

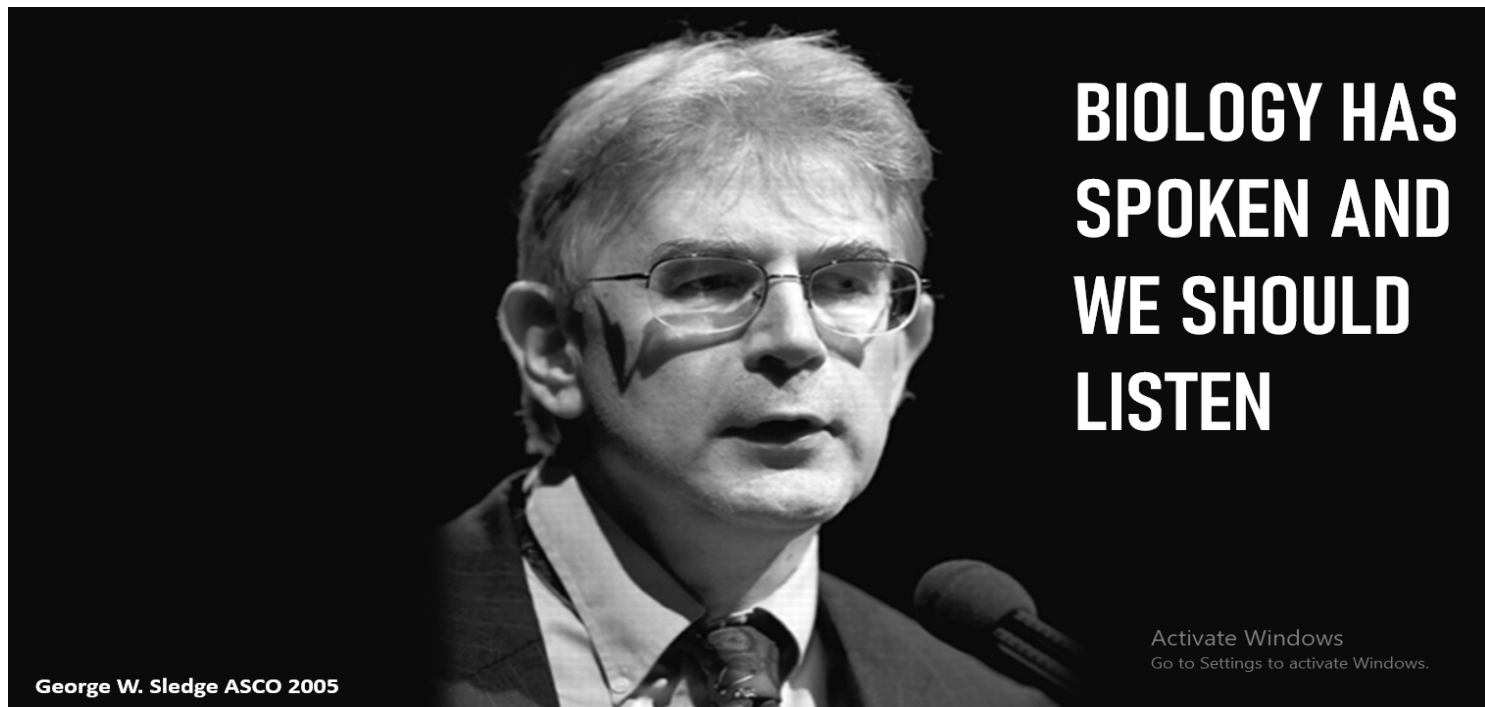
WHY IS NGS IMPORTANT IN GI ONCOLOGY TREATMENT?

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TIMISOARA, 11.09.2026.

molecular tumor profiling that help to identified patient populations most likely to benefit from targeted therapy and/or immunotherapy and predict response to treatment

—that is, precision medicine



PRECISION MEDICINE IN ONCOLOGY

instead of one-size-fits-all approaches, this strategy considers molecular features specific to the tumor (DNA mutations, gene expression and protein alterations) dramatic changes in the treatment paradigms for many cancer types with molecularly targeted agents and immunotherapy

nature reviews drug discovery

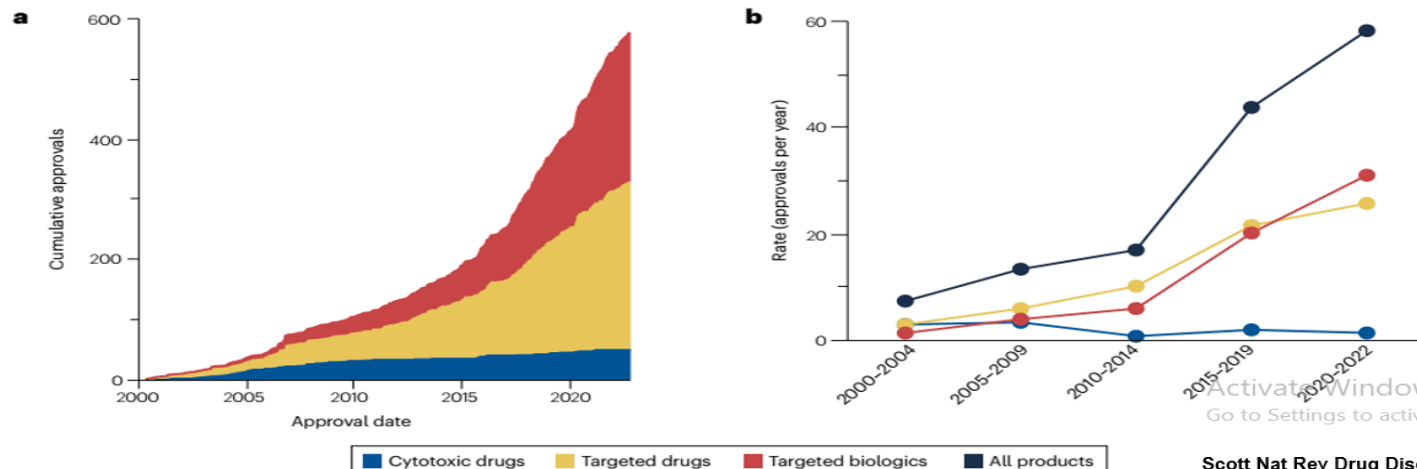
<https://doi.org/10.1038/s41573-023-00723-4>

Review article

Check for updates

Trends in the approval of cancer therapies by the FDA in the twenty-first century

Emma C. Scott¹✉, Andrea C. Baines¹, Yutao Gong¹, Rodney Moore Jr², Gulsum E. Pamuk¹, Haleh Saber¹, Ashim Subedee^{1,2}, Matthew D. Thompson¹, Wenming Xiao¹, Richard Pazdur³, V. Ashutosh Rao⁴, Julie Schneider³ & Julia A. Beaver^{1,3}



Scott Nat Rev Drug Disc 2023

TUMOR TISSUE REMAINS THE GOLD STANDARD FOR MOLECULAR DIAGNOSTIC ANALYSIS

NGS AND LIQUID BIOPSIES PROVIDE REAL-TIME AND LESS INVASIVE ACCESS TO TUMOR GENETICS ENHANCING TREATMENT PRECISION

- **IDENTIFIES TARGETED THERAPIES:**

NGS screens multiple genes simultaneously to identify specific targetable mutations (*BRAF*, *KIT*, *EGFR*, *ERBB2*, *FGFR3*, *PIK3CA*, *AKT1*, *TSC1*, *ESR1*, *ROS1*, AND *ALK* REARRANGEMENTS)

- **DETERMINES IMMUNOTHERAPY ELIGIBILITY:**

detects key biomarkers such as microsatellite instability (MSI -H) and tumor mutational burden (TMB) which predict response to immunotherapy.

- **REPLACES MULTIPLE SINGLE-GENE TESTS:**

traditional testing looks at one gene at a time, which wastes valuable time and tumor tissue (checks hundreds of genes at once)

- **TRACKS RESISTANCE AND PROGRESSION BY LIQUID BIOPSIES**

monitoring of tumor evolution over time and treatment, picking up minimal residual disease (MDR) and identifying emergent resistance clones.

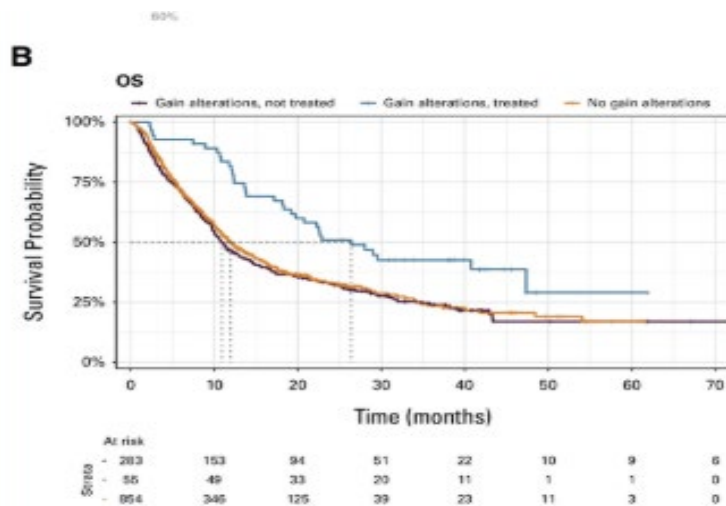
ESMO RECOMMENDATIONS FOR GI TUMORS ROUTINE MULTIGENE NGS

- **COLORECTAL CANCER (CRC):** is recommended for advanced or metastatic CRC to detect actionable alterations (such as MSI/dMMR, *BRAF*, *RAS*, and *HER2*).
- **CHOLANGIOCARCINOMA:** routine NGS is recommended in advanced disease to identify targetable fusions or mutations (such as *IDH1* mutations and *FGFR2* fusions)
- **GASTROINTESTINAL STROMAL TUMORS (GIST):** Updated ESMO guidelines expanded tumor NGS recommendations to encompass rare tumors like advanced GIST to check for *KIT* and *PDGFRA* mutations.
- **TUMOR-AGNOSTIC ALTERATIONS:** Recommended in metastatic cancers where matched therapies or clinical trials are accessible

Performance and Clinical Benefit of Comprehensive Genomic Profiling of GI Tumors in a Comprehensive Cancer Center

Giulia Maddalena, MD, PhD¹ ; Valentina Angerilli, MD²; Federico Nichetti, MD¹ ; Gianmarco Ricagno, MD^{1,3} ; Jessica Gasparello, PhD⁴ ; Elena Mattiuzzo, PhD¹; Maria Caterina De Grandis, MD¹; Elena Carcea, PhD¹; Carlotta Ceccon, PhD^{2,3} ; Anna Roma, MD⁵; Eleonora Perissinotto, MD^{1,3}; Sara Sperotto, MD^{1,3} ; Giacomo Di Paolo, MD^{1,3}; Marta Sbaraglia, MD⁴; Marco Maruzzo, MD, PhD⁵ ; Francesca Bergamo, MD¹ ; Angelo Paolo Dei Tos, MD⁴; Matteo Fassan, MD, PhD^{4,6} ; and Sara Lonardi, MD¹

DOI <https://doi.org/10.1200/PO-25-01168>



RESULTS Of the 1,450 samples, 140 (9.7%) were inadequate for CGP. Failure was mainly due to low quantity of extracted tumor DNA ($P = .002$). Of the 1,265 metastatic patients, GAs were detected in 355 (28.1%) cases, of whom 55 (15.5%) were treated with targeted therapy. Survival did not differ between patients with no GAs and those with GAs who were not treated accordingly (median overall survival 12.0 v 10.9 months), whereas it was significantly longer for those receiving treatment for actionable GAs (26.4 months). This advantage was confirmed in an exploratory, inverse probability of treatment-weighted analysis (adjusted hazard ratio, 0.72 [95% CI, 0.58 to 0.89]; $P = .002$). Among 283 (83.7%) untreated patients with complete follow-up, 41.6% did not receive targeted therapy due to lack of clinical trial or failure to meet inclusion criteria.

CONCLUSION Appropriate specimen selection and early molecular assessment at the time of advanced disease diagnosis are essential to detect clinically actionable molecular alterations and therapeutic opportunities in patients with GI cancers. Our results support CGP in comprehensive cancer centers.

We must move away from reactive, sequential single-gene testing.

It exhausts valuable tissue samples and delays time-to-treatment

Overall survival according to the presence of gain alterations and subsequent implementation of targeted therapy in patients with advanced-stage disease and complete follow-up.

HOW DOES GENETIC TESTING INFLUENCE CHEMOTHERAPY RISK FOR GASTROINTESTINAL CANCER PATIENTS?

- Genetic testing evaluates variants in genes such as [DPYD and UGT1A1 variants](#) that affect the metabolism of chemotherapy drugs used in GI cancers.
- DPYD gene variants impair the breakdown of fluoropyrimidine, leading to toxic drug accumulation
- UGT1A1 gene variants affect irinotecan metabolism, increasing risks of severe diarrhea and low white blood cell counts.
- identifying these variants before treatment and tailoring chemotherapy doses- reduce adverse side effects from 65% to 38% and lowering treatment discontinuation rates

COLORECTAL CANCER

Table 4. List of genomic alterations level I/II according to ESCAT in advanced colorectal cancer

Gene/Signature ^a	Alteration	Estimated prevalence	ESCAT score	Drug class matched	References
<i>KRAS</i> , <i>NRAS</i>	Mutations (exon 2, 3 and 4)	53%	NA ^b	Anti-EGFR monoclonal antibodies	Douillard et al., <i>N Engl J Med</i> 2013 ⁷⁶ Van Cutsem et al., <i>J Clin Oncol</i> 2015 ⁷⁷
<i>BRAF</i>	Mutations (p. V600E)	8.5%	IA	BRAF inhibitors + EGFR inhibitors	Kopetz et al., <i>N Engl J Med</i> 2019 ⁷⁸
MSI-H/dMMR ^a	MSI-H/dMMR	4.5%	IA	PD-1 checkpoint inhibitors	André et al., <i>N Engl J Med</i> 2020 ⁷⁹
<i>KRAS</i>	Mutations (p. G12C)	4%	IA	<i>KRAS</i> ^{G12C} TKIs + anti-EGFR monoclonal antibodies	Fakih et al., <i>N Engl J Med</i> 2023 ⁸⁰
<i>ERBB2</i>	Amplifications	2%	IIB	Anti-HER2 monoclonal antibodies ± anti-HER2 TKIs	Meric-Bernstam et al., <i>Lancet Oncol</i> 2019 ⁸¹ Siena et al., <i>Lancet Oncol</i> 2021 ⁸²
<i>POLE</i>	Mutations	<1%	IIB	Anti-HER2 ADCs PD-1 checkpoint inhibitors	Strickler et al., <i>Lancet Oncol</i> 2023 ⁸³ Rousseau et al., <i>Cancer Discov</i> 2022 ⁸⁴

ADCs, antibody–drug conjugates; dMMR, mismatch repair deficient; HER, human epidermal growth factor receptor; EGFR, epidermal growth factor receptor; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; MSI-H, microsatellite instability-high; NA, not applicable; PD-1, programmed cell death protein 1; TKIs, tyrosine kinase inhibitors.

^aSignature.

^bbiomarker of resistance.

a recent study estimated that over 1,100 patients would require NGS-based MSI testing to identify one MSI-H case that IHC would miss. In contrast, nearly 500 patients would require IHC to identify one dMMR case missed by NGS.⁵ Similarly, these numbers were comparable between MMR IHC and PCR-based MSI test

MCRC ESMO CLINICAL RECOMENDATION 2026.

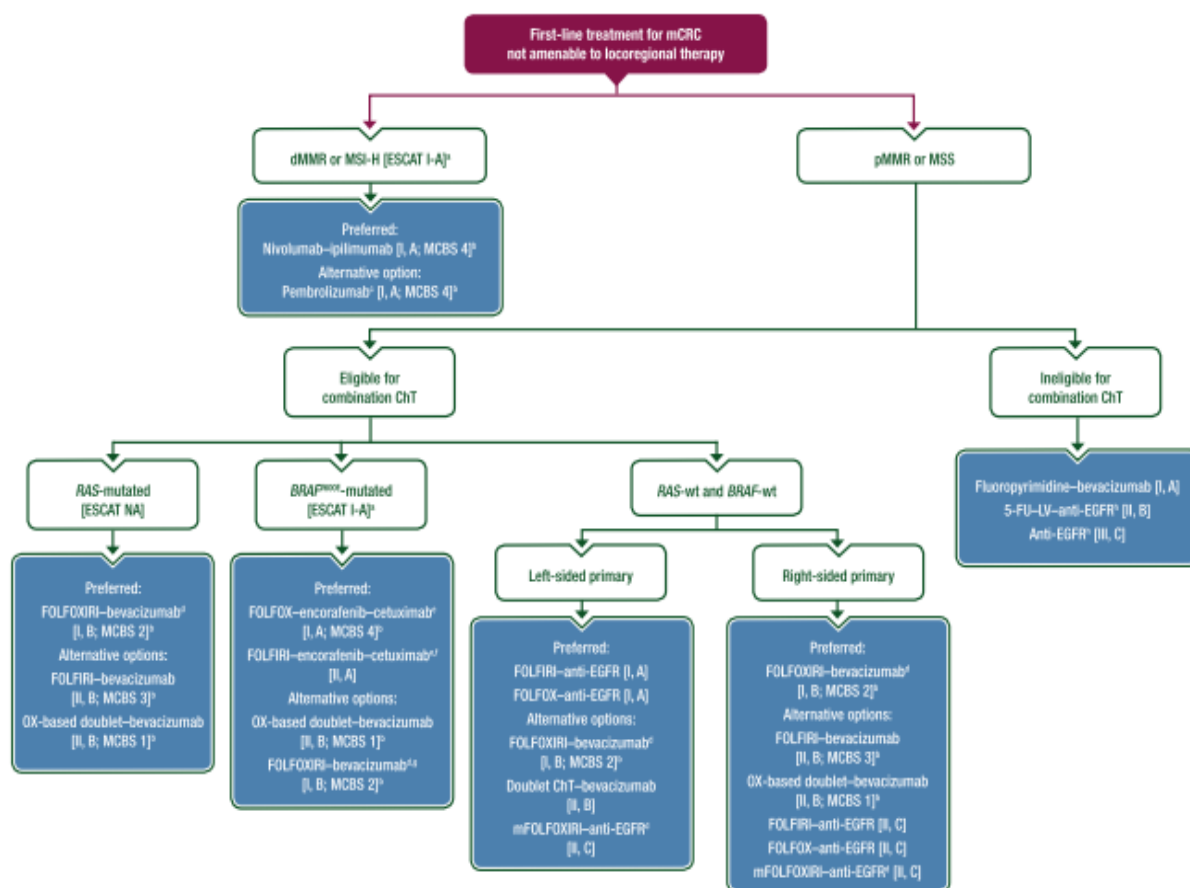
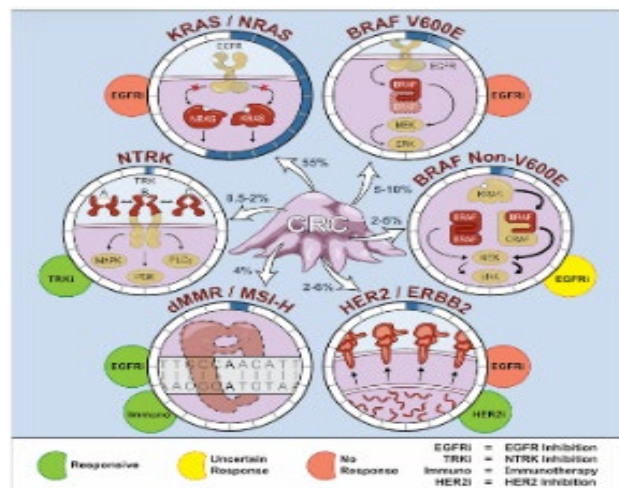
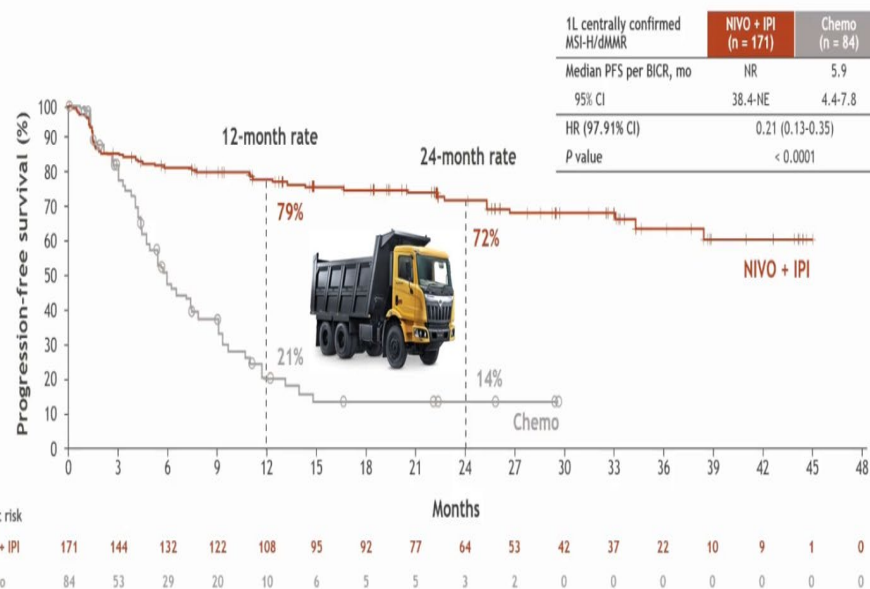


Figure 2. First-line treatment for mCRC not amenable to locoregional therapy.

Progression-free survival



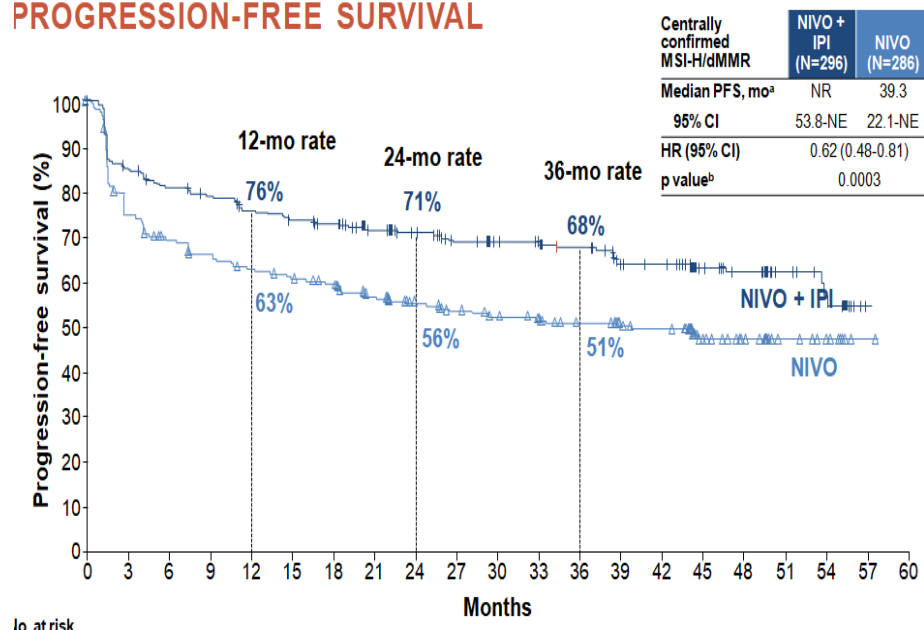
- At the prespecified interim analysis, 1L NIVO + IPI showed superior PFS vs chemo in patients with centrally confirmed MSI-H/dMMR mCRC (HR, 0.21; 97.91% CI, 0.13-0.35; $P < 0.0001$)

– 24-month PFS rates for NIVO + IPI vs chemo: 72% vs 14%

Activate Windows
Go to Settings to activate Windows.

CheckMate 8HW: Nivo +/- Ipi across all lines of therapy in dMMR/MSI-h mCRC

PROGRESSION-FREE SURVIVAL



At 24 months, the restricted mean survival time was 10.6 months longer with nivolumab plus ipilimumab than with chemotherapy

24-month OS of **74%** with dual IPI/NIVO blockade

A RANDOMISED STUDY OF ENCORAFENIB, CETUXIMAB, AND FOLFIRI VERSUS FOLFIRI WITH OR WITHOUT BEVACIZUMAB IN *BRAF* V600E-MUTANT COLORECTAL CANCER: BREAKWATER COHORT 3

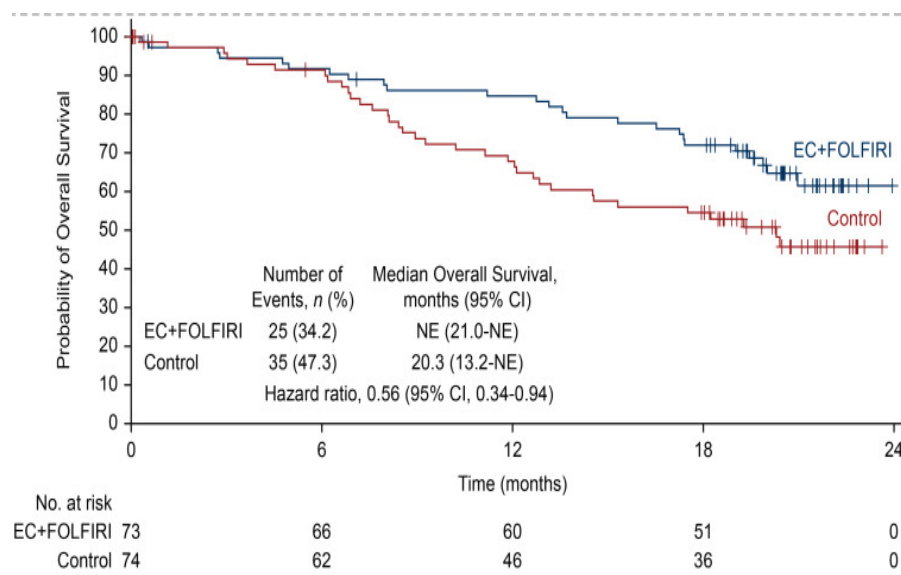
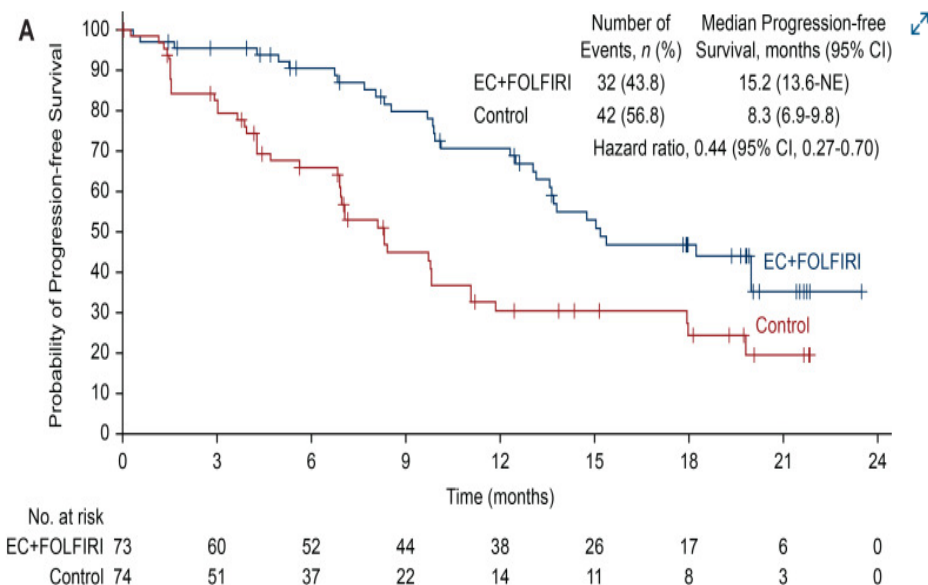
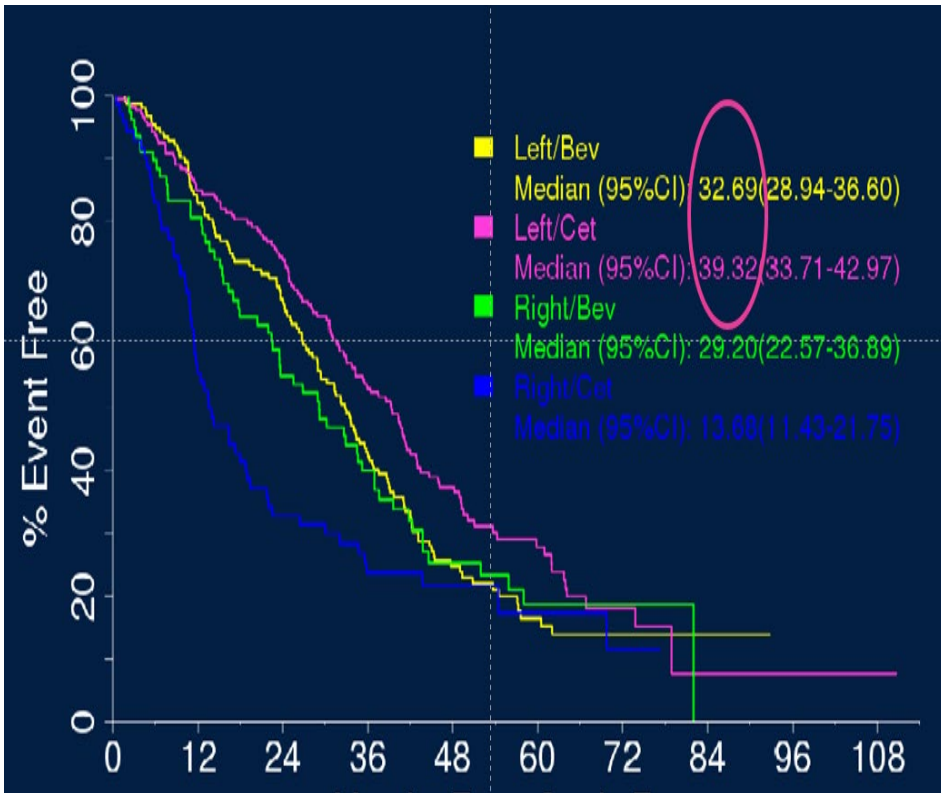
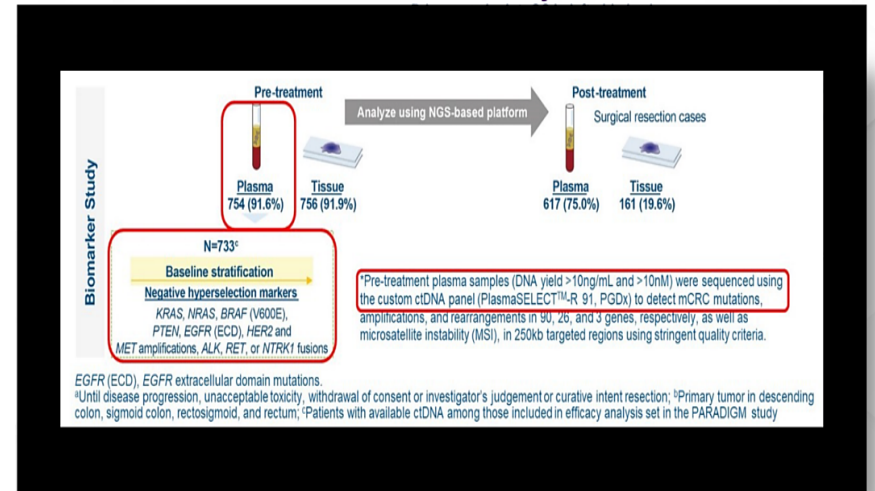


Figure 4 Overall survival (full analysis set; data cutoff: 6 January 2026).

CALGB 80405 „POST- HOC “ ANALYSIS RAS WT(KRAS, NRAS) LEFT VS RIGHT SIDES TUMOR OS



Is Sidedness Enough to Explain Benefit from anti EGFR? There Must Be More to the Story

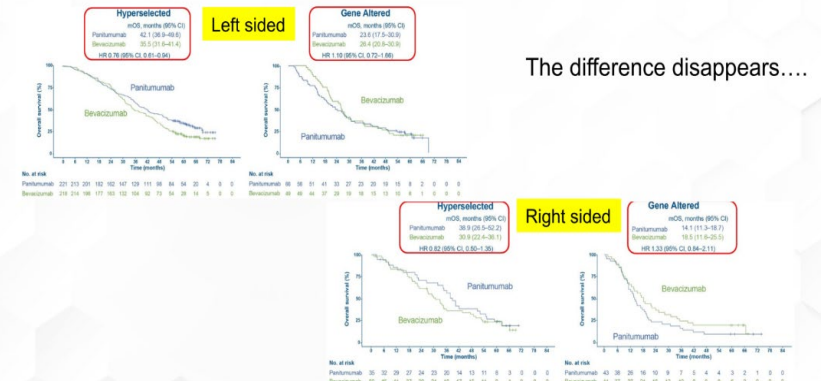


Cremolini C, et.al. Presented at: ASCO;2022.

Shitara K, et.al. Presented at: ASCO GI;2023.

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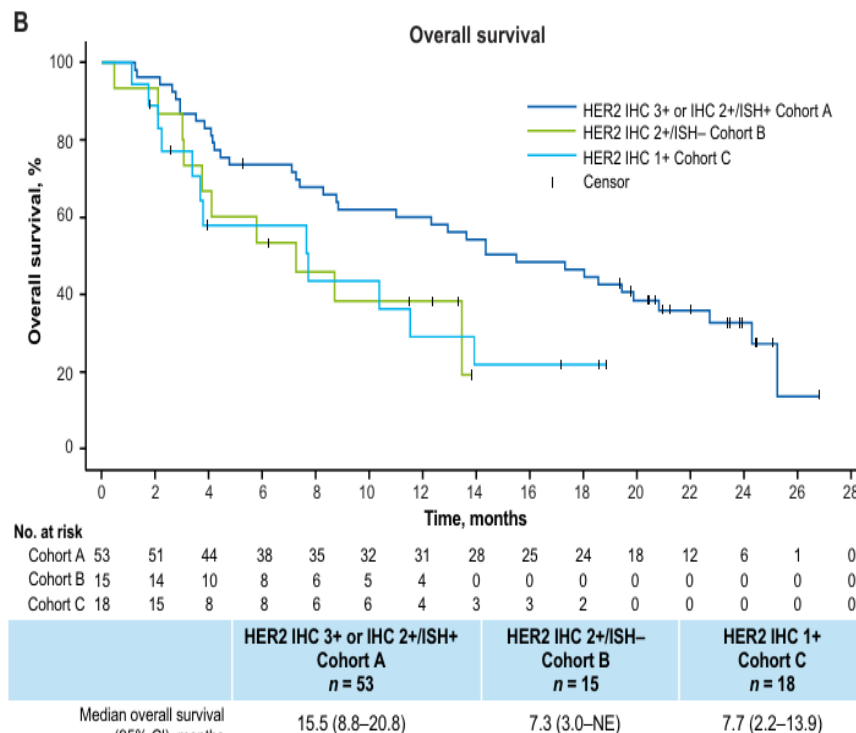
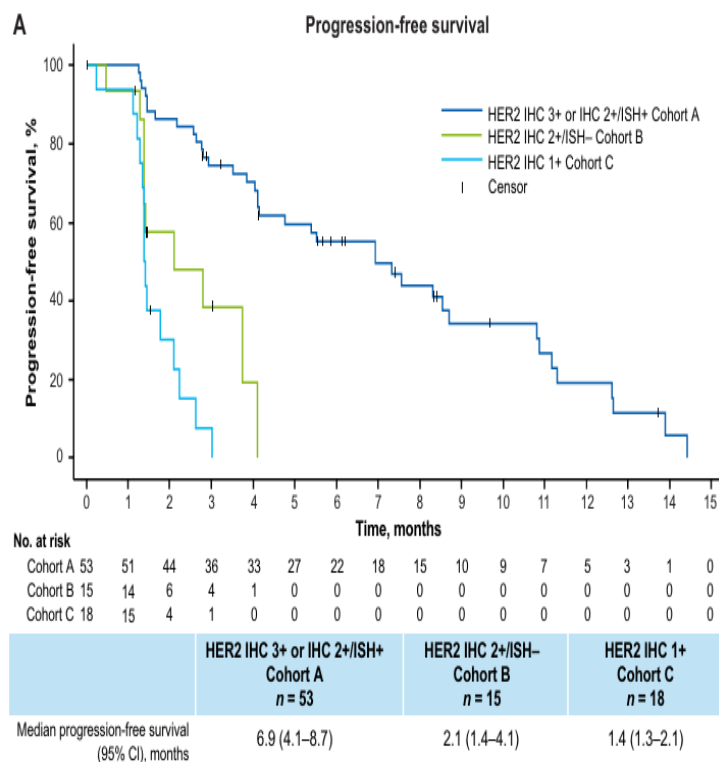
Survival by Sidedness Based on Hyper-selection



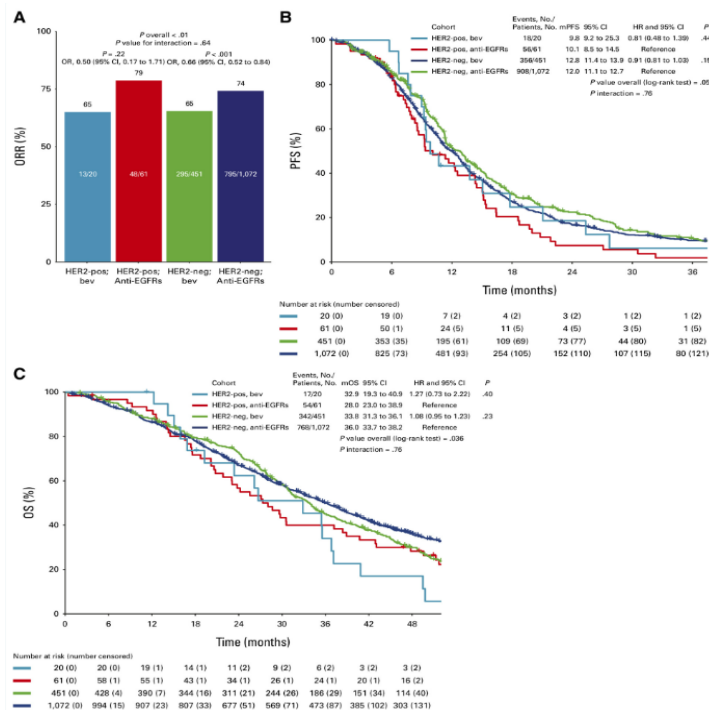
Shitara K, et.al. Presented at: ASCO GI;2023.

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Final results of DESTINY-CRC01 investigating trastuzumab deruxtecan in patients with HER2-expressing metastatic colorectal cancer

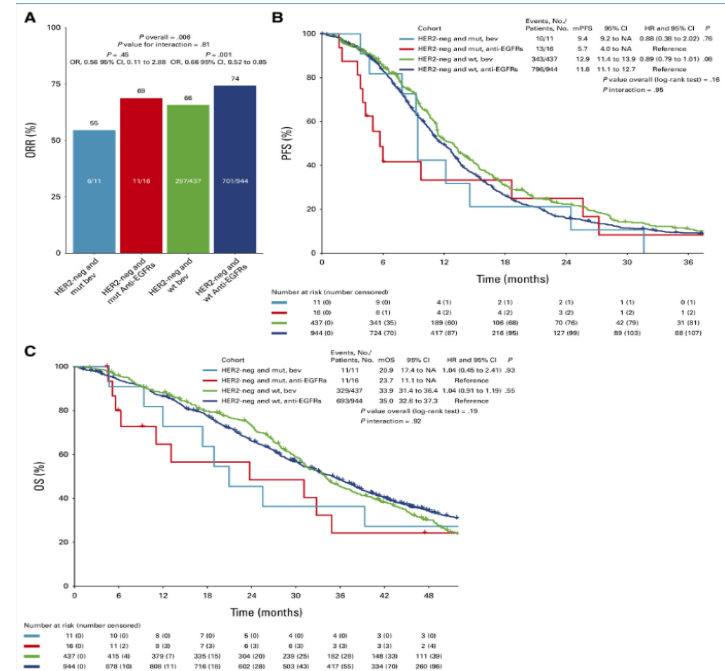


IMPACT OF HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 IN PATIENTS WITH METASTATIC COLORECTAL CANCER TREATED WITH CHEMOTHERAPY PLUS BEVACIZUMAB OR ANTI-EGFRs: EXPLORATORY ANALYSIS OF EIGHT RANDOMIZED TRIALS



(A) ORR, (B) PFS, and (C) OS according to *HER2* expression/amplification status and monoclonal antibody received

left-sided pMMR *RAS/BRAF* wild-type tumors ($n_{\text{HER2-pos}} = 30$), showing shorter PFS in HER2-pos and no predictive effect on the use of bev or anti-EGFRs with chemotherapy doublets.

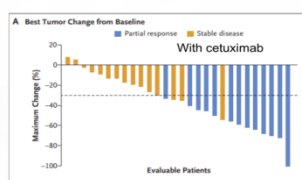
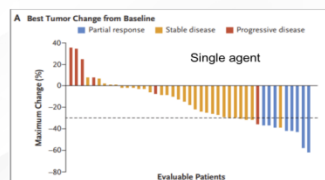


(A) ORR, (B) PFS, and (C) OS according to *HER2* mutational status in HER2-negative tumors and monoclonal antibody received.

KRAS G12C INHIBITION (4% OF COLORECTAL CANCERS) IS IDENTIFIED THROUGH COMPREHENSIVE TUMOR GENETIC SEQUENCING

KRAS G12C Inhibition: Adagrasib

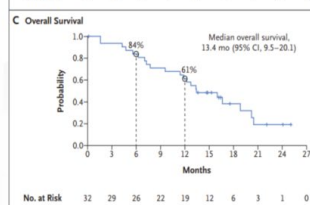
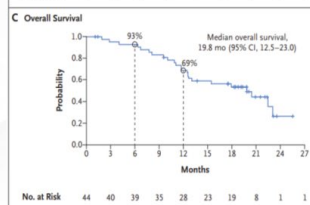
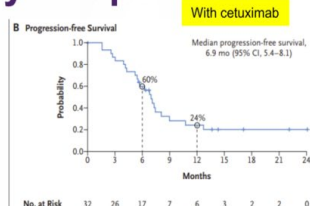
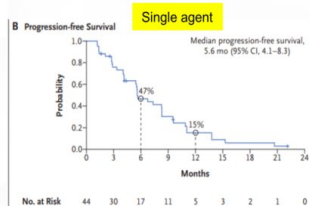
- Adagrasib: tested as single agent as well as in combination with cetuximab in KRYSTAL-1 study
- Longer half-life, some reports of better brain penetration



Yaeger R, et al. *N Engl J Med.* 2023;388(1):44-54.

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KRYSTAL-1: Efficacy Endpoints



Yaeger R, et al. *N Engl J Med.* 2023;388(1):44-54.

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Targeting the Untargetable: KRAS G12C Sotarasib

- A new era of targeting KRASG12C
- Sotarasib: in pretreated patients with KRAS G12C mutant metastatic colorectal cancer
 - Single agent
 - ORR of 10%
 - median response duration of 4.2 months
 - Combination with cetuximab
 - ORR of 30%
 - Disease control rate 90%
 - Rate of grade 3 or higher AEs was 22.5%

Fakih MG, et al. *Lancet Oncol.* 2022;23:115-24.

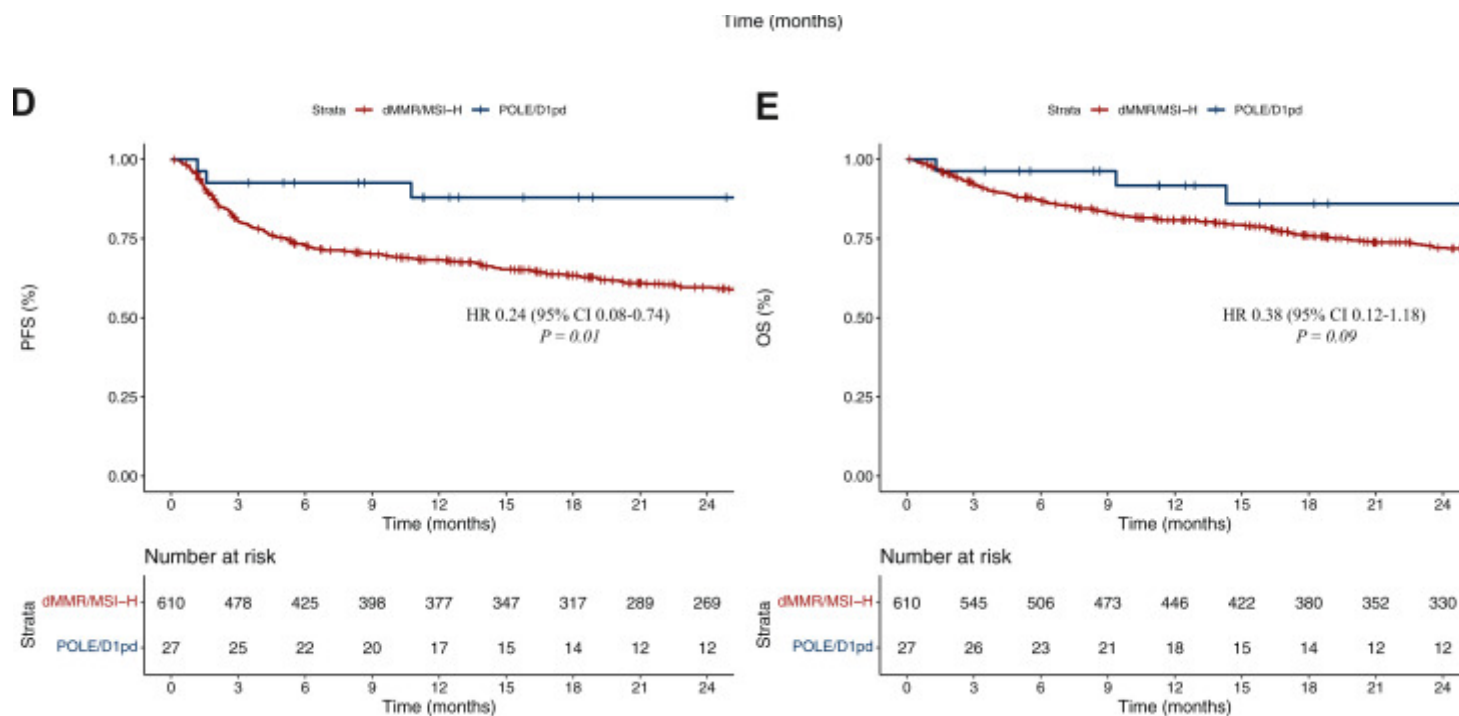
Kuboki Y, et al. *Ann Oncol.* 2022;33:Suppl. 1:136-S196.

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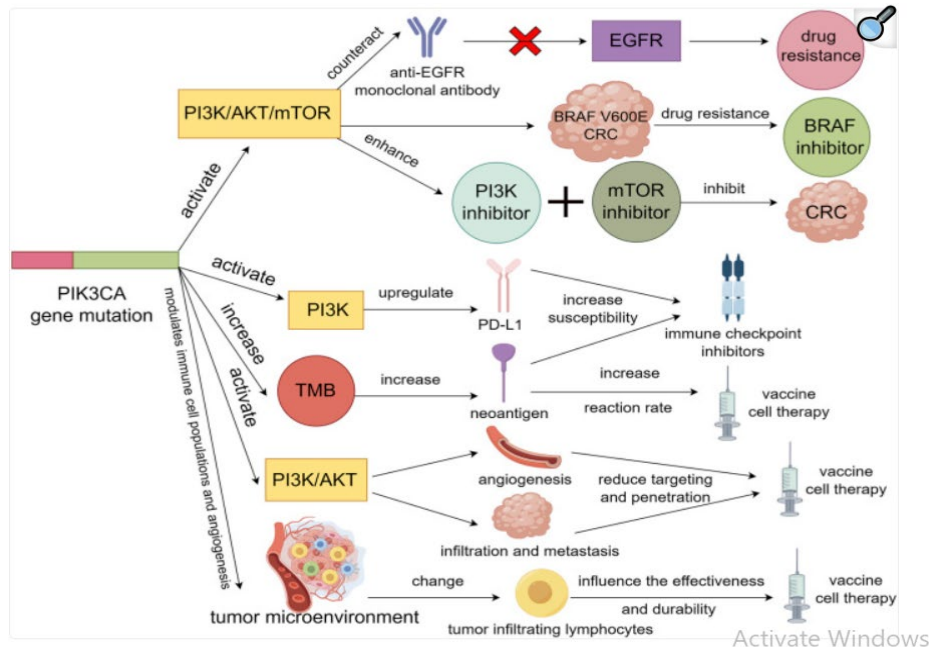
AMBROSINI M, ROUSSEAU B, MANCA P ...

IMMUNE CHECKPOINT INHIBITORS FOR *POLE* OR *POLD1* PROOFREADING-DEFICIENT METASTATIC COLORECTAL CANCER

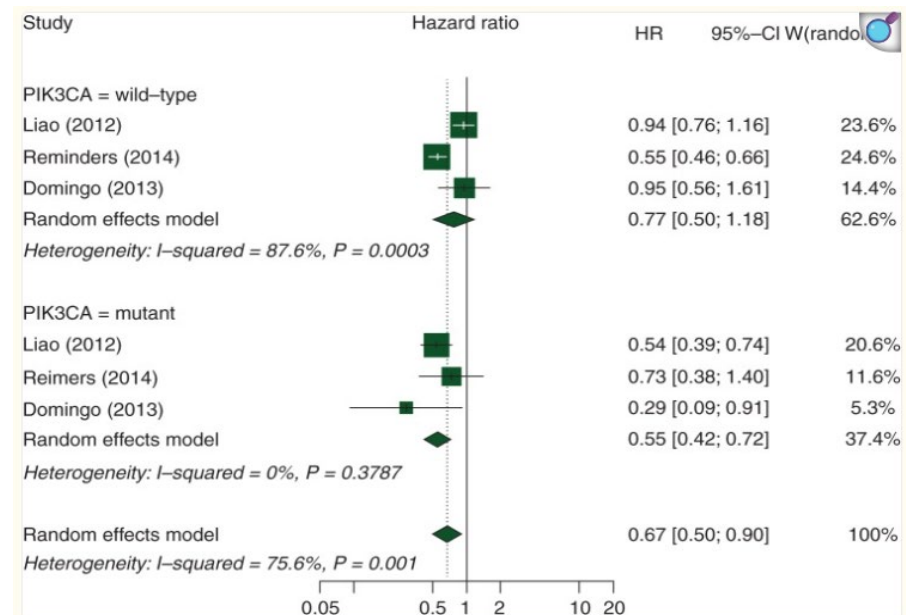
ANNALS OF ONCOLOGY, 2024; 35, 643-655

Figure 2 Tumor response of *POLE/D1pd* mCRC and survival compared to dMMR/MSI-H mCRC.

PROGNOSTIC ROLE OF TUMOR *PIK3CA* MUTATION IN COLORECTAL CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS



Summary estimates of the hazard ratio (and 95% confidence interval) for the overall survival of colorectal cancer (CRC) patients with mutated versus wild-type *PIK3CA* in patients who regularly ingested aspirin after a CRC diagnosis.



affecting about 15%–20% of CRC patients.

PIK3CA mutations significantly associated with worse PFS and shorter OS in CRC with anti-EGFR treatment.

causes resistance to BRAF inhibitors in BRAF V600E colorectal cancer.

RECOMMENDATIONS FOR THE USE OF NEXT-GENERATION SEQUENCING (NGS) FOR PATIENTS WITH ADVANCED CANCER IN 2024: A REPORT FROM THE ESMO PRECISION MEDICINE WORKING GROUP

Table 8 List of genomic alterations level I/II according to ESCAT in advanced cholangiocarcinoma

Gene	Alteration	Estimated prevalence	ESCAT score	Drug class matched	References
IDH1	Mutations	8%-18% ICCA	IA	IDH1 inhibitors	Abou-Alfa et al., <i>Lancet Oncol</i> 2020 ¹²⁴
FGFR2	Fusions	5%-15% ICCA	IB	Pan-FGFR TKIs	Javle et al., <i>J Clin Oncol</i> 2018 ¹²⁵ Abou-Alfa et al., <i>Lancet Oncol</i> 2020 ¹²⁶ Pant et al., <i>J Clin Oncol</i> 2023 ¹²⁷ Goyal et al., <i>N Engl J Med</i> 2023 ¹²⁸
ERBB2	Amplifications	10%-20% dCCA, pCCA, GBC	IB	Anti-HER2 monoclonal antibodies Anti-HER2 ADCs Anti-HER2 bispecific antibodies HER2 TKIs	Javle et al., <i>Lancet Oncol</i> 2021 ¹²⁹ Meric-Bernstam et al., <i>JCO</i> 2023 ¹³⁰ Harding et al., <i>Lancet Oncol</i> 2023 ¹³¹ Nakamura et al., <i>J Clin Oncol</i> 2023 ¹³²
	Mutations	3%-5%	IIB	Anti-HER2 monoclonal antibodies Pan-HER TKIs	Hyman et al., <i>Nature</i> 2018 ¹³³ Cannon et al., <i>J Clin Oncol</i> 2023 ¹³³ Harding et al., <i>Nat Comm</i> 2023 ¹³⁴
BRAF	Mutations (p. V600E)	50%	IB	BRAF inhibitors + MEK inhibitors	Subbiah et al., <i>Lancet Oncol</i> 2020 ¹³⁵ Salama et al., <i>J Clin Oncol</i> 2020 ¹³⁶ Subbiah et al., <i>Nature Med</i> 2023 ¹³⁶
KRAS	Mutations (p. G12C)	<1%	IC	KRAS ^{G12C} TKIs	Bekaii-Saab et al., <i>J Clin Oncol</i> 2022 ¹⁰²

BILIARY TRACT CANCER: ESMO CLINICAL PRACTICE GUIDELINE

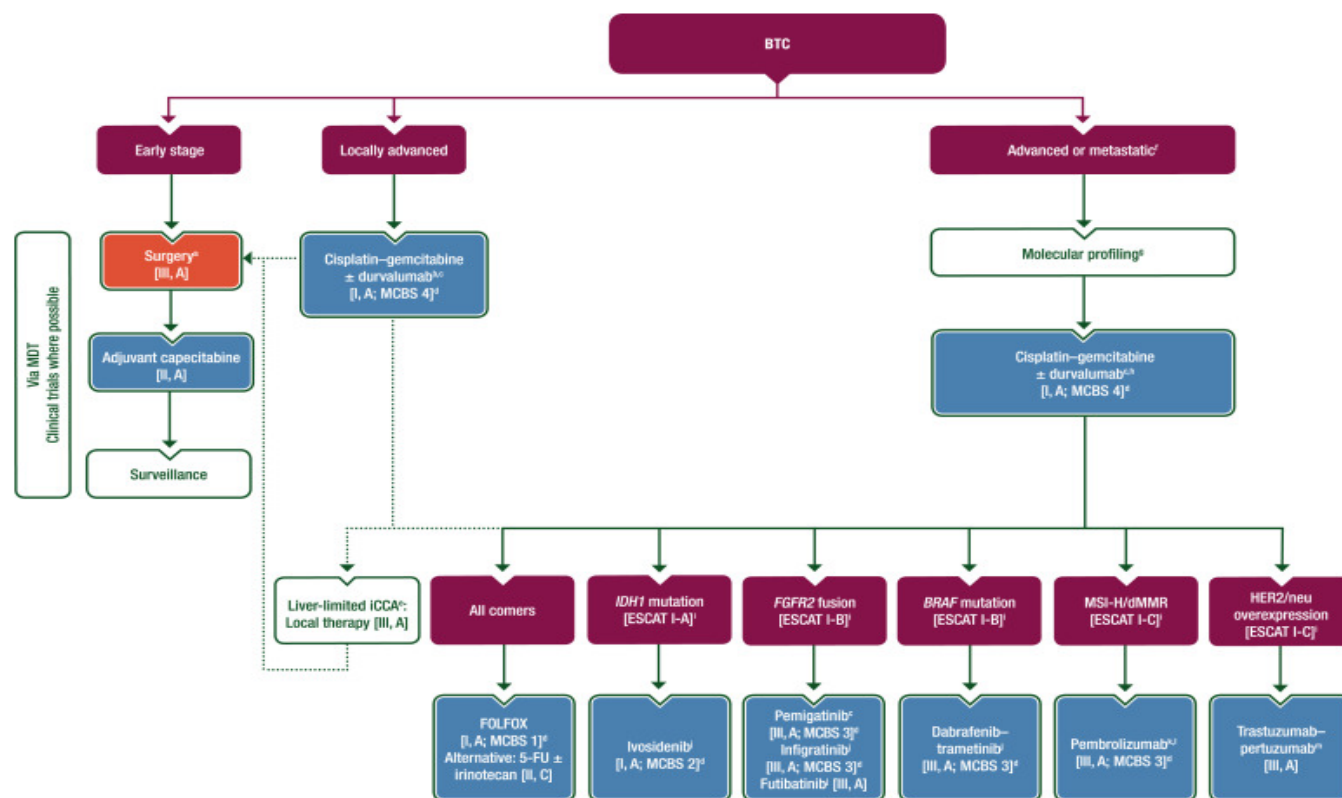
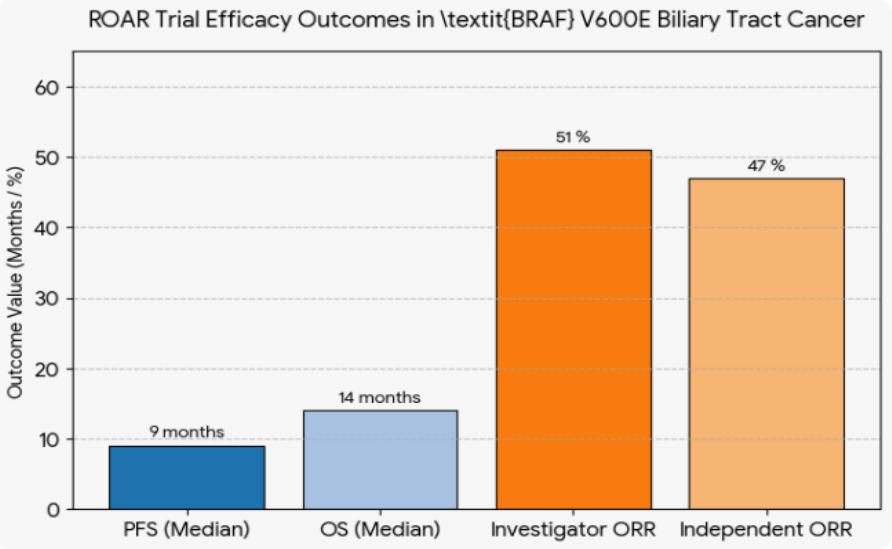


Figure 1 Treatment algorithm for BTC. Purple: general categories or stratification; red: surgery; white: other aspects of management; blue: systemic anticancer therapy.



Dabrafenib plus trametinib in patients with *BRAF*^{V600E}-mutated biliary tract cancer (ROAR): a phase 2, open-label, single-arm, multicentre basket trial

Clinical Trial	Tumor Shrinkage Rate (ORR)	Disease Control Rate (DCR)	Key Finding
MyPathway Trial	23%	51%	Showed promising, durable anti-tumor activity in heavily pretreated patients.
TAPUR Study	32%	40%	Confirmed significant clinical benefit specifically for patients with HER2 amplifications.

TRASTUZUMAB AND PERTUZUMAB (DUAL ANTI-HER2 BLOCKADE) HER2-POSITIVE CHOLANGIOCARCINOMA

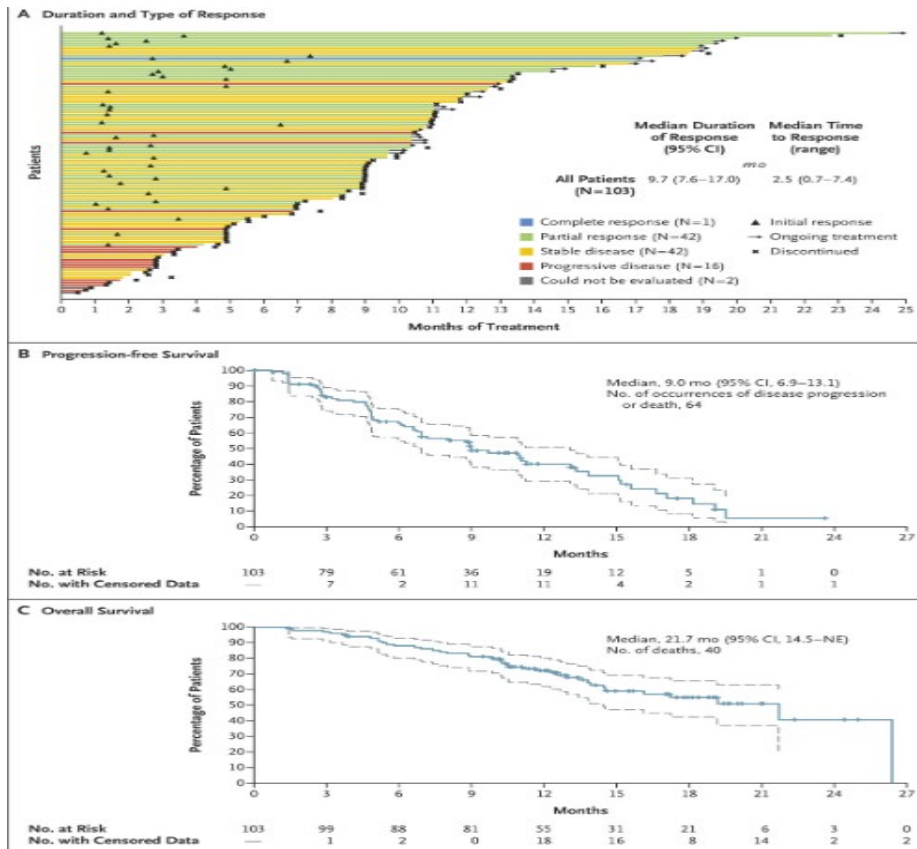
BRAF&HER2

Side-by-Side Trial Comparison

Efficacy Parameter	HERIZON-BTC-01 (Zanidatamab)	DESTINY-PanTumor02 (Enhertu - BTC Cohort)
Trial Focus	Exclusively designed for Biliary Tract Cancer (BTC)	Pan-tumor study (BTC was one of several tumor sub-cohorts)
Objective Response Rate (ORR)	41.3% overall; 51.6% specifically for the IHC 3+ subgroup	22.0% overall for the BTC cohort; up to 61.3% across the entire trial for IHC 3+ patients
Median Duration of Response (mDOR)	14.9 months (Shows sustained tumor shrinkage over a longer period)	8.6 months (Within the specific biliary tract cancer subgroup)
Median Progression-Free Survival (mPFS)	5.5 months	4.6 months
Median Overall Survival (mOS)	15.5 months overall; 18.1 months for the IHC 3+ subgroup	7.0 months within the specific biliary tract cancer subgroup

HER2 alteration happens more often in extrahepatic (outside the liver) cholangiocarcinoma (5–20%) and gallbladder cancer (15–35%) than in intrahepatic (inside the liver) cholangiocarcinoma (about 5%)

FUTIBATINIB FOR *FGFR2*-REARRANGED INTRAHEPATIC CHOLANGIOCARCINOMA N ENGL J MED 2023;388:228-239



Futibatinib demonstrated clinically meaningful and durable activity in previously treated patients with *FGFR2*-rearranged intrahepatic CCC

This study established *FGFR2* alterations as an actionable molecular target and reinforced the role of comprehensive molecular profiling in advanced iCCA.

Real-world impact of NGS in advanced GI cancers

Grover A, Makan NS · J Clin Oncol. 2025;43(4_suppl):814 · Retrospective cohort, n = 77

77

ADVANCED GI
CANCERS

59.7%

TARGETABLE
MUTATIONS

44.2%

FDA-APPROVED
TARGETED THERAPY

6.5%

NGS IMPACTED
1L TREATMENT

79.2%

Eligible for a clinical trial

11 vs 7.5

months of treatment
biomarker vs no biomarker

TAKE-HOME

NGS identifies therapeutic opportunities far more often than they translate into first-line treatment.

Real-world community setting; small retrospective cohort. Percentages are presented as reported and are not shown as a mathematical funnel.

THANK YOU FOR ATTENTION

YOUR COLONOSCOPY SHOWED NOTHING
ABNORMAL ASIDE FROM THE THANK YOU
CARD LEFT IN YOUR LARGE INTESTINE.
THAT WAS A NICE TOUCH.

CS635910

