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GI CONNECT

HIGHLIGHTS FROM ASCO GI 2025
BRAF-MUTATED CRC

Dr Elena Élez, MD, PhD
Vall d'Hebron University Hospital, Barcelona, Spain

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CRC, colorectal cancer

DEVELOPED BY GI CONNECT

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CLINICAL TAKEAWAYS

- **BREAKWATER:** demonstrated a statistically significant and clinically meaningful benefit in ORR with EC + mFOLFOX6 that was rapid and durable in *BRAF* V600E-mutant mCRC. The results support EC + mFOLFOX6 as a new first-line SOC for patients with *BRAF* V600E-mutant CRC

- **CHECKMATE 8HW:** NIVO + IPI demonstrated statistically significant and clinically meaningful improvement in PFS vs NIVO in patients with MSI-H/dMMR mCRC across all lines of therapy and across prespecified subgroups, including patients who also harboured a *BRAF* mutation

dMMR, deficient mismatch repair; EC, encorafenib plus cetuximab; IPI, ipilimumab; mCRC, metastatic colorectal cancer; mFOLFOX6, modified fluouracil/leucovorin/oxaliplatin; MSI-H, microsatellite instability-high; NIVO, nivolumab; ORR, overall response rate; PFS, progression-free survival; SOC, standard of care

EDUCATIONAL OBJECTIVES

- Understand the **latest highlights** on practice changing ***BRAF*-mutated colorectal cancer data** from the ASCO GI 2025 conference, accentuating the implementation of the latest data into clinical practice

BREAKWATER: ANALYSIS OF FIRST-LINE ENCORAFENIB + CETUXIMAB + CHEMOTHERAPY IN *BRAF* V600E-MUTANT mCRC

Kopetz S, et al. Abstract 16, ASCO GI 2025

mCRC, metastatic colorectal cancer

BREAKWATER: BACKGROUND AND STUDY DESIGN

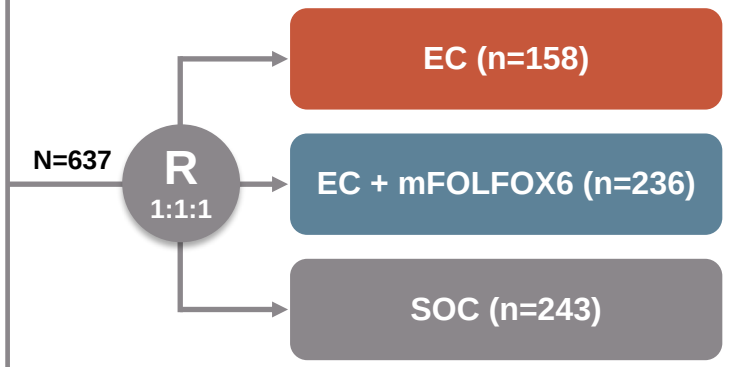
- 8%-12% of patients with mCRC have *BRAF* V600E mutations, which confer poor prognosis[1]
- Encorafenib plus cetuximab was approved for the treatment of previously treated patients with *BRAF* V600E-mutant mCRC based on the phase 3 BEACON trial[2,3]
- First-line treatment options remain an unmet need for patients with *BRAF* V600E-mutant mCRC[4,5]
- BREAKWATER is an open-label phase 3 trial in first-line *BRAF* V600E-mutant mCRC[6]

Inclusion criteria

- Age ≥16 years (or ≥18 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 tumours (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)

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

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

The EC arm was dropped following a protocol amendment

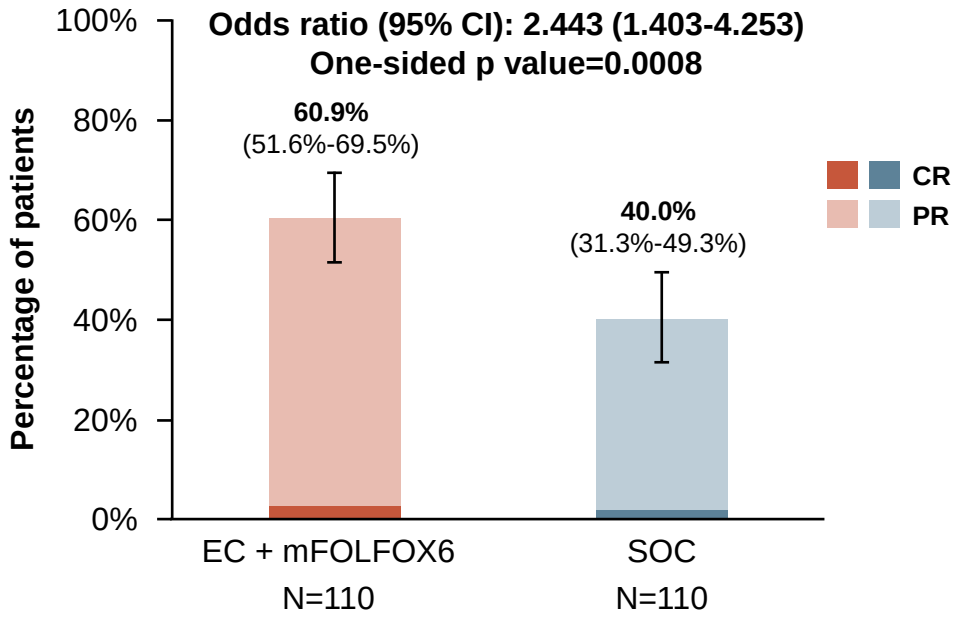
BICR, blinded independent central review; dMMR, deficient mismatch repair; EC, encorafenib plus cetuximab; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; mCRC, metastatic colorectal cancer; mFOLFOX6, modified fluorouracil / leucovorin / oxaliplatin; 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

1. Tabernero J, et al. ASCO Educ Book. 2022;42:254-263; 2. Tabernero J, et al. J Clin Oncol. 2021;39:273-284; 3. FDA Approves Cetuximab Plus Encorafenib for BRAF V600E-Mutant Metastatic CRC After Prior Therapy. Available here (accessed January 2025); 4. Van Cutsem E, et al. J Clin Oncol. 2023;412628-2637; 5. Cohen R, et al. J Natl Cancer Inst. 2021;113:1386-1395; 6. Kopetz S, et al. Abstract 16, ASCO GI 2025

BREAKWATER: RESPONSE RESULTS (CO-PRIMARY)

- Four-hundred-and-seventy-nine pts were randomised to the EC + mFOLFOX6 and SOC arms (EC + mFOLFOX6: n=236; SOC: n=243)
- Baseline demographics and disease characteristics were similar across arms (median age: 61.0 years; male: 50.5%; ECOG PS 0: 54.3%)

CONFIRMED ORR BY BICR



CONFIRMED BOR, TTR, AND DoR BY BICR

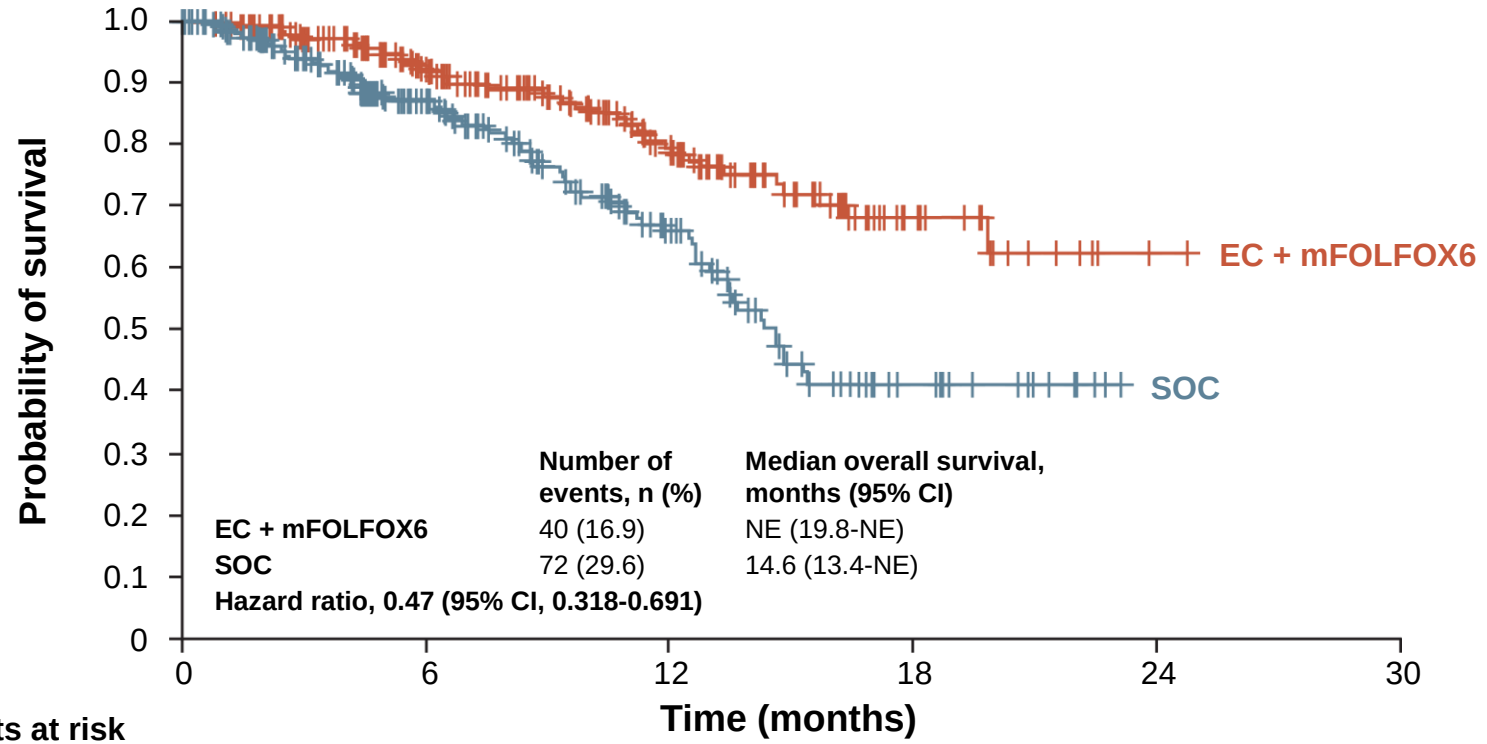
	EC + mFOLFOX6 N=110	SOC N=110
Confirmed best overall response, n (%)		
CR	3 (2.7)	2 (1.8)
PR	64 (58.2)	42 (38.2)
SD	31 (28.2)	34 (30.9)
Non-CR/non-PD	3 (2.7)	4 (3.6)
PD	3 (2.7)	9 (8.2)
NE	6 (5.5)	19 (17.3)
	N=67	N=44
TTR, median (range), weeks	7.1 (5.7-53.7)	7.3 (5.4-48.0)
Estimated DoR, median (range), months	13.9 (8.5-NE)	11.1 (6.7-12.7)
Patients with a DoR of ≥6 months, n (%)	46 (68.7)	15 (34.1)
Patients with a DoR of ≥12 months, n (%)	15 (22.4)	5 (11.4)

BICR, blinded independent central review; BOR, best overall response; CI, confidence interval; CR, complete response; DoR, duration of response; EC, encorafenib plus cetuximab; ECOG PS, Eastern Cooperative Oncology Group performance status; mFOLFOX6, modified fluouracil / leucovorin / oxaliplatin; NE, not estimable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; SOC, standard of care; TTR, time to response

Kopetz S, et al. Abstract 16, ASCO GI 2025; Kopetz S, et al. Nat Med. 2025. doi: 10.1038/s41591-024-03443-3. Online ahead of print.

BREAKWATER: OVERALL SURVIVAL (INTERIM) RESULTS

- There was a trend towards an improvement in overall survival but data are immature at this point



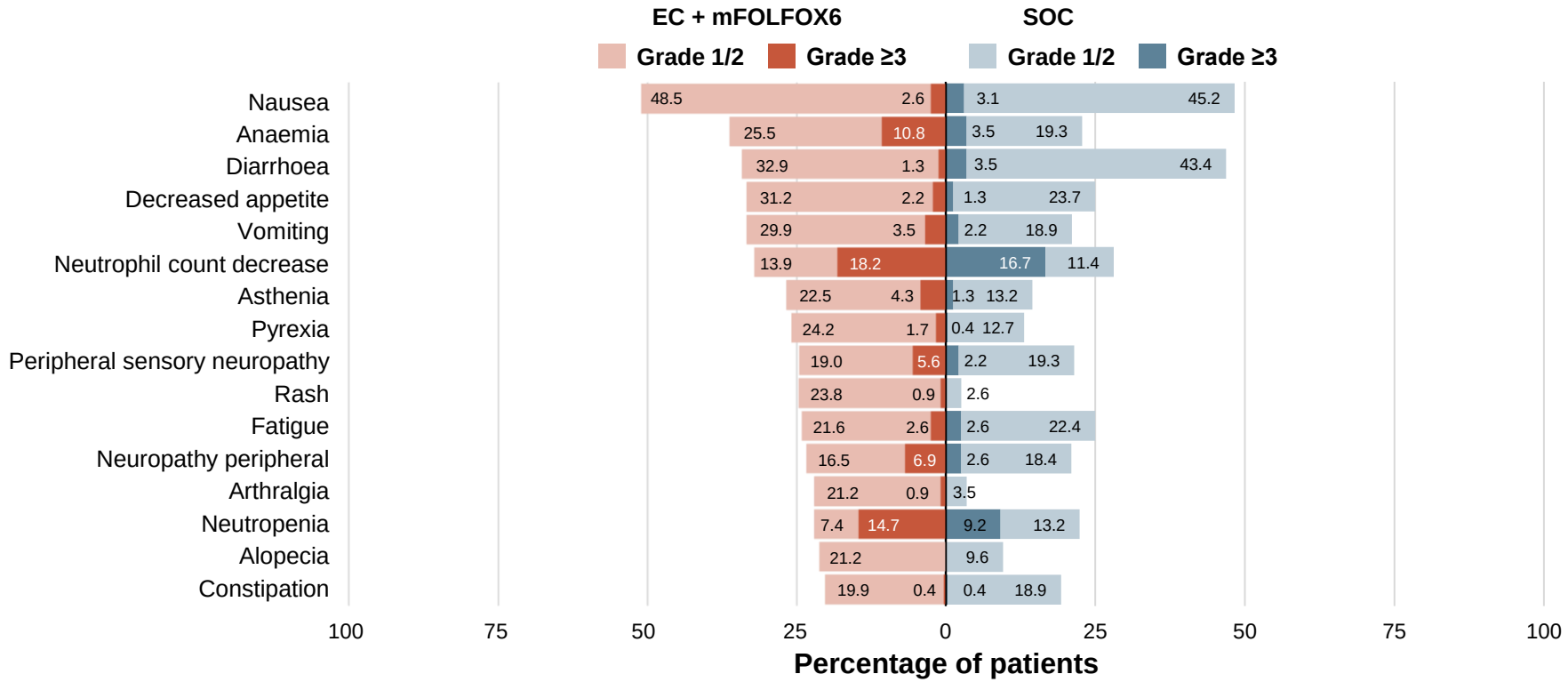
No. of patients at risk						
EC + mFOLFOX6	236	156	81	20	1	0
SOC	243	138	64	14	0	0

CI, confidence interval; EC, encorafenib plus cetuximab; mFOLFOX6, modified fluouracil / leucovorin / oxaliplatin; NE, not estimable; SOC, standard of care

Kopetz S, et al. Abstract 16, ASCO GI 2025; Kopetz S, et al. Nat Med. 2025. doi: 10.1038/s41591-024-03443-3. Online ahead of print.

BREAKWATER: SAFETY RESULTS

MOST FREQUENT (≥20%)[a] ALL–CAUSALITY TEAEs



- Serious treatment-emergent adverse events (EC+mFOLFOX6: n=231; SOC: n=228) occurred in 37.7% vs 34.6% of pts in the respective arms
- The safety profile was consistent with that known for each agent

[a] Frequency based on the EC + mFOLFOX6 arm

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

Kopetz S, et al. Abstract 16, ASCO GI 2025

BREAKWATER: SUMMARY

- BREAKWATER demonstrated a statistically significant and clinically meaningful benefit in ORR with EC + mFOLFOX6 that was rapid and durable in *BRAF* V600E-mutant mCRC
- A trend towards an OS improvement was observed with EC + mFOLFOX6 vs SOC; data are immature at this point
- EC + mFOLFOX6 was generally well-tolerated, with the most frequently reported TEAEs being consistent with those expected for each of the study treatments

Clinical Perspective

- BREAKWATER supports EC + mFOLFOX6 as a new first-line SOC for patients with *BRAF* V600E-mutant CRC

EC, encorafenib plus cetuximab; (m)CRC, (metastatic) colorectal cancer; mFOLFOX6, modified fluouracil / leucovorin / oxaliplatin; ORR, objective response rate; OS, overall survival; SOC, standard of care; TEAE, treatment emergent adverse event

Kopetz S, et al. Abstract 16, ASCO GI 2025; Kopetz S, et al. Nat Med. 2025. doi: 10.1038/s41591-024-03443-3. Online ahead of print.

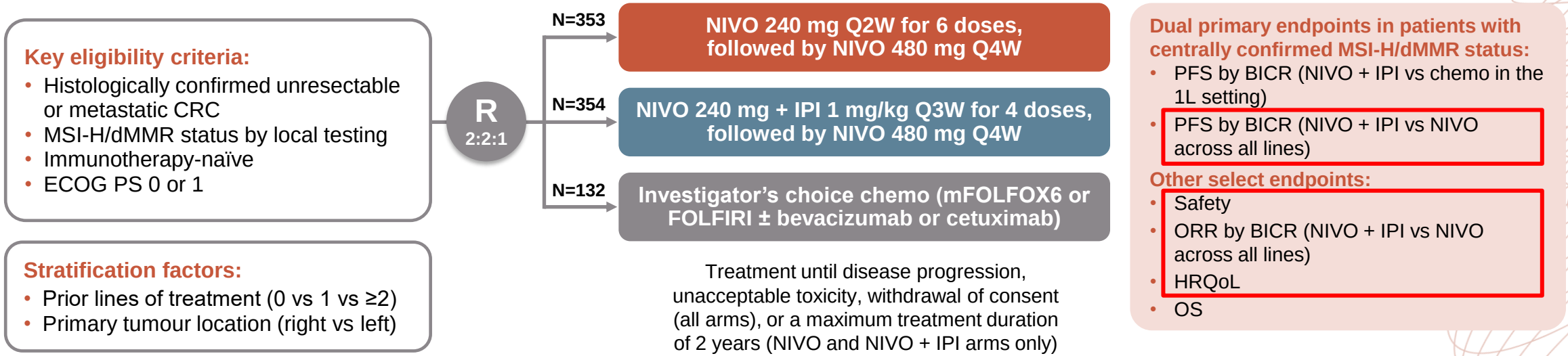
FIRST RESULTS OF NIVOLUMAB PLUS IPILIMUMAB VS NIVOLUMAB MONOTHERAPY FOR MSI-H/dMMR mCRC FROM CHECKMATE 8HW

André T, et al. Abstract LBA143, ASCO GI 2025

dMMR, deficient mismatch repair; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high

CHECKMATE 8HW: BACKGROUND AND STUDY DESIGN

- Tumours with MSI-H/dMMR status are found in 5-7% of mCRC patients[1-3] and are associated with poor outcomes with chemotherapy ± targeted therapies[4]
- Concurrent *BRAF*m and dMMR/MSI-H status is a rare (≈2 %) subtype of mCRC with a poor prognosis[1,5]
- CheckMate 8HW is a randomised, phase 3 trial comparing NIVO + IPI with NIVO or chemotherapy in patients with MSI-H/dMMR mCRC across different lines of therapy[6,7]



1L, first-line; BICR, blinded independent central review; BRAFm, BRAF mutated; dMMR, deficient mismatch repair; ECOG PS, Eastern Cooperative Oncology Group performance status; FOLFIRI, fluorouracil / leucovorin / irinotecan; HRQoL, health related quality of life; IPI, ipilimumab; (m)CRC, (metastatic) colorectal cancer; 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

1. Venderbosch S, et al. Clin Cancer Res. 2014;20:5322-5330; 2. Gutierrez C, et al. JCO Precis Oncol. 2023;7:e2200179; 3. Innocenti F, et al. J Clin Oncol. 2019;37:1217-1227; 4. André T, et al. Abstract LBA768, ASCO GI 2024; 5. Ambrosini M, et al. Eur J Cancer. 2024;210:114290; 6; André T, et al. Abstract LBA143, ASCO GI 2025; 7. André T, et al. Lancet. 2025. doi: 10.1016/S0140-6736(24)02848-4. Online ahead of print

CHECKMATE 8HW: RESULTS

BASELINE CHARACTERISTICS

- 30% of the patients in the NIVO + IPI arm and 24% in the NIVO arm had *BRAF* mutations

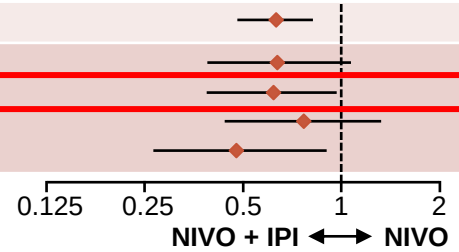
Characteristic (all randomised patients)	Category	NIVO + IPI (n=354)	NIVO (n=353)
BRAF, KRAS, NRAS mutation status, n (%)[a]	*BRAF/KRAS/NRAS* all wild type	83 (23)	103 (29)
	BRAF mutant	106 (30)	85 (24)
	KRAS or *NRAS* mutant	83 (23)	89 (25)
	Unknown	73 (21)	74 (21)

[a] Percentages may not add up to 100% due to rounding

RESULTS: PROGRESSION-FREE SURVIVAL

- NIVO + IPI demonstrated significant and clinically meaningful PFS benefit vs NIVO in patients with MSI-H/dMMR mCRC across all lines of therapy
- This benefit was consistently seen in prespecified subgroups across all lines of therapy, including patients who also harboured a *BRAF* mutation

Category (centrally confirmed MSI-H/dMMR)	Subgroup	Median PFS,[a] mo		Unstratified HR	Unstratified HR (95% CI)
		NIVO + IPI	NIVO		
Overall (N=582)		NR	39.3	0.63	
BRAF, KRAS, NRAS mutation status	*BRAF/KRAS/NRAS* all wild type (n=156)	NR	44.3	0.64	
	BRAF mutant (n=179)	NR	25.9	0.62	
	KRAS or *NRAS* mutant (n=125)	NR	NR	0.76	
	Unknown (n=114)	54.1	38.1	0.48	



[a] Per BICR

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; NIVO, nivolumab; PFS, progression-free survival

André T, et al. Abstract LBA143, ASCO GI 2025; André T, et al. Lancet. 2025. doi: 10.1016/S0140-6736(24)02848-4. Online ahead of print

CHECKMATE 8HW: SAFETY

- A higher incidence of TRAEs was observed with NIVO + IPI versus nivolumab
- The safety profile of NIVO + IPI was manageable and no new safety signals were reported

	NIVO + IPI (N=352)		NIVO (N=351)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
TRAEs, n (%)[a]				
Any TRAEs	285 (81)	78 (22)	249 (71)	50 (14)
Serious TRAEs	65 (18)	55 (16)	29 (8)	24 (7)
TRAEs leading to discontinuation	48 (14)	33 (9)	21 (6)	14 (4)
Treatment-related deaths, n (%)[c]	2 (<1)[d]		1 (<1)[e]	
TRAEs[a] reported in ≥10% of patients, n (%)				
Pruritus	91 (26)	0	63 (18)	0
Diarrhoea	71 (20)	3 (<1)	59 (17)	2 (<1)
Hypothyroidism	61 (17)	2 (<1)	31 (9)	0
Asthenia	58 (16)	2 (<1)	44 (13)	2 (<1)
Fatigue	42 (12)	1 (<1)	35 (10)	1 (<1)
Hyperthyroidism	40 (11)	0	16 (5)	0
Arthralgia	38 (11)	1 (<1)	23 (7)	0
Rash	34 (10)	3 (<1)	29 (8)	1 (<1)
Adrenal insufficiency	34 (10)	8 (2)	12 (3)	3 (<1)

[a] Includes events reported between first dose and 30 days after last dose of study therapy. [b] Discontinuation of any component of the combination regimen was counted as a drug discontinuation event. [c] Treatment-related deaths were reported regardless of timeframe. [d] Includes 1 event each of myocarditis and pneumonitis. No new treatment-related deaths were reported since the previous interim analysis. [e] One event of pneumonitis

IPI, ipilimumab; NIVO, nivolumab; TRAE, treatment related adverse event

André T, et al. Abstract LBA143, ASCO GI 2025; André T, et al. Lancet. 2025. doi: 10.1016/S0140-6736(24)02848-4. Online ahead of print

CHECKMATE 8HW: SUMMARY

- NIVO + IPI demonstrated statistically significant and clinically meaningful improvement in PFS vs NIVO in patients with MSI-H/dMMR mCRC across all lines of therapy
- The PFS benefit was consistent across prespecified subgroups and all lines of therapy, including patients who also harboured a *BRAF* mutation
- No new safety signals were identified; grade 3/4 TRAEs were reported in 22% of patients of NIVO + IPI and 14% with NIVO

Clinical Perspective

- Nivolumab + ipilimumab may be a treatment option in the future for dMMR/MSI-H mCRC patients, including *BRAF*-mutant mCRC *patients*
- There will need to be consideration about the optimal treatment sequence for this patient subgroup

BRAF-mutated; dMMR, deficient mismatch repair; IPI, ipilimumab; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high; NIVO, nivolumab; PFS, progression-free survival; TRAE, treatment related adverse event

André T, et al. Abstract LBA143, ASCO GI 2025; André T, et al. Lancet. 2025. doi: 10.1016/S0140-6736(24)02848-4. Online ahead of print

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