# Systemic Therapy in Metastatic Colorectal Cancer – Past Present and Future

Medical Oncology Perspective
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## Outline

- **CRC Statistics**
- **Key Clinical Pieces of Data**
- **Foundation of 1st line chemotherapy**
  - **6 decades under 6 minutes**
- **Targeted therapies**
  - **VEGF directed**
  - **EGFR directed**
  - **MSI-H**
  - **BRAF directed**
- **ASCO GI 2026 CRC updates (BREAKWATER and COMMIT)**

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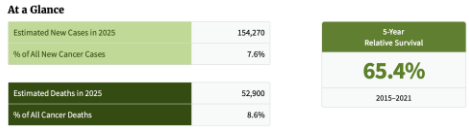


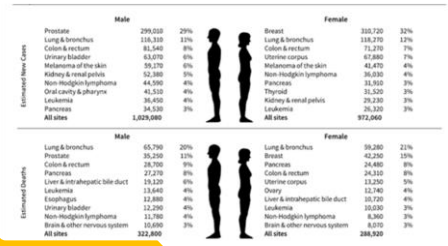


# SEER DATA 2025 Statistics CRC

- Increasing incidence in YA
  - 20% < 55 (doubled since 2019)
- Screening C-scope at 45
- Environmental, Dietary, Genetics

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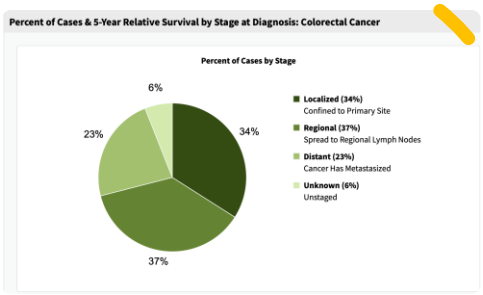


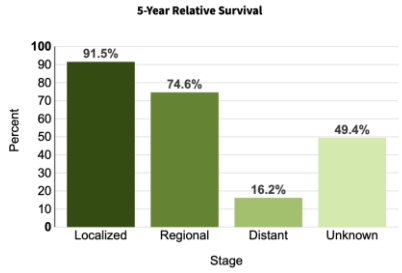


# SEER DATA

- 23% Stage IV
- 5 year survival 16%

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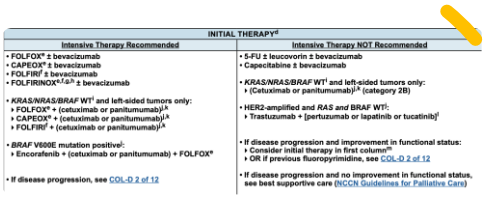
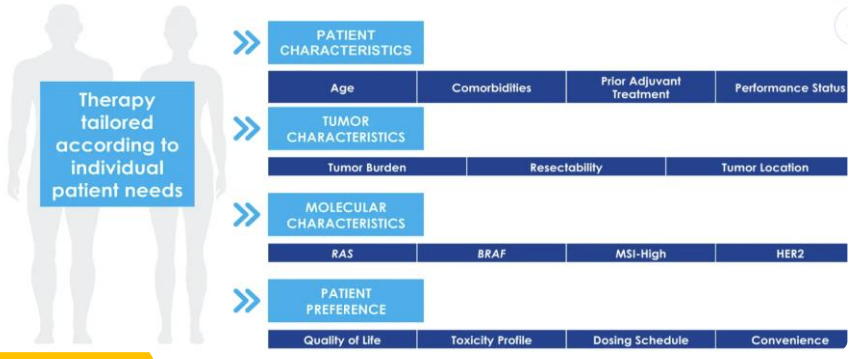


| INITIAL THERAPY[d] | |
|---|---|
| Intensive Therapy Recommended | Intensive Therapy NOT Recommended |
| • FOLFOX[e] ± bevacizumab<br>• CAPEOX[e] ± bevacizumab<br>• FOLFIRI[f] ± bevacizumab<br>• FOLFIRINOX[f,i,j,k] ± bevacizumab<br><br>• *KRAS/NRAS/BRAF* WT[l] and left-sided tumors only:<br>› FOLFOX[e] + (cetuximab or panitumumab)[j,k]<br>› CAPEOX[e] + (cetuximab or panitumumab)[j,k]<br>› FOLFIRI[f] + (cetuximab or panitumumab)[j,k]<br><br>• *BRAF* V600E mutation positive[l]:<br>› Encorafenib + (cetuximab or panitumumab) + FOLFOX[e]<br><br>• If disease progression, see COL-D 2 of 12 | • 5-FU ± leucovorin ± bevacizumab<br>• Capecitabine ± bevacizumab<br><br>• *KRAS/NRAS/BRAF* WT[l] and left-sided tumors only:<br>› (Cetuximab or panitumumab)[j,k] (category 2B)<br><br>• HER2-amplified and *RAS* and BRAF WT[l]:<br>› Trastuzumab + [pertuzumab or lapatinib or tucatinib][l]<br><br>• If disease progression and improvement in functional status:<br>› Consider initial therapy in first column[m]<br>› OR if previous fluoropyrimidine, see COL-D 2 of 12<br><br>• If disease progression and no improvement in functional status, see best supportive care (NCCN Guidelines for Palliative Care) |

# Key Pieces of Clinical Data: So many options !

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| ERA | TIMELINE | DRUG | BENEFIT | TRIAL | NOTES | |
|---|---|---|---|---|---|---|
| 5FU ERA | 1957-1990 | 5FU Bolus vs BSC | 6m | | | |
| COMBO 1996-2004 | 1998 - 2000 | Irinotecan<br>IFL vs 5FU+Leu | OS 14.8 vs 12.6 | Saltz | IFL (Irinotecan + Bolus 5FU/Leu) | |
| | 2002 - 2004 | FOLFOX vs IFL | OS 19.5m vs 15m | De Gramont and N9741 | FOLFOX > 5FU and IFL<br>Bolus 5FU > SE than infusional | |
| | 2004 | FOLFIRI vs FOLFOX | 21 m either sequence | Tournigand et al | Equivalent efficacy, sequence does not matter<br>OX: neuropathy/neutropenia<br>IRI: alopecia/diarrhea | |
| | 2001 (mCRC)<br>2004 (adj) | Capecitabine<br>CAPEOX vs FOLFOX | Equivalent | X-ACT and other Meta-analysis | Hand foot syndrome<br>CAPIRI (NO !) | |
| | 2006 | (FOLFOX cont vs 6cycles-><br>Maint 5FU->Ox on POD | 19.3 vs 21.2m<br>Better QOL<br>Less SE | OPTIMOX1 and CAIRO | | |
| | | | | | | |

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| ERA | TIMELINE | DRUG | BENEFIT | TRIAL | NOTES |
|---|---|---|---|---|---|
| Targeted<br>2004-2020 | 2004 | VGEFi Bev<br>Bev+IFL vs IFL + ?<br>Bev+Ox(F or C)<br>Bev+FOLFOXIRI vs Bev+FOLFIRI * | OS 20 vs 15.6 *(4m)<br>PFS but not OS<br>OS 31 vs 25.8 | AVF2107g<br>N016966<br>TRIBE1 | Ben benefit maintenance than upfront setting |
| | 2004<br>2006 | AntiEGFR (RAS wt)<br>Cetuximab<br>Panitumumab vs Chemo or Bev | OS 3-4 months | CRYSTAL/FIRE/<br>PARADIGM | Extended RAS (exon 2 vs 2,3,4)<br>Additional 11% that don't benefit from EGFR<br>Side matters (LEFT sided only) |
| Biomarker***<br>Directed<br>MSI High<br>2020-present | 2020 | Pembrolizumab vs Chemo+Bev+/-Cetux<br><br>Ipi+Nivo | 5 yr OS 77.5 vs 36.7m (29% primary progressive disease)<br><br>2 yr PFS 72% (48%)<br>ORR 71% ( 45%)<br><br>Progression 10% (29%) | KEYNOTE 177<br><br>CheckMate 8HW | Benefit not seen in RAS mutated<br><br>Dual ICI superior efficacy<br>RAS mutation |
| | | | | | |
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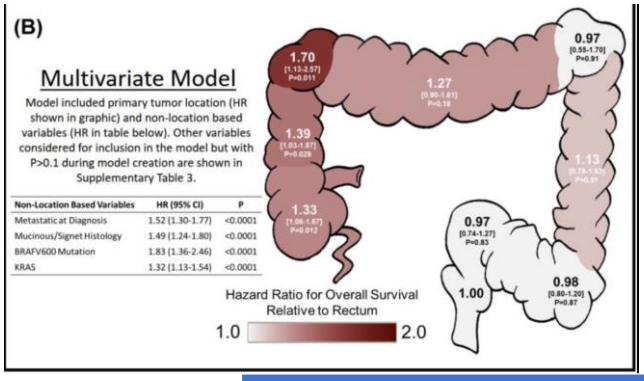
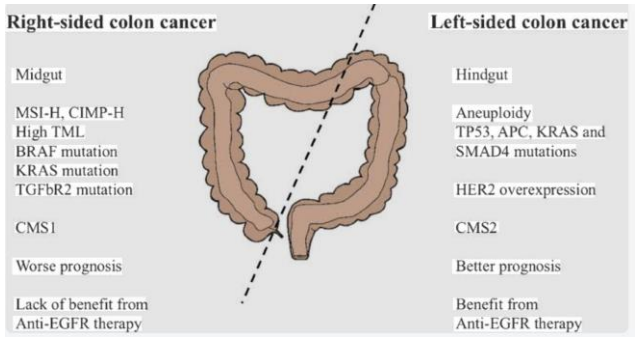
# Mutational Analysis and Sidedness




| RIGHT (worse) Transverse to Cecum | LEFT (better) Splenic Flex onwards |
|---|---|
| Sessile, serrated, mucinous | Villous and typical adenoCA |
| Flat, larger, advanced, poorly diff | polypoid |
| BRAF, KRAS | HER2 amp |
| MSI high, dMMR | |
| Lack of benefit from Anti-EGFR Rx | Benefit from Anti-EGFR Rx***(RAS Wt) |
| | |

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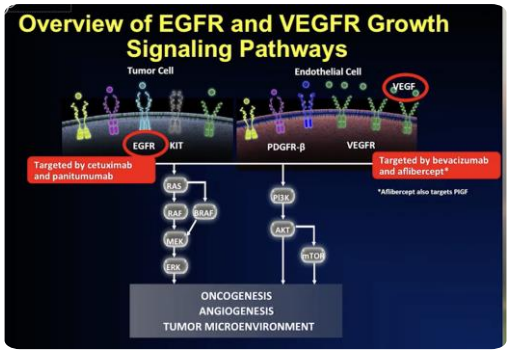
# RAS mutation




- EGFR inhibitors (Cetuximab and Panitumumab)
- Blockade at the top of the chain
- Pathway broken by RAS mutation, upstream inhibition is futile
- MAPK and PIK3/AKT pathway remains intact

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# Summary of 1L Systemic therapy

- 5FU + oxaliplatin or irinotecan or capecitabine is back bone
- FOLFOX = FOLFIRI and CAPEOX (sequence does not matter)
- Stop and go approach * = less SE, better QOL, still efficacious
- Bevacizumab better in maintenance setting but still option in combination with 5FU regimen
- FOLFOXIRI (oxaliplatin + irinotecan): young, fit, aggressive tumors
- Sidedness matters: Rt side: no EGFRi Cetux/Panitumumab
- Extended RAS testing: EGFRi won't work if RAS mutated
- MSI-H: Pembrolizumab is approved; Dual ICI better response, more ICI SE

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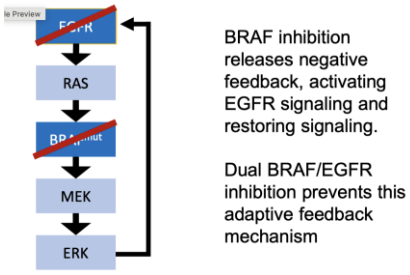
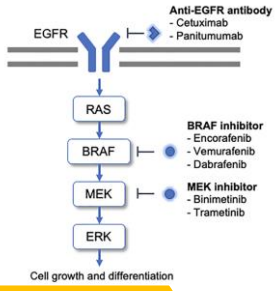



BRAF inhibition releases negative feedback, activating EGFR signaling and restoring signaling.

Dual BRAF/EGFR inhibition prevents this adaptive feedback mechanism




# 2nd line Targeted therapies: BRAF mutation **

- Occurs in exon 15 (BRAF v600E) - only actionable BRAF mutation ( 4-7% )
- Associated with poor OS and atypical patterns of metastases
- BEACON trial
  - Progression after 1-2 regimens
  - TRIPLET:Encorafenib + Binimetinib+ Cetux
  - DOUBLET:Encorafenib+Cetux
  - CONTROL: Cetuximab + Irinotecan or FOLFIRI
  - Triplet+Doublet showed OS benefit (9m + 8.4m vs 5.9m)
  - 40% reduction in risk of death
  - Doublet with better SE profile so SOC

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# Anti - HER 2 directed therapies (2nd line +)

| Trial | Regimen | ORR | Median PFS | Median OS | Key Notes |
|---|---|---|---|---|---|
| **MOUNTAINEER** | Tucatinib + trastuzumab | 38.1% | 8.2 months | 24.1 months | FDA-approved Jan 2023; RAS WT only |
| **DESTINY-CRC01** | Trastuzumab deruxtecan 6.4 mg/kg | 45.3% | 6.9 months | 15.5 months | IHC 3+ or IHC 2+/ISH+; RAS WT |
| **DESTINY-CRC02** | Trastuzumab deruxtecan 5.4 mg/kg | 37.8% | 5.8 months | NR | Active in RAS-mutant; IHC 3+ preferred |
| **MyPathway** | Trastuzumab + pertuzumab | 32% | 2.9 months | 11.5 months | RAS WT; heavily pretreated |
| **HERACLES-A** | Trastuzumab + lapatinib | 28% | 4.7 months | 10.0 months | First proof-of-concept trial |

4% of CRC

Depends on RAS and IHC stain

Tucatinib + Trastuzumab (1st FDA approved)

Trastuzumab Deruxtecan – ADC IHC 3+ or 2+ with FISH+, RAS mutated

Trastuzumab + Pertuzumab: dual HER2 therapy, better in KRAS wt

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# KRAS G 12 C and NTRK fusions (2nd line and beyond)

KRYSTAL 1: Adagrasib monotherapy vs in combination with cetuximab for KRAS G12C mutatant mCRC; mPFS of 6.9m vs 5.6

NTRK fusions are rare: Larotrectinib. Entrectinib, Repotrectinib

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# 3rd line and beyond

- **For disease that has progressed through all available regimens:**
  - **Fruquintinib**
  - **Regorafenib**
  - **Trifluridine + tipiracil ± bevacizumab (bevacizumab combo preferred)**

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ORIGINAL ARTICLE

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

Authors: Elena Elez, M.D., Ph.D., Takayuki Yoshino, M.D., Ph.D., Lin Shen, M.D., Sara Lonardi, M.D., Eric Van Cutsem, M.D., Ph.D., Cathy Eng, M.D., Tae Won Kim, M.D., Ph.D., +11 , for the BREAKWATER Trial Investigators* Author Info & Affiliations

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# BREAKWATER

## ABSTRACT 16: BREAKWATER: Analysis of first-line encorafenib + cetuximab + chemotherapy in BRAF V600E-mutant metastatic colorectal cancer (Kopetz)

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)

- prespecified hierarchical testing
- Initial analysis is RR -> OS

Kopetz et al, *GI Symposium* 2025

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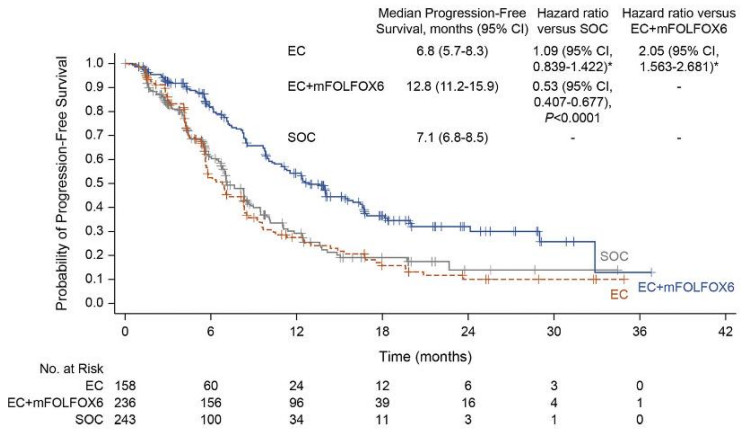


**Objective response rate**

- **60.9% with EC FOLFOX vs 40% with SOC**
- **Median Duration of response 13.9m vs 11.9m**

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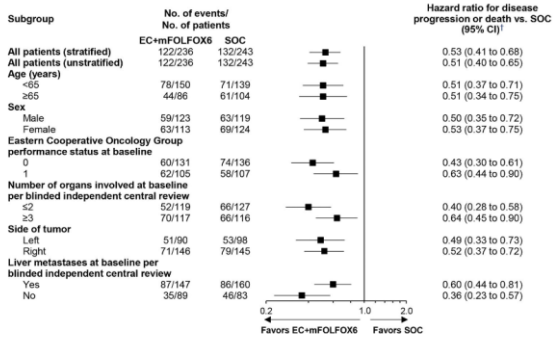


**Figure 1. Analysis of Progression-Free Survival by Blinded Independent Central Review.**
**Panel A** shows Kaplan–Meier estimates of progression-free survival in the EC, EC+mFOLFOX6 and SOC arms. **Panel B** shows a forest plot of the analyses in pre-specified subgroups in the EC+mFOLFOX6 and SOC arms.
*Analyses of EC versus SOC and EC versus EC+mFOLFOX6 are descriptive. CIs are not adjusted for multiplicity and should not be mistaken for hypothesis tests. Following a protocol amendment, enrollment into the EC arm was discontinued prematurely.
†Subgroup analyses are exploratory and descriptive in nature; CIs are not adjusted for multiplicity and should not be interpreted as hypothesis tests.
CI, confidence interval; EC, encorafenib and cetuximab; EC+mFOLFOX6, encorafenib and cetuximab plus oxaliplatin, leucovorin and 5-FU; HR, hazard ratio; SOC, standard of care.

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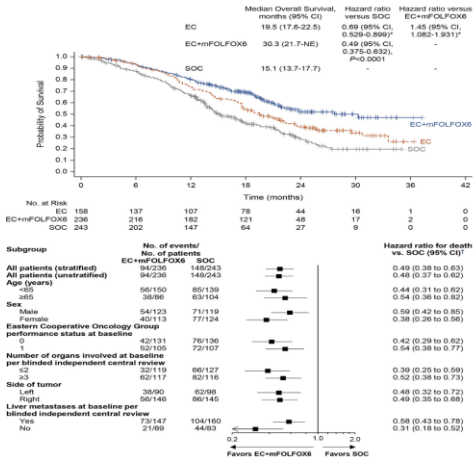


**Figure 2. Analysis of Overall Survival.**
**Panel A** shows Kaplan–Meier estimates of overall survival in the EC, EC+mFOLFOX6 and SOC. **Panel B** shows a forest plot of the analyses in pre-specified subgroups in the EC+mFOLFOX6 and SOC arms.
Because the result of the interim analysis of overall survival was statistically significant, no further statistical test will be performed.
*Analyses of EC versus SOC and EC versus EC+mFOLFOX6 are descriptive. CIs are not adjusted for multiplicity and should not be mistaken for hypothesis tests. Following a protocol amendment, enrollment into the EC arm was discontinued prematurely.
†Subgroup analyses are exploratory and descriptive in nature; CIs are not adjusted for multiplicity and should not be interpreted as hypothesis tests.

**Median OS**
EC: 19.5m
EC+mFOLFOX: 30.3m
SOC: 15.1m

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| Adverse Event | EC N = 153 | EC+mFOLFOX6 N = 232 | SOC N = 229 |
|---|---|---|---|
| Treatment-emergent adverse events — no. (%) | | | |
| Intestinal obstruction | 6 (3.9) | 11 (4.7) | 5 (2.2) |
| Pyrexia | 0 | 9 (3.9) | 3 (1.3) |
| Anemia | 0 | 8 (3.4) | 1 (0.4) |
| Disease progression | 4 (2.6) | 8 (3.4) | 1 (0.4) |
| Abdominal pain | 3 (2.0) | 6 (2.6) | 7 (3.1) |
| Vomiting | 1 (0.7) | 6 (2.6) | 1 (0.4) |
| Sepsis | 1 (0.7) | 4 (1.7) | 1 (0.4) |
| ALT increased | 0 | 3 (1.3) | 1 (0.4) |
| Ascites | 0 | 3 (1.3) | 0 |
| Ileus | 2 (1.3) | 3 (1.3) | 4 (1.7) |
| Pneumonia | 0 | 3 (1.3) | 5 (2.2) |
| Pulmonary embolism | 0 | 3 (1.3) | 1 (0.4) |
| Small intestinal obstruction | 1 (0.7) | 3 (1.3) | 1 (0.4) |
| Urinary tract infection | 6 (3.9) | 3 (1.3) | 2 (0.9) |

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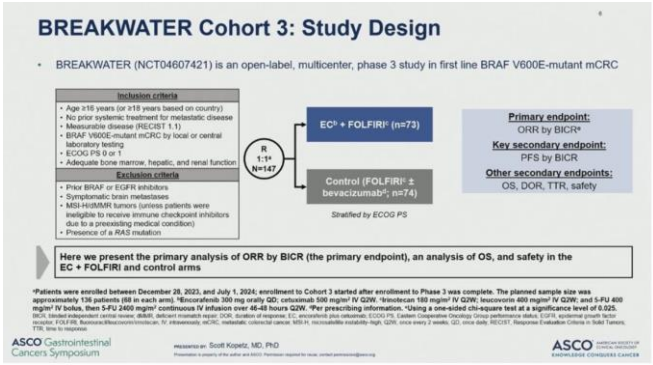


## BREAKWATER ASCO GI 2026 cohort 3 Primary analysis

- Primary analysis of 1L Encorafenib + Cetuximab + FOLFIRI
- 147 untreated patients with BRAF V600E
- 1:1 EC+FOLFIRI vs FOLFIRI +/- Bevacizumab
- ORR 64.4% vs 39.2%
- Median time to response 6.9 weeks
- At 6m: 57.4% vs 34.5% maintained response
- OS data immature
- SE: 39.4% vs 36.8%

CONCLUSION: The targeted therapy backbone is the key driver of better disease control in BRAF v600E mutated CRC

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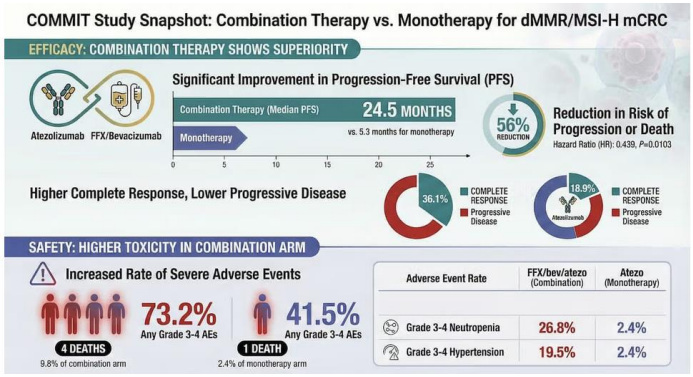
# COMMIT TRIAL




- Initially 3 arm study
  - FOLFOX + Bev (removed)
  - FOLFOX+Bev+Atezo
  - Atezo alone
  - Accrual stopped 3/25 (CHECKMATE)
- 29% in Keynote 177 had POD
- 45% progressed in 12m
- III, RCT
- 41 patients
- Untreated MSI-H
- 1:1
- Atezo vs mFOLFOX+Bev+Atezo
- Met primary end point: PFS
- ORR 86% vs 46%
- Combo arm more SE

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| Parameter | COMMIT (mFOLFOX6/Bev/At... | CheckMate 8HW (Nivo + Ipi) | KEYNOTE-177 (Pembrolizumab) |
|---|---|---|---|
| **2-Year PFS** | Significantly improved vs. atezo alone | **72%** | 48% |
| **Median PFS** | Not yet reported | Not reached (47 mo f/u) | 16.5 months |
| **ORR** | 86%** | **71%** | 43-45% |
| **Complete Response** | 36%** | **30%** | ~11% |
| **Progressive Disease as Best Response** | 32%** | **10%** | 29% |
| **Grade 3-4 TRAEs** | Expected higher (chemo-based) | 22% | 22% |

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# PROGRESS MADE

- Oligometastatic colon cancer: Gold standard for Curative metastectomy
- Remarkable transformation with mOS of 6m with 5FU only to then 12m to now 30m even in BRAF mutated cancers; higher in MSI-H (95m)

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# UNMET NEEDS

| Unmet Need | Patient Population | Current Status |
|---|---|---|
| **MSS/pMMR tumors** | ~85% of mCRC | Do not respond to immunotherapy; sensitizing MSS tumors to ICI is the **greatest unmet need** |
| **RAS-mutant disease** | ~40% of mCRC | Effective targeted therapies lacking (except KRAS G12C ~3%) |
| **Right-sided tumors** | ~30% of mCRC | Inferior outcomes; minimal anti-EGFR benefit; mOS ~19 vs. 34 months (left-sided) |
| **True cure** | All mCRC | 20% achieve 5-year survival; cure remains rare |
| **Acquired resistance** | All targeted therapy | Limits durability of responses |

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# FUTURE NEEDS

- Immunotherapy for MSS tumors (anti-angiogenesis + ICI, Bispecific antibodies
- ctDNA for residual disease monitoring and adaptive Rx strategies
- ADC: T-DXd for HER2+; expanding indications

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# REFERENCES


- Colucci G, Gebbia V, Paoletti G, Giuliani F, Caruso M, Gebbia N, Cartenì G, Agostara B, Pezzella G, Manzione L, Borsellino N, Misino A, Romito S, Durini E, Cordio S, Di Seri M, Lopez M, Maiello E, Montemurro S, Cramarossa A, Lorusso V, Di Bisceglie M, Chiarenza M, Valerio MR, Guida T, Leonardi V, Pisconti S, Rosati G, Carrozza F, Nettis G, Valdesi M, Filippelli G, Fortunato S, Mancarella S, Brunetti C; Gruppo Oncologico Dell'Italia Meridionale. Phase III randomized trial of FOLFIRI versus FOLFOX4 in the treatment of advanced colorectal cancer: a multicenter study of the Gruppo Oncologico Dell'Italia Meridionale. J Clin Oncol. 2005 Aug 1;23(22):4866-75. doi: 10.1200/JCO.2005.07.113. Epub 2005 Jun 6. PMID: 15939922.
- Richard M. Goldberg et al. A Randomized Controlled Trial of Fluorouracil Plus Leucovorin, Irinotecan, and Oxaliplatin Combinations in Patients With Previously Untreated Metastatic Colorectal Cancer . *J Clin Oncol* **22**, 23-30(2004)
- Loree JM, Pereira AAL, Lam M, Willauer AN, Raghav K, Dasari A, Morris VK, Advani S, Menter DG, Eng C, Shaw K, Broaddus R, Routbort MJ, Liu Y, Morris JS, Luthra R, Meric-Bernstam F, Overman MJ, Maru D, Kopetz S. Classifying Colorectal Cancer by Tumor Location Rather than Sidedness Highlights a Continuum in Mutation Profiles and Consensus Molecular Subtypes. Clin Cancer Res. 2018 Mar 1;24(5):1062-1072. doi: 10.1158/1078-0432.CCR-17-2484. Epub 2017 Nov 27. PMID: 29180604; PMCID: PMC5844818.
- Cremolini C, Loupakis F, Antoniotti C, Lupi C, Sensi E, Lonardi S, Mezi S, Tomasello G, Ronzoni M, Zaniboni A, Tonini G, Carlomagno C, Allegrini G, Chiara S, D'Amico M, Granetto C, Cazzaniga M, Boni L, Fontanini G, Falcone A. FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study. Lancet Oncol. 2015 Oct;16(13):1306-15. doi: 10.1016/S1470-2045(15)00122-9. Epub 2015 Aug 31. PMID: 26338525.
- Cremolini C, Antoniotti C, Rossini D, Lonardi S, Loupakis F, Pietrantonio F, Bordonaro R, Latiano TP, Tamburini E, Santini D, Passardi A, Marmorino F, Grande R, Aprile G, Zaniboni A, Murgioni S, Granetto C, Buonadonna A, Moretto R, Corallo S, Cordio S, Antonuzzo L, Tomasello G, Masi G, Ronzoni M, Di Donato S, Carlomagno C, Clavarezza M, Ritorto G, Mambrini A, Roselli M, Cupini S, Mammoliti S, Fenocchio E, Corgna E, Zagonel V, Fontanini G, Ugolini C, Boni L, Falcone A; GONO Foundation Investigators. Upfront FOLFOXIRI plus bevacizumab and reintroduction after progression versus mFOLFOX6 plus bevacizumab followed by FOLFIRI plus bevacizumab in the treatment of patients with metastatic colorectal cancer (TRIBE2): a multicentre, open-label, phase 3, randomised, controlled trial. Lancet Oncol. 2020 Apr;21(4):497-507. doi: 10.1016/S1470-2045(19)30862-9. Epub 2020 Mar 9. PMID: 32164906.
- Encorafenib, Binimetinib, and Cetuximab in BRAF V600E–Mutated Colorectal Cancer; S. Kopetz, A. Grothey, R. Yaeger, E. Van Cutsem, J. Desai, T. Yoshino, H. Wasan, F. Ciardiello, F. Loupakis, Y.S. Hong, N. Steeghs, T.K. Guren, H.-T. Arkenau, P. Garcia-Alfonso, P. Pfeiffer, S. Orlov, S. Lonardi, E. Elez, T.-W. Kim,J.H.M. Schellens, C. Guo, A. Krishnan, J. Dekervel, V. Morris, A. Calvo Ferrandiz, L.S. Tarpgaard, M. Braun, A. Gollerkeri, C. Keir, K. Maharry, M. Pickard, J. Christy-Bittel, L. Anderson, V. Sandor, and J. Tabernero
- Pembrolizumab in Microsatellite-Instability–High Advanced Colorectal Cancer T. André, K.-K. Shiu, T.W. Kim, B.V. Jensen, L.H. Jensen, C. Punt, D. Smith, R. Garcia-Carbonero, M. Benavides, P. Gibbs, C. de la Fouchardiere, F. Rivera, E. Elez, J. Bendell, D.T. Le, T. Yoshino, E. Van Cutsem, P. Yang, M.Z.H. Farooqui, P. Marinello, and L.A. Diaz, Jr., for the KEYNOTE-177 Investigators


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