VIII SIMPOSIO NACIONAL
de ONCOLOGÍA de PRECISIÓN
Vigo, 19 y 20 de febrero de 2026

Lo mejor de 2025 en 20 diapositivas

CÁNCER DE ORIGEN DIGESTIVO COLO-RECTAL

Ana Mª López Muñoz
Hospital Universitario de Burgos

Disclosure information

Employment: Medical Oncologist Hospital Universitario Burgos

Consultant or Advisory Role: Amgen, Astra Zeneca, Eisai, Roche.

Speaking: Bristol-Myers, Amgen, Astra Zeneca, Eisai, MSD, Roche, Servier, Astellas, Takeda, Be One

- **ENFERMEDA AVANZADA:**
  - 1ª LÍNEA GUIADA POR BK
  - ENFERMEDAD REFRACTARIA
    - SIN BK
    - CON BK
- **ENFERMEDAD LOCALIZADA:**
  - ADYUVANCIA/NEOADYUVANCIA
  - ctDNA
  - Otros…

ENFERMEDAD AVANZADA:

1ª LÍNEA GUIDADA POR BK

2025 ASCO ANNUAL MEETING

Precision Oncology in the First-Line Setting of Colorectal Cancer

- Precision oncology has now fully entered the first-line setting of mCRC, with early combinations tailored to molecular subtypes delivering clinically transformative outcomes:

ASCO Gastrointestinal Cancers Symposium

BREAKWATER: Analysis of first-line encorafenib + cetuximab + chemotherapy in BRAF V600E-mutant metastatic colorectal cancer

2025 ASCO ANNUAL MEETING

First-line encorafenib + cetuximab + mFOLFOX6 in BRAF V600E-mutant metastatic colorectal cancer (BREAKWATER): progression-free survival and updated overall survival analyses

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. Lalibere,[19] S.S. Dychter,[20] X. Zhang,[21] J. Tabernero,[1,22] and S. Kopetz,[10] for the BREAKWATER Trial Investigators*

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

R 1:1:1[a,b] N=637

- EC (n=158)
- EC + mFOLFOX6 (n=236)
- SOC (n=243)[c]

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

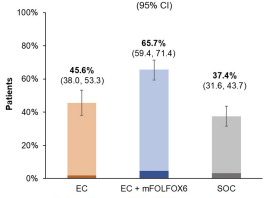
Dual primary endpoints:
PFS and ORR[d] by BICR (EC + mFOLFOX6 vs SOC)

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

Here we present the primary analysis of ORR by BICR (one of the dual primary endpoints), an interim analysis of OS, and safety in the EC + mFOLFOX6 and SOC arms

Best Overall Response by BICR (All Randomized Patients)

Confirmed ORR by BICR (95% CI)

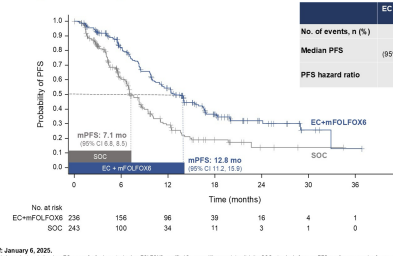


Confirmed Best Overall Response, TTR, and DOR by BICR

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.
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.

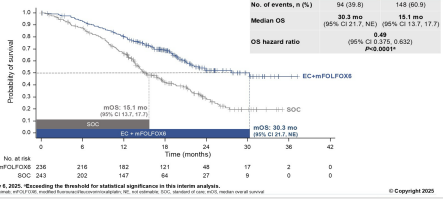
PFS by BICR (EC + mFOLFOX6 and SOC)



	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	

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

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]	

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

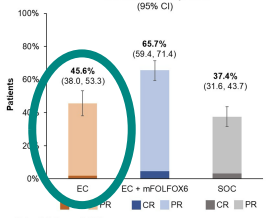
The BREAKWATER study supports EC + mFOLFOX6 as a new first-line SOC for patients with BRAF V600E-mutant mCRC

S. Kopetz. ASCO GI 2025. E. Elez. ASCO-2025. NEJM 2025

VIII SIN

- EC showed a numerically higher ORR, comparable PFS, longer median OS, and early separation of OS Kaplan-Meier curves vs SOC; and EC has a more tolerable safety profile than SOC
  - EC may be considered for patients in the first-line setting who are unable to tolerate chemotherapy

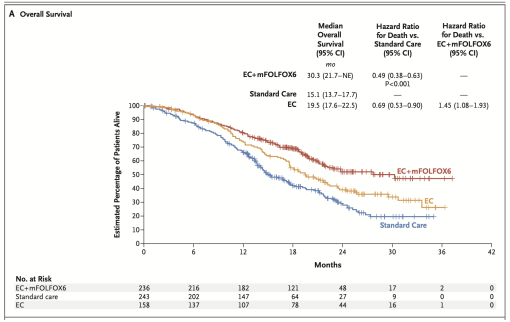
Best Overall Response by BICR (All Randomized Patients)



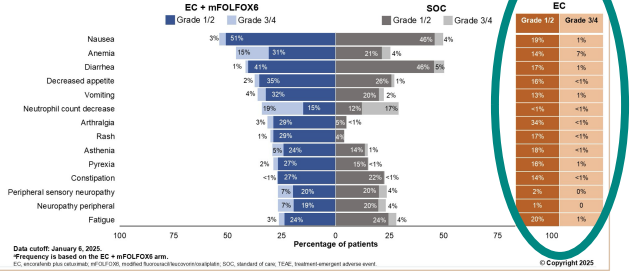
Confirmed Best Overall Response, TTR, and DOR by BICR

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.

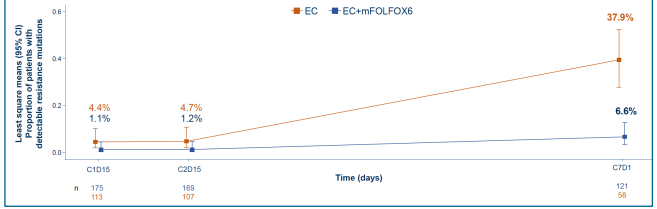
BERLIN 2025 ESMO congress

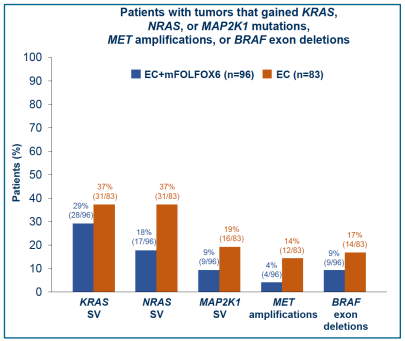
Circulating tumor (ct) DNA analysis of *BRAF* V600E dynamics and changes in genomic landscape in patients (pts) with first-line (1L) *BRAF* V600E-mutant metastatic colorectal cancer (mCRC) treated in BREAKWATER

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



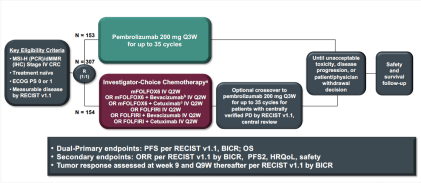


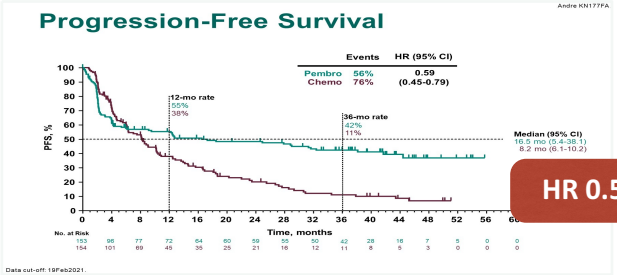
The BREAKWATER study supports EC + mFOLFOX6 as a new first-line SOC for patients with BRAF V600E-mutant mCRC

E. Elez. ASCO-2025. NEJM 2025. S Kopetz ESMO 2025

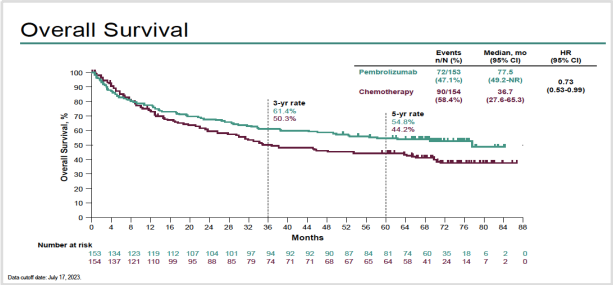
The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 DECEMBER 3, 2020 VOL. 383 NO. 23

Pembrolizumab in Microsatellite-Instability–High Advanced Colorectal Cancer





HR 0.59

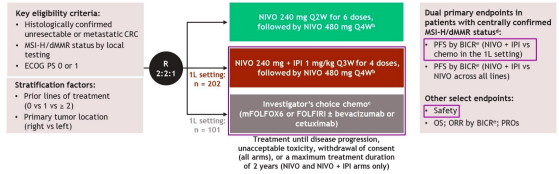


The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE

Nivolumab plus Ipilimumab in Microsatellite-Instability–High Metastatic Colorectal Cancer

CheckMate 8HW study design

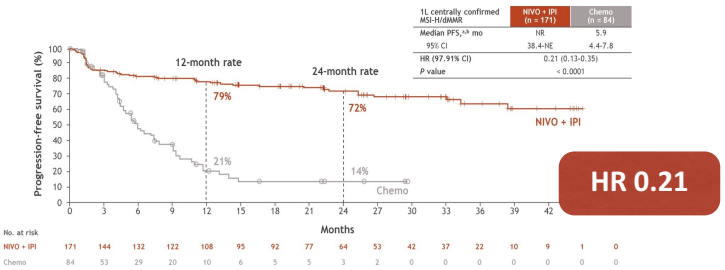
- CheckMate 8HW is a randomized, multicenter, open-label phase 3 study[a]



IPILIMUMAB-NIVOLUMAB vs QT-Inv FIRST LINE

CheckMate 8HW: first results of 1L NIVO + IPI vs chemo

Progression-free survival



HR 0.21

- PFS benefit with NIVO + IPI vs chemo was robust and consistent across the sensitivity analyses, including PFS by BICR in 1L all randomized patients (HR, 0.32; 95% CI, 0.23-0.46)

[a]Per BICR. [b]Median follow-up, 24.3 months.

. André. N Engl J Med 2020;383:2207-18. L.A. Diaz. Kai-Keen Shiu,ESMO- 2023

T. Andre ASCO-GI 2024 # LBA 768. H.J. Lenz ASCO 2024 # 3503 . T. André, N Engl J Med 2024;391:2014-26.

ASCO Gastrointestinal Cancers Symposium

First results of nivolumab plus ipilimumab vs nivolumab monotherapy for microsatellite instability-high/ mismatch repair-deficient metastatic colorectal cancer from CheckMate 8HW

Nivolumab plus ipilimumab versus nivolumab in microsatellite instability-high metastatic colorectal cancer (CheckMate 8HW): a randomised, open-label, phase 3 trial

2025 ASCO ANNUAL MEETING

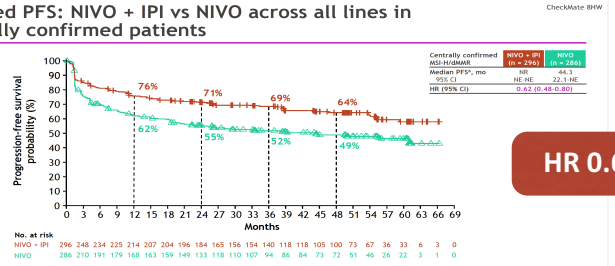
Nivolumab plus ipilimumab versus chemotherapy or nivolumab monotherapy for microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: expanded analyses from CheckMate 8HW

ESMO BERLIN, GERMANY 17-21 OCTOBER 2025 ESMO

Nivolumab plus ipilimumab vs nivolumab monotherapy for microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: new results from CheckMate 8HW

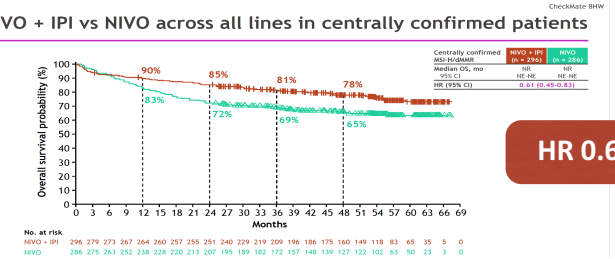
IPILIMUMAB-NIVOLUMAB vs NIVOLUMAB ALL LINES

Updated PFS: NIVO + IPI vs NIVO across all lines in centrally confirmed patients



HR 0.62

OS: NIVO + IPI vs NIVO across all lines in centrally confirmed patients



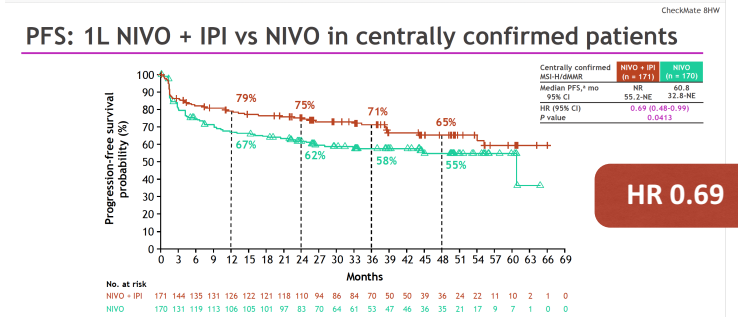
HR 0.61

Response and duration of response

Centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 296)	NIVO (n = 286)
ORR,[a] % (95% CI)	71 (65-76)	58 (52-64)
Difference in ORR,[b] % (95% CI)	13 (5-21)	
P value[c]	0.0011	
Best overall response,[a,d] %		
Complete response	30	28
Partial response	40	30
Stable disease	14	19
Progressive disease	10	19
Median TTR (range),[a,e] mo	2.8 (1.2-44.5)	2.8 (1.2-29.5)
Median DOR (95% CI),[a,e] mo	NR (NE)	NR (NE)

IPILIMUMAB-NIVOLUMAB vs NIVOLUMAB FIRST LINE

PFS: 1L NIVO + IPI vs NIVO in centrally confirmed patients



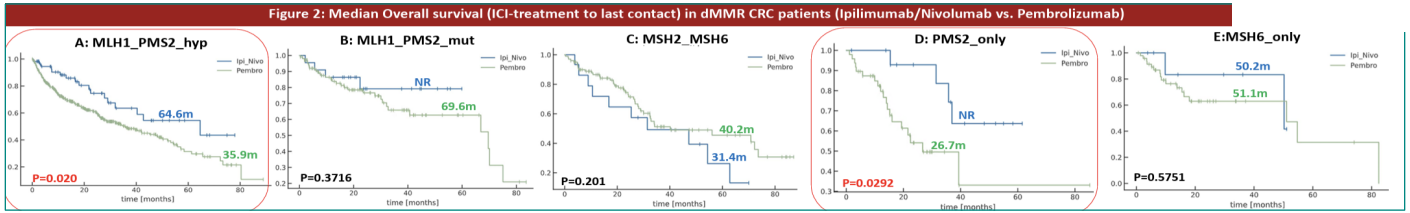
HR 0.69

ORR: 1L NIVO + IPI vs NIVO in centrally confirmed patients

	NIVO + IPI (n = 171)	NIVO (n = 170)
ORR,[a,b] %	73	61
95% CI	65-79	53-79
Best overall response,[b,c] %		
CR	35	31
PR	37	31
SD[c]	12	19
PD	11	16
Median time to response (range),[d] months	2.8 (1.2-38.6)	2.7 (1.2-29.5)
Median duration of response (95% CI),[d,e] months	NR (NE)	NR (59.4-NE)

T. Andre ASCO GI 2025. Lancet 2025. H-J Lenz ASCO 2025. Sara Lonardi ESMO 2025

Optimizing Immunotherapy in Mismatch Repair-Deficient Colorectal Cancers Through Tailored, Subtype-Specific Treatment Approaches (795P)



Moh'd Khushman. ESMO 2025 # 795 p

nature communications

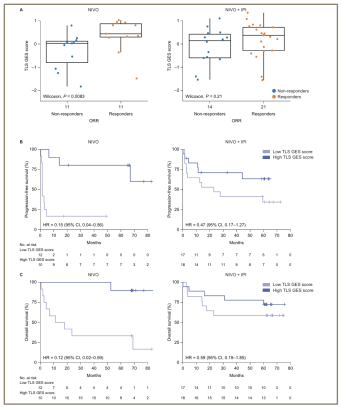
Article

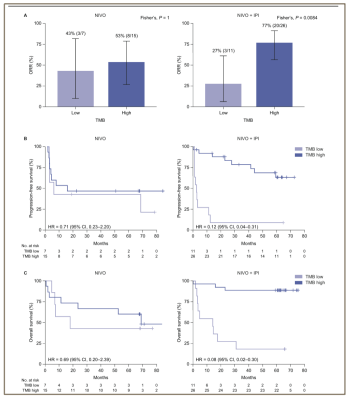
https://doi.org/10.1038/s41467-025-63960-8

Inflammation and mutational burden differentially associated with nivolumab or ipilimumab combination efficacy in colorectal cancer

Higher expression of inflammation-related gene expression signatures is associated with improved response and survival benefit with nivolumab monotherapy.

Higher tumor mutational burden, tumor indel burden, and degrees of microsatellite instability are associated with improved survival benefit with nivolumab plus ipilimumab





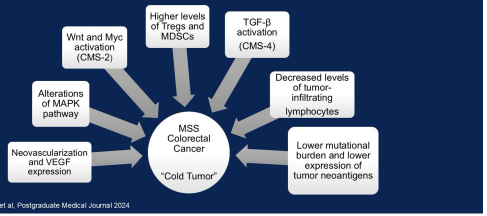
Ming Lei. Nature Communications 2025

The CM8HW supports NIVO + IPI as a standard of care option for the 1L treatment of MSI-H/dMMR mCRC

ENFERMEDAD AVANZADA: REFRACTARIA

- SIN BK
- CON BK

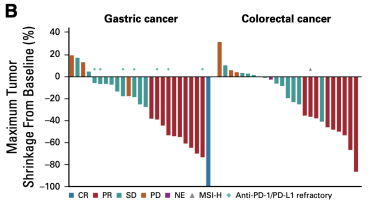
What we know: the tumor microenvironment of MSS colorectal cancer is consistent with a "cold tumor"



Han YJ et al. Postgraduate Medical Journal 2024

de

REGONIVO (EPOC 1603)

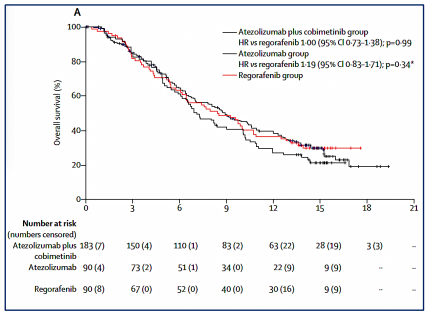


Regorafenib plus nivolumab in patients with mismatch repair-proficient/microsatellite stable metastatic colorectal cancer: a single-arm, open-label, multicentre phase 2 study

Response, n (%)	Without liver metastases (n = 23)	With liver metastases (n = 47)	All patients (N = 70)
Complete response	0	0	0
Partial response	5 (22)	0	5 (7)
Stable disease	8 (35)	14 (30)	22 (31)
Progressive disease	9 (39)	27 (57)	36 (51)
Not evaluable	1 (4)	6 (13)	7 (10)
Objective response rate	5 (22)	0	5 (7)
Disease control rate ≥8 weeks	13 (57)	14 (30)	27 (39)
Median duration of stable disease, weeks	30	21	30

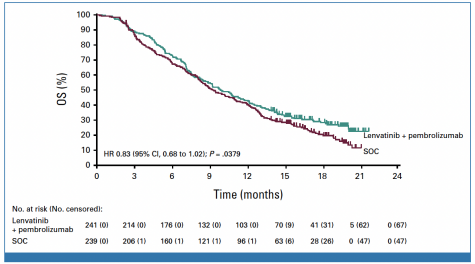
Demonstrated level of activity in patients without liver metastases

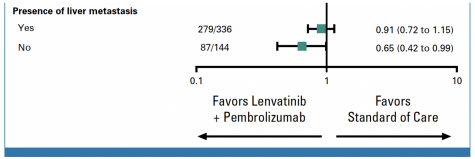
Atezolizumab with or without cobimetinib versus regorafenib in previously treated metastatic colorectal cancer (IMblaze370): a multicentre, open-label, phase 3, randomised, controlled trial



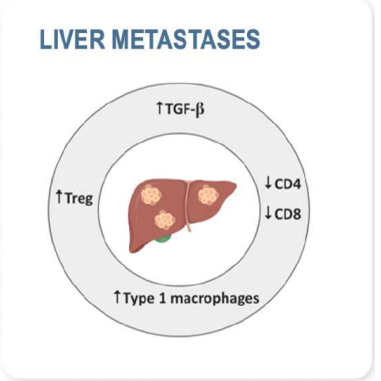
Cathy Eng. Lancet Oncol 2019

Lenvatinib Plus Pembrolizumab Versus Standard of Care for Previously Treated Metastatic Colorectal Cancer: Final Analysis of the Randomized, Open-Label, Phase III LEAP-017 Study





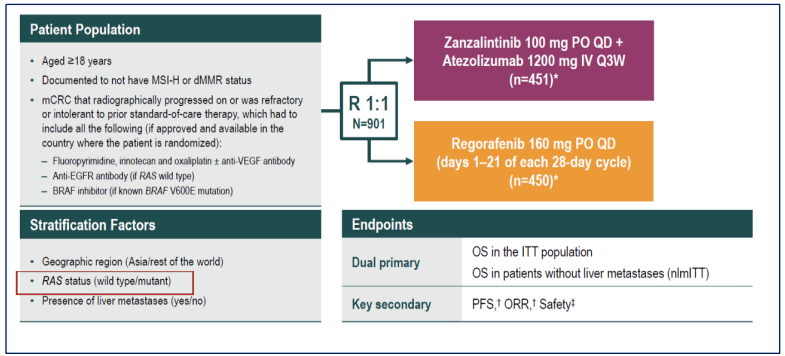
Akihito kawazoe. JCO 2024; 42: 2918-2927

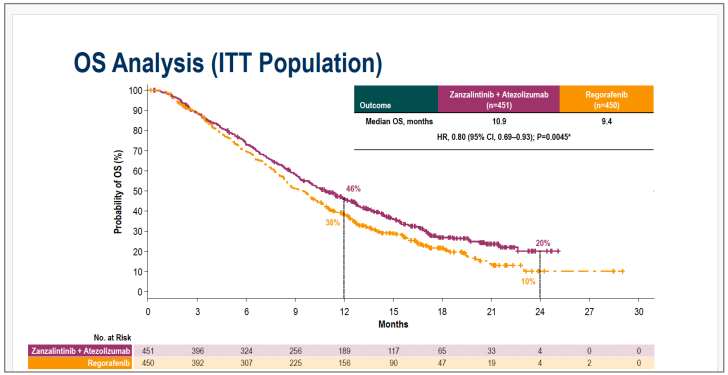


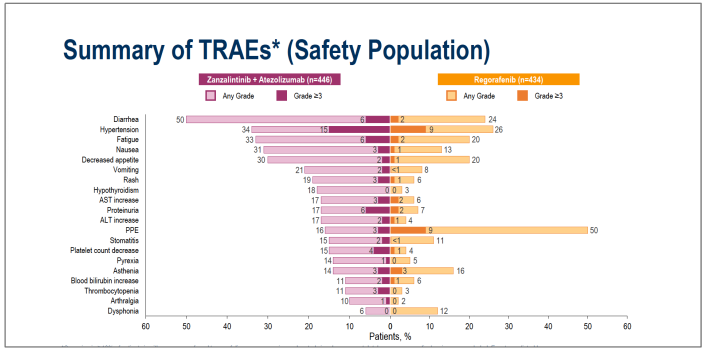
Zanzalintinib plus Atezolizumab vs Regorafenib in Patients with Previously Treated Metastatic Colorectal Cancer:
Primary Overall Survival Analysis from the Randomized, Open-Label, Phase 3 STELLAR-303 Study

Zanzalintinib plus atezolizumab versus regorafenib in refractory colorectal cancer (STELLAR-303): a randomised, open-label, phase 3 trial

ZANZALINTINIB + ATEZOLIZUMAB vs REGORAFENIB







Outcome	Overall population (ZZ-atz vs Reg)	Without liver metastases
mOS, months	10'9 vs 9'4 (HR 0'8, p 0'0045)	15'9 vs 12'8 m (HR 0'79, p 0'0875)
mPFS, months	3'7 vs 2'0 (HR 0'68)	–
ORR, %	4% vs 1%	–

Anwaar Saeed ESMO 2025. J Randolph Hecht Lancet 2025

ASCO Gastrointestinal Cancers Symposium

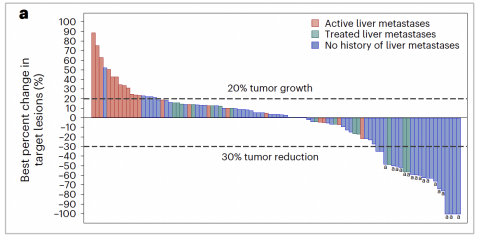
Preliminary results from a randomized, open-label, phase 2 study of botensilimab with or without balstilimab in refractory microsatellite stable metastatic colorectal cancer with no liver metastases

BOTENSILIMAB + BALSTILIMAB

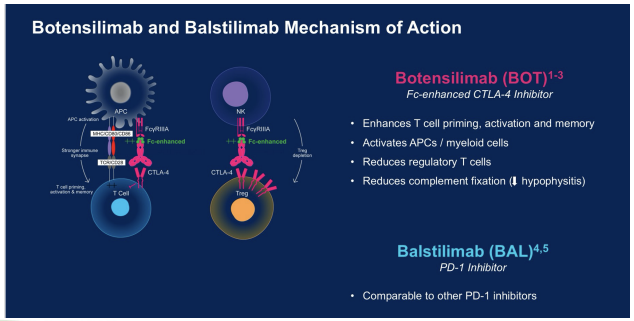
nature medicine

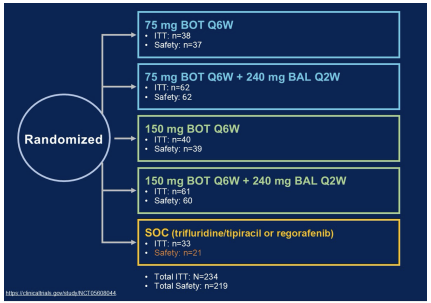
Article https://doi.org/10.1038/s41591-024-03083-7

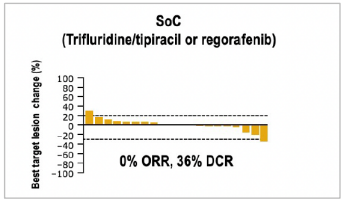
Botensilimab plus balstilimab in relapsed/ refractory microsatellite stable metastatic colorectal cancer: a phase 1 trial

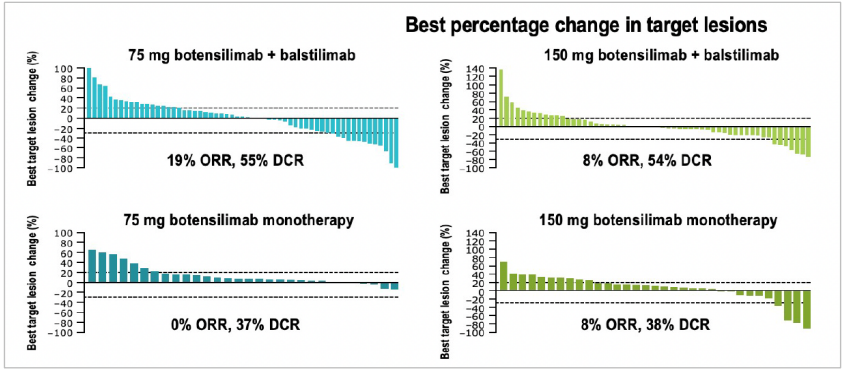


Andrea J. Bullock. Nature Medicine 2024; 30: 2558







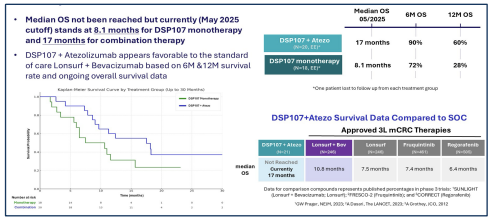


Faklh MG. ASCO GI 2025

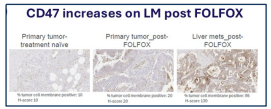
NEW TARGETS, NEW CONTEXTS, NEW BKs, NEW AGENTS……

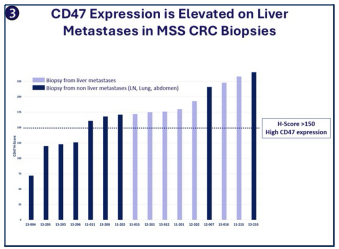
BI-SPECIFIC

Phase 2 dose expansion study of DSP107, a first-in-class bi-specific 4-1BB T-cell engager, with and without Atezolizumab in metastatic MSS Colorectal Cancer patients



CD47 a Targeted Tumor Antigen in Liver Metastases





Anwaar Saeed ASCO 2025

ADC

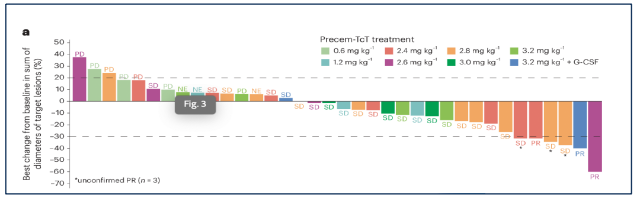
nature medicine

Article

https://doi.org/10.1038/s41591-025-03843-z

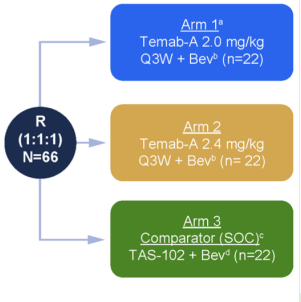
Precemtabart tocentecan, an anti-CEACAM5 antibody–drug conjugate, in metastatic colorectal cancer: a phase 1 trial

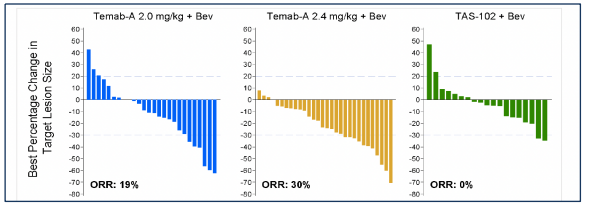
Kopetz S. et al. Nature Medicine 2025

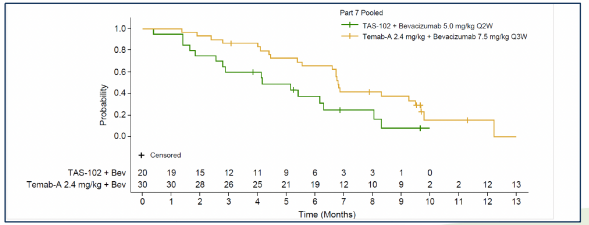


Telisotuzumab Adizutecan in Combination With Bevacizumab Versus Standard of Care in Patients With 3L+ Colorectal Cancer: Dose Expansion Results of a Phase 1 Study

Ceccini M. et al. ESMO 2025

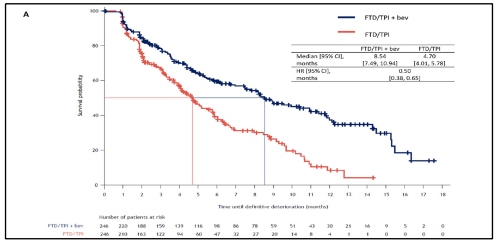






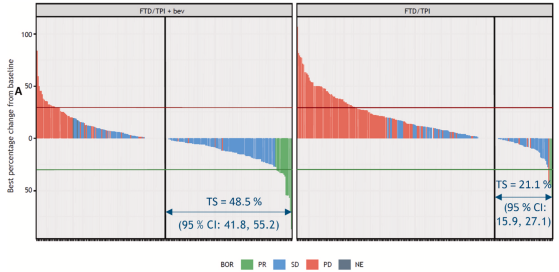
NO SELECCIÓN MOLECULAR.....

Impact of Treatment With Trifluridine/Tipiracil in Combination With Bevacizumab on Health-Related Quality of Life and Performance Status in Refractory Metastatic Colorectal Cancer: An Analysis of the Phase III SUNLIGHT Trial



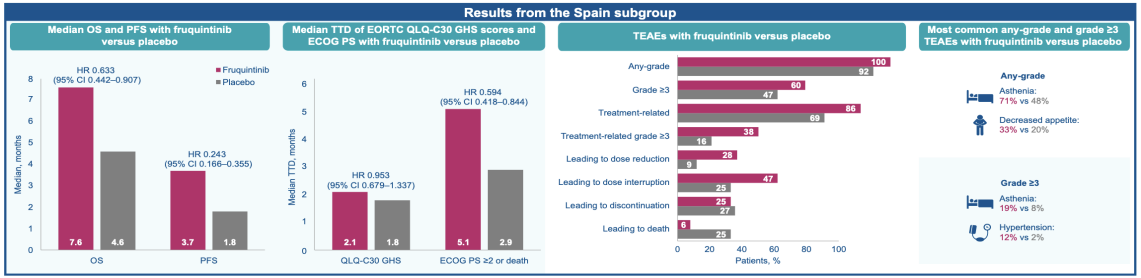
Julien Taieb. Clinical Colorectal Cancer June 2025

Impact of trifluridine/tipiracil plus bevacizumab on tumor shrinkage and depth of response in refractory metastatic colorectal cancer: analysis of the SUNLIGHT trial



Julien Taieb. European Journal of Cancer 227 (2025) 115644

Analysis of fruquintinib in patients with metastatic colorectal cancer who were enrolled in Spain: results from the global FRESCO-2 study



R. Garcia-Carbonero. ESMO Gastrointestinal Oncology 2025

HER-2

	MyPathway N = 57	TAPUR N = 28	TRIUMPH N = 27 (tissue+) N = 25 (ctDNA+)	MOUNTAINEER N = 84	HERACLES-A N = 27	HERACLES-B N = 31	DESTINY- CRC01 N = 86 (ARM1)	DESTINY-CRC02 N = 82 (ARM1)	PHASE 1 ZANIDATAMAB N = 28
Phase	II	II	II	II	II	II	II	II	I
RAS mutation (%)	22	17	0	0	0	0	1-2	17	0
Previous treatment lines (N –)	3	3	3	2	4	4	3	3	4
Prior anti-HER2 therapy	No	No	No	No	No	No	Yes	Yes	Yes
Definition of HER 2 positive status	Amplification/ Overexpression IHC/ISH +Mutations	Amplification/ Overexpression IHC/ISH +Mutations	Amplification/ Overexpression: -Tissue: IHC3 + or IHC2 + /ISH+ -ctDNA: NGS	Amplification/ Overexpression IHC3 + or IHC2 + / ISH+ And/or NGS	Amplification/ Overexpression IHC3 + or IHC2 + /FISH+	Amplification/ Overexpression IHC3 + or IHC2 + /FISH+	Amplification/ Overexpression IHC3 + or IHC2 + /FISH+	Amplification/ Overexpression IHC3 + or IHC2 + /FISH+	Amplification/ Overexpression IHC3 + or IHC2 + /FISH+
Anti HER2 regimen	Trastuzumab +Pertuzumab	Trastuzumab +Pertuzumab	Trastuzumab +Pertuzumab	Tucatinib +Trastuzumab (Cohort A and B)	Lapatinib +Trastuzumab	Trastuzumab-Emtansine	Trastuzumab-Deruxtecan 6,4 mg/kg	Trastuzumab-Deruxtecan 5,4 mg/kg	Zanidatamab
ORR (%)	32	25	30 (tissue+) 28 (ctDNA+)	38.1	28	9.7	45.3	37.8	38
mPFS (months)	2.9	4.3	4 (tissue+) 3.1 (ctDNA+)	8.1	4.7	4.1	6.9	5.8	6.8
mOS (months)	11.5	13.8	10.1 (tissue+) 8.8 (ctDNA+)	24.1	10	/	15.5	13.4	/

BERLIN 2025 ESMO congress

Trastuzumab deruxtecan (T-DXd) in patients with HER2-positive (HER2+) metastatic colorectal cancer (mCRC): Final analysis of DESTINY-CRC02, a randomized, phase 2 trial

Final analysis
(DCO, December 4, 2024)

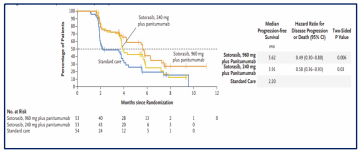
T-DXd dose	5.4 mg/kg n = 82	6.4 mg/kg n = 40
Treatment duration, median (range), mo	5.5 (0.7-34.3)[a]	4.9 (0.7-29.2)[a]
Follow-up, median (range), mo	14.2 (0.5-34.0)	12.7 (0.7-36.6)
cORR (95% CI), %	37.8 (27.3-49.2)	27.5 (14.6-43.9)
DOR, median (95% CI), mo	5.5 (4.2-8.1)	5.5 (3.7-9.8)
PFS, median (95% CI), mo	5.8 (4.6-7.0)	5.5 (4.2-7.0)
OS, median (95% CI), mo	15.9 (12.6-18.8)	19.7 (9.9-25.8)
Drug-related grade ≥3 TEAE,%[a]	42.2	48.7
Adjudicated drug-related ILD, %[a]	9.6 (2 grade 1; 6 grade 2)	17.9 (2 grade 1; 4 grade 2; 1 grade 5[b])

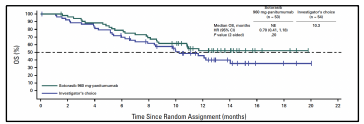
These findings support T-DXd 5.4 mg/kg as the optimal single-agent dose for patients with previously treated HER2+ mCRC, irrespective of *RAS* mutations and prior anti-HER2 therapy

KRAS MT

Overall Survival Analysis of the Phase III CodeBreaK 300 Study of Sotorasib Plus Panitumumab Versus Investigator's Choice in Chemorefractory *KRAS* G12C Colorectal Cancer

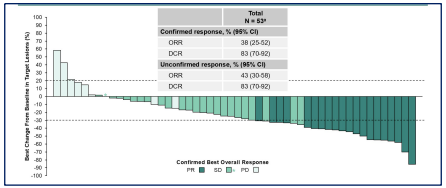
CODE-BREAK 300

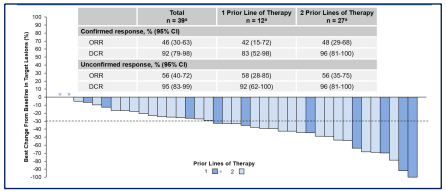




M.G. Fakih. NEJM 2023. ASCO 2024
Filippo Pietrantonio. JCO 2025

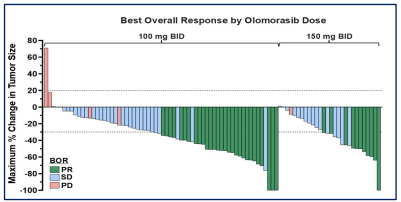
The KRAS G12C Inhibitor MK-1084 for *KRAS* G12C-Mutated Advanced Colorectal Cancer: Results From KANDLELIT-001





Iwona Lugowska. ASCO 2025

Efficacy and safety of olomorasib, a second-generation KRAS G12C inhibitor, plus cetuximab in KRAS G12C-mutant advanced colorectal cancer



Parameter	All Patients N=83	Olomorasib (100 mg BID) + cetuximab (N=54)	Olomorasib (150 mg BID) + cetuximab (N=29)
BOR, n (%)			
PR[a]	40 (43.0)	29 (45.3)	11 (37.9)
SD	46 (49.5)	30 (46.9)	16 (55.2)
PD	7 (7.5)	5 (7.8)	2 (6.9)
ORR[a], % (95% CI)	**43.0 (32.8, 53.7)**	**45.3 (32.8, 58.3)**	**37.9 (20.7, 57.7)**
DCR, % (95% CI)	92.5 (85.1, 96.9)	92.2 (82.7, 97.4)	93.1 (77.2, 99.2)
Median TTR, mo (Min - Max)	1.4 (1.0 - 4.2)	1.4 (1.0 - 4.2)	1.4 (1.2 - 2.8)
Median DOR, mo (95% CI)	6.5 (6.0, 11.9)	8.3 (5.6, 12.2)	6.2 (2.8, NE)
Median PFS, mo (95% CI)	7.4 (6.6, 7.8)	7.5 (6.8, 9.7)	6.6 (4.2, 7.6)
6-mo PFS rate, % (95% CI)	62.8 (52.0, 71.8)	65.1 (51.9, 75.4)	57.6 (37.3, 73.4)

Antoine Hollebecque. ASCO 2025

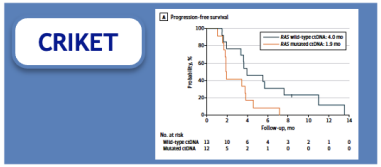
WT: Rechallenge

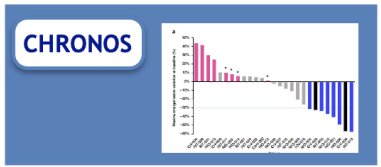
VIII SIMPOSIO NACIC

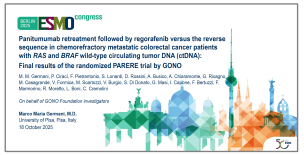
Table 3 | Phase II trials investigating retreatment with anti-EGFR antibodies

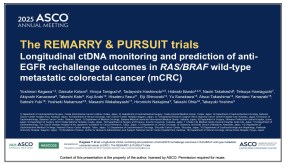
Trial	Patient population	Interventions (number of patients)	ORR	mPFS	mOS	Grade ≥3 AEs (% of patients)
Santini et al.[42]	KRAS codons 12–13 WT	FOLFIRI/irinotecan + cetuximab (n=39)	53.8%*	6.6 months	NR	Skin rash (38.5%), neutropenia (10.0%) and diarrhoea (7.7%)
IACORO CC-08 (ref. 143)	KRAS exon 2 WT	Irinotecan + cetuximab (n=34)	2.9%	2.4 months (3-month PFS 44.1%)*	8.2 months	neutropenia (29.6%)
IACORO CC-09 (ref. 143)	KRAS exon 2 WT	Irinotecan + panitumumab (n=20)	8.3%	3.1 months (3-month PFS 50%)*	8.9 months	Acneiform rash (17%), hypomagnesaemia (15%) and dry skin (12%)
CRICKET[44]	RAS/BRAF WT	Irinotecan + cetuximab (n=28)	21%*	3.4 months	9.8 months	Diarrhoea (18%), skin toxicity (14%), neutropenia (14%) and HFS (7%)
E-Rechallenge[145]	RAS WT	Irinotecan + cetuximab (n=33)	15.6%*	2.9 months	8.6 months	NR
CHRONOS[141]	RAS, BRAF and EGFR ECD WT	Panitumumab (n=27)	30%*	4 months	13.8 months	Skin rash (9%), folliculitis (9%)
PURSUIT[43]	RAS/BRAF WT (and RAS WT*)	Panitumumab + irinotecan (n=90)	14%*	3.6 months	NR	56.5%
CAVE[47]	RAS WT	Avelumab + cetuximab (n=77)	6.5%	3.6 months	11.6 months*	Cutaneous eruption (14%) and diarrhoea (4%)
VELO[146]	RAS WT	FTD–TPI (n=20) vs FTD–TPI + panitumumab (n=21)	0% vs 9.7%	2.5 vs 4.0 months; HR 0.72, 95% CI 0.28–0.82; P=0.007*	13.1 vs 15.8 months; HR 0.90, 95% CI 0.54–1.71; P=0.8	Rash (59%) in the experimental arm
CITRIC[144]	RAS, BRAF and EGFR ECD WT*	Irinotecan + cetuximab (n=31) vs investigator choice (n=27)	12.9% vs 0%; P=0.03	4.4 vs 2.2 months; HR 0.72, 95% CI 0.40–1.28, P=0.26	NR	Diarrhoea (16.1%), skin rash (9.7%), mucositis (6.5%) and neutropenia (6.4%) in the experimental arm

Paolo Ciraci. Nature Reviews Clinical Oncology 2025 (22); 28–45









2025 ASCO ANNUAL MEETING

fire AIO

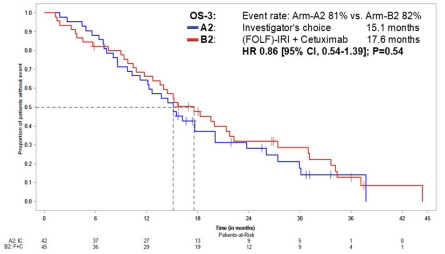
FIRE-4 study (AIO KRK-0114):
Randomized study evaluating the efficacy of cetuximab re-challenge in patients with metastatic RAS wild-type colorectal cancer responding to first-line treatment with FOLFIRI plus cetuximab

Lenaq Weiss. ASCO 2025

Objective Response

		Arm A2: Investigator's choice N=42	Arm B2: (FOLF)-IRI + Cetuximab N=45	Odds Ratio 95% CI; P-value*
Best Response, N (%)				
	CR	1 (2.4)	1 (2.2)	
	PR	4 (9.5)	11 (24.4)	
	SD	21 (50.0)	15 (33.3)	
	PD	13 (31.0)	11 (24.4)	
	NE	3 (7.1)	7 (15.6)	
Objective Response Rate (ORR)	n (%) 95% CI	5 (**11.9**) 4 - 25.6	12 (**26.7**) 14.6 - 41.9	0.37 (0.12 - 1.17) 0.08
Disease Control Rate (DCR)	n (%) 95% CI	26 (**61.9**) 45.6 -76.4	27 (**60.0**) 44.3 -74.3	1.08 (0.46 - 2.57) 0.86

*Fisher's exact test, α = 5%

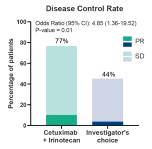


Circulating Tumour (ct) DNA-Guided Anti-EGFR Rechallenge Strategy in Metastatic Colorectal Cancer (mCRC): Final results of the phase II randomized CITRIC trial

C. Montagout. ESMO 2025

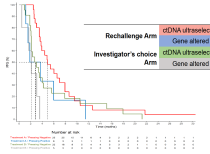
Response in ITT population

	Cetuximab + Irinotecan Rechallenge N=31	Investigator's choice N=27	p-value
ORR (90% CI), %	9.7 (2.7 – 23.2)	3.7 (0.2– 16.4)	0.6
PR, %	3 (9.7)	1 (3.7)	
SD, %	21 (67.7)	11 (40.7)	
PD, %	7 (22.6)	15 (55.6)	
NE, %	0 (0)	0 (0)	
Disease control rate (90% CI), %	77.7 (61.7 – 88.9)	44.4 (28.1 - 61.8)	0.01



ORR was numerically higher and DCR was statistically higher with irinotecan + cetuximab rechallenge compared to investigator's choice

ctDNA ultraselection to anti-EGFR rechallenge



		mPFS, months	HR (95% CI)	P-value
Rechallenge Arm	ctDNA ultraselected	5.1	1.7 (0.7-4.2)	0.2
	Gene altered	2.8	--	--
Investigator's choice Arm	ctDNA ultraselected	2.8	2.1 (0.7-5.9)	0.1
	Gene altered	2.1	--	--

ctDNA anti-EGFR ultraselection panel = mutation in RAS, BRAF V600E, EGFR ECD, MAP2K1, PTEN; amplification in ERBB2, MET (MSK-ACCESS powered by SOPHIA DDM)

Pre-planned exploratory analysis showed higher PFS in patients ultraselected by ctDNA treated with cetuximab + irinotecan rechallenge

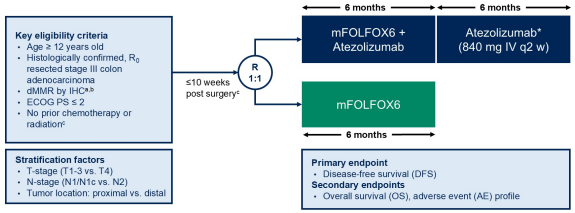
ENFERMEDAD LOCALIZADA

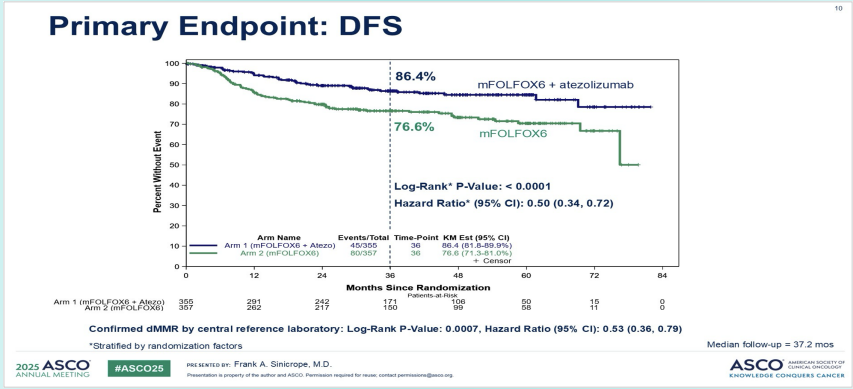
- ADYUVANCIA/NEOADYUVANCIA
- CTDNA
- OTROS: AAS, EJERCICIO

¿Equiparables a QT adyuvnate?

2025 ASCO ANNUAL MEETING

LBA1: **Randomized trial of standard chemotherapy alone or combined with atezolizumab as adjuvant therapy for patients with stage III deficient DNA mismatch repair** (dMMR) **colon cancer** (Alliance A021502; ATOMIC)



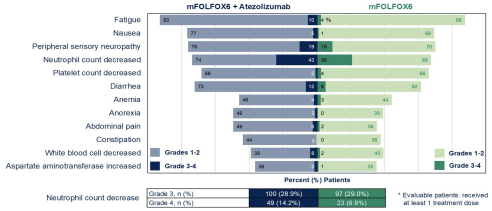


Safety Summary

Characteristics	mFOLFOX6 + Atezo (N=346)[#]	mFOLFOX6 (N=334)[#]
Any Grade AE, % (n) Treatment-related	100% (346) 99.7% (345)	95.1% (329) 94.2% (326)
Grade 3-4 AE, % (n) Treatment-related	83.8% (290) 72.3% (250)	69.1% (239) 59.2% (205)
Grade 5 AE, % (n) Treatment-related	1.7% (6) 0.6% (2)*	0.6% (2) 0.0% (0)

Patient Safety

AEs Occurring in > 35% of Evaluable* Patients



Immune-Related AEs

No clinically significant differences in r greater immune-related AEs

		mFOLFOX6 + Atezo (N=346, %)[#]		mFOLFOX6 (N=334, %)[#]	
		Grades 1-2	Grades 3-4	Grades 1-2	Grades 3-4
Endocrinopathies	Adrenal insufficiency	0.3	0.9	0	0
	Hyperglycemia	17.9	2.6	9.0	1.2
	Hypothyroidism	20.5	0	3.6	0
Colitis	Colitis	5.5	1.2	0.6	0
	Diarrhea	60.1	12.1	53.3	8.4
Myositis	Generalized muscle weakness	7.8	0.9	3.3	0
Dermatitis	Rash maculo-papular	13.3	0.9	6.0	0

Grade 3-4

Hepatitis, n (%)		
ALT or AST increase	5.2%	1.8%
Alk phos or bilirubin increase	1.8%	0%
Pneumonitis, n (%)	2%	0.9%

Atezolizumab plus mFOLFOX6 is a practice changing treatment for patients with dMMR stage III colon cancer

How big of a blast is ATOMIC?

Myriam Chalabi, MD PhD
Netherlands Cancer Institute
Amsterdam, the Netherlands

2025 ASCO ANNUAL MEETING #ASCO25 PRESENTED BY: Myriam Chalabi, MD, PhD

Folfox + atezolizumab should be considered in patients with dMMR colon cancers who undergo upfront surgery

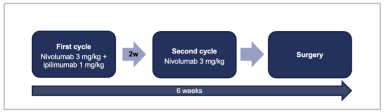
- In the era of immunotherapy: do patients with dMMR colon cancers need adjuvant chemotherapy?
- Is neoadjuvant immunotherapy better than adjuvant chemotherapy in dMMR colon cancers?

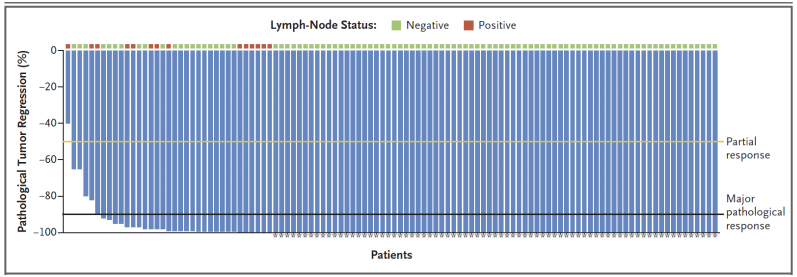
Neoadjuvant immunotherapy for dMMR colon cancer

NICHE-2

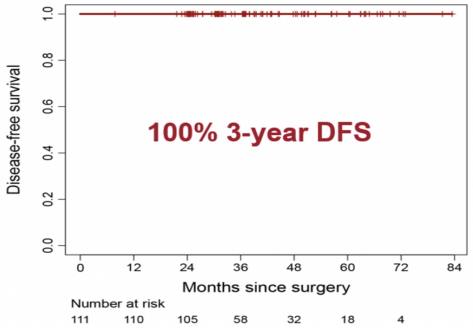
The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JUNE 6, 2024 VOL. 390 NO. 21

Neoadjuvant Immunotherapy in Locally Advanced Mismatch Repair–Deficient Colon Cancer

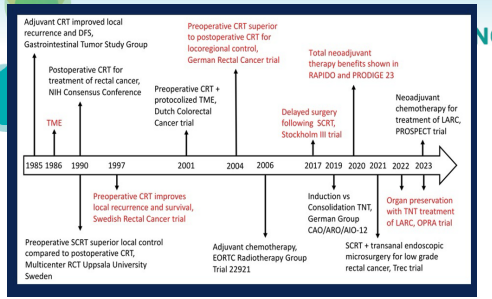


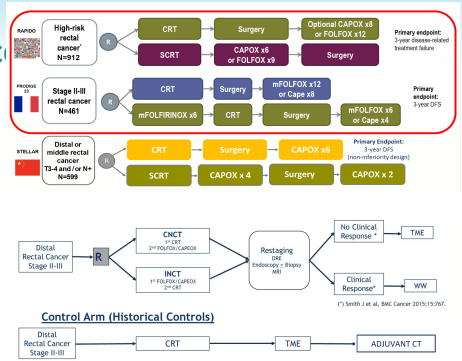


	no. (%)
≤50% Residual viable tumor	109 (98)
≤10% Residual viable tumor: major pathological response	105 (95)
0% Residual viable tumor: complete pathological response	75 (68)



Neoadjuvant immunotherapy is more effective, and allows for de-escalation of chemotherapy

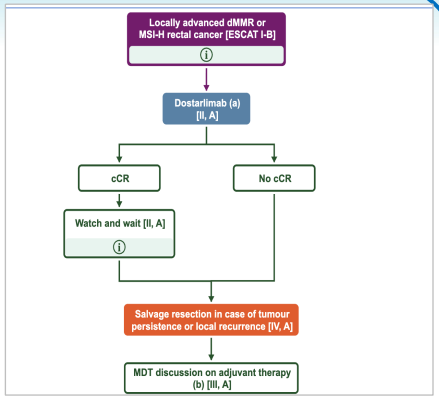




SPECIAL ARTICLE

Localised rectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

R.-D. Hofheinz. Ann Oncol. 2025

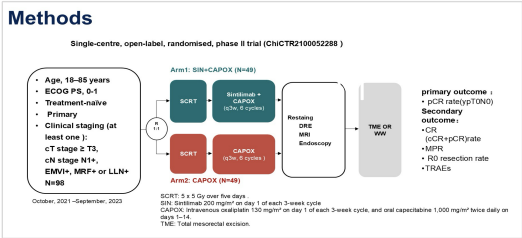


INMUNOTERAPIA: NEOADYUVANCIA ADENOCARCINOMA RECTO MSS

SPRING-01

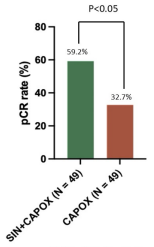
Short-course radiotherapy followed by sintilimab and CAPOX as total neoadjuvant treatment in locally advanced rectal cancer: a prospective, randomized controlled trial (SPRING-01)

Changqing Jing. ASCO 2025



ITT population	SIN+CAPOX (N = 49)	CAPOX (N = 49)
pCR (ypT0N0) *	29(59%)	16(33%)
Complete response (pCR+cCR) *	30(61%)	16(33%)
Major pathological response *	36(74%)	23(47%)
Surgical population	**SIN+CAPOX (N = 45)**	**CAPOX (N = 44)**
Tumor regression grading *		
0	29(64%)	16(36%)
1	7(16%)	7(16%)
2	5(11%)	13(30%)
3	4(9%)	8(18%)
NAR score		
Low	32(71%)	21(48%)
Intermediate	9(20%)	17(39%)
High	4(9%)	6(14%)

•ITT: pCR: (29 [59%] of 49 [95% CI 45-73] vs 16 [33%] of 49 [95% CI 20-46];
• difference, 27% [95% CI 8-46]; p=0.015)



2025 ESMO GASTROINTESTINAL CANCERS
Annual Congress

Use of ctDNA in treatment strategy

Localised colon cancer

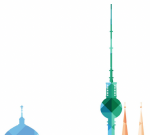
2025 ASCO ANNUAL MEETING

ctDNA Guiding Treatment of Colorectal Cancer: Ready for primetime?

BERLIN 2025 ESMO congress

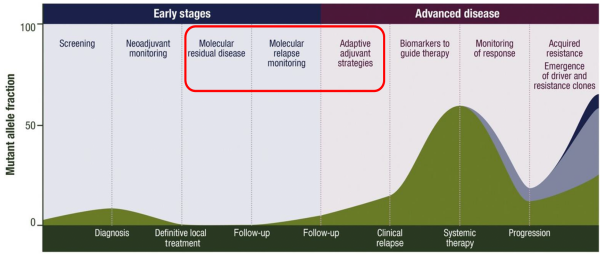
MINIMAL RESIDUAL DISEASE

Special Session on ctDNA



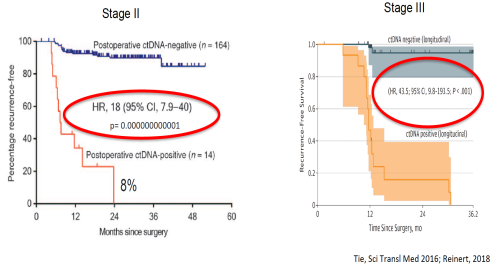
__In the era of precision oncology__, the need to identify patients who genuinely require adjuvant therapy and those who can be spared from it has become increasingly urgent.

Potential ctDNA applications



Pascual J. Ann Oncol 2022

ctDNA after surgery in localized colon cancer is THE MOST IMPORTANT prognostic factor



Tie, Sci Transl Med 2016; Reinert, 2018

#1. ctDNA predicts recurrence: specificity>95%; PPV>95%

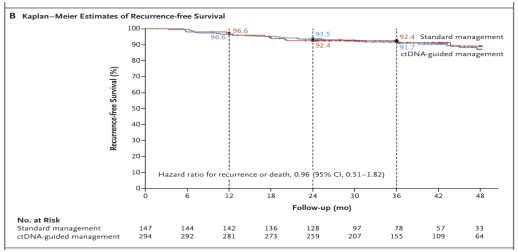
Tumor-informed and tissue-free ctDNA MRD tests

ctDNA+: 10% stage II; 25% stage III

DYNAMIC

Circulating Tumor DNA Analysis Guiding Adjuvant Therapy in Stage II Colon Cancer

Jeanne Tie, M.D., Joshua D. Cohen, M.Phil., Kamel Lahouel, Ph.D., Serigne N. Lo, Ph.D.,



2025 ASCO ANNUAL MEETING

ctDNA-Guided Adjuvant Chemotherapy Escalation in Stage III Colon Cancer

Primary Analysis of the ctDNA-Positive Cohort from the Randomized AGITG DYNAMIC-III Trial (Intergroup Study of AGITG and CCTG)

Jeanne Tie

BERLIN 2025 ESMO congress

ctDNA-Guided Adjuvant Chemotherapy De-Escalation in Stage III Colon Cancer

Primary Analysis of the ctDNA-Negative Cohort from the Randomised AGITG DYNAMIC-III Trial (Intergroup Study of AGITG and CCTG)

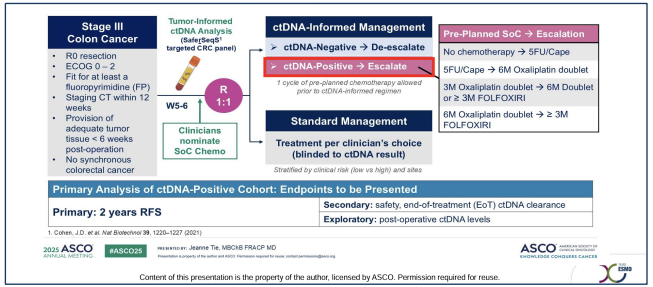
Jeanne Tie

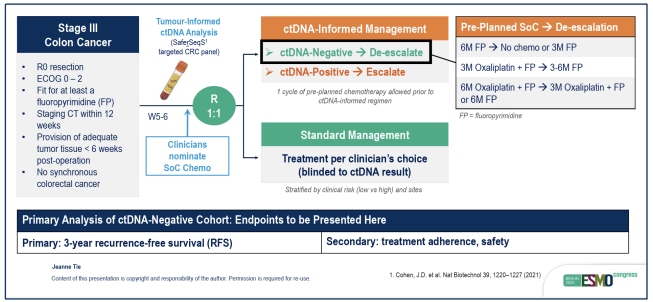
nature medicine

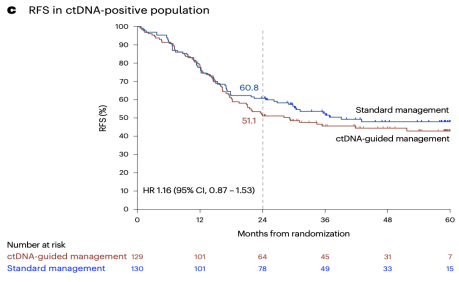
Article

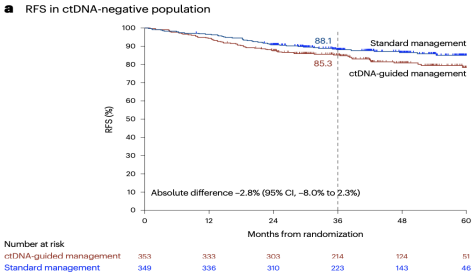
https://doi.org/10.1038/s41591-025-04030-w

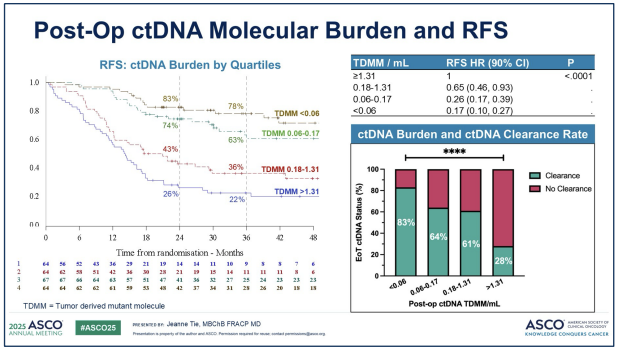
Circulating tumor DNA-guided adjuvant therapy in locally advanced colon cancer: the randomized phase 2/3 DYNAMIC-III trial





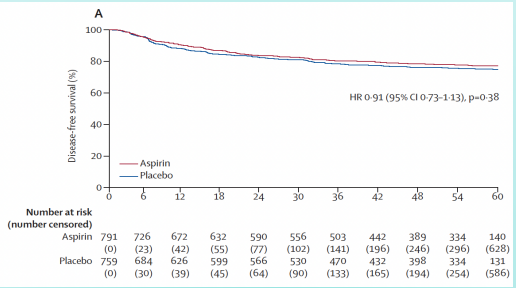






Jeanne Tie. ASCO 2025. Nature Medicine 2025

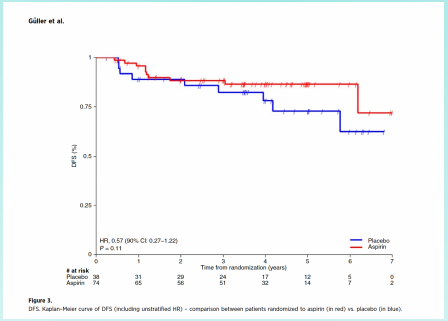
Aspirin after completion of standard adjuvant therapy for colorectal cancer (ASCOLT): an international, multicentre, phase 3, randomised, double-blind, placebo-controlled trial



John W K Chia . Lancet Gastroenterol Hepatol 2025

CLINICAL CANCER RESEARCH | CLINICAL TRIALS: TARGETED THERAPY

Adjuvant Aspirin Treatment in *PIK3CA*-Mutated Colon Cancer Patients: The SAKK 41/13 Prospective Randomized Placebo-Controlled Double-Blind Trial



Ulrich Güller. Clin Cancer Res 2025

ASCO Gastrointestinal Cancers Symposium

ALASCCA

Low-Dose Aspirin Reduces Recurrence Rate in Colorectal Cancer Patients with PI3K Pathway Alterations

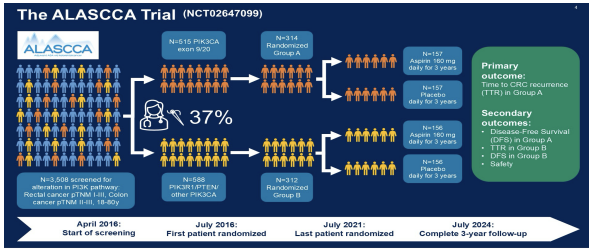
3-Year Results from the ALASCCA Trial

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 18, 2025 VOL. 393 NO. 11

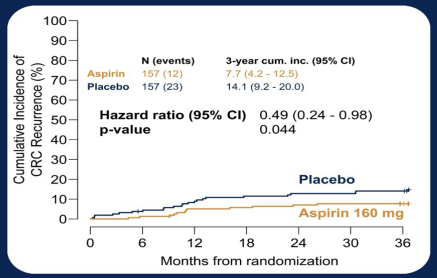
Low-Dose Aspirin for PI3K-Altered Localized Colorectal Cancer

ALASCCA

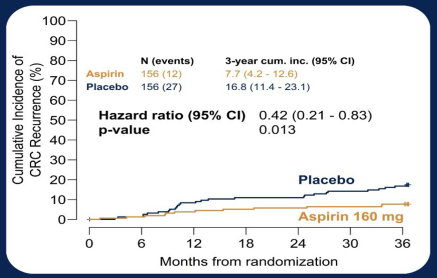


Primary Outcome: CRC Recurrence

Group A (PIK3CA Exons 9/20)



Group B (PIK3R1/PTEN/Other PIK3CA)



Aspirin 160 mg reduced recurrence rate by 50% in CRC patients with tumors harboring mutations in the PI3K pathway

Can change clinical practice for around one third of patients with non-metastasized CRC

A. Martling. N Engl J Med 2025;393:1051-64.

2025 ASCO ANNUAL MEETING

Can Lifestyle Save Lives in Colorectal Cancer?

EXERCISE

Exercise improves muscle strength, cardiorespiratory fitness, emotional distress, physical activity, fatigue, and sleep quality …… in colorectal

Precision Oncology?

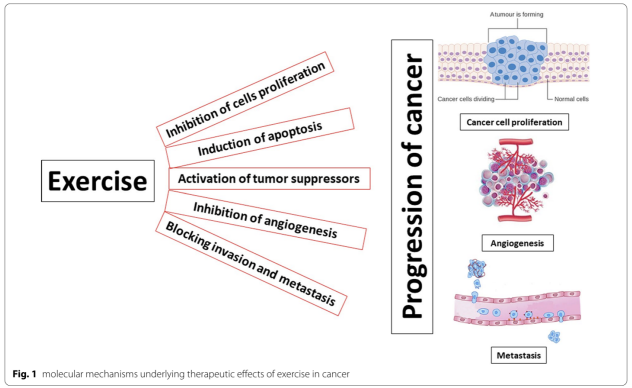


Fig. 1 molecular mechanisms underlying therapeutic effects of exercise in cancer

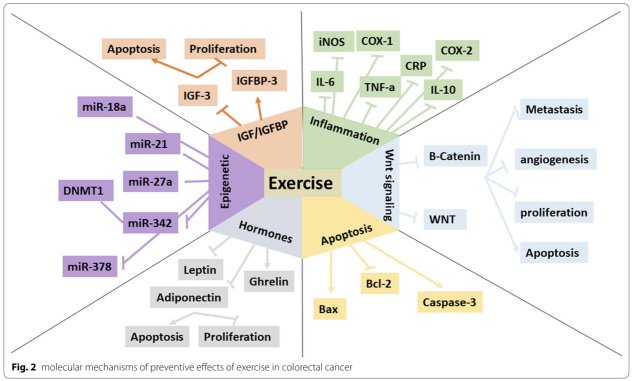


Fig. 2 molecular mechanisms of preventive effects of exercise in colorectal cancer

Amirsasan et al. Cancer Cell International 2022; 22: 247

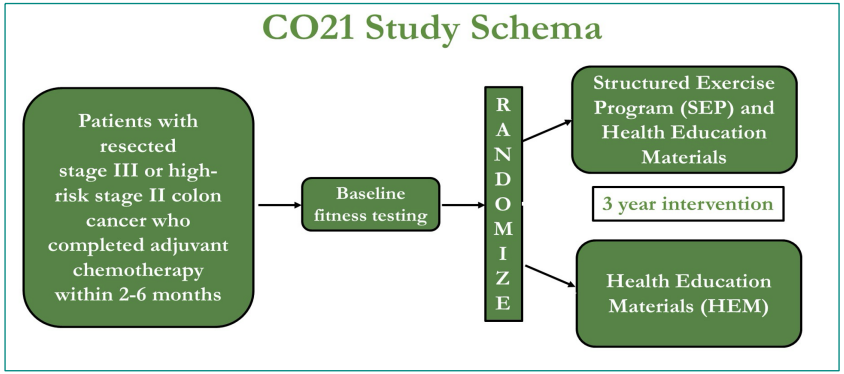
Canadian Cancer Trials Group / Groupe canadien des essais sur le cancer

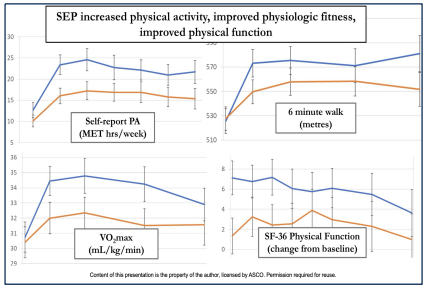
A Phase III Study of the Impact of a Physical Activity Program on Disease-Free Survival in Patients with High-Risk Stage II or Stage III Colon Cancer: The CHALLENGE Trial (CO.21)

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JULY 3, 2025 VOL. 393 NO. 1

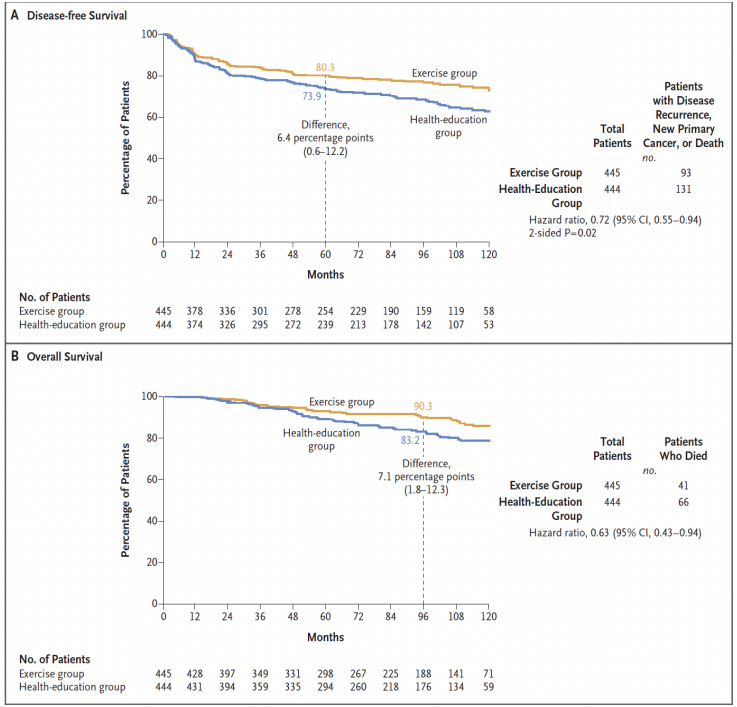
Structured Exercise after Adjuvant Chemotherapy for Colon Cancer

CO21 Study Schema





	SEP (n=445)	HEM (N=444)
DFS event	93 (21%)	131 (30%)
Recurrence	65 (15%)	81 (18%)
Local colon	12	12
Liver	16	29
Lung	20	19
Other	30	33
New Primary	23 (5%)	43 (10%)
Breast	2	12
Prostate	5	9
CRC	0	5
Other	17	17



Kerry S. Courneya. NEJM 2025

2025 ASCO ANNUAL MEETING

First-line encorafenib + cetuximab + mFOLFOX6 in BRAF V600E-mutant metastatic colorectal cancer (BREAKWATER): progression-free survival and updated overall survival analyses

2025 ASCO ANNUAL MEETING

Nivolumab plus ipilimumab versus chemotherapy or nivolumab monotherapy for microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: expanded analyses from CheckMate 8HW

2025 ASCO ANNUAL MEETING

LBA1: **Randomized trial of standard chemotherapy alone or combined with atezolizumab as adjuvant therapy for patients with stage III deficient DNA mismatch repair** (dMMR) **colon cancer** (Alliance A021502; ATOMIC)

2025 ASCO ANNUAL MEETING

ctDNA-Guided Adjuvant Chemotherapy Escalation in Stage III Colon Cancer

Primary Analysis of the ctDNA-Positive Cohort from the Randomized AGITG DYNAMIC-III Trial (Intergroup Study of AGITG and CCTG)

Jeanne Tie

ASCO Gastrointestinal Cancers Symposium

ALASCCA

Low-Dose Aspirin Reduces Recurrence Rate in Colorectal Cancer Patients with PI3K Pathway Alterations

3-Year Results from the ALASCCA Trial

Canadian Cancer Trials Group / Groupe canadien des essais sur le cancer

A Phase III Study of the Impact of a Physical Activity Program on Disease-Free Survival in Patients with High-Risk Stage II or Stage III Colon Cancer:

The CHALLENGE Trial (CO.21)

ASCO Gastrointestinal Cancers Symposium

BREAKWATER: Primary analysis of first-line (1L) encorafenib + cetuximab (EC) + FOLFIRI in BRAF V600E-mutant metastatic colorectal cancer (mCRC)

NRG ONCOLOGY

ASCO Gastrointestinal Cancers Symposium

January 8-10, 2026

NRG-GI004/SWOG-S1610: COlorectal cancer dMMR Immuno-Therapy (COMMIT) study

A randomized phase III study of atezolizumab monotherapy versus mFOLFOX6/bevacizumab/atezo in the first-line treatment of patients with dMMR or MSI-H metastatic colorectal cancer

ASCO Gastrointestinal Cancers Symposium

The Role of (Total) Neoadjuvant Therapy in Colorectal Cancer: Above and Beyond the Rectum

ASCO Gastrointestinal Cancers Symposium

ctDNA-Guided Adjuvant Treatment in Colorectal Cancer

ASCO Gastrointestinal Cancers Symposium

Glucagon-Like Peptide-1 Receptor Agonist vs Aspirin For Primary Prevention Of Colorectal Cancer: Evidence From A Real-World Head-to-Head Comparison

ASCO Gastrointestinal Cancers Symposium

Cedars Sinai

Longitudinal Study on the Influence of Physical Activity in Managing Cancer-Related Fatigue in Patients with Colorectal Cancer

Horizonte 2026: Oportunidades

PRÓXIMO SIMPOSIO NACIONAL DE ONCOLOGÍA DE PRECISIÓN

2027