI CONNECT

This programme is developed by GI CONNECT, an international group of experts in the field of gastrointestinal oncology.



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CLINICAL TAKEAWAYS

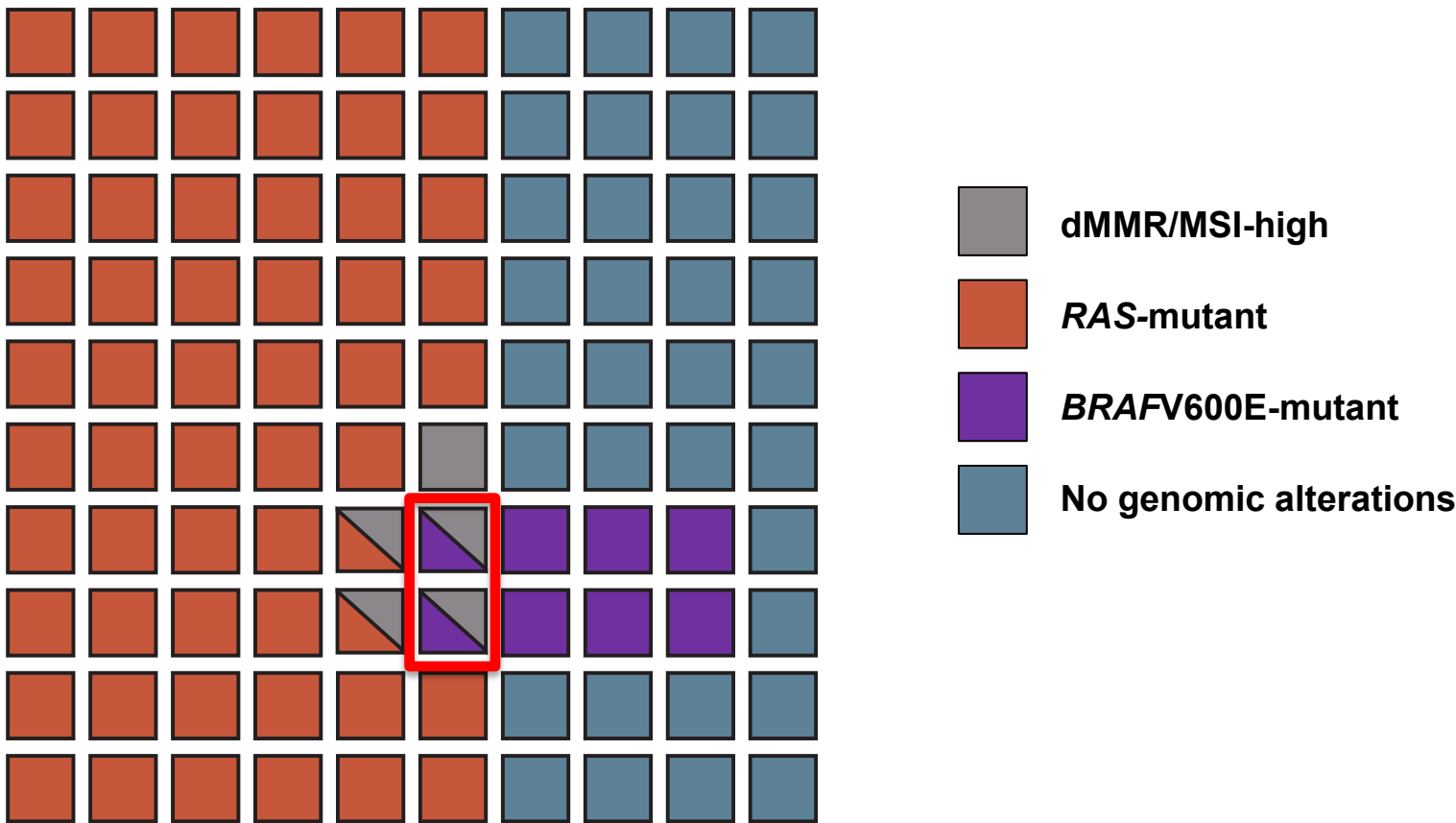
- **Dual immunotherapy is now 1st line for dMMR mCRC patients:** CheckMate 8HW demonstrated significant benefit from adding ipilimumab to nivolumab in dMMR patients regardless of *BRAF* status
- **FOLFOX + encorafenib/cetuximab is a new 1st line standard for *BRAF*-mutant/pMMR mCRC:** BREAKWATER showed the combination of encorafenib/cetuximab with FOLFOX chemotherapy significantly improves outcomes, doubling survival in *BRAF*V600E-mutant patients
- **Encorafenib + cetuximab remains effective post-immunotherapy:** for dMMR and *BRAF*-mutant patients progressing after immunotherapy, 2nd line treatment with encorafenib + cetuximab is effective, showing comparable benefit regardless of MMR status, supported by real-world evidence
- **Clear treatment sequencing is emerging:**
 - **dMMR/*BRAF*-mutant mCRC:** 1) immunotherapy (ipi-nivo), 2) targeted therapy (encorafenib + cetuximab), and 3) chemotherapy as a third-line option
 - **pMMR/*BRAF*-mutant mCRC:** 1) FOLFOX +EC, 2) chemotherapy/anti-angiogenesis), and 3) FTD-TPI/bevacizumab as a third-line option

EDUCATIONAL OBJECTIVES

1. Understand **clinical trial data and real-world evidence** of therapies for the **treatment of *BRAFV600E*-mutant and MSI-H CRC** and relevant patient subgroups
2. Recognise the appropriate **sequencing of therapies** for the treatment of ***BRAFV600E*-mutant and MSI-H CRC** across the patient journey to ensure **optimal outcomes**

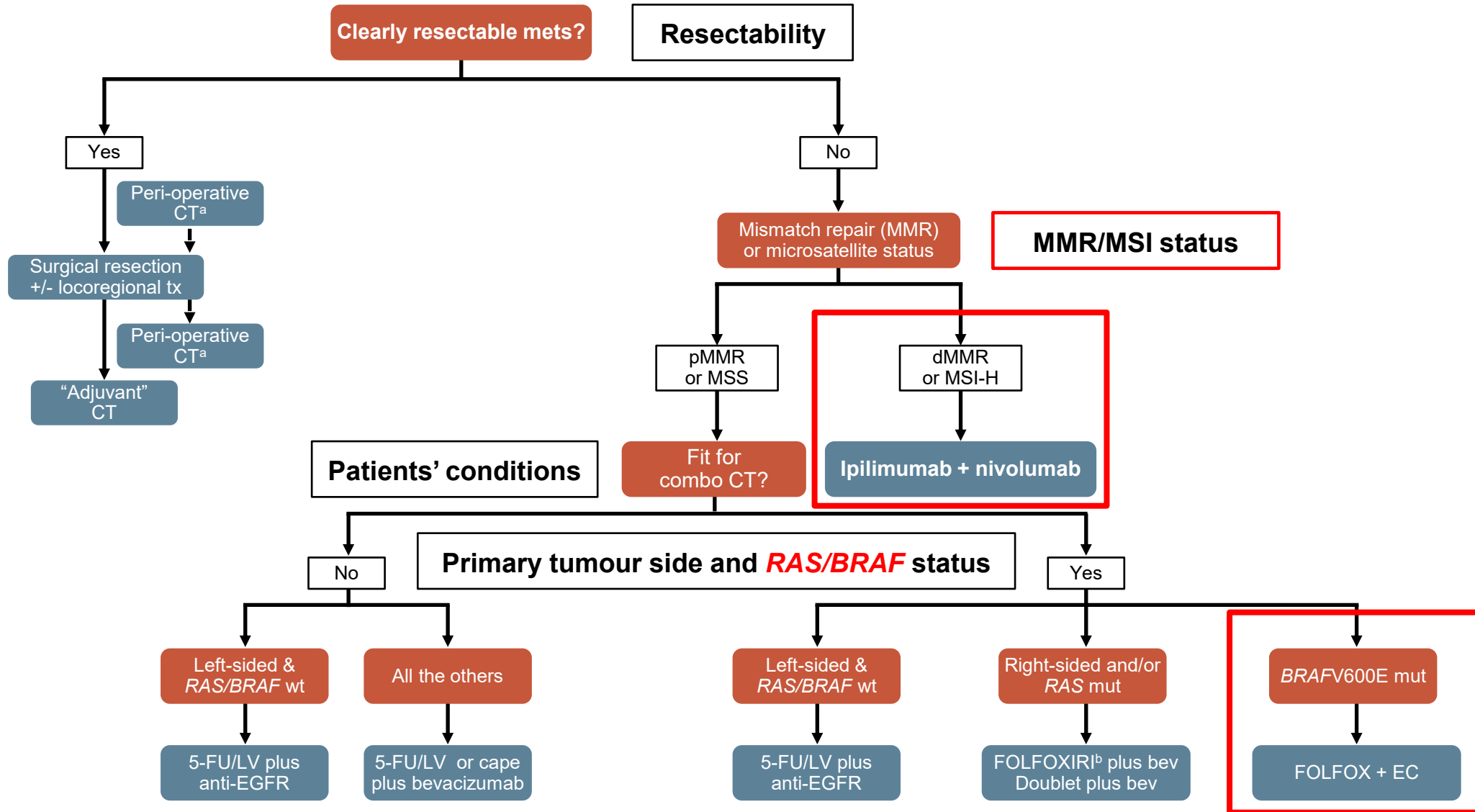
MOLECULAR SUBGROUPS OF mCRC

ACCORDING TO INTERNATIONAL GUIDELINES



dMMR, deficient mismatch repair; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high
Cervantes A, et al. Ann Oncol 2023;34(1):10-32; Cervantes A, et al. Ann Oncol. 2024;35(2):241-243

CHOICE OF THE FIRST-LINE



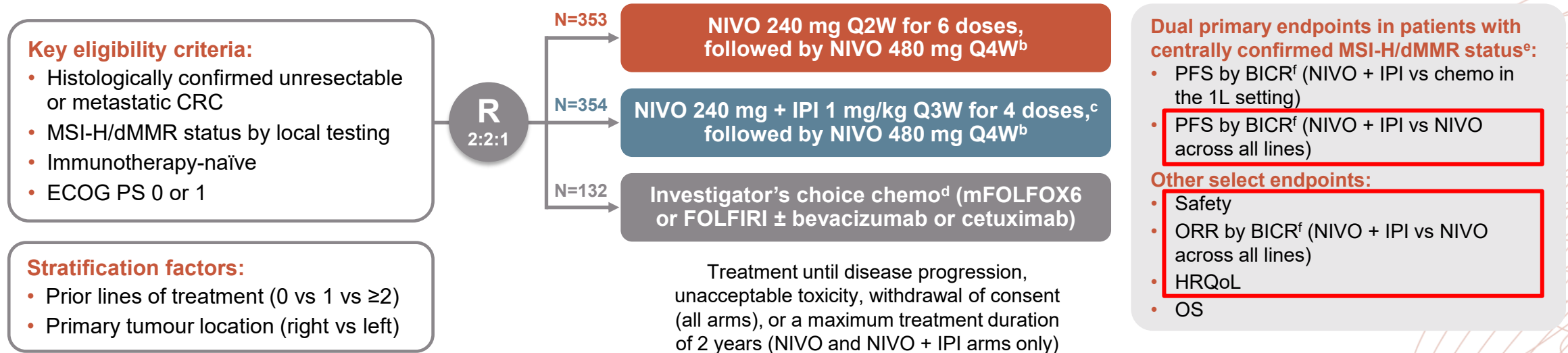
^a Not in dMMR/MSI-H?; ^b Only if <75 years old (71-75 years old with ECOG performance status 0)

bev, bevacizumab; cape, capecitabine; CT, chemotherapy; (d/p)MMR, (deficient/proficient) mismatch repair; EC, encorafenib-cetuximab; FOLFOX(IRI), fluorouracil / leucovorin / oxaliplatin (irinotecan); mets, metastases; MSI-H, microsatellite instability-high; MSS, microsatellite stable; mut, mutant; tx, treatment; wt, wild-type

Adapted from Cremolini C, ESMO 2022, Educational Session

CHECKMATE 8HW – STUDY DESIGN

- CheckMate 8HW is a randomised, multicentre, open-label phase 3 study^a



- At data cutoff (August 28, 2024), the median follow-up^g was 47.0 months (range, 16.7-60.5)

^a ClinicalTrials.gov. NCT04008030; ^b Patients with ≥2 prior lines are randomised only to the NIVO or NIVO + IPI arms; ^c Patients can continue NIVO treatment upon early IPI discontinuation;

^d Patients receiving investigator's choice of chemo are eligible to receive NIVO + IPI upon progression (crossover treatment);

^e Confirmed using either IHC and/or polymerase chain reaction-based tests; ^f Evaluated using RECIST v1.1; ^g Time between randomisation and data cutoff among all randomised patients across all 3 treatment arms

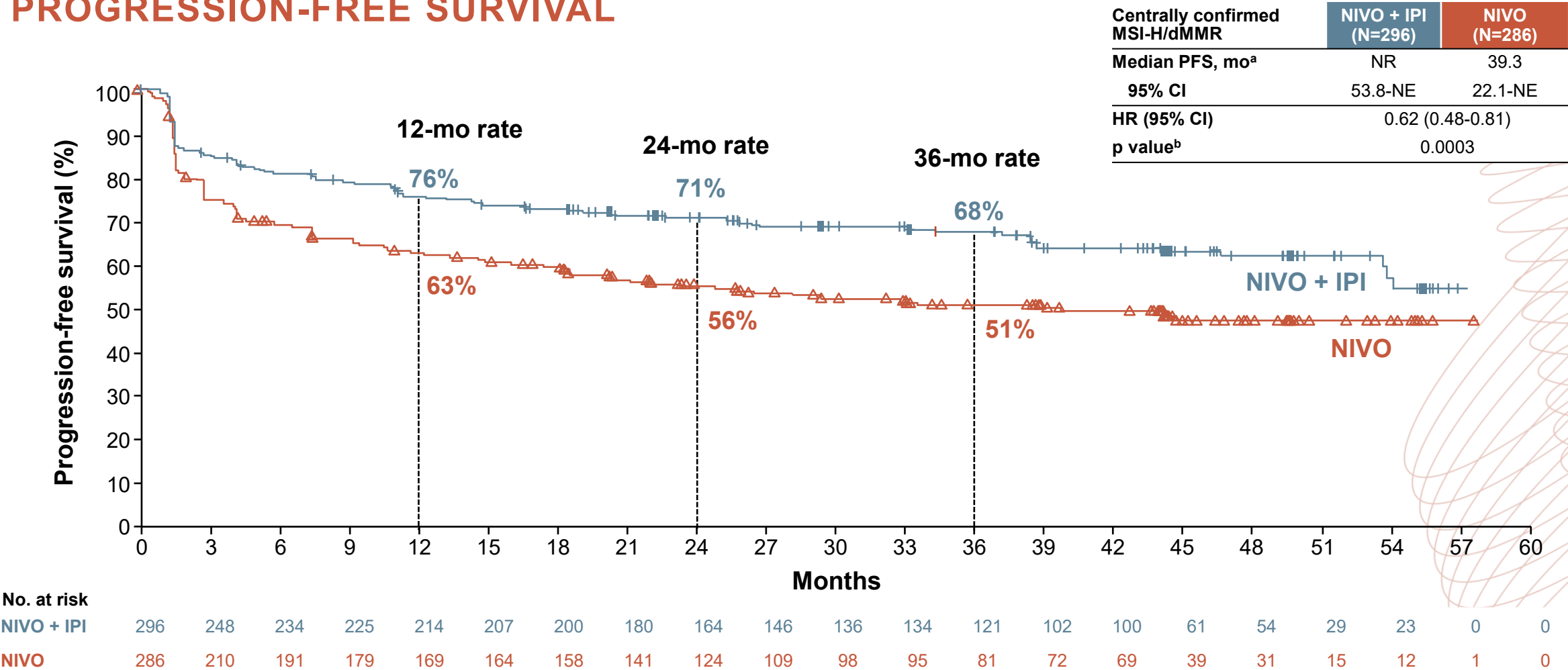
1L, first-line; BICR, blinded independent central review; chemo, chemotherapy; CRC, colorectal cancer; dMMR, deficient mismatch repair; ECOG PS, Eastern Cooperative Oncology Group performance status; FOLFIRI, fluorouracil / leucovorin / irinotecan; HRQoL, health related quality of life; IPI, ipilimumab; IHC, immunohistochemistry; mFOLFOX6, modified fluorouracil / leucovorin / oxaliplatin; MSI-H, microsatellite instability-high; NIVO, nivolumab; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q2/3/4W, every 2/3/4 weeks;

R, randomisation; RECIST, Response Evaluation Criteria in Solid Tumours

André T, et al. J Clin Oncol. 43(Number 4_suppl; abstract LBA143) [ASCO GI 2025; oral presentation]; André T, et al. Lancet. 2025;405:383-395

CHECKMATE 8HW: NIVO +/- IPI ACROSS ALL LINES OF THERAPY IN dMMR/MSI-H mCRC

PROGRESSION-FREE SURVIVAL



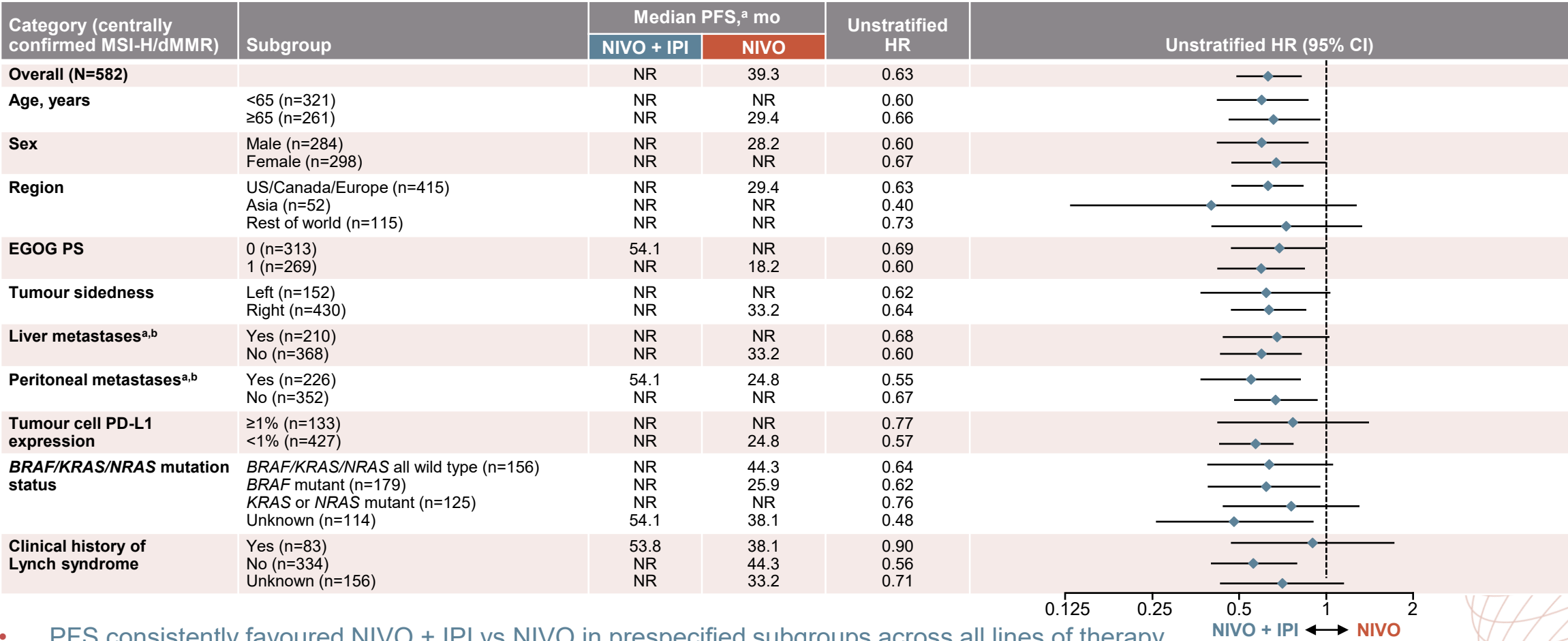
^a Per BICR; ^b Boundary for statistical significance: p<0.0095

BICR, blinded independent central review; CI, confidence interval; dMMR, deficient mismatch repair; HR, hazard ratio; IPI, ipilimumab; mCRC, metastatic colorectal cancer; mo, months; MSI-H, microsatellite instability-high; NE, not evaluable; NIVO, nivolumab; NR, not reached; PFS, progression-free survival

André T, et al. J Clin Oncol. 43(4_suppl; abstract LBA143) [ASCO GI 2025; oral presentation]; André T, et al. Lancet. 2025;405:383-395

CHECKMATE 8HW – NIVO +/- IPI ACROSS ALL LINES OF THERAPY IN dMMR/MSI-HIGH mCRC

PROGRESSION-FREE SURVIVAL SUBGROUP ANALYSIS



- PFS consistently favoured NIVO + IPI vs NIVO in prespecified subgroups across all lines of therapy

^a Per BICR; ^b Patients may have had more than one site of metastasis

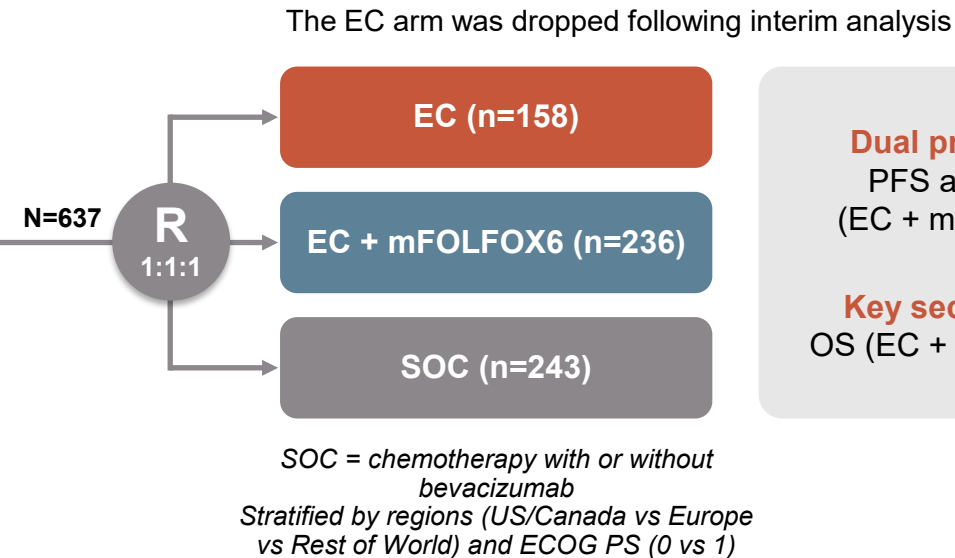
BREAKWATER: FOLFOX/ENCO/CET VS SOC IN FIRST-LINE BRAF-MUTANT mCRC

Inclusion criteria

- Age ≥ 16 years (or ≥ 18 years based on country)
- No prior systemic treatment for metastatic disease
- Measurable disease (RECIST 1.1)
- BRAFV600E-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 tumours (unless patients were ineligible to receive immune checkpoint inhibitors due to a pre-existing medical condition)
- Presence of a RAS mutation



Dual primary endpoints:
PFS and ORR by BICR
(EC + mFOLFOX6 vs SOC)

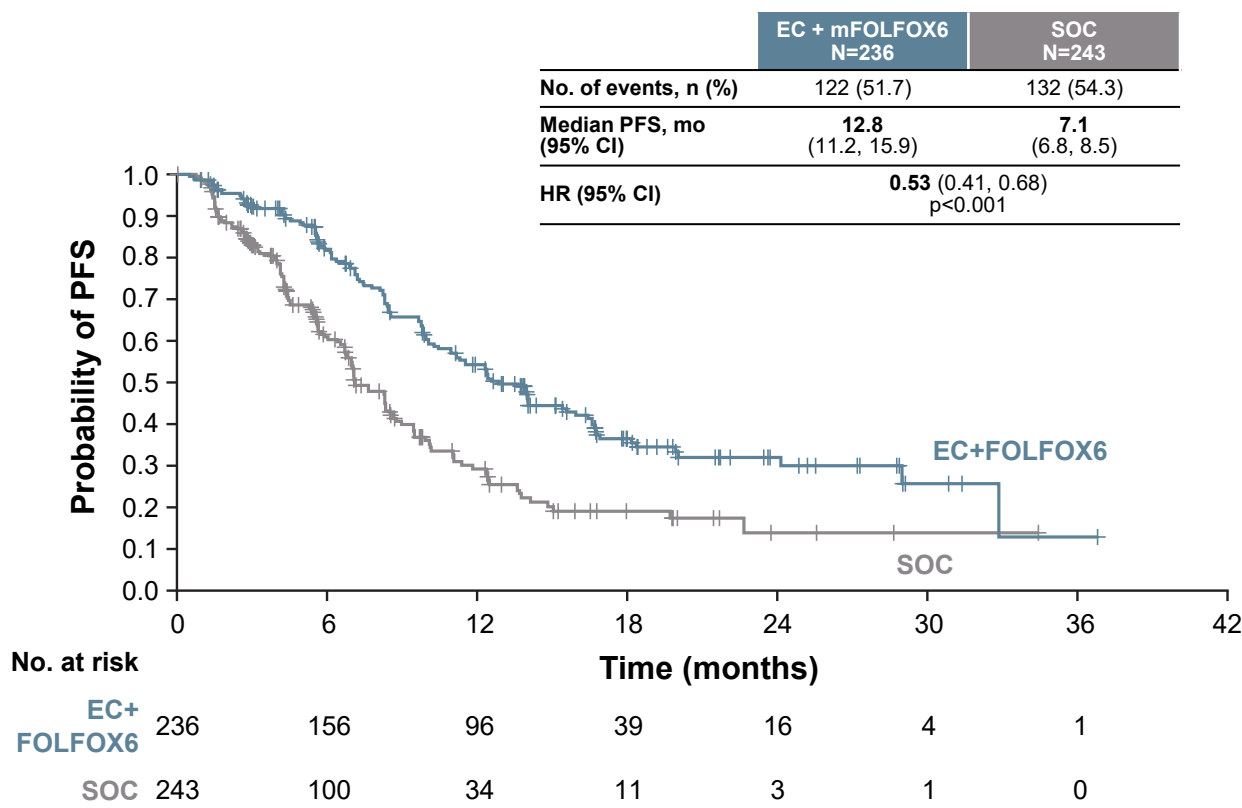
Key secondary endpoint:
OS (EC + mFOLFOX6 vs SOC)

BICR, blinded independent central review; CET, cetuximab; dMMR, deficient mismatch repair; EC, encorafenib plus cetuximab; ECOG PS, Eastern Cooperative Oncology Group performance status; ENCO, encorafenib; mCRC, metastatic colorectal cancer; (m)FOLFOX(6), (modified) fluorouracil / leucovorin / oxaliplatin; MSI-H, microsatellite instability-high; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomisation; RECIST, Response Evaluation Criteria in Solid Tumours; SOC, standard of care

Elez E, et al. N Eng J Med. 2025; 392:2425-37; Kopetz S, et al. J Clin Oncol. 43(4_suppl; abstract 16) [ASCO GI 2025; oral presentation]

BREAKWATER: FOLFOX/ENCO/CET VS SOC IN FIRST-LINE BRAF-MUTANT mCRC

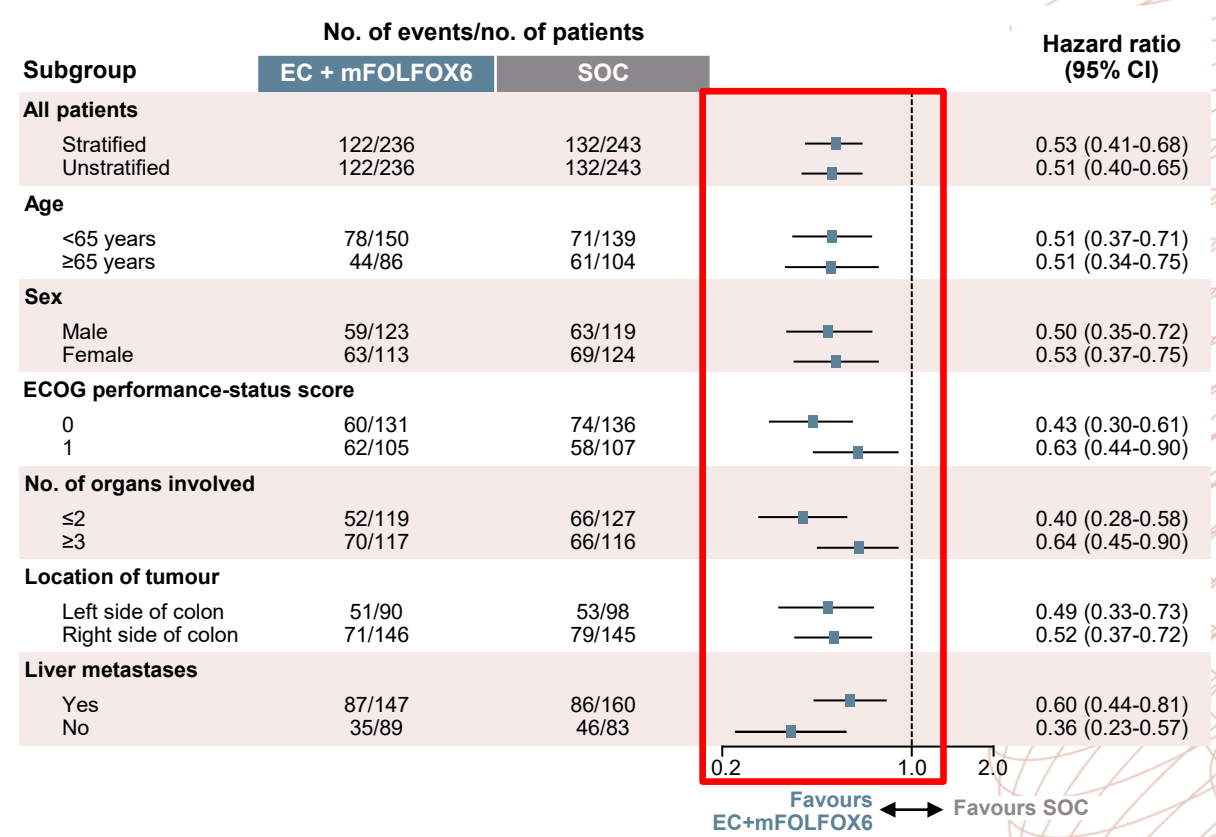
PROGRESSION-FREE SURVIVAL



Data cutoff: January 6, 2025.

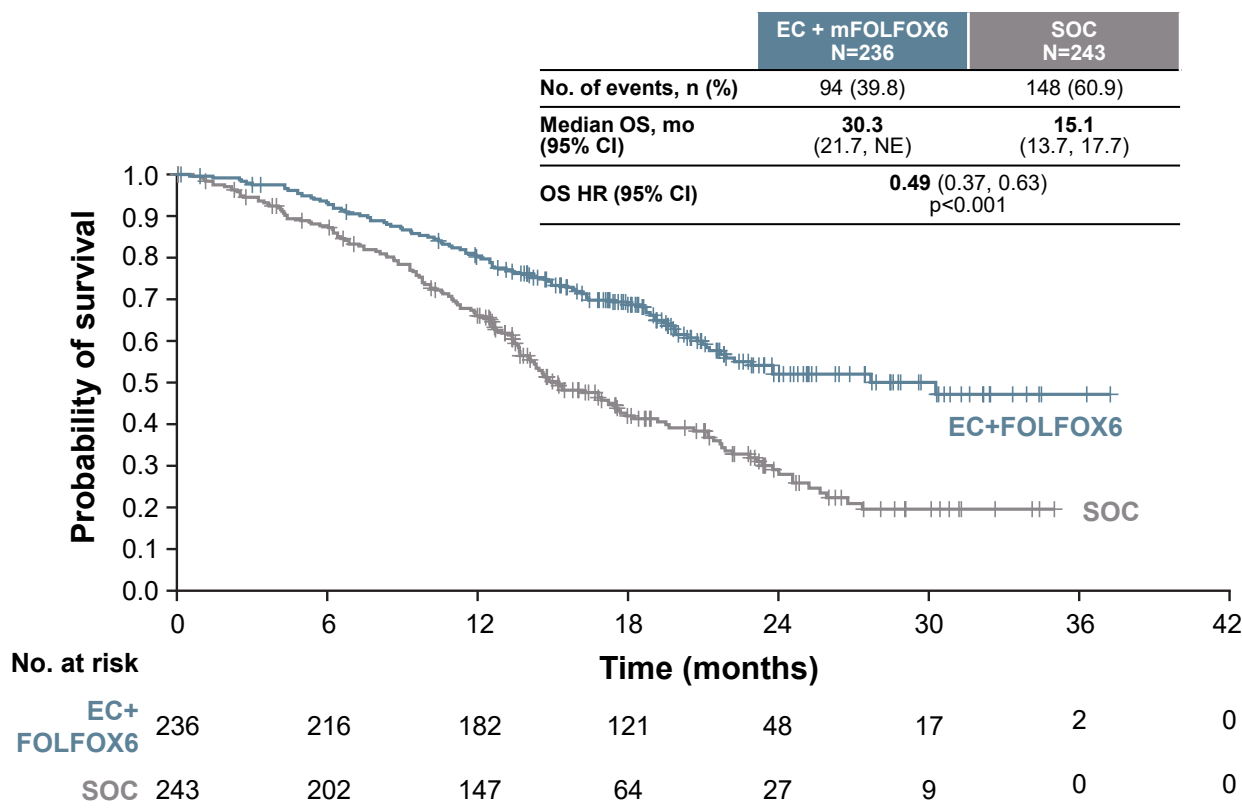
CET, cetuximab; CI, confidence interval; EC, encorafenib plus cetuximab; ECOG PS, Eastern Cooperative Oncology Group; ENCO, encorafenib; HR, hazard ratio; mCRC, metastatic colorectal cancer; (m)FOLFOX(6), (modified) fluorouracil / leucovorin / oxaliplatin; mo, months; PFS, progression-free survival; SOC, standard of care

Elez E, et al. N Eng J Med. 2025; 392: 2425-37



BREAKWATER: FOLFOX/ENCO/CET VS SOC IN FIRST-LINE BRAF-MUTANT mCRC

OVERALL SURVIVAL



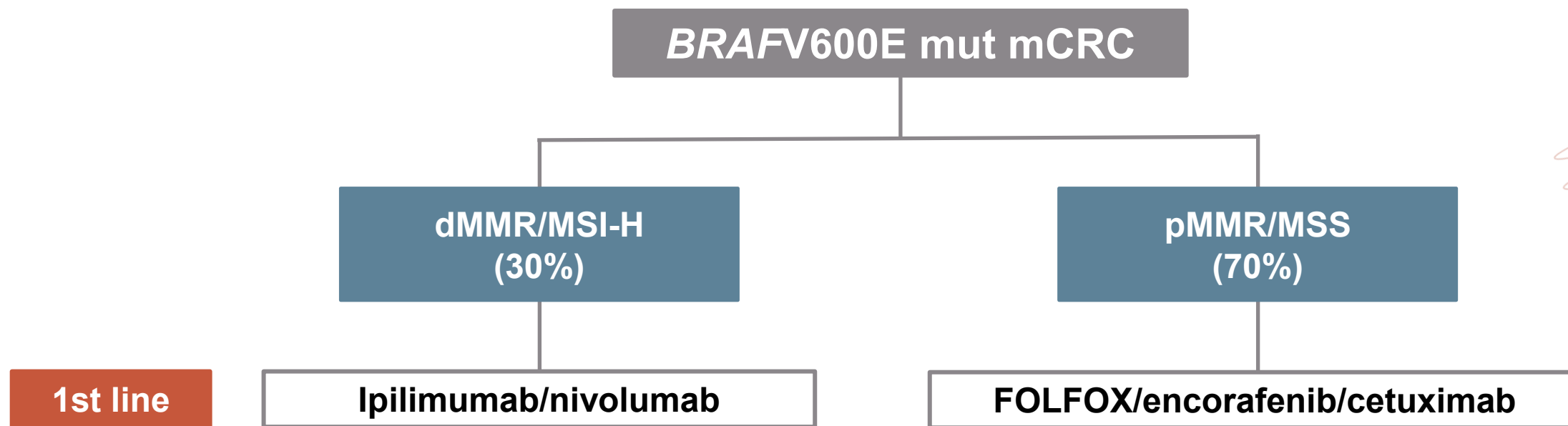
Subgroup	No. of events/no. of patients		Hazard ratio (95% CI)
	EC + mFOLFOX6	SOC	
All patients			
Stratified	94/236	148/243	0.49 (0.38-0.63)
Unstratified	94/236	148/243	0.48 (0.37-0.62)
Age			
<65 years	56/150	85/139	0.44 (0.31-0.62)
≥65 years	38/86	63/104	0.54 (0.36-0.82)
Sex			
Male	54/123	71/119	0.59 (0.42-0.85)
Female	40/113	77/124	0.38 (0.26-0.56)
ECOG performance-status			
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			
≤2	32/119	66/127	0.39 (0.25-0.59)
≥3	62/117	82/116	0.52 (0.38-0.73)
Side of tumour			
Left	38/90	62/98	0.48 (0.32-0.72)
Right	56/146	86/145	0.49 (0.35-0.68)
Liver metastases			
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.

CET, cetuximab; CI, confidence interval; EC, encorafenib plus cetuximab; ECOG PS, Eastern Cooperative Oncology Group; ENCO, encorafenib; HR, hazard ratio; mCRC, metastatic colorectal cancer; (m)FOLFOX(6), (modified) fluorouracil / leucovorin / oxaliplatin; mo, months; OS, overall survival; SOC, standard of care

Elez E, et al. N Eng J Med. 2025;392: 2425-37

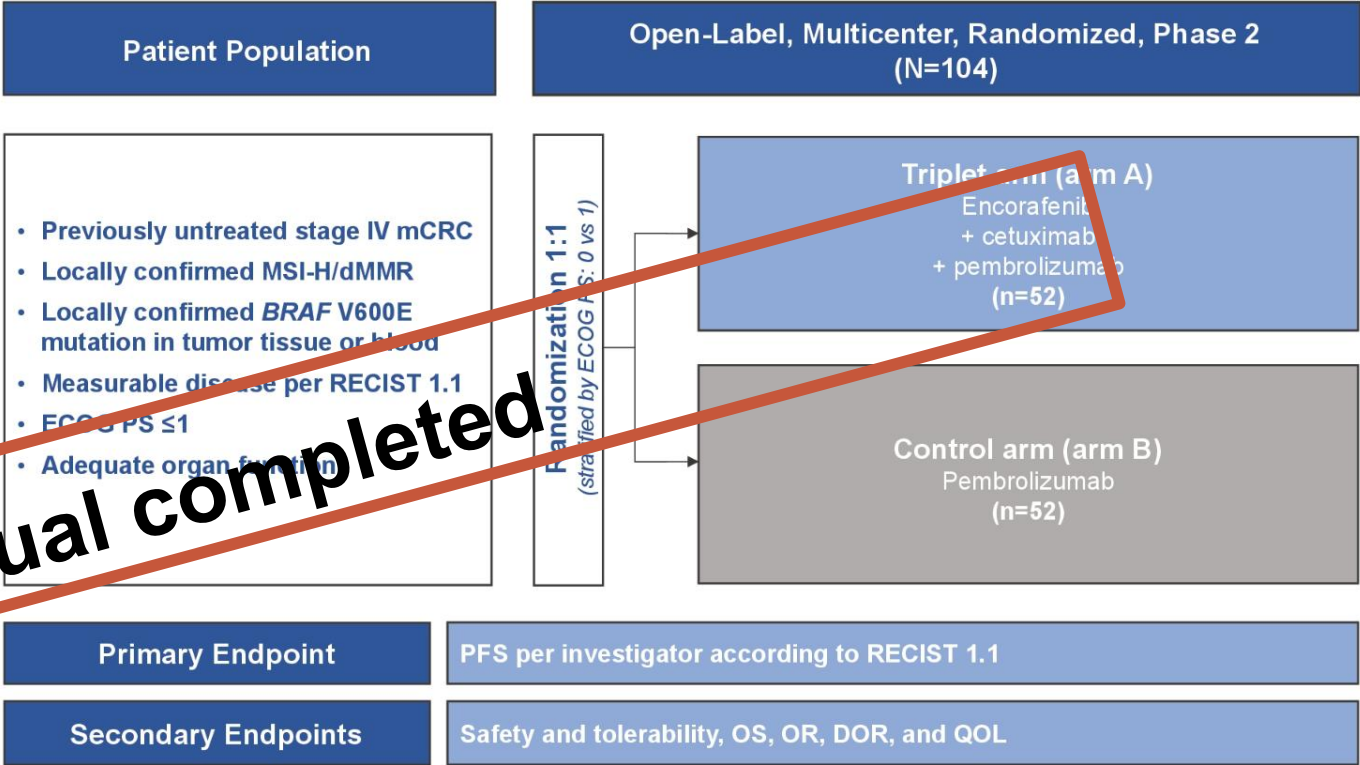
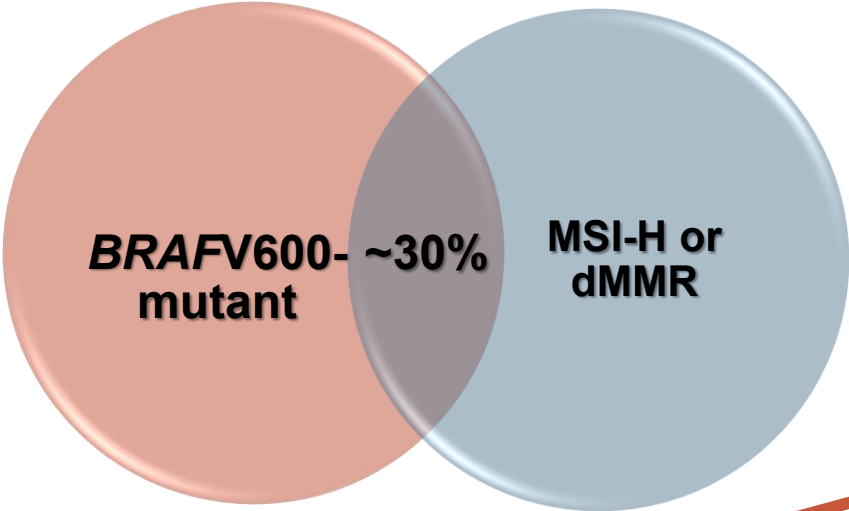
CONTINUUM OF CARE FOR *BRAF*V600E-MUTANT mCRC PATIENTS



Cremolini C. Personal communication

d/pMMR, deficient/proficient mismatch repair; FOLFOX, fluorouracil / leucovorin / oxaliplatin; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high; MSS, microsatellite stable; mut, mutant

ON THE HORIZON FOR UNTREATED dMMR/MSI-H AND BRAF-MUTANT mCRC



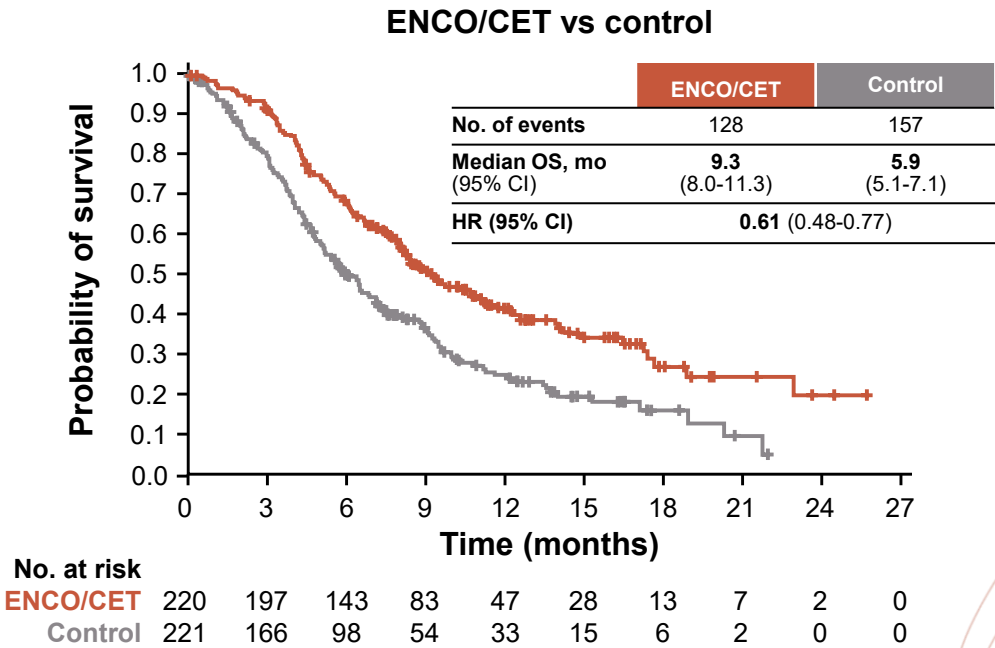
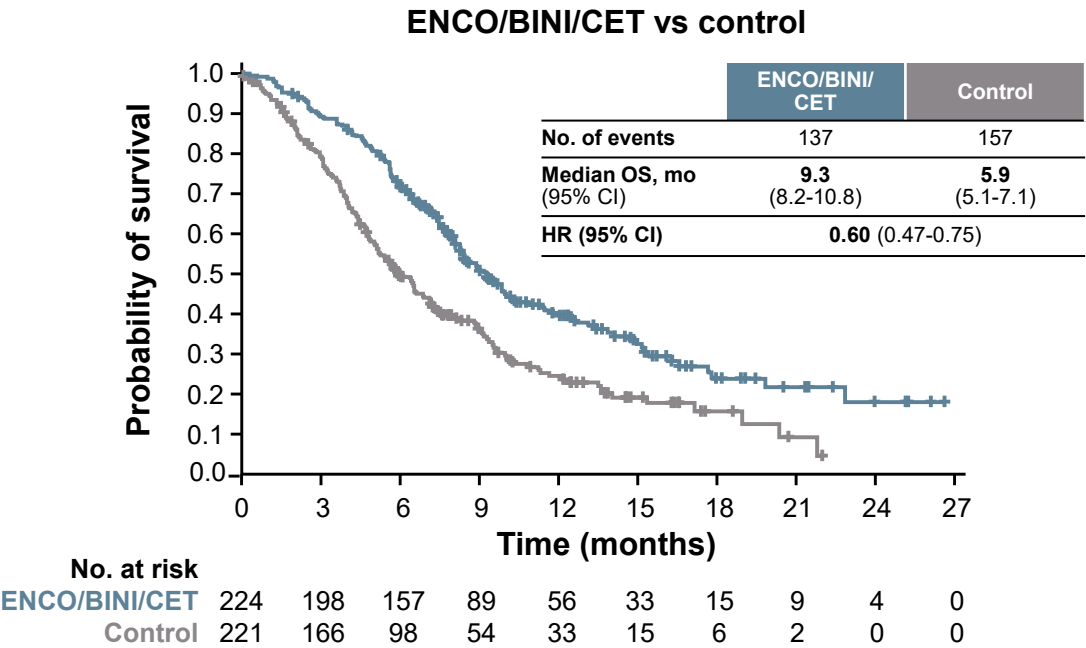
Accrual completed

NCT05217446

dMMR, deficient mismatch repair; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high; OR, objective response; OS, overall survival; PFS, progression-free survival; QOL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumours
Kopetz S, et al. J Clin Oncol. 2022;40(16_suppl; abstract TPS3634) [ASCO 2022; oral presentation]

BEACON: ENCO/CET VS SOC IN PRE-TREATED BRAF-MUTANT mCRC

OVERALL SURVIVAL RESULTS^a



OBJECTIVE RESPONSE RATE

Confirmed response by blinded central review	ENCO/BINI/CET (triplet) N=224	ENCO/CET (doublet) N=220	Control N=221
Objective response rate, %	27%	20%	2%
95% CI	21%, 33%	15%, 25%	<1%, 5%
p value vs control	<0.0001	<0.0001	NA

^a Median follow-up: 12.8 months

BINI, binimetinib; CET, cetuximab; CI, confidence interval; ENCO, encorafenib; HR, hazard ratio; mCRC, metastatic colorectal cancer; mo, months; NA, not applicable; OS, overall survival; SOC, standard of care

Tabernero J, et al. J Clin Oncol. 2021;39:273-284

CONFIRMATORY REAL-WORLD EVIDENCE: FINDINGS CONSISTENT WITH THE BEACON TRIAL, FOR EC TREATMENT IN *BRAF*-MUTATED CRC

BEACON EFFICACY FINDINGS (DOUBLET THERAPY)

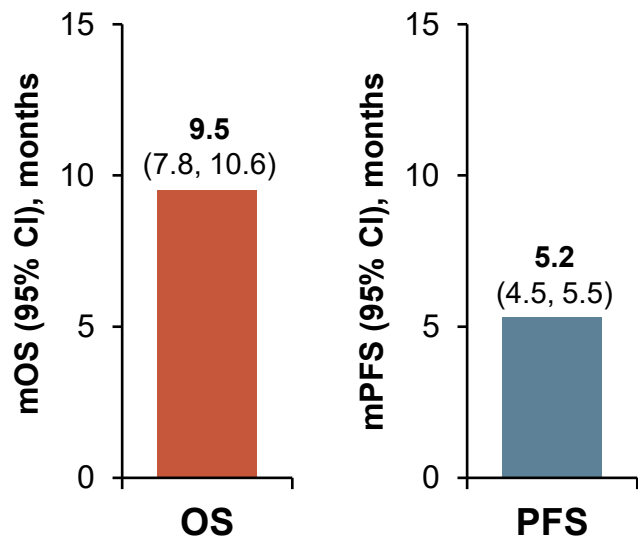
Median PFS: 4.3 months; median OS: 9.3 months

BERING CRC (N=150)

(3 Sep 2020 to 26 Apr 2024; ongoing)¹



Encorafenib + cetuximab (n=141; FAS)

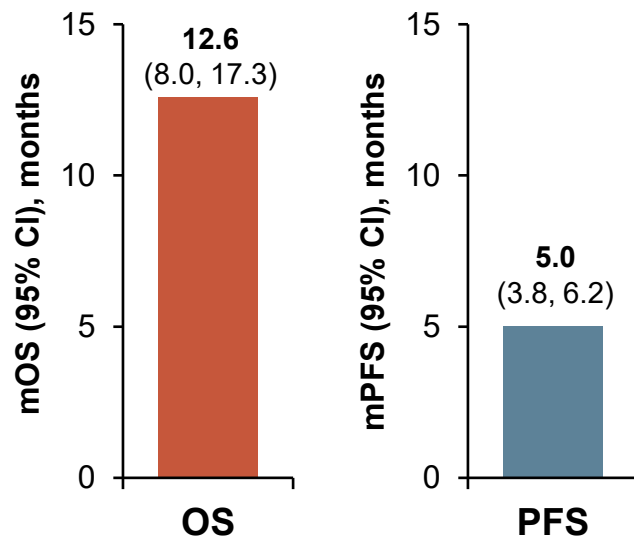


CONFIDENCE (N=81)

(Mar to Jul 2022)²



Encorafenib + cetuximab (N=81)

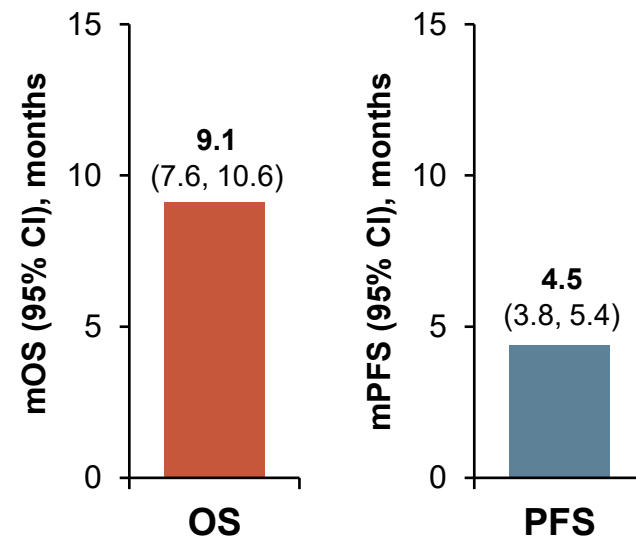


B-REAL, an AGEO study (N=201)

(Jan 2020 to Jun 2022)³



Encorafenib + cetuximab (n=176)



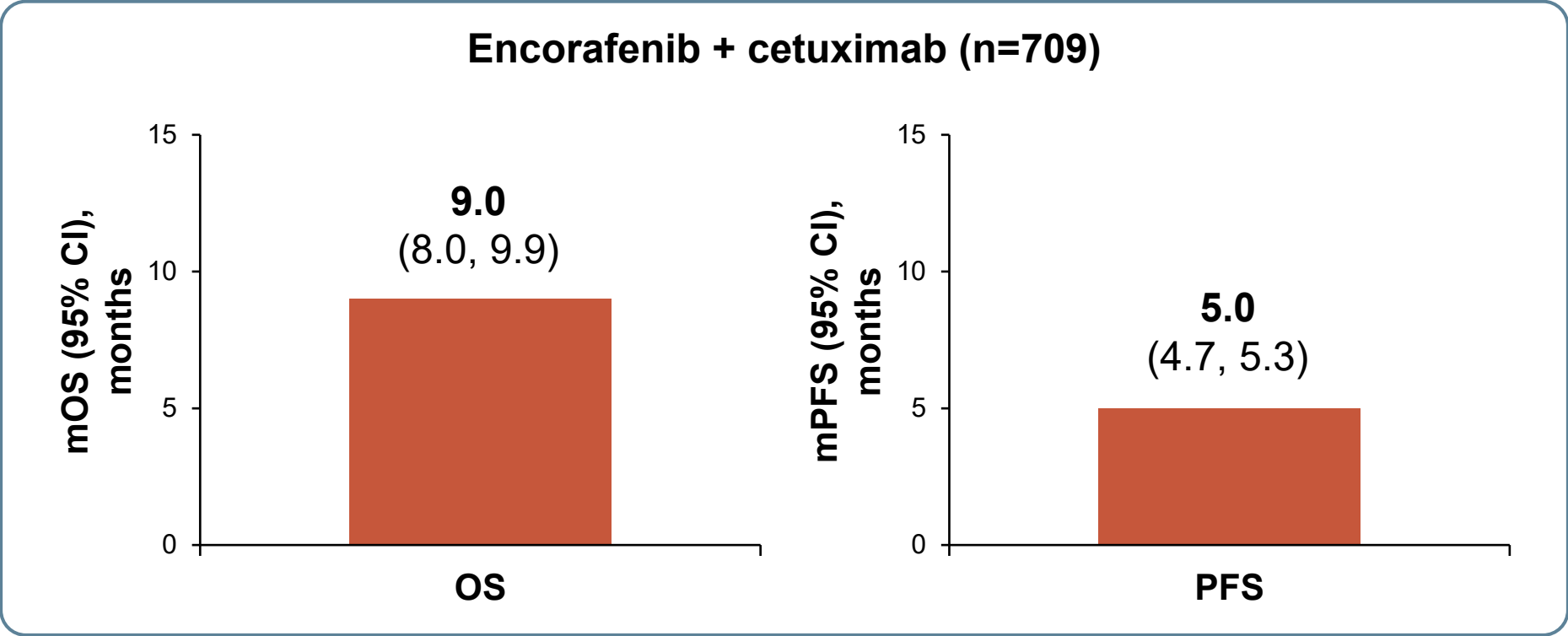
AGEO, Association des Gastro-Entérologues Oncologues; CI, confidence interval; FAS, full analysis set; (m)OS, (median) overall survival; (m)PFS, (median) progression-free survival

1. Stintzing S, et al. Annals of Oncology (2025) 36 (suppl_1): S1-S65. 10.1016/annonc/annonc1820 (ESMO GI 2025; poster presentation); 2. Fernandez Montes A, et al. ESMO Real World Data and Digital Oncology 2024; 5:100055; 3. Gallois C, et al. ESMO Open 2024; 9: doi.org/10.1016/j.esmoop.2024.103696

CONFIRMATORY REAL-WORLD EVIDENCE: FINDINGS CONSISTENT WITH THE BEACON TRIAL, FOR EC TREATMENT IN BRAF-MUTATED CRC

RETROSPECTIVE, LONGITUDINAL, POOLED ANALYSIS

Results from pooled dataset (N=709)
(BERING CRC, B-REAL, CATAMARAN, CONFIDENCE, GONO Cohort)



CI, confidence interval; EC, encorafenib +cetuximab; (m)OS, (median) overall survival; (m)PFS, (median) progression-free survival
Cremolini C, et al. Ann Oncol. 2025;36(supplement 1: S23-S24) [ESMO GI 2025; poster presentation]

BRAFi + EGFRi ± MEKi FOLLOWING ICI_s IN BRAF-MUTANT AND dMMR/MSI-H mCRC^{1,2}

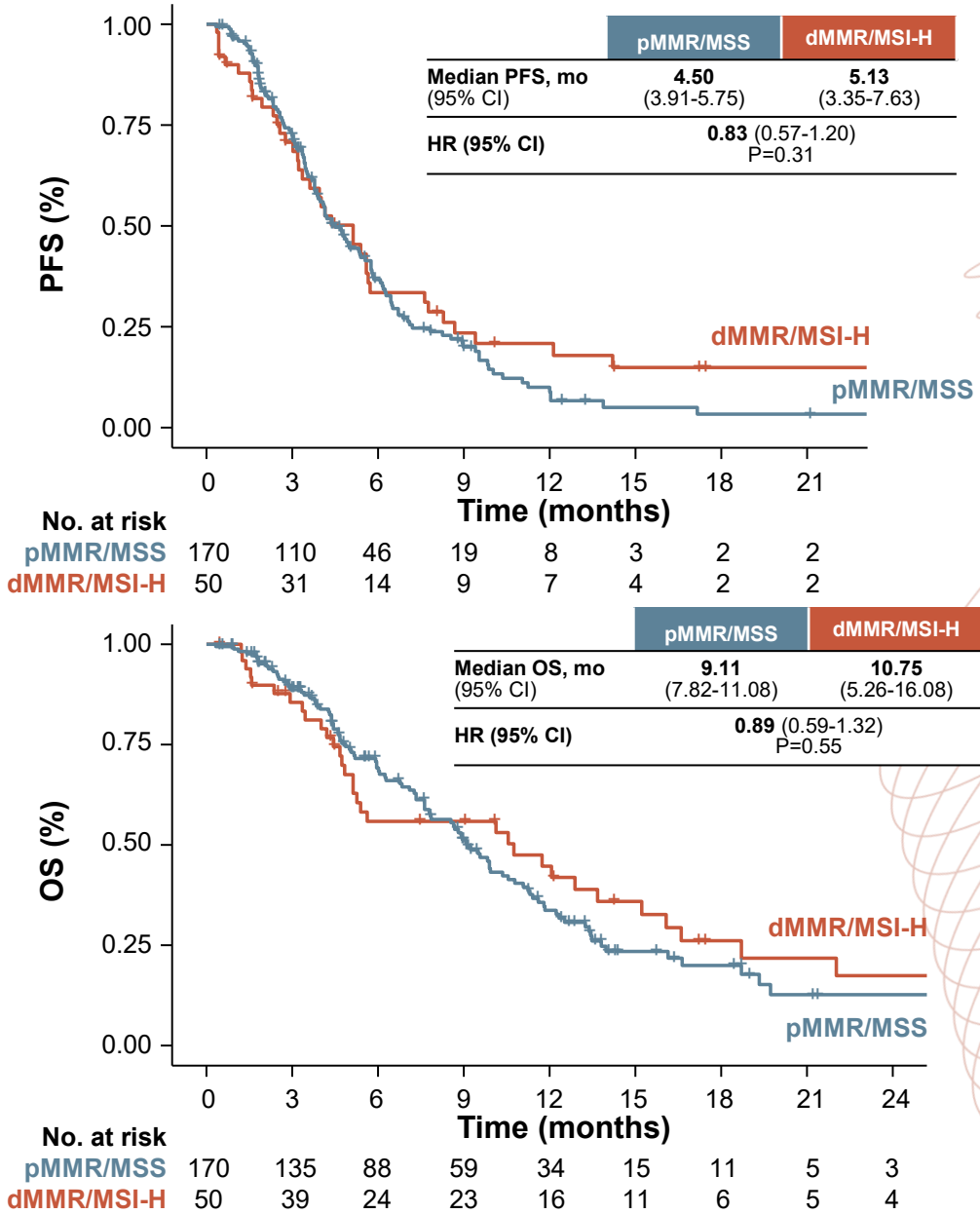
B-REAL and AGEO-IMMUNODIG MSI, AGEO studies (N=220) (Jan 2017 to Jan 2024)



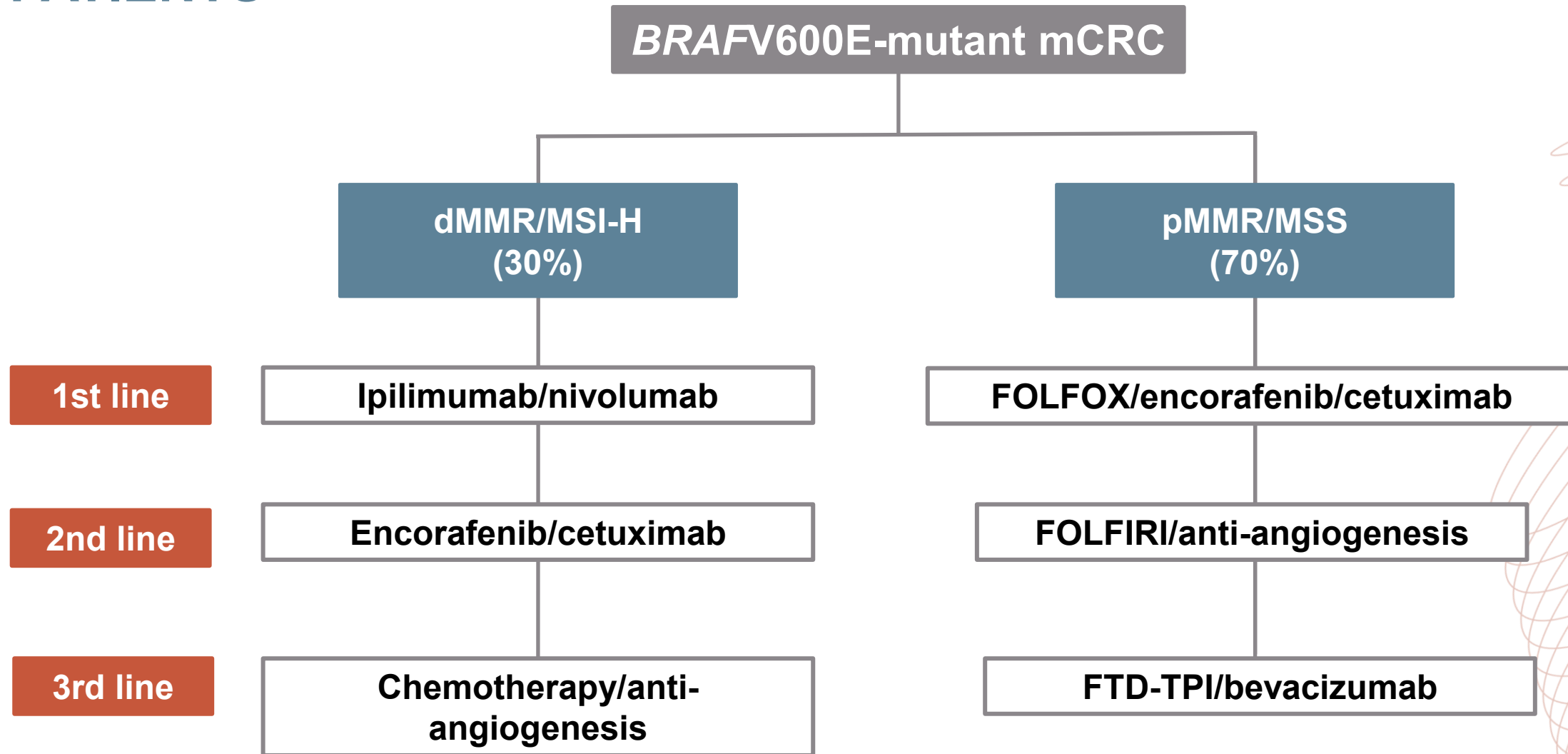
	BRAFV600E-mut pMMR/MSS (n=170)	BRAFV600E-mut dMMR/MSI-H (n=50)	HR (95% CI)	p value
ORR, %	32	18		0.09
DCR, %	73	60		0.11
mPFS, months	4.50	5.13	0.83	0.31
mOS, months	9.11	10.75	0.89	0.55

AGEO, Association des Gastro-Entérologues Oncologues; BRAFi, BRAF inhibitor; CI, confidence interval;
BRAFi, BRAF inhibitor; DCR, disease control rate; d/pMMR, deficient/proficient mismatch repair;
EGFRi, EGFR inhibitor; HR, hazard ratio; ICI, immune checkpoint inhibitor; mCRC, metastatic colorectal cancer; MEKi, MEK inhibitor; MSI-H, microsatellite instability-high;
(m)OS, (median) overall survival; (m)PFS, (median) progression-free survival; MSS, microsatellite stability; mut, mutant; ORR, overall response rate

1. Ambrosini M, et al. Ann Oncol. 2024;35(Supplement 1; S32) [ESMO GI Congress 2024; poster presentation]; 2. Ambrosini M, et al. Eur J Cancer. 2024;210:114290



CONTINUUM OF CARE FOR *BRAF*V600E-MUTANT mCRC PATIENTS

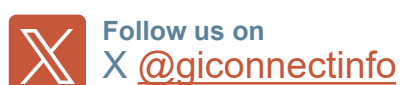


d/pMMR, deficient/proficient mismatch repair; FOLFIRI, fluorouracil / leucovorin / irinotecan; FOLFOX, fluorouracil / leucovorin / oxaliplatin; FTD-TPI, trifluridine-tipiracil; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high; MSS, microsatellite stable

Cremolini C. Personal communication.



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