Year in Review: Clinical Investigator Perspectives on the Most Relevant New Datasets and Advances in Oncology

Colorectal Cancer

A CME/MOC-Accredited Live Webinar

Thursday, April 16, 2026
5:00 PM – 6:00 PM ET

Faculty

Arvind Dasari, MD, MS
Anwaar Saeed, MD

Moderator

Neil Love, MD

RTP Year in Review 2026

Faculty

Arvind Dasari, MD, MS
Professor
Department of Gastrointestinal Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

MODERATOR
Neil Love, MD
Research To Practice
Miami, Florida

Anwaar Saeed, MD
Associate Professor
University of Pittsburgh School of Medicine
Section Chief, Gastrointestinal Oncology
Director, Gastrointestinal Disease Center
Co-Leader, Cancer Therapeutics Program
UPMC Hillman Cancer Center
Pittsburgh, Pennsylvania

Commercial Support

This activity is supported by educational grants from Exelixis Inc, GSK, and Natera Inc.

Dr Love — Disclosures

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following companies: Aadi Bioscience, AbbVie Inc, ADC Therapeutics, Agendia Inc, Alexion Pharmaceuticals, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Arvinas, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeOne, Biotheranostics Inc, A Hologic Company, Black Diamond Therapeutics Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Celcuity, Clovis Oncology, Coherus BioSciences, Corcept Therapeutics Inc, CTI BioPharma, a Sobi Company, Daiichi Sankyo Inc, Eisai Inc, Elevation Oncology Inc, Exact Sciences Corporation, Exelixis Inc, Genentech, a member of the Roche Group, Genmab US Inc, Geron Corporation, Gilead Sciences Inc, GSK, Helsinn Therapeutics (US) Inc, ImmunoGen Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Jazz Pharmaceuticals Inc, Johnson & Johnson, Karyopharm Therapeutics, Kite, A Gilead Company, Kura Oncology, Legend Biotech, Lilly, MEI Pharma Inc, Merck, Mersana Therapeutics Inc, Mirati Therapeutics Inc, Mural Oncology Inc, Natera Inc, Novartis, Novartis Pharmaceuticals Corporation on behalf of Advanced Accelerator Applications, Novocure Inc, Nuvalent, Nuvation Bio Inc, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Revolution Medicines Inc, Rigel Pharmaceuticals Inc, R-Pharm US, Sanofi, Seagen Inc, Servier Pharmaceuticals LLC, SpringWorks Therapeutics Inc, Stemline Therapeutics Inc, Sumitomo Pharma America, Summit Therapeutics, Syndax Pharmaceuticals, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, TerSera Therapeutics LLC, and Tesaro, A GSK Company.

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Dr Dasari — Disclosures

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Contracted Research	Bristol Myers Squibb, Crinetics Pharmaceuticals, Eisai Inc, Enterome, Guardant Health, Hutchison MediPharma, Natera Inc, NeoGenomics, Personalis, RayzeBio, Taiho Oncology Inc, Xencor

Dr Saeed — Disclosures

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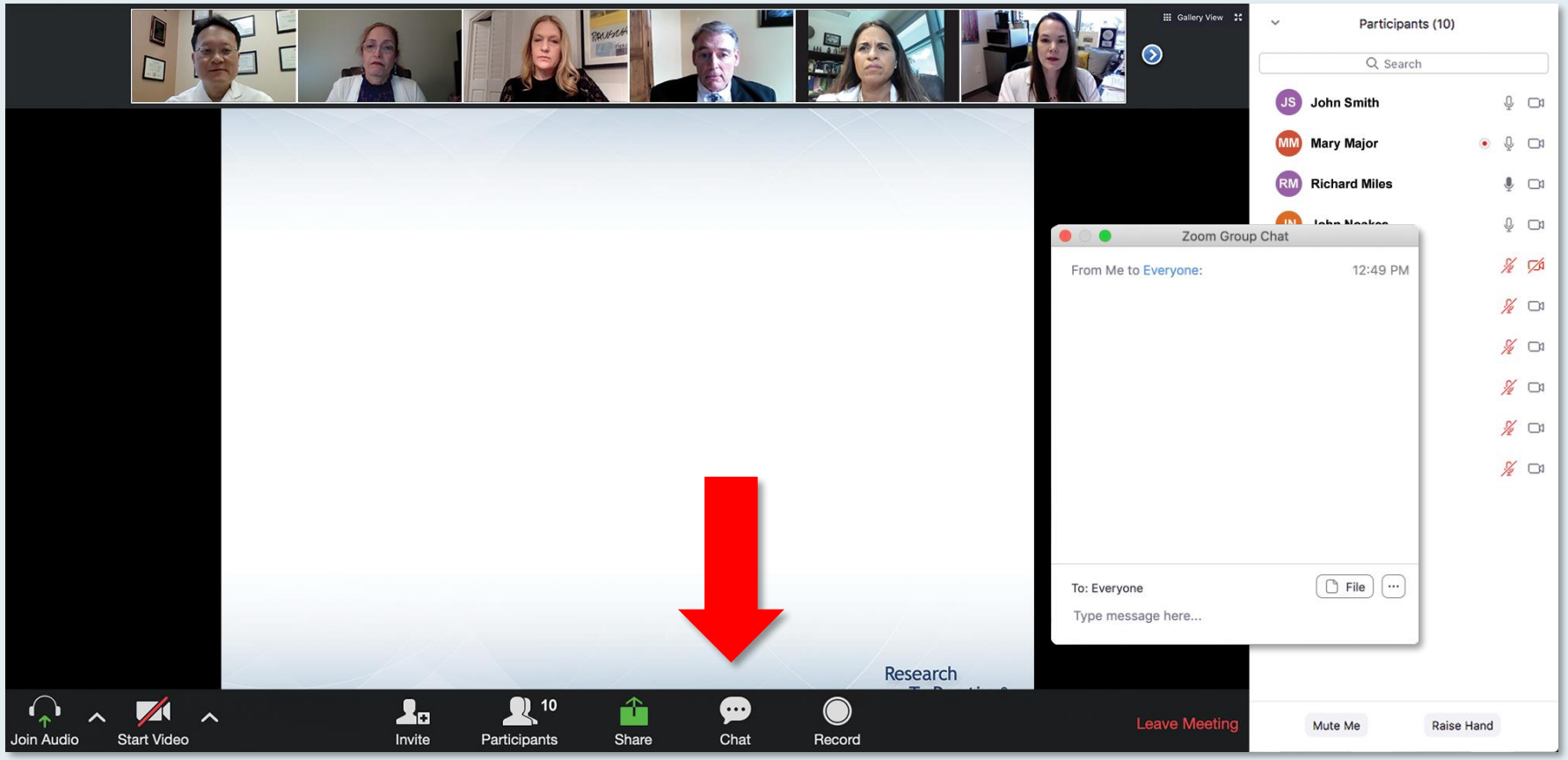

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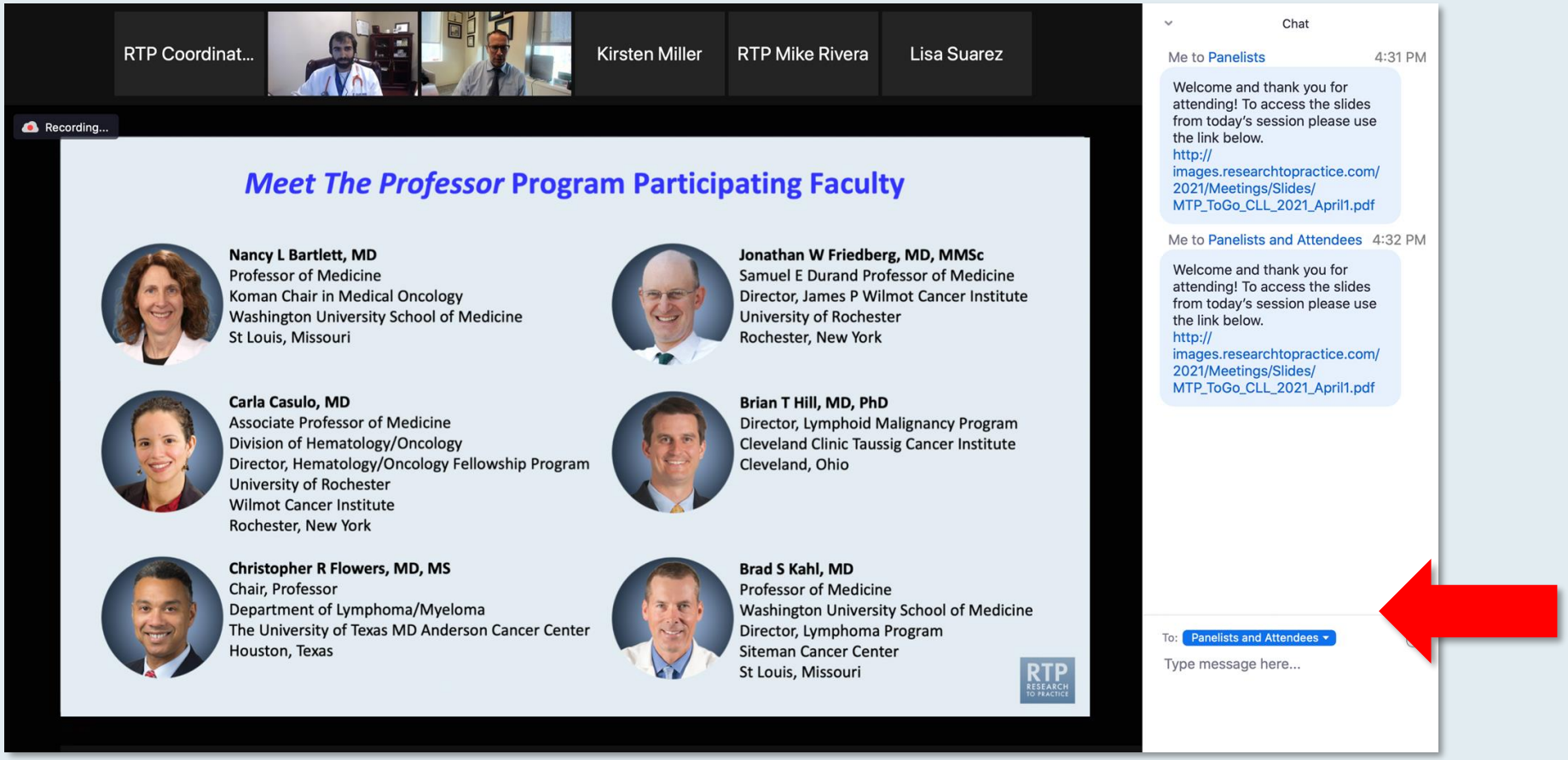

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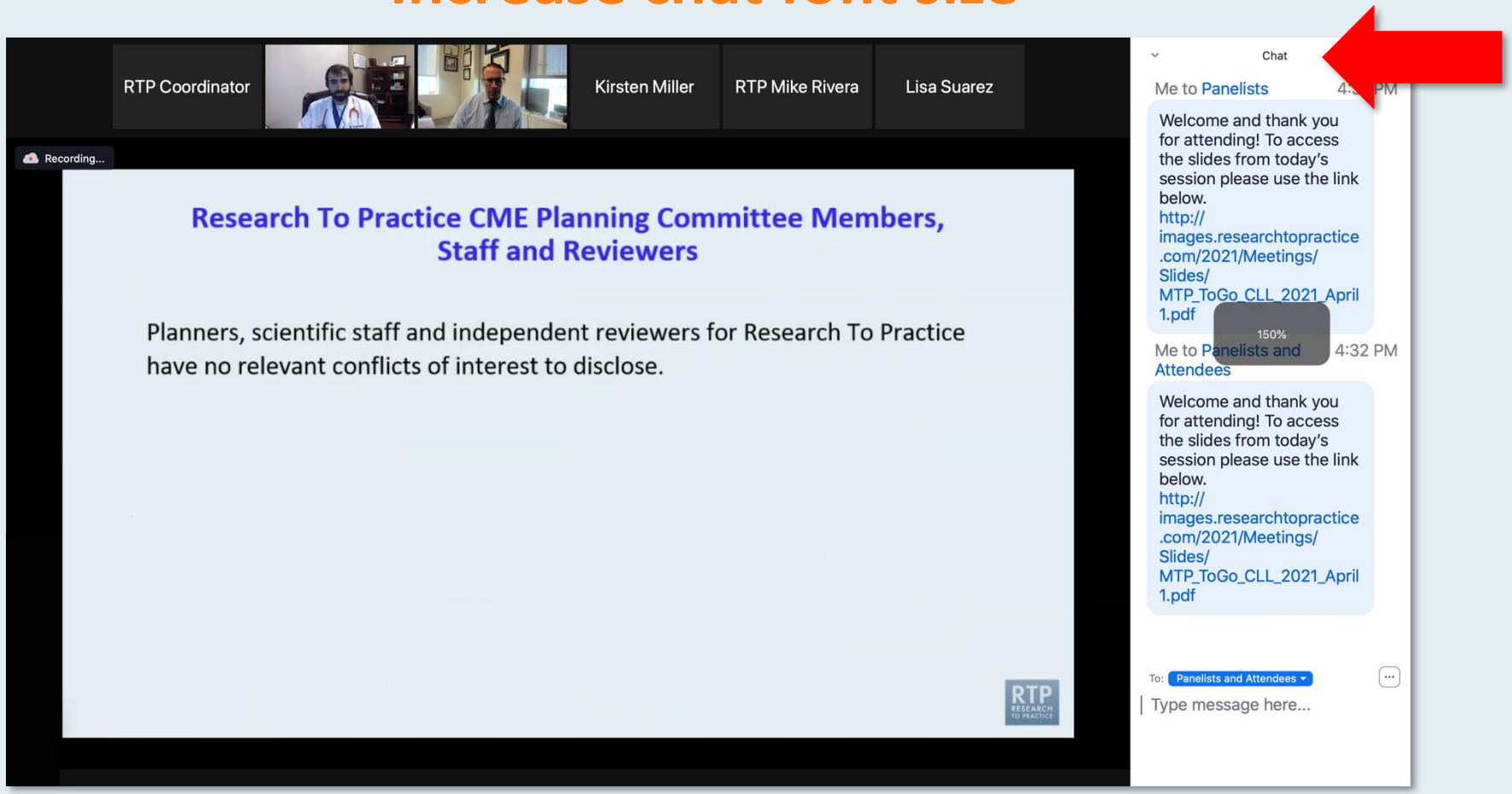

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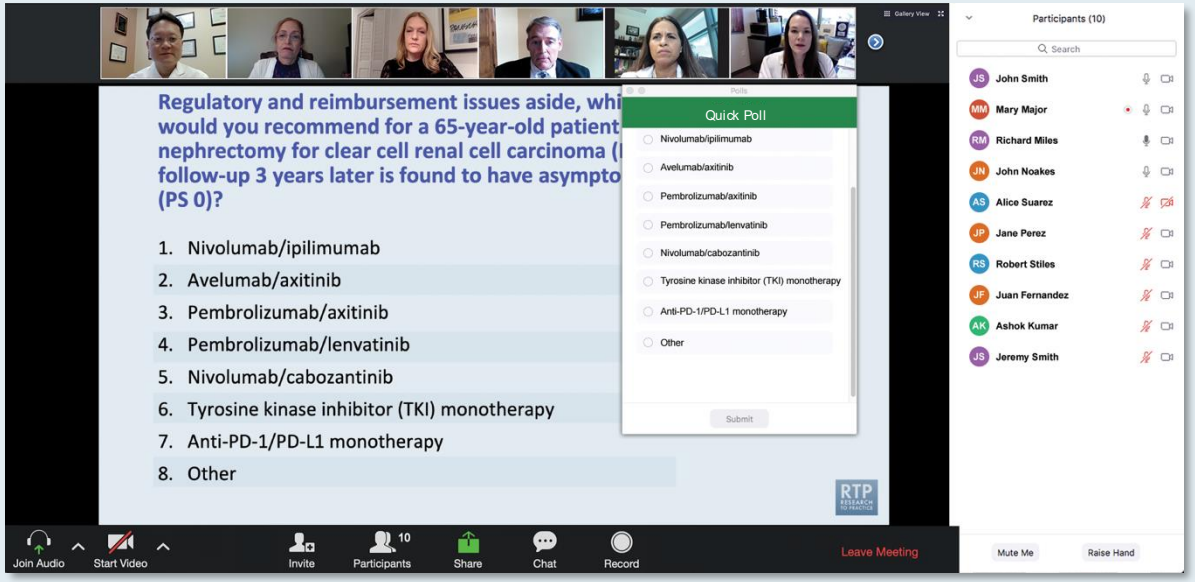

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Developed in Partnership with Florida Cancer Specialists & Research Institute

The Ritz-Carlton Orlando, Grande Lakes | Orlando, Florida

Friday, April 24, 2026

7:00 PM – 9:00 PM

Keynote Session: Diffuse Large B-Cell Lymphoma and Follicular Lymphoma

Manali Kamdar, MD, MBBS
Krish Patel, MD
Gilles Salles, MD, PhD

Fellows Welcome!

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John N Allan, MD

Adam Kittai, MD

8:50 AM – 9:40 AM

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RTP RESEARCH TO PRACTICE

Year in Review:
Colorectal Cancer

INTRODUCTION: RTP Paper of the Year!

MODULE 1: Checkpoint Inhibitors for Localized MSI-High Tumors

MODULE 2: Circulating Tumor DNA Assays

MODULE 3: Checkpoint Inhibitors for Metastatic Disease

MODULE 4: Other Important Papers

RTP Year in Review 2026

Thank you for joining us!

Please take a moment to complete the survey currently up on Zoom.
Your feedback is very important to us.

Information on how to obtain CME, ABIM MOC and ABS credit will be provided in the Zoom chat room.
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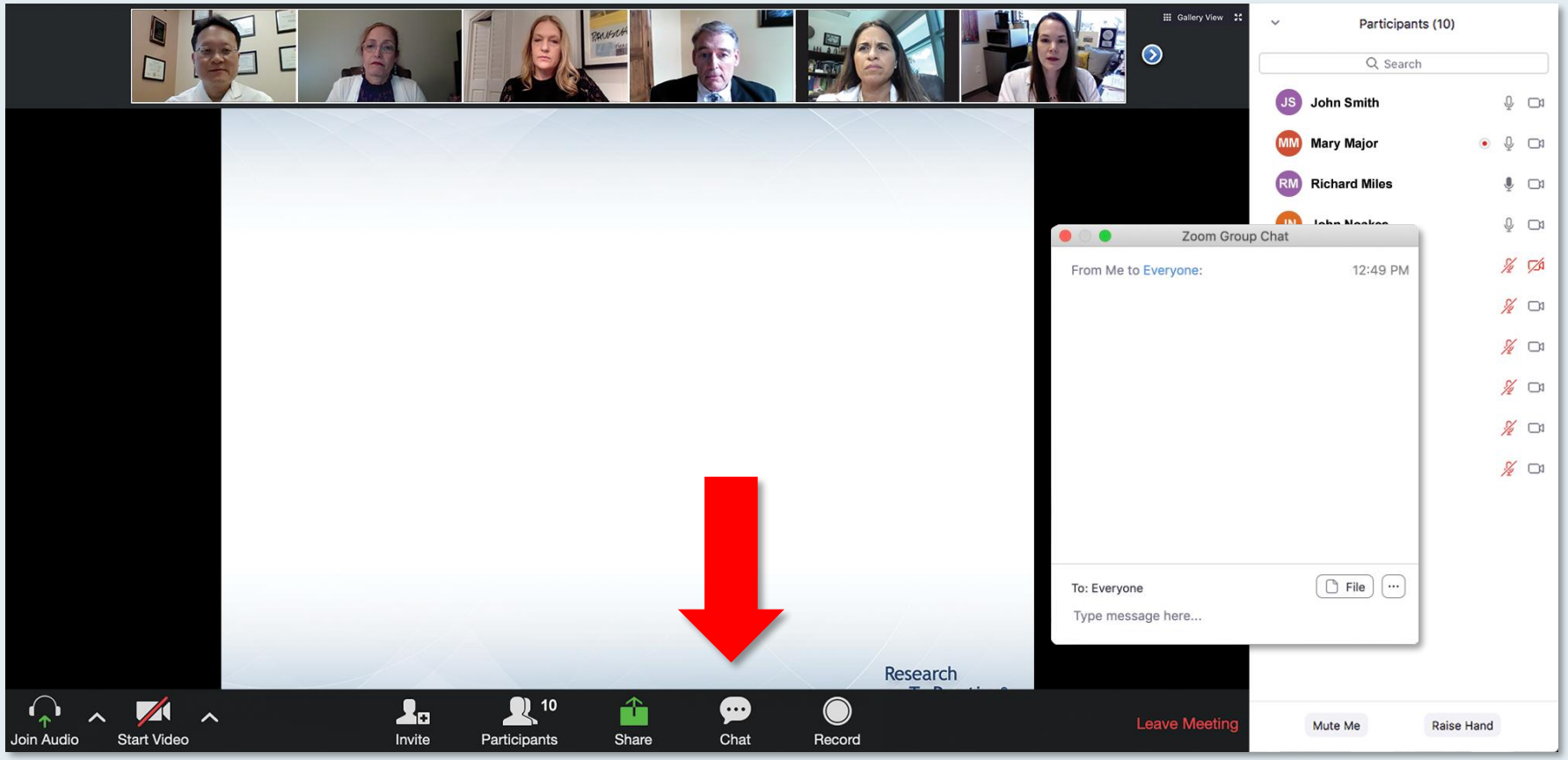

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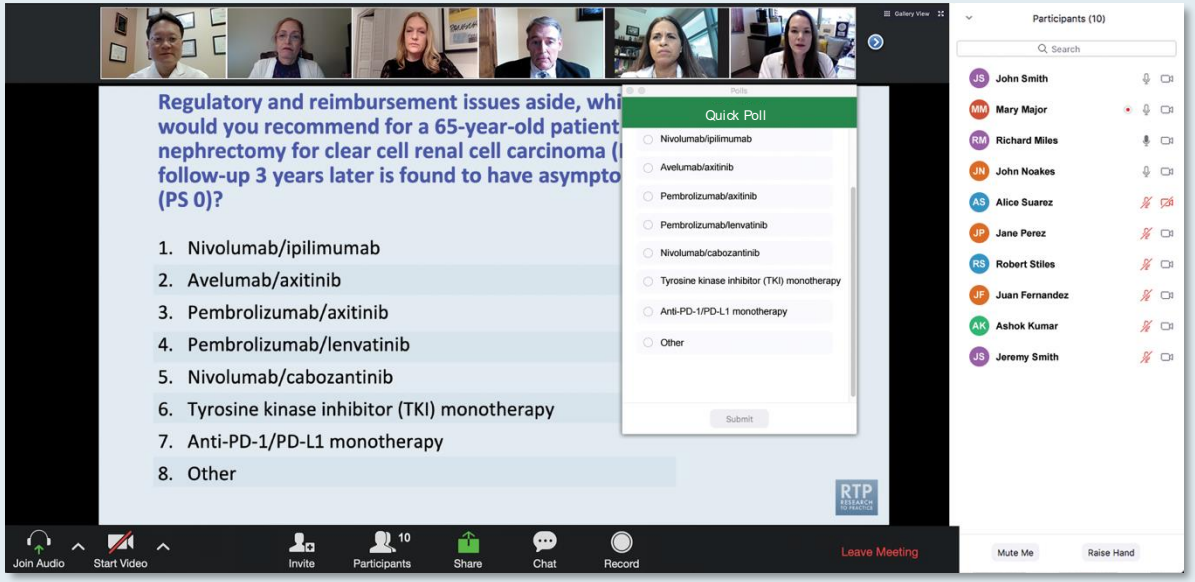

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CRC Year in Review

2025 – 2026 | Recent Advances in the Management of Metastatic CRC (mCRC)

Anwaar Saeed, MD
Associate Professor of Medicine
Section Chief, Gastrointestinal Oncology

UPMC | HILLMAN CANCER CENTER UPMC | CHILDREN'S HOSPITAL OF PITTSBURGH University of Pittsburgh NCI Comprehensive Cancer Center

Year in Review 2025: Optimizing the Care of Patients with Nonmetastatic Colorectal Cancer

Arvind Dasari, MD, MS
Professor,
Department of GI Medical Oncology
Division of Cancer Medicine
UT MD Anderson

RTP Year in Review 2026

Key Datasets

Arvind Dasari, MD, MS

- Shi Q et al. Proposed changes to the pathologic staging for colon cancer (CC): AJCC Colon Cancer Expert Panel (AJCCCCEP). ASCO 2025;Abstract 3520.
- Ando K et al. Correlation between the timing of recurrence and circulating tumor DNA (ctDNA) doubling time in patients (pts) with resected colon cancer. Gastrointestinal Cancers Symposium 2026;Abstract 220.
- Tie J et al. Circulating tumor DNA analysis guiding adjuvant therapy in stage II colon cancer: 5-year outcomes of the randomized DYNAMIC trial. *Nat Med* 2025;31(5):1509-18.
- Tie J et al. Circulating tumor DNA-guided adjuvant therapy in locally advanced colon cancer: The randomized phase 2/3 DYNAMIC-III trial. *Nat Med* 2025;31(12):4291-300.
- Cohen SA et al. Real-world monitoring of ctDNA reliably predicts cancer recurrence and treatment efficacy in patients with resected stages I-III colon cancer. *Ann Surg* 2025;[Online ahead of print].
- Bando H et al. Impact of postoperative ctDNA dynamics on eligibility for the ALTAIR randomized trial in patients with colorectal cancer: Implications for clinical trial enrollment. Gastrointestinal Cancers Symposium 2026;Abstract 12.

Key Datasets

Arvind Dasari, MD, MS (continued)

- Zhang GQ et al. Predictive role of circulating tumor DNA in stage III colon cancer treated with celecoxib: A post hoc analysis of the CALGB (Alliance)/SWOG 80702 phase 3 randomized cinical trial. *JAMA Oncol* 2026;12(2):149-58.
- Martling A et al. Low-dose aspirin for PI3K-altered localized colorectal cancer. *N Engl J Med* 2025;393(11):1051-64.
- Courneya KS et al. Structured exercise after adjuvant chemotherapy for colon cancer. *N Engl J Med* 2025;393(1):13-25.
- Cercek A et al. Nonoperative management of mismatch repair-deficient tumors. *N Engl J Med* 2025;392(23):2297-308.
- Rasschaert G et al. AZUR-4, a phase 2, open label, randomized study of neoadjuvant dostarlimab plus capecitabine plus oxaliplatin (CAPEOX) versus CAPEOX alone in previously untreated T4N0 or stage III mismatch repair proficient/microsatellite stable resectable colon cancer. ASCO 2025;Abstract TPS3649.
- Sinicrope FA et al. 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). ASCO 2025;Abstract LBA1.

Key Datasets

Anwaar Saeed, MD

- André T et al. Pembrolizumab versus chemotherapy in microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer: 5-year follow-up from the randomized phase III KEYNOTE-177 study. *Ann Oncol* 2025;36(3):277-84.
- Lonardi S et al. Nivolumab plus ipilimumab vs nivolumab monotherapy for microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): New results from CheckMate 8HW. ESMO 2025;Abstract LBA29.
- Rocha Lima CM et al. Colorectal Cancer Metastatic dMMR Immunotherapy (COMMIT) study: A randomized phase III study of atezolizumab (atezo) monotherapy versus mFOLFOX6/bevacizumab/atezo (FFX/bev) in the first-line treatment of patients (pts) with deficient DNA mismatch repair (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal cancer (mCRC) — NRG-GI004/SWOG-S1610. Gastrointestinal Cancers Symposium 2026;Abstract 14.
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Key Datasets

Anwaar Saeed, MD (continued)

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Year in Review:
Colorectal Cancer

INTRODUCTION: RTP Paper of the Year!

MODULE 1: Checkpoint Inhibitors for Localized MSI-High Tumors

MODULE 2: Circulating Tumor DNA Assays

MODULE 3: Checkpoint Inhibitors for Metastatic Disease

MODULE 4: Other Important Papers

RTP Year in Review 2026

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RTP Year in Review 2026

What's a good metaphor for a small cell cancer of the lung?

A particularly fitting metaphor for **small cell lung cancer** is:

⚡ "A wildfire sparked in dry grass"

- **Ignites quickly:** Small cell can arise and grow rapidly, often before it's detected


AGREE
IN BETWEEN
DISAGREE

If I had to shrink that to the **single most important shortlist,** I would probably choose: **BREAKWATER, MATTERHORN, FLAURA2 OS, DeLLphi-304, SERENA-6, INAVO120 OS, AMPLIFY/CLL17, and MajesTEC-3.** Those are the studies I think are most likely to be remembered as the ones that actually changed treatment patterns or treatment philosophy.

If this was a drug, we'd be giving it

Thomas Lynch, MD
June 3, 2010

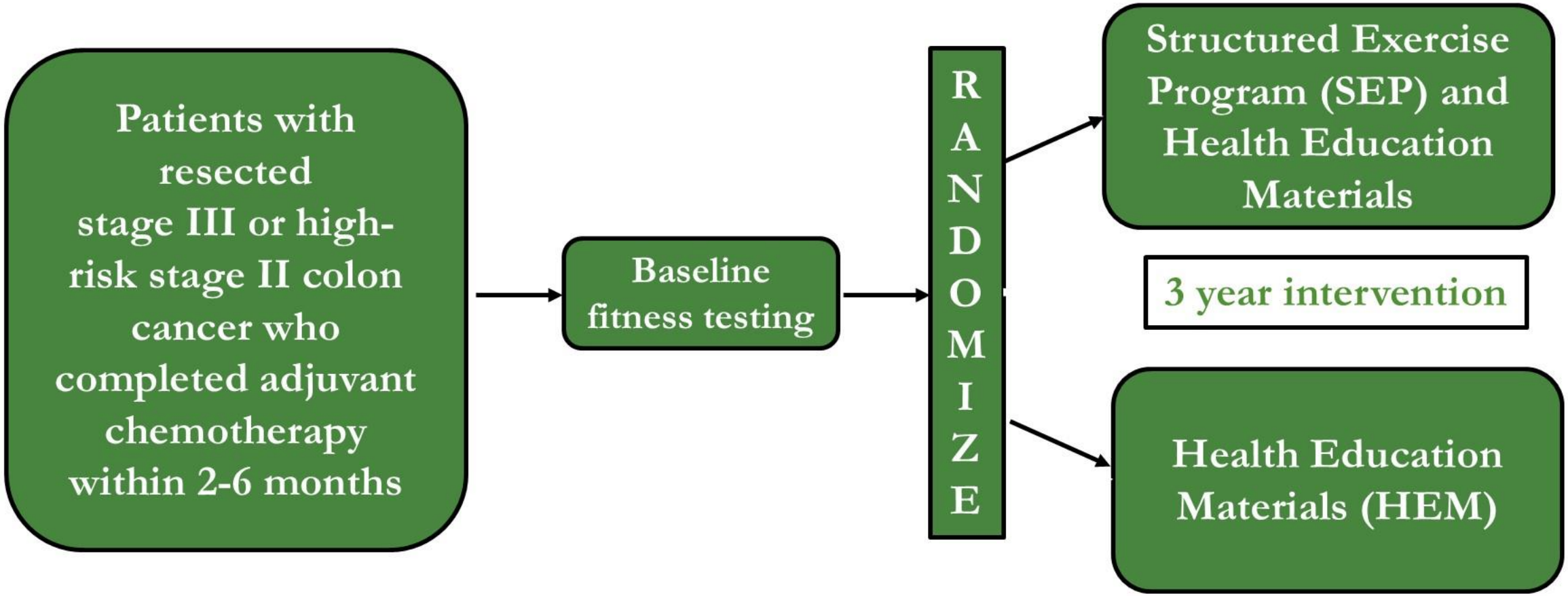
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 3, 2025 VOL. 393 NO. 1

Structured Exercise after Adjuvant Chemotherapy for Colon Cancer

Kerry S. Courneya, Ph.D.,[1] Janette L. Vardy, M.D., Ph.D.,[2,3] Christopher J. O'Callaghan, D.V.M., Ph.D.,[4] Sharlene Gill, M.D.,[5] Christine M. Friedenreich, Ph.D.,[6,7] Rebecca K.S. Wong, M.B., Ch.B.,[8] Haryana M. Dhillon, Ph.D.,[9] Victoria Coyle, M.B., B.Ch., Ph.D.,[10] Neil S. Chua, M.D.,[11] Derek J. Jonker, M.D.,[12] Philip J. Beale, Ph.D.,[13] Kamal Haider, M.D.,[14] Patricia A. Tang, M.D.,[15] Tony Bonaventura, M.D.,[16] Ralph Wong, M.D.,[17] Howard J. Lim, M.D., Ph.D.,[5,18] Matthew E. Burge, M.B., B.S.,[19,20] Stacey Hubay, M.D.,[21] Michael Sanatani, M.D.,[22] Kristin L. Campbell, Ph.D.,[18,23] Fernanda Z. Arthuso, Ph.D.,[1] Jane Turner, M.Phil.,[3] Ralph M. Meyer, M.D.,[24] Michael Brundage, M.D.,[25] Patti O'Brien, M.Sc.,[4] Dongsheng Tu, Ph.D,[4] and Christopher M. Booth, M.D.,[25] for the CHALLENGE Investigators*

CO21 Study Schema



Primary Endpoint: PFS

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

Courneya. ESMO 2025.

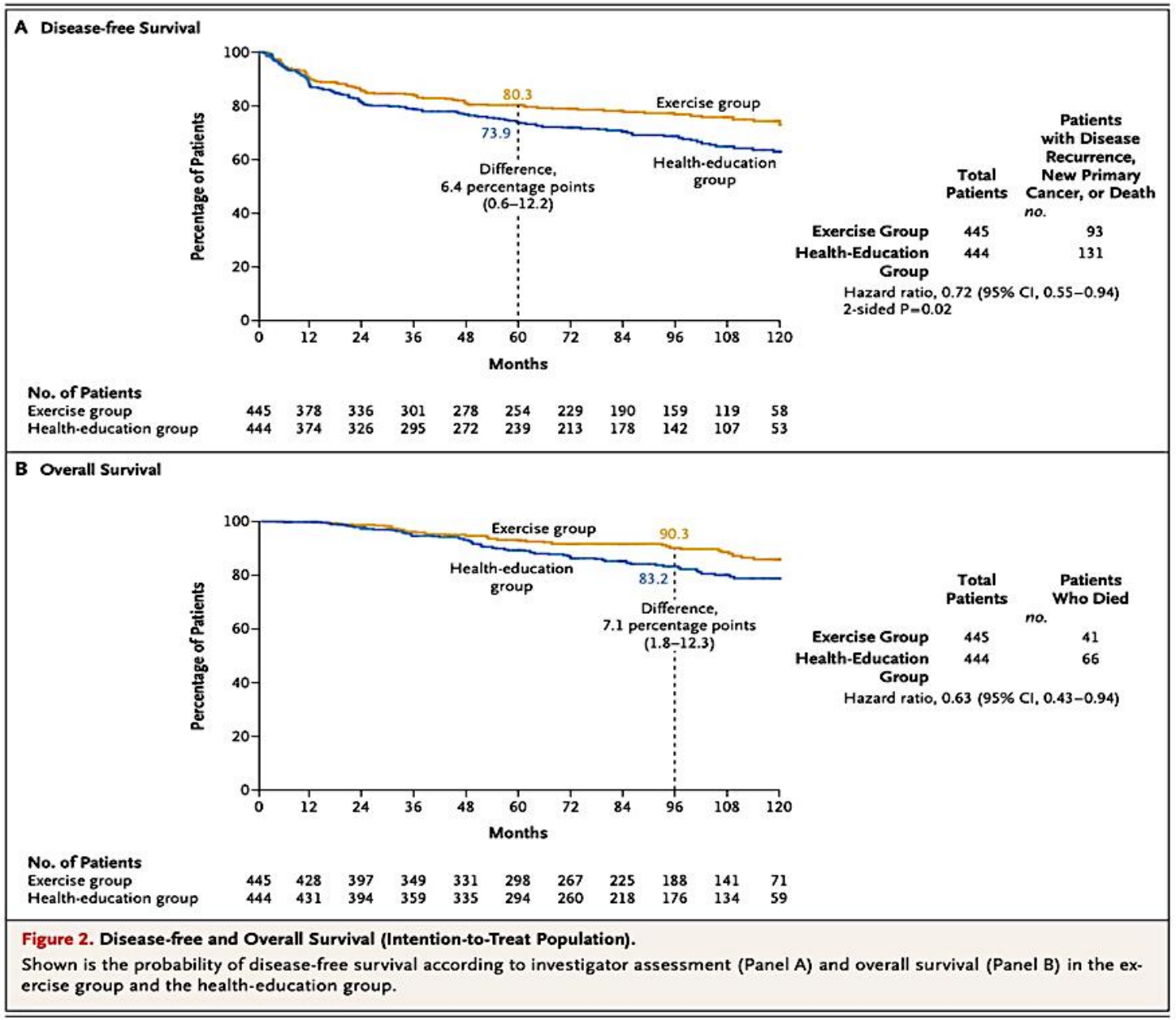


Figure 2. Disease-free and Overall Survival (Intention-to-Treat Population).
Shown is the probability of disease-free survival according to investigator assessment (Panel A) and overall survival (Panel B) in the exercise group and the health-education group.

DFS
HR 0.72

OS
HR 0.63

Courneya. NEJM 2025.

Discussion

- Practice changing and must be considered standard of care
- We can apply these findings immediately in clinic
- Cost effective and safe

ASCO Gastrointestinal Cancers Symposium

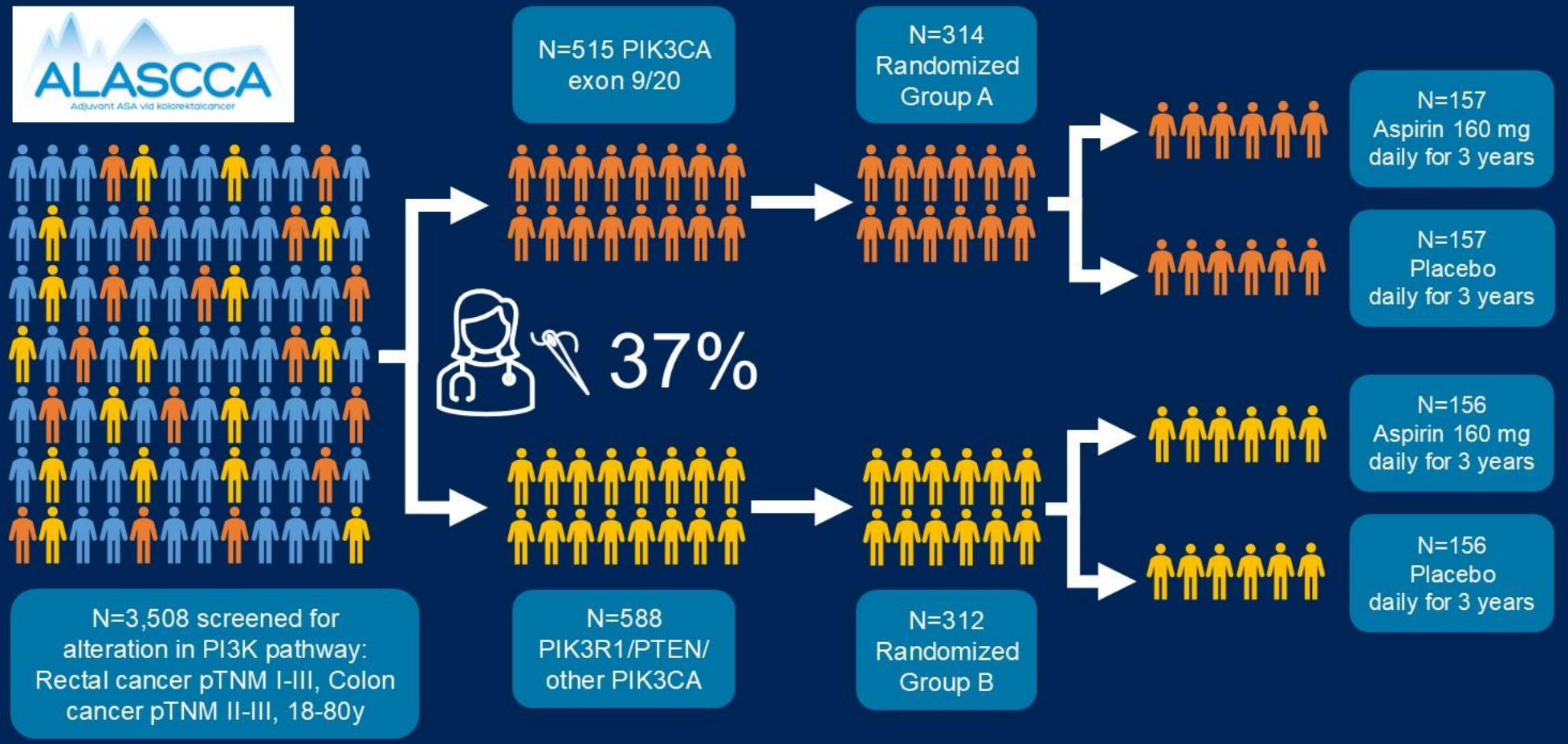
ALASCCA
Adjuvant ASA vid kolorektalcancer

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

3-Year Results from the ALASCCA Trial

Prof. Anna Martling M.D, PhD, FACS (Hon), FASCRS (Hon)
Karolinska Institutet & Karolinska University Hospital, Stockholm, Sweden

The ALASCCA Trial (NCT02647099)



Primary outcome:
Time to CRC recurrence (TTR) in Group A

Secondary outcomes:
- Disease-Free Survival (DFS) in Group A
- TTR in Group B
- DFS in Group B
- Safety

April 2016: Start of screening

July 2016: First patient randomized

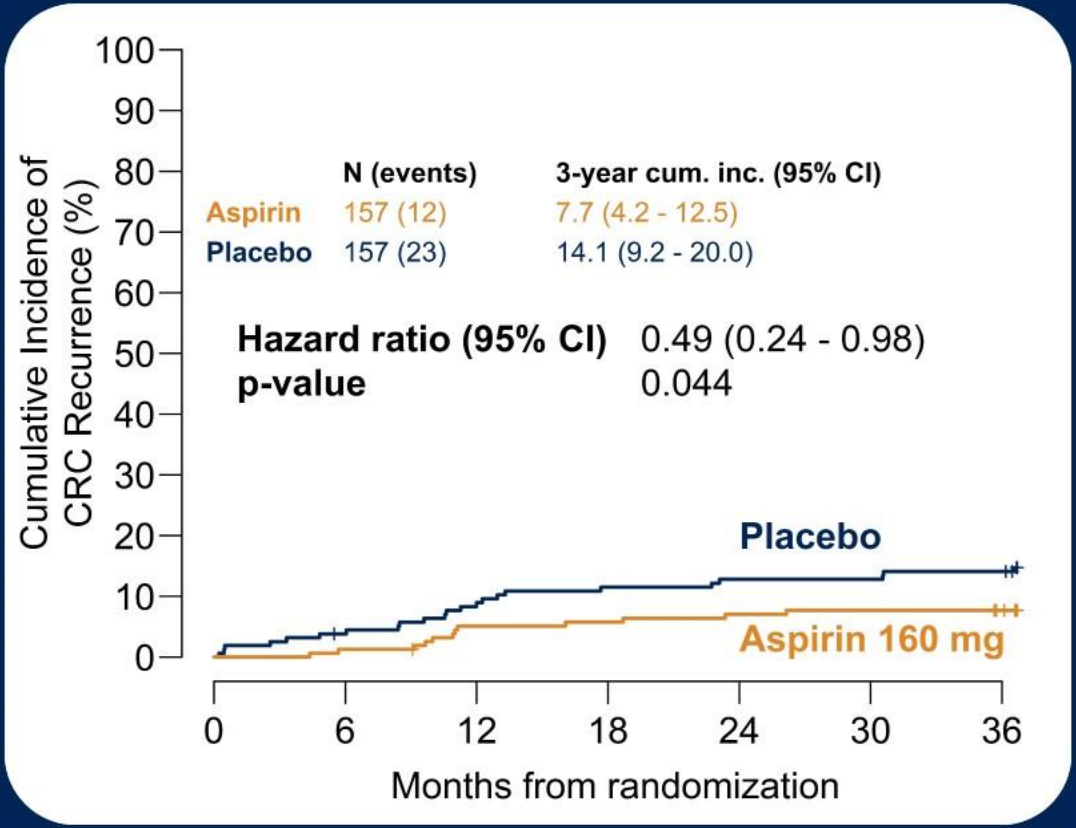
July 2021: Last patient randomized

July 2024: Complete 3-year follow-up

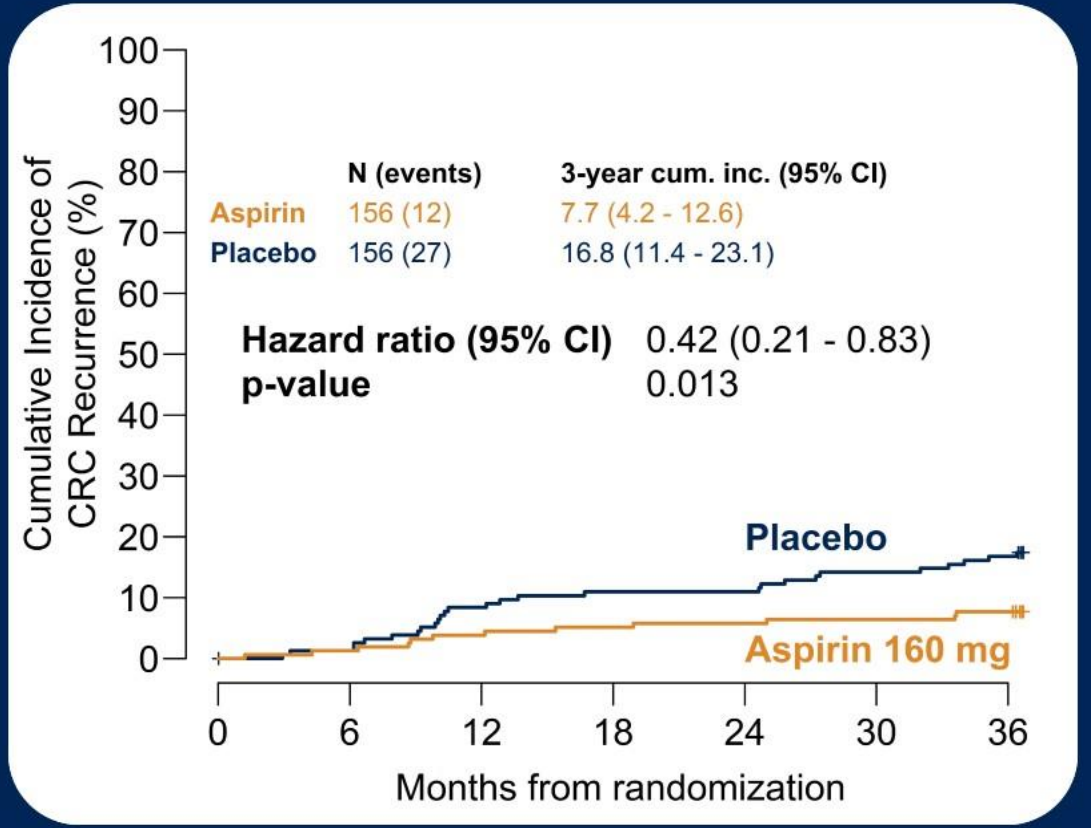
PRESENTED BY: Anna Martling: Low-Dose Aspirin Reduces Recurrence Rate in Colorectal Cancer Patients with PI3K Pathway Alterations: 3-Year Results from a Randomized Placebo-Controlled Trial (Abstract Number: LBA125)

Primary Outcome: CRC Recurrence

Group A (PIK3CA Exons 9/20)



Group B (PIK3R1/PTEN/Other PIK3CA)



Key Takeaway Points

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

Repurposing of safe, inexpensive, globally available drug

Importance of upfront genomic testing

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Colorectal Cancer

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RTP Year in Review 2026

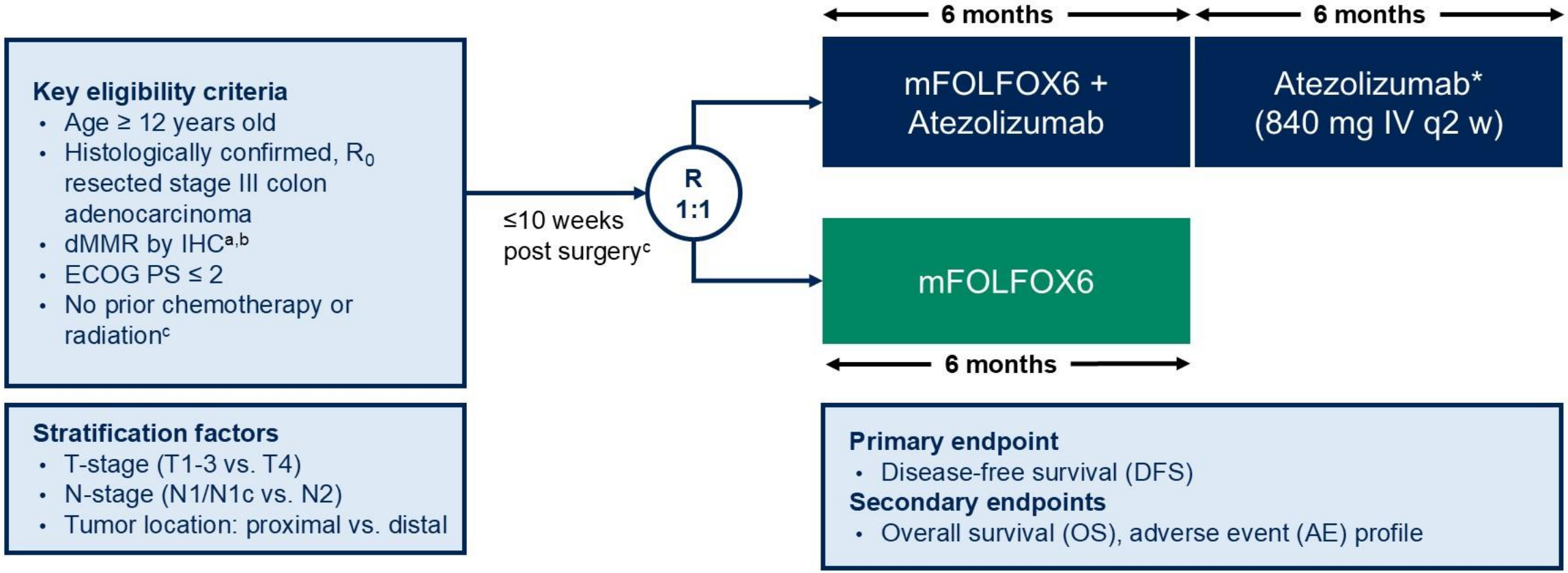
2025 ASCO ANNUAL MEETING

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)

Frank A. Sinicrope, Fang-Shu Ou, Dirk Arnold, Walter R. Peters, Robert J. Behrens, Christopher H. Lieu, Khalid Matin, Deirdre J. Cohen, Samara L. Potter, Wendy L. Frankel, Ardaman Shergill, Dennis Hsu, Anke C. Reinacher-Schick, Tyler Zemla, Clare A. Gatten, Eileen O'Reilly, Jeffrey A. Meyerhardt

Study Design

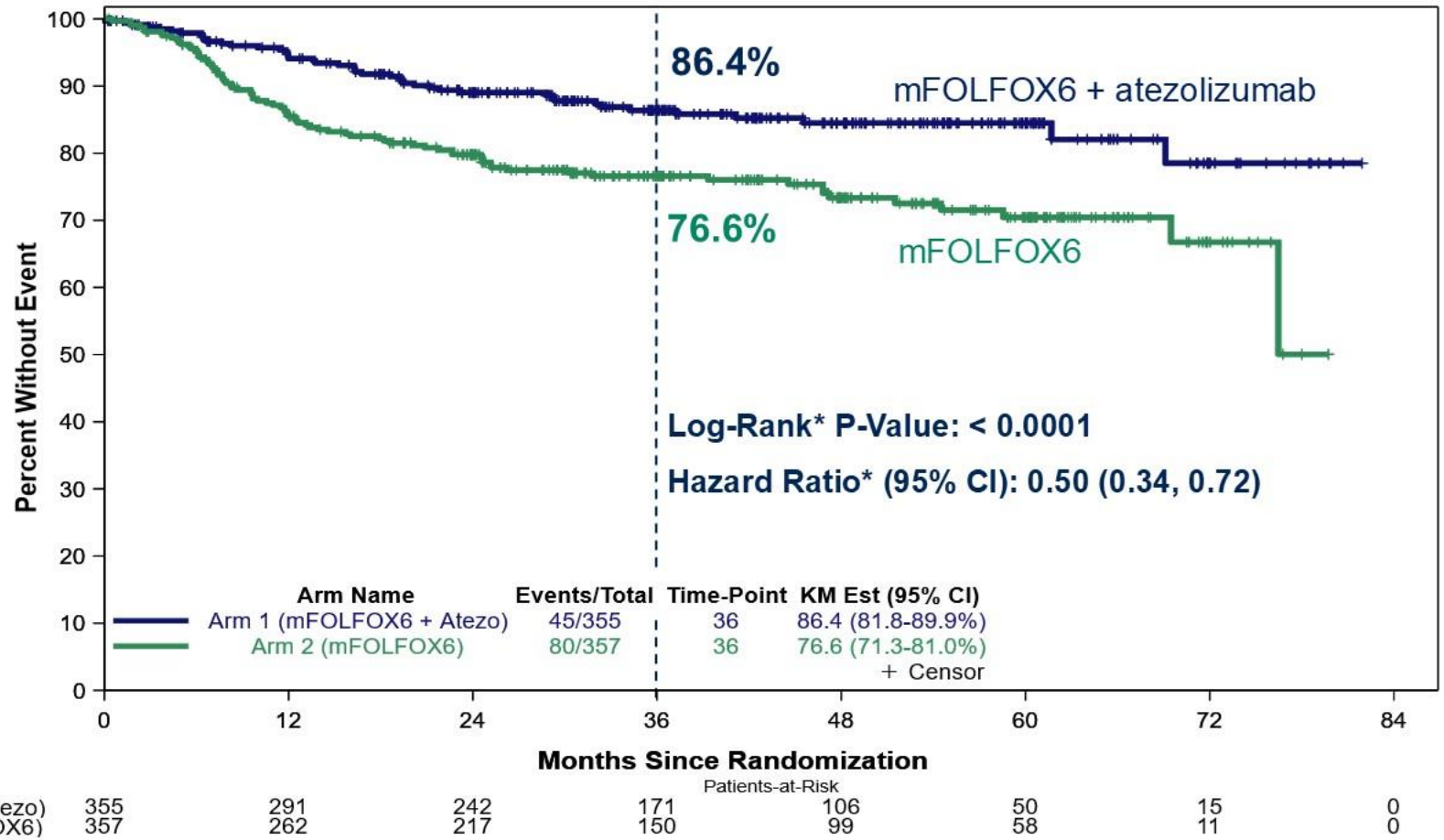
ATOMIC is a randomized, multicenter, open label phase 3 study



[a] **dMMR by immunohistochemistry (IHC) locally or at site-selected reference laboratory. Retrospective central confirmation of dMMR also performed.**
[b] Lynch syndrome included.
[c] One cycle of mFOLFOX6 prior to randomization permitted.

*Atezolizumab (anti-PD-L1)

Primary Endpoint: DFS



Confirmed dMMR by central reference laboratory: Log-Rank P-Value: 0.0007, Hazard Ratio (95% CI): 0.53 (0.36, 0.79)

*Stratified by randomization factors

Median follow-up = 37.2 mos

Discussion

- Practice changing and must be considered standard of care for stage III colon cancer patients
- Reasonable to extrapolate to the minority of stage II colon cancer patients who receive adjuvant therapy
- Future trials must look at duration & intensity of adjuvant immunotherapy:

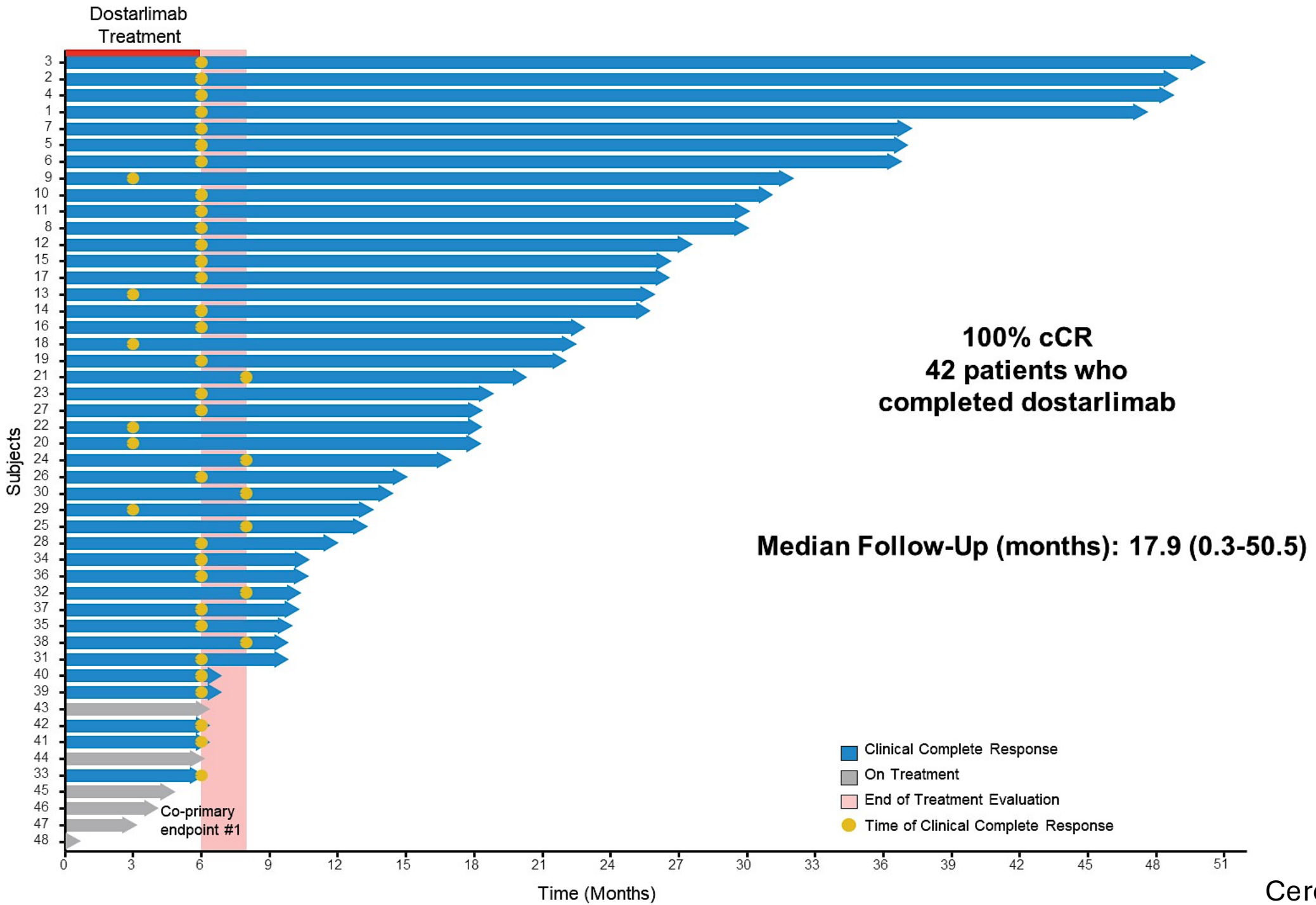
- Is 12-months required in all patients?
- Approximately 15% still with recurrence. Can these patients be identified and be offered dual checkpoint inhibitors?

The NEW ENGLAND JOURNAL of MEDICINE

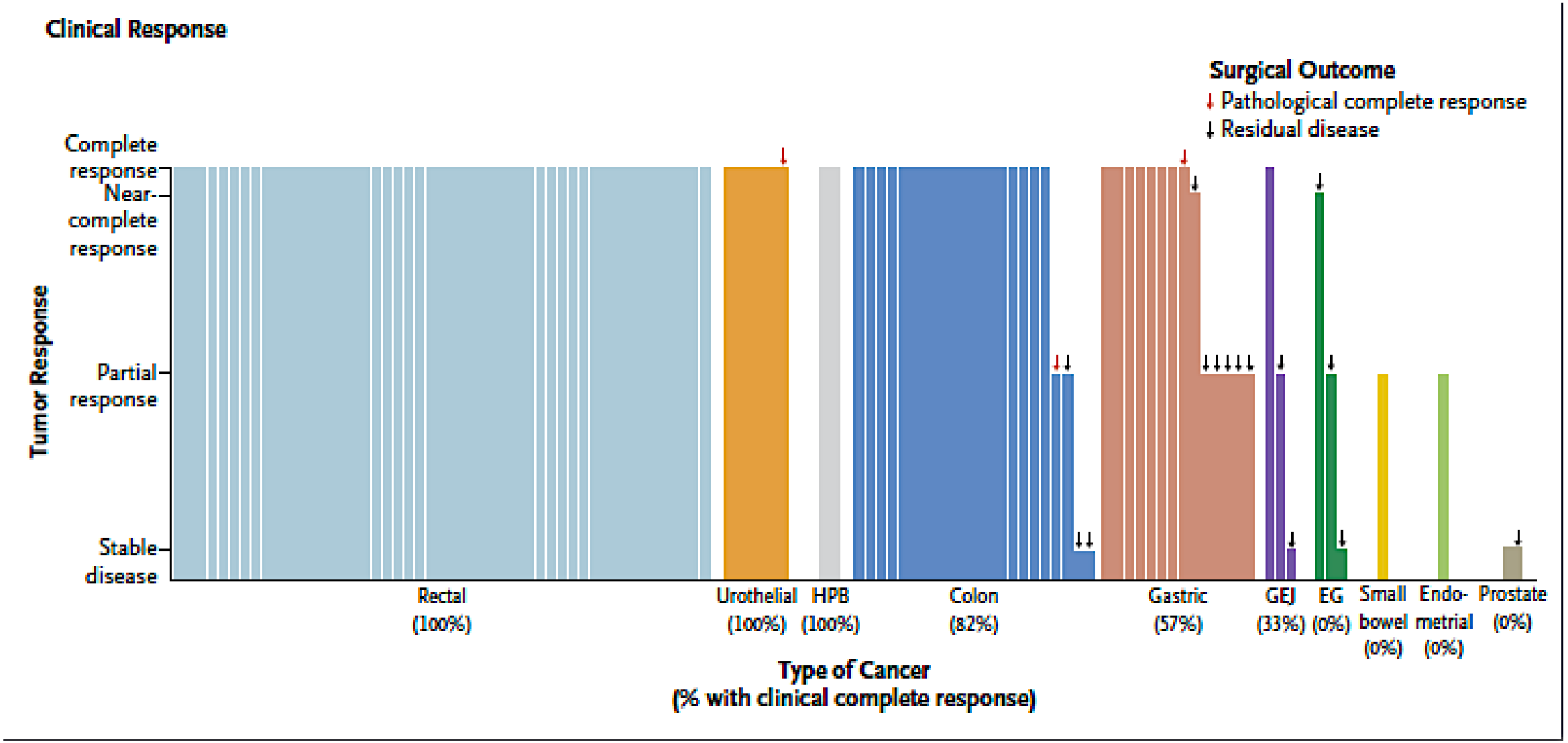
ESTABLISHED IN 1812 JUNE 19, 2025 VOL. 392 NO. 23

Nonoperative Management of Mismatch Repair–Deficient Tumors

A. Cercek,[1] M.B. Foote,[1] B. Rousseau,[1] J.J. Smith,[2] J. Shia,[3] J. Sinopoli,[1] J. Weiss,[1] M. Lumish,[4] L. Temple,[1] M. Patel,[1] C. Wilde,[1] L.B. Saltz,[1] G. Argiles,[1] Z. Stadler,[1] O. Artz,[1] S. Maron,[1] G. Ku,[1] P. Gu,[1] Y.Y. Janjigian,[1] D. Molena,[2] G. Iyer,[1] J. Coleman,[2] W. Abida,[1] S. Cohen,[1] K. Soares,[2] M. Schattner,[1] V.E. Strong,[2] R. Yaeger,[1] P. Paty,[2] M. Shcherba,[1] R. Sugarman,[1] P.B. Romesser,[5] A. Zervoudakis,[1] A. Desai,[1] N.H. Segal,[1] I. El Dika,[1] M. Widmar,[2] I. Wei,[2] E. Pappou,[2] G. Fumo,[6] S. Aparo,[7] M. Gonen,[8] M. Gollub,[9] V.S. Jayaprakasam,[9] T.-H. Kim,[9] J. Garcia Aguilar,[2] M. Weiser,[2] and L.A. Diaz, Jr.[1]



Cercek A. ASCO 2024.

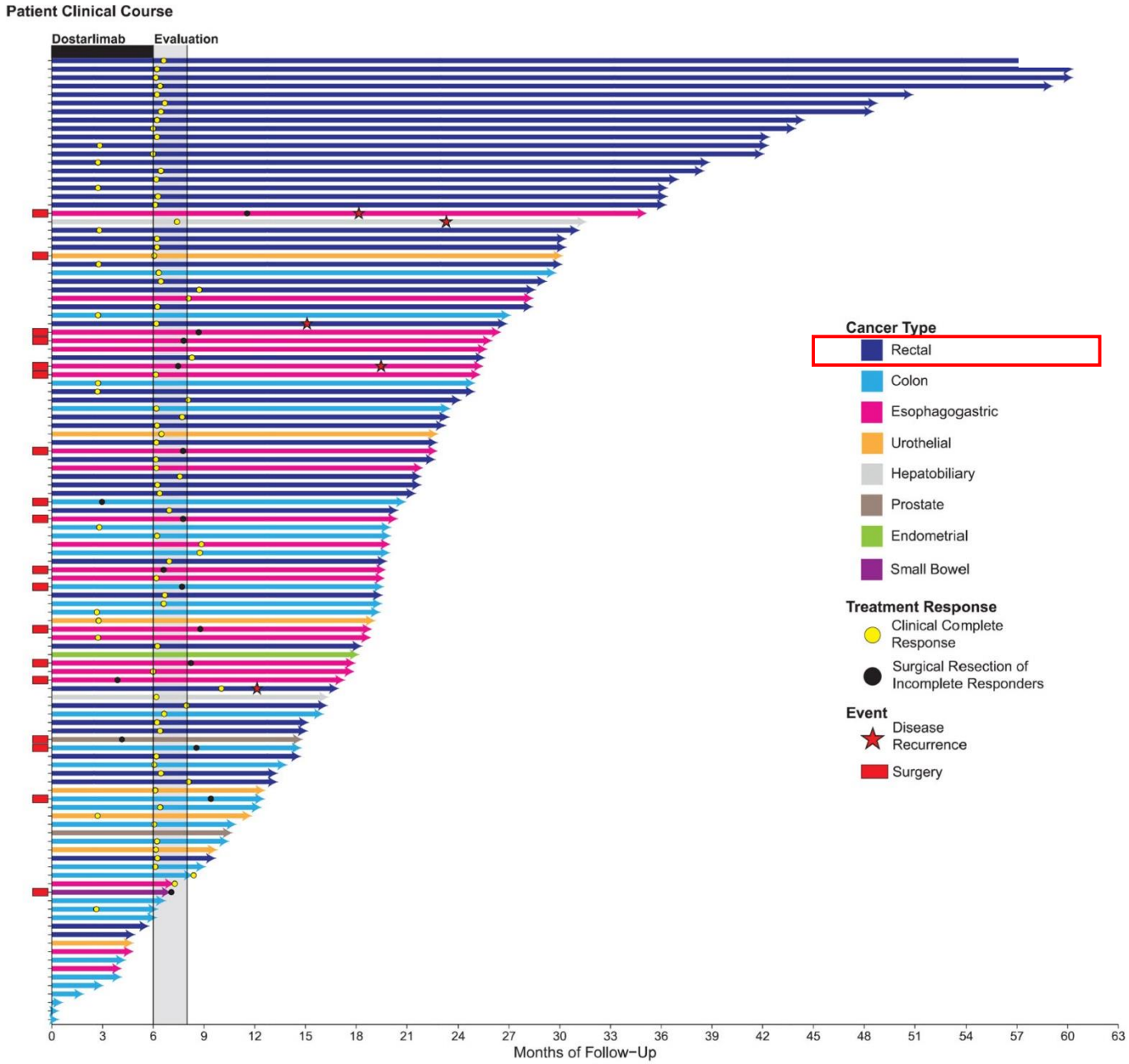


- All pts underwent NOM
-5 pts with local recurrence (4/ 4 responded to IO re-challenge)
- 96% without recurrence at 2-years

- 65% underwent NOM
- 85% without recurrence at 2-years

Cercek A. NEJM 2025.

Clinical Outcomes by Tumor Type



Cercek A. NEJM 2025.

Discussion

- Practice changing and must be considered standard of care for MSI-H / dMMR rectal cancer.

- Should neoadjuvant IO be considered for MSI-H / dMMR colon cancer outside of a clinical trial?

In certain circumstances such as bulky tumors or high risk for surgical complications.

- Should neoadjuvant IO be considered for MSS / pMMR colon or rectal cancer?

Only as part of clinical trials

Phase II AZUR 4 Study: Design

Trial Design: 120 patients stratified by T4N0 or stage III

Key inclusion criteria:

- Aged 18 years
- Resectable pMMR/MSS colon aca with no prior treatment
- T4N0 or stage III
- ECOG PS 0-1

Primary endpoints

- Major pathological response
- Safety

Rasschaert G. ASCO 2025. TPS3649.

Year in Review:
Colorectal Cancer

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RTP Year in Review 2026

2025 ASCO® ANNUAL MEETING

Proposed Changes to the Pathologic Staging for Colon Cancer (CC): American Joint Committee on Cancer (AJCC) Colon Cancer Expert Panel (CCEP)

Qian Shi[1], George J. Chang[2], Levi D. Pederson[1], Elliot Amponsah Asare[3], Zhaohui Jin[4], Romain Cohen[5], Jeffrey A. Meyerhardt[6], Thierry Andre[5], Jeanne Tie[7], Takayuki Yoshino[8], Eiji Oki[9], Yuichiro Tsukada[10], Koji Ando[9], Marloes AG Elferink[11], Iris D Nagtegaal[12], Jesse G. Dixon[1], Bryan E Palis[13], Karla V. Ballman[1], Greg Yothers[14], Zeliang Ma[4], Steven R Alberts[4], Chanjuan Shi[15], Mary Kay Washington[16], Julien Taieb[17], Scott Steele[18], and Richard M Goldberg[19]

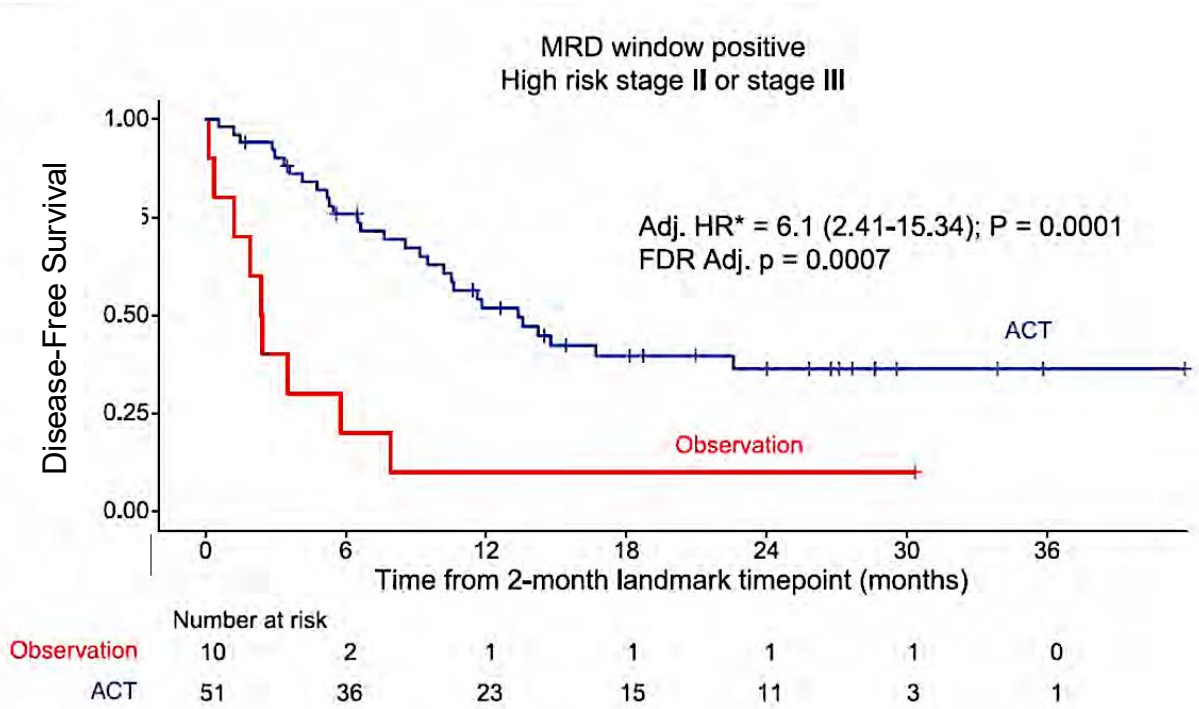
Qian Shi, Professor of Biostatistics and Oncology, Mayo Clinic

[1]Department of Quantitative Health Science, Mayo Clinic, Rochester, MN; [2]The University of Texas MD Anderson Cancer Center, Houston, TX; [3]University of Utah Huntsman Cancer Institute, Salt Lake City, UT; [4]Division of Medical Oncology, Mayo Clinic, Rochester, MN; [5]Sorbonne University, Department of Medical Oncology, Saint-Antoine Hospital, AP-HP, Paris, France; [6]Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Harvard University, Boston, MA; [7]Department of Medical Oncology, Peter MacCallum Cancer Centre and Personalized Oncology Division, Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia; [8]Department of Gastrointestinal Oncology, National Cancer Center Hospital East, Japan; [9]Department of Surgery and Science, Kyushu University, Japan; [10]Department of Colorectal Surgery, National Cancer Center Hospital East; [11]Department of Research and Development, Netherlands Comprehensive Cancer Organization, the Netherlands; [12]Department of Pathology, Radboud University Medical Center, the Netherlands; [13]American College of Surgeons, Chicago, IL; [14]NSABP/NRG Oncology, and The University of Pittsburgh Department of Biostatistics, Pittsburgh, PA; [15]Duke University Trent Center for Bioethics Humanities and History of Medicine, Durham, NC; [16]Vanderbilt University Medical Center, Vanderbilt-Ingram Cancer Center, Nashville, TN; [17]Paris Cité University, Georges Pompidou European Hospital GI Oncology Department, Paris, France; [18]Cleveland Clinic, Cleveland, OH; [19]West Virginia University Cancer Institute and the Mary Babb Randolph Cancer Center, Morgantown, WV

Real-world monitoring of ctDNA reliably predicts cancer recurrence and treatment efficacy in patients with resected stages I to III colon cancer

Cohen SA et al. *Ann Surg*. 2025;[Online ahead of print]

Improved DFS with ACT vs observation



ctDNA status	ACT	Observation
Events %	56.86 (29/51)	90 (9/10)
24M-DFS % (95% CI)	36.3 (22.2–50.6)	10 (0.6–35.8)
mDFS (mo)	13.38 (10.9–NR)	2.41 (1.22–NR)

*adjusted for age, gender, stage and MSI

Cohen SA. Ann Surg. 2025

Conclusions: Postsurgical ctDNA detection is prognostic of relapse and potentially predictive of ACT benefit in patients with resectable colon cancer, which may enable personalized surveillance, intervention, and/or trial options, ultimately improving patient outcomes.

Cohen SA. Ann Surg. 2025

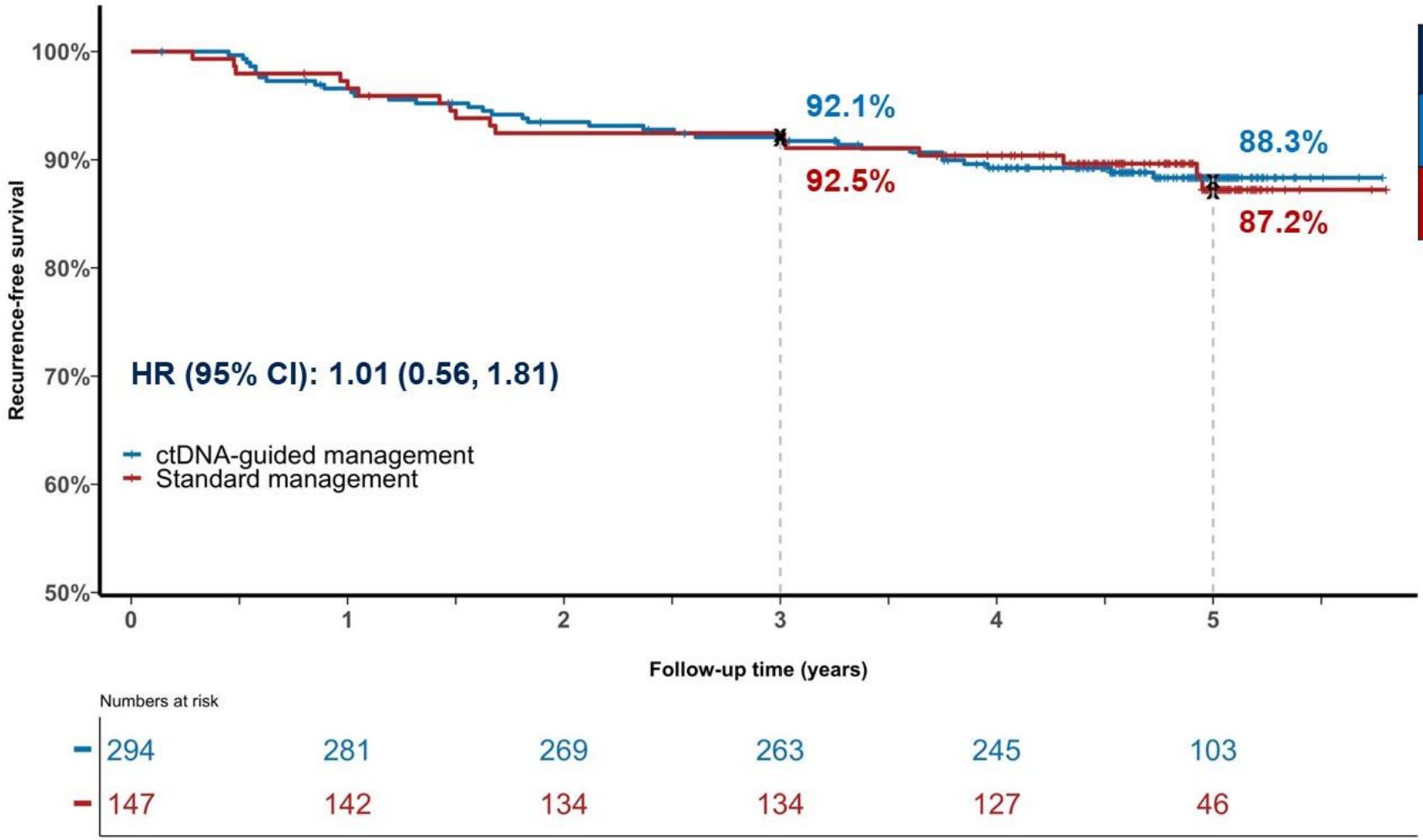
nature medicine

Article

https://doi.org/10.1038/s41591-025-03579-w

Circulating tumor DNA analysis guiding adjuvant therapy in stage II colon cancer: 5-year outcomes of the randomized DYNAMIC trial

Updated 5-Year RFS Analysis



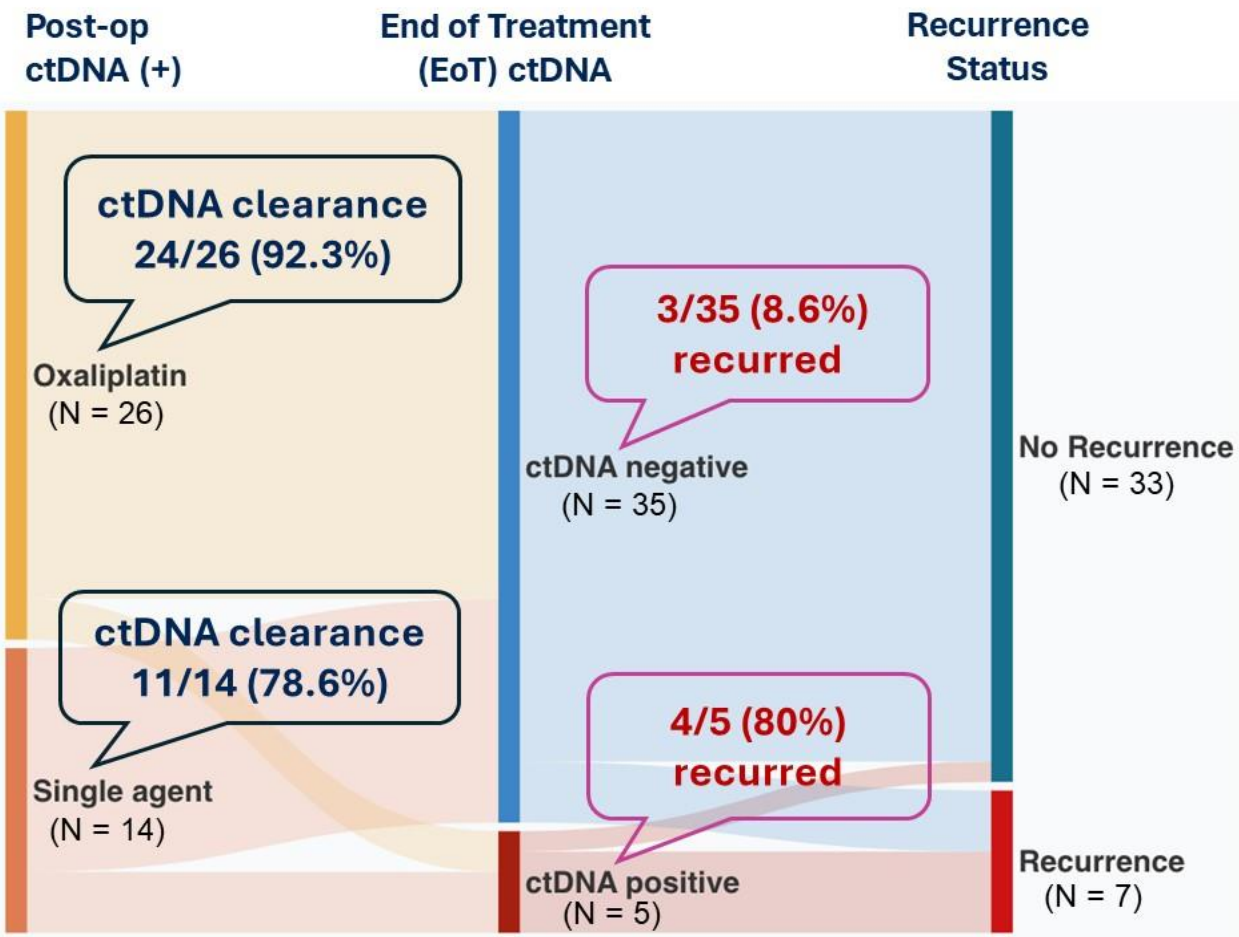
5-Year RFS Rate, %	
ctDNA	88.3
SoC	87.2

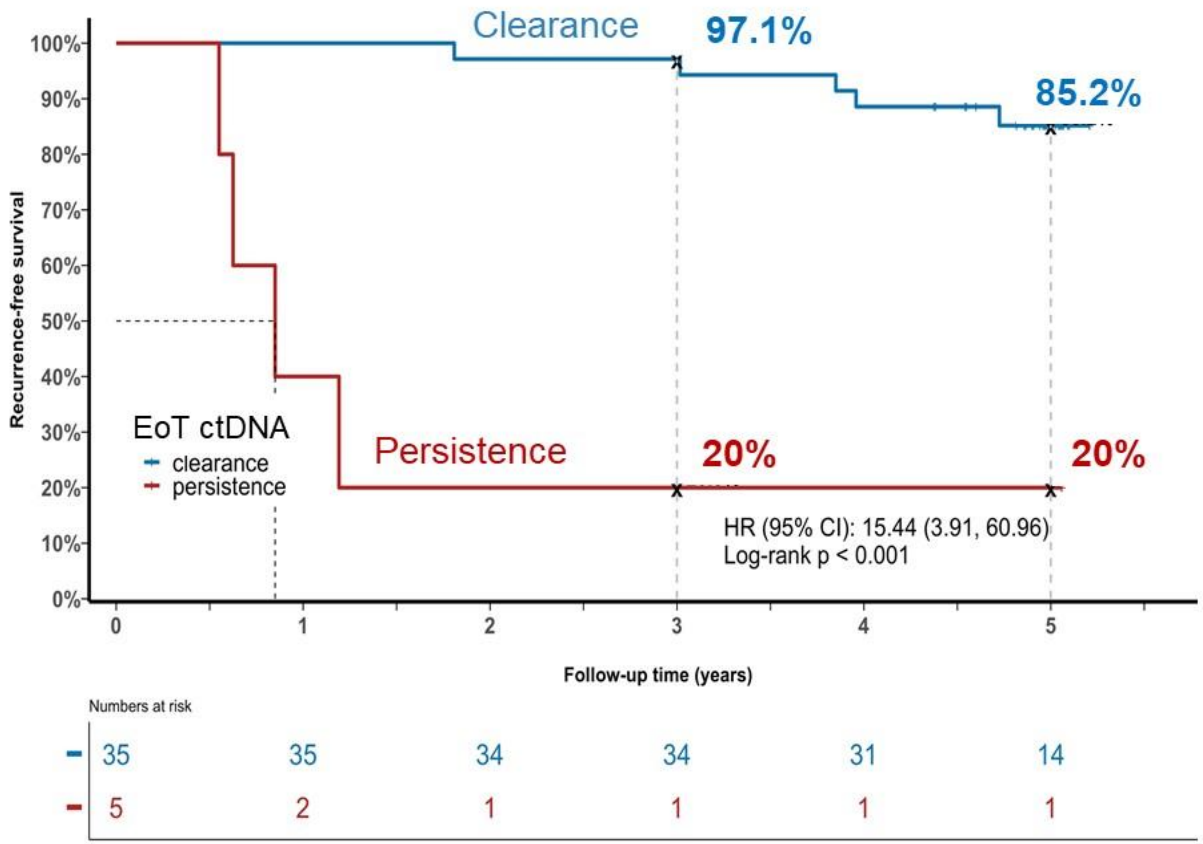
Difference in 5-year RFS rate +1.1%
(95% CI for difference, -5.8 to 8.0%)

Median Follow-Up
ctDNA-Guided 59.7 months
SoC 59.7 months
(IQR 55.0 – 61.5)

Data cut-off: 17 Jan 2024

Post-op ctDNA Positive: EoT ctDNA Clearance and RFS





EoT = 4 weeks post chemo

Conclusions

- More mature follow-up data confirms the initial findings of the DYNAMIC study → a ctDNA-guided approach to adjuvant treatment in stage II colon cancer reduces use of chemotherapy compared to standard-of-care without compromising survival outcomes
- A ctDNA-guided approach achieves excellent survival outcomes, including in patients with T4 disease
- ctDNA clearance can be achieved with adjuvant chemotherapy in a high proportion of post-op ctDNA-positive patients and is associated with favorable outcomes
- There is potential for improved precision of the ctDNA-informed approach (by increasing variant number and incorporating ctDNA molecular burden), but further validation of these preliminary findings is required

Discussion

- Compelling data confirming earlier observations
- NCCN guidelines currently do not recommend using MRD assays to make treatment decisions BUT….
- Reasonable to consider after thorough discussion with patients and their families in low-risk stage II (or when adjuvant therapy may be high risk and / or not in line with patient preferences)

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

Conclusions

For patients with ctDNA-positive stage III colon cancer post-surgery

- Recurrence risk remains high (3-year RFS ~50%) despite adjuvant chemotherapy
- Recurrence risk increases with rising ctDNA burden
- ctDNA-informed treatment escalation, including from oxaliplatin doublet to FOLFOXIRI, did not reduce recurrence risk (2-year RFS 52% vs 61%)
- ctDNA clearance post treatment was associated with a favorable outcome (3-year RFS 84% vs 12% in patients without clearance), reflecting treatment efficacy
- Future studies should explore novel escalation strategies, with ctDNA clearance as a strong preliminary signal of efficacy

Conclusions

For patients with ctDNA-negative stage III colon cancer post-surgery

- Recurrence risk is low, with 3-year RFS of 87%
- ctDNA-informed treatment de-escalation was feasible with high adherence (90%)
  - Markedly reduced oxaliplatin exposure (88.6% → 34.8%)
  - Better safety profile: fewer treatment-related hospitalisations and grade ≥3 adverse events
  - Non-inferiority versus SoC was not confirmed, though outcomes were close (3-yr RFS 85.3% vs 88.1%), particularly in low-risk (T1-3N1) disease (3-yr RFS 91.0% vs 93.2%)
  - Could inform risk-benefit discussions for individual patients
- ctDNA-informed de-escalation strategies warrant further investigation

Discussion

- Trial used an older generation assay and treatment escalation decisions were not consistent
- Will need to await results of ongoing trials such as CIRCULATE-North America
- No role for treating ctDNA+ patients outside of clinical trials with systemic chemotherapy

ASCO Gastrointestinal Cancers Symposium

Prognostic and predictive role of circulating tumor DNA (ctDNA) in stage III colon cancer treated with celecoxib: Findings from CALGB (Alliance)/SWOG 80702

Jonathan A. Nowak, Qian Shi, Tyler Twombly, Levi Pederson, Chao Ma, Juha P. Väyrynen, Melissa Zhao, Yasutoshi Takashima, Ardaman Shergill, Pankaj Kumar, Felix Couture, Philip Kuebler, Smitha Krishnamurthi, Benjamin Tan, Eileen M. O'Reilly, Anthony F. Shields, Shuji Ogino, Alexey Aleshin, and Jeffrey A. Meyerhardt

Discussion

- Compelling hypothesis generating data
- Reminiscent of atezolizumab in muscle invasive bladder cancer development and approval (Powles et al, NEJM, 2025)
- Need further validation prior to use in clinic; should enroll patients onto trials

ASCO Gastrointestinal Cancers Symposium

Impact of Postoperative ctDNA Dynamics on Eligibility for ALTAIR Randomized Trial in Patients with Colorectal Cancer: Implications for Clinical Trial Enrollment

Hideaki Bando, on behalf of Yoshiaki Nakamura and the CIRCULATE-Japan investigators

National Cancer Center Hospital East, Kashiwa, Japan

Yoshiaki Nakamura, Vasily N. Aushev, Jun Watanabe, Yusuke Takahashi, Masahito Kotaka, Nobuhisa Matsuhashi, Eiji Oki, Yoshito Komatsu, Manabu Shiozawa, Keiji Hirata, Yuji Miyamoto, Kentaro Yamazaki, Kun-Huei Yeh, Adham Jurdi, Saori Mishima, Daisuke Kotani, Hiroya Taniguchi, Takayuki Yoshino, and Takeshi Kato

Conclusions

- Among patients enrolled in the GALAXY trial at the ALTAIR-participating sites:
  - ~15% of patients with stage II–III disease and ~30% with stage IV disease who received adjuvant chemotherapy (ACT) met the ctDNA-based ALTAIR eligibility criteria
  - 77% of patients who had ctDNA positivity after ACT were eligible
  - 6.5% overall were enrolled in ALTAIR
- Higher MRD positivity and ALTAIR enrollment rates were observed with increasing colorectal cancer stage.
- Higher ctDNA levels correlated with clinical relapse within 3 months of ctDNA positivity.

Serial ctDNA testing during ACT and surveillance is crucial to identify patients eligible for Treat on Molecular Recurrence (TOMR) trials.

Year in Review:
Colorectal Cancer

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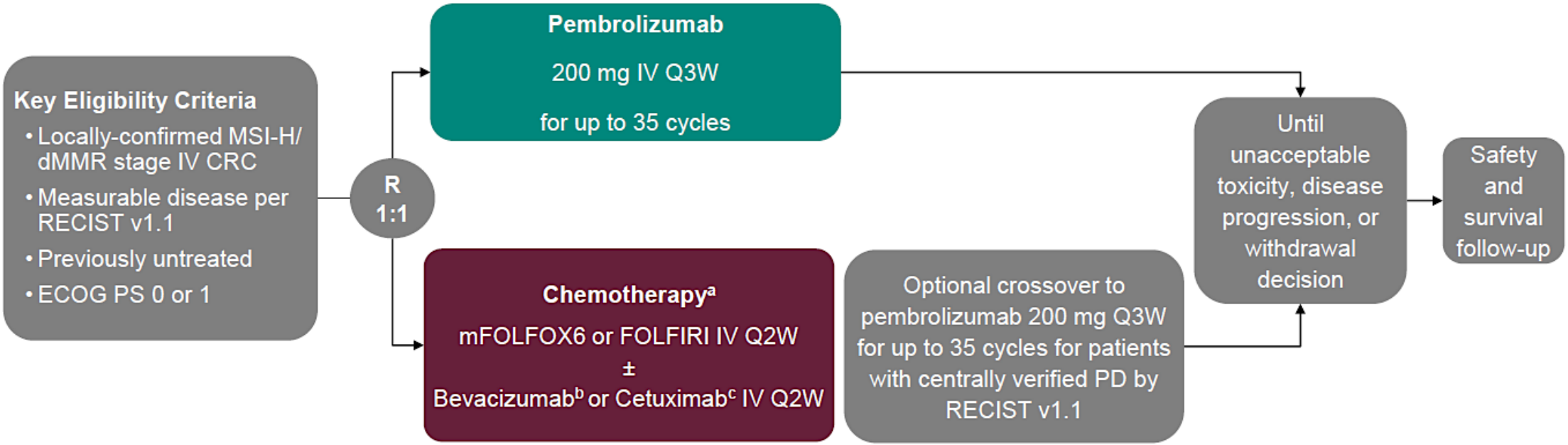
RTP Year in Review 2026

Trial 1 | KEYNOTE-177 5yr

KEYNOTE-177 Study Design (NCT02563002)



- **Dual primary end points:** PFS per RECIST v1.1 by BICR; OS
- **Secondary end point:** Safety
- **Exploratory end point:** DOR per RECIST v1.1 by BICR

- **Median time from randomization to data cutoff:** 73.3 months (6.1 years; range, 64.9-89.2 months)

Data cutoff date: July 17, 2023. FOLFIRI, irinotecan 180 mg/m² IV day 1, leucovorin 400 mg/m² IV day 1, 5-fluorouracil 400 mg/m² IV day 1 then 2400 mg/m² IV over 46-48 hours; mFOLFOX6, oxaliplatin 85 mg/m² IV day 1, leucovorin 400 mg/m² IV day 1, and 5-fluorouracil 400 mg/m² IV day 1 then 2400 mg/m² over 46-48 hours. [a]Chosen by investigator before randomization. [b]Bevacizumab 5 mg/kg IV day 1. [c]Cetuximab 400 mg/m² IV over 2 hours, then 250 mg/m² IV over 1 hour once per week.

André et al. Ann Oncol 2025;36:277-284.

Trial 1 | KEYNOTE-177 5yr

IMPLICATIONS

1. Cements pembrolizumab as 1L SOC for MSI-H/dMMR mCRC
2. OS > 6 years with IO-first — transformative
3. Durable responses (mDOR > 6 yrs) support IO biology
4. Crossover-adjusted benefit likely even greater (mOS doubled: 77.5 vs 36.7 mo despite 62% crossover)
5. Benchmark for dual IO comparisons (CM8HW, COMMIT)

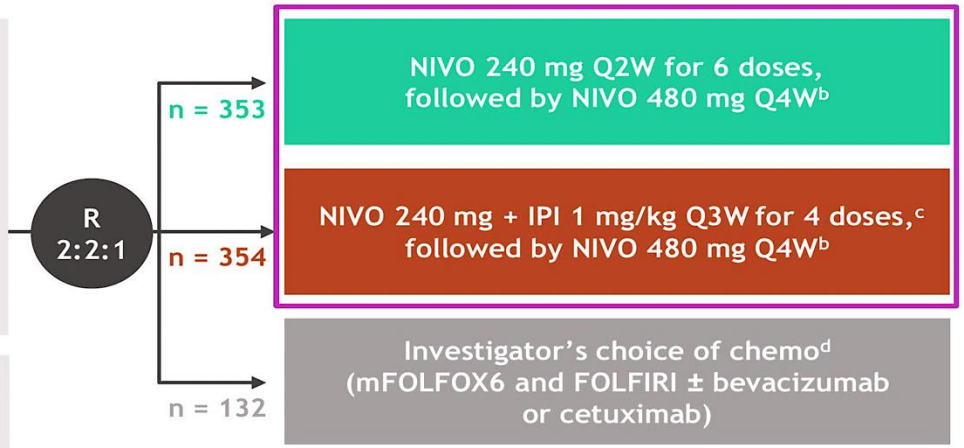
André et al. Ann Oncol 2025;36:277-284.

Study design: CheckMate 8HW

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

Key eligibility criteria:
- Histologically confirmed unresectable or metastatic CRC
- MSI-H/dMMR status by local testing
- Immunotherapy-naïve
- ECOG PS 0 or 1

Stratification factors:
- Prior lines of treatment (0 vs 1 vs ≥ 2)
- Primary tumor location (right vs left)



Treatment until disease progression, unacceptable toxicity, withdrawal of consent (all arms), or a maximum treatment duration of 2 years (NIVO and NIVO + IPI arms only)

Dual primary endpoints in patients with centrally confirmed MSI-H/dMMR status[e]:
- PFS by BICR[f] (NIVO + IPI vs chemo in 1L)
- PFS by BICR[f] (NIVO + IPI vs NIVO across all lines)

Secondary endpoints in patients with centrally confirmed MSI-H/dMMR status[e]:
- PFS by BICR[f] (NIVO + IPI vs NIVO in 1L)
- ORR by BICR[f] (NIVO + IPI vs NIVO in 1L)
- OS (NIVO + IPI vs NIVO across all lines)
- ORR by BICR[f] (NIVO + IPI vs NIVO across all lines)

Other key endpoints in 1L treated patients
- Safety

- At data cutoff (April 30, 2025), median follow-up[g,h] for all randomized 1L patients was 50.1 (range 24.7-67.3) months

[a]ClinicalTrials.gov. NCT04008030. [b]Patients with ≥ 2 prior lines are randomized only to the NIVO or NIVO + IPI arms. [c]Patients can continue NIVO treatment upon early IPI discontinuation. [d]Patients receiving investigator's choice of chemo are eligible to receive NIVO + IPI upon progression (crossover treatment). [e]Confirmed using either immunohistochemistry and/or polymerase chain reaction-based tests. [f]Evaluated using RECIST v1.1. [g]Time between randomization and data cutoff across all 3 treatment arms. [h]Median follow-up was 55.1 (range 24.7-68.5) months in all lines.

Crossover from chemo allowed at PD

Lonardi S et al ESMO 2025; Abstract LBA49

Trial 2 | CheckMate 8HW

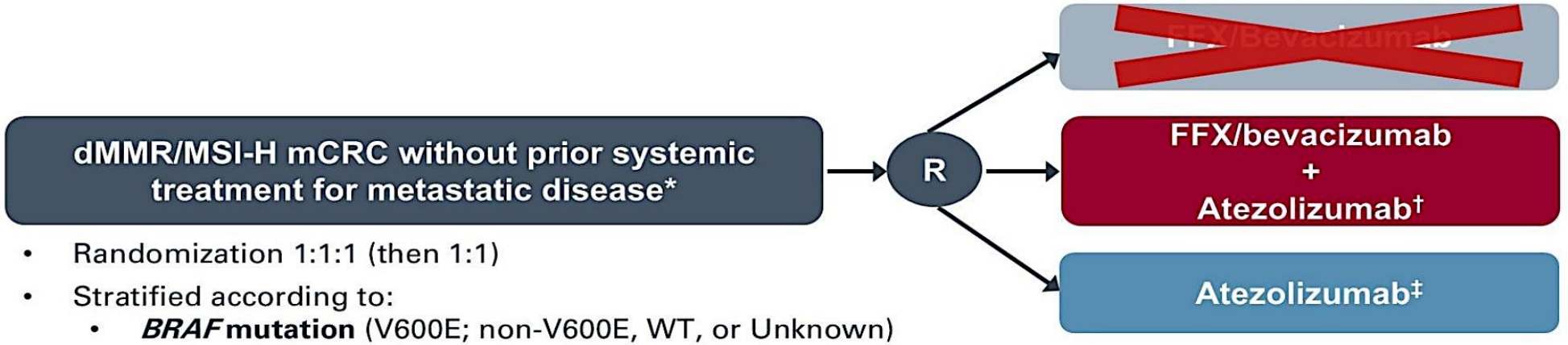
IMPLICATIONS

1. First phase 3: dual IO > chemo AND mono IO in MSI-H
2. PFS HR 0.21 vs chemo — unprecedented in mCRC
3. Led to FDA approval nivo+ipi for MSI-H/dMMR
4. Nivo mono viable — PFS > 3 years
5. Key Q: which patients need dual vs mono?

Lonardi S et al ESMO 2025; Abstract LBA49

Trial 3 | COMMIT

Study Design



- Randomization 1:1:1 (then 1:1)
- Stratified according to:
  - ***BRAF* mutation** (V600E; non-V600E, WT, or Unknown)
  - **Metastatic disease:** (liver-only; extra-hepatic)
  - **Prior adjuvant therapy for CRC**

Due to KEYNOTE 177 results, COMMIT's FFX/bev arm was closed (trial amended 6/4/20), leaving two arms:
- **FFX/bev/atezo**
- **Atezo monotherapy**

The study was also modified to enroll 120 total patients.
- **80% power to detect a hazard ratio of 0.6 for PFS, one-sided alpha=0.025.**

* One cycle of FOLFOX or CAPOX with or without bev (or biosimilar) allowed prior to enrollment

† **FFX/bev/atezo:** oxaliplatin 85 mg/m2 IV + leucovorin 400 mg/m2 IV + bevacizumab 5 mg/kg IV+ 5-FU 400 mg/m2 IV bolus on Day 1 followed by 5-FU 2400 mg/m2 IV over 46 hours plus atezo (840mg IV q2wks)

‡ **Atezo monotherapy:** 840mg IV q2wks

ASCO Gastrointestinal Cancers Symposium

Primary endpoint: PFS
Key secondary: ORR, DCR, OS, safety
N=102 (41 combo vs 41 atezo mono)

Rocha Lima et al. ASCO GI 2026; Abstract 14.

Trial 3 | COMMIT

IMPLICATIONS

1. Chemo+Bev+IO combo superior to IO mono in dMMR mCRC
2. Nearly eliminates early PD (2.8% vs 32.4%)
3. Challenges IO-mono paradigm from KN-177
4. BRAF V600E benefit: PFS HR 0.23 — key subgroup
5. Complementary to CM8HW dual-IO; defines IO+chemo role

Rocha Lima et al. ASCO GI 2026; Abstract 14.

The Manufacturer Announces US FDA Accepted the New Drug Application for Zanzalintinib in Combination with an Immune Checkpoint Inhibitor for Patients with Metastatic Colorectal Cancer

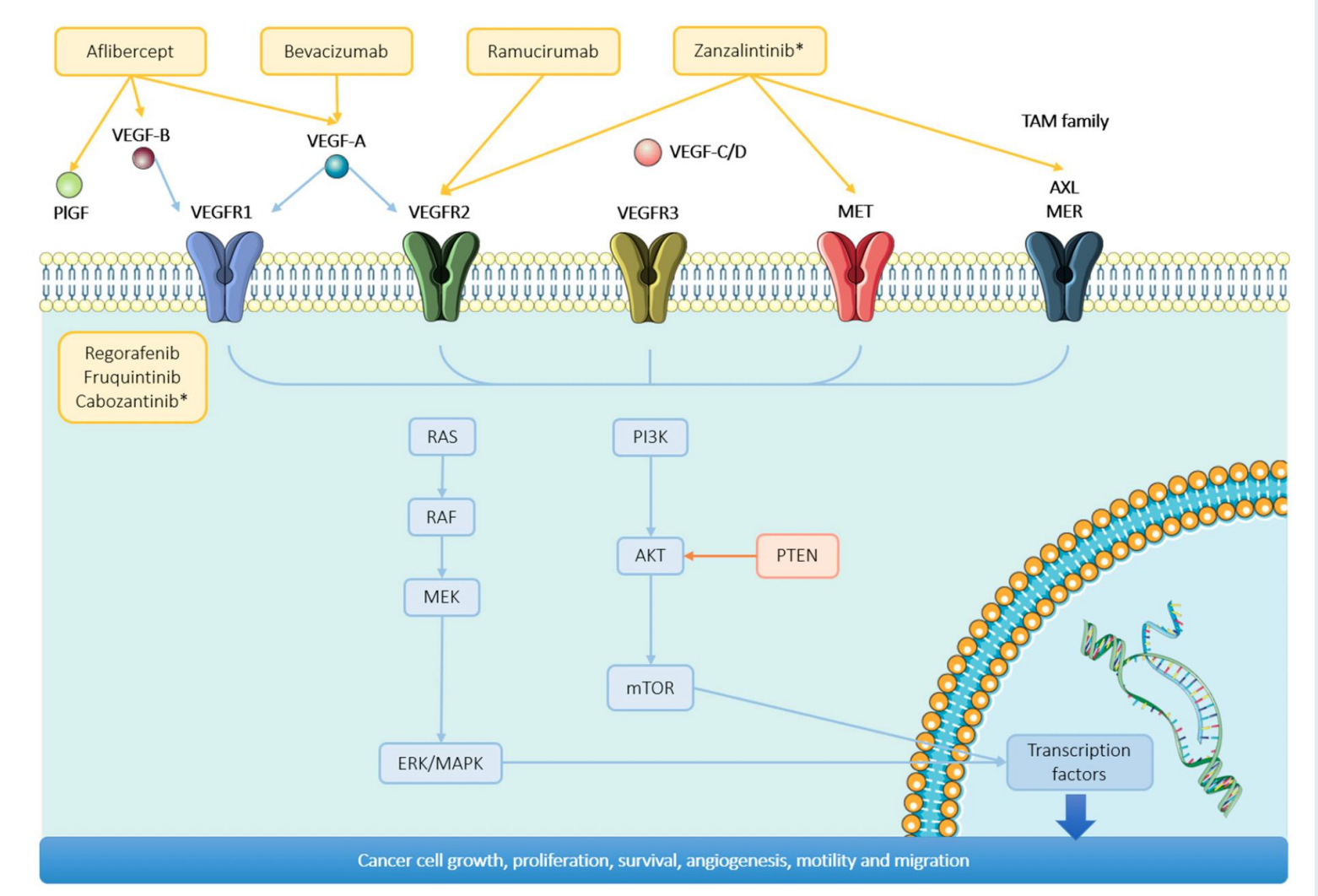
Press Release: February 2, 2026

"[The manufacturer] today announced that its New Drug Application (NDA) for zanzalintinib, in combination with atezolizumab, has been accepted for review in the U.S. for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, and, if RAS wild-type, an anti-epidermal growth factor receptor (EGFR) therapy. The Food and Drug Administration(FDA) assigned a standard review with a Prescription Drug User Fee Act target action date of December 3, 2026.

The NDA is based on the results of the phase 3 STELLAR-303 pivotal trial, in which zanzalintinib in combination with atezolizumab demonstrated a statistically significant improvement in overall survival (OS) versus regorafenib in the intention-to-treat (ITT) population of patients with previously treated CRC. Detailed results, including OS and progression-free survival (PFS) in the ITT population and in the subset of patients without liver metastases (non-liver metastases, NLM), were presented at the 2025 European Society for Medical Oncology (ESMO) Congress and published in The Lancet. Data pertaining to the other dual primary endpoint, OS inpatients without active liver metastases, were immature at the data cutoff, and the trial is proceeding to the planned final analysis for this endpoint, which is expected in mid-2026, based on current event rates."

https://ir.exelixis.com/news-releases/news-release-details/exelixis-announces-us-fda-accepted-new-drug-application

Zanzalintinib Mechanism of Action



* Not FDA approved

de Torres CS et al. *Int J Mol Sci* 2024;25,6967.

Trial 4 | STELLAR-303

STELLAR-303 (NCT05425940) Study Design

Patient Population

- Aged ≥18 years
- Documented to not have MSI-H or dMMR status
- mCRC that radiographically progressed on or was refractory or intolerant to prior standard-of-care therapy, which had to include all the following (if approved and available in the country where the patient is randomized):
  - Fluoropyrimidine, irinotecan and oxaliplatin ± anti-VEGF antibody
  - Anti-EGFR antibody (if *RAS* wild type)
  - BRAF inhibitor (if known *BRAF* V600E mutation)

Stratification Factors

- Geographic region (Asia/rest of the world)
- *RAS* status (wild type/mutant)
- Presence of liver metastases (yes/no)

R 1:1
N=901

Zanzalintinib 100 mg PO QD + Atezolizumab 1200 mg IV Q3W (n=451)*

Regorafenib 160 mg PO QD (days 1–21 of each 28-day cycle) (n=450)*

Endpoints

Dual primary	OS in the ITT population OS in patients without liver metastases (nlmITT)
Key secondary	PFS,† ORR,† Safety‡

*Treatment beyond radiographic progression was allowed per Investigator discretion. †According to Response Eval... both the ITT and non-liver metastasis ITT populations has been demonstrated in the final analysis. ‡According to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. dMMR, deficient mismatch repair; EGFR, epidermal growth factor receptor; ITT, intention to treat; IV, intravenous; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high; nlmITT, subset of patients without liver metastases; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, oral administration; Q3W, every 3 weeks; QD, once daily; VEGF, vascular endothelial growth factor.

Anwaar Saeed, MD

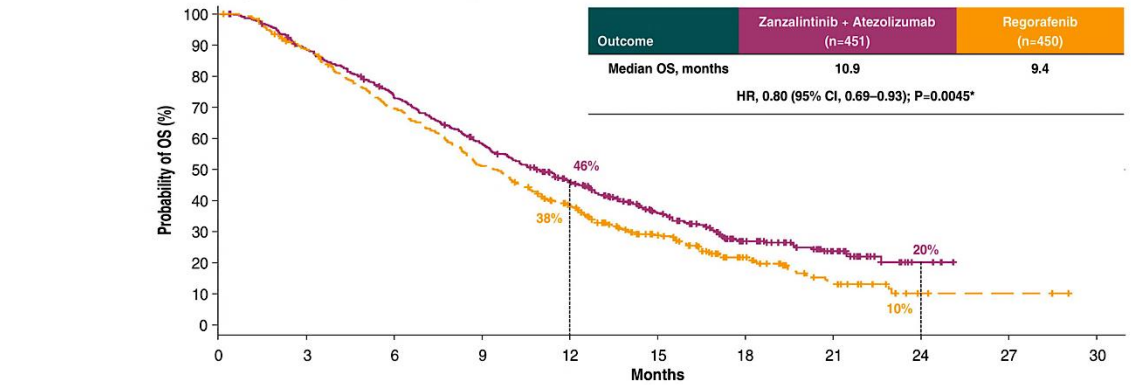
BERLIN 2025 ESMO congress

Hecht et al. Lancet 2025; 406: 2360–70.

Trial 4 | STELLAR-303

RESULTS

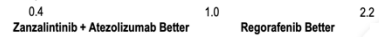
OS Analysis (ITT Population)



*Two-sided alpha = 0.015. CI, confidence interval; HR, hazard ratio; ITT, intention to treat; OS, overall survival.

OS Subgroup Analyses (ITT Population)

Subgroup		Zanzalintinib + Atezolizumab Events, n/Patients, n	Regorafenib Events, n/Patients, n	HR (95% CI)
Overall		312/451	343/450	0.80 (0.69–0.93)
Sex	Male	177/260	213/268	0.73 (0.60–0.90)
	Female	135/191	130/182	0.91 (0.71–1.15)
Age	< 65	201/293	222/300	0.84 (0.69–1.01)
	≥ 65	111/158	121/150	0.73 (0.56–0.94)
Geographic region	Asia	103/158	120/159	0.77 (0.59–1.00)
	Rest of the world	209/293	223/291	0.82 (0.68–0.99)
RAS status	Wild type	117/183	133/182	0.79 (0.61–1.01)
	Mutant	195/268	210/268	0.80 (0.66–0.98)
Liver metastases	Yes	214/264	224/254	0.78 (0.65–0.94)
	No	98/187	119/196	0.77 (0.59–1.01)
ECOG PS	0	135/210	140/200	0.85 (0.67–1.07)
	≥1	175/239	203/250	0.76 (0.62–0.93)
Primary tumor location	Rectum	106/167	121/154	0.63 (0.48–0.82)
	Colon	206/284	222/296	0.92 (0.76–1.11)
Time since diagnosis of mCRC	<18 months	67/85	92/110	0.80 (0.58–1.09)
	≥18 months	245/366	251/340	0.82 (0.69–0.98)
Prior anti-VEGF antibody	Yes	252/363	285/375	0.80 (0.68–0.95)
	No	60/88	58/75	0.80 (0.56–1.15)
Prior anti-EGFR antibody	Yes	121/184	138/190	0.81 (0.64–1.04)
	No	191/267	205/260	0.78 (0.64–0.95)
BRAF status	Wild type	236/338	276/349	0.75 (0.63–0.89)
	Mutant	10/15	12/17	0.96 (0.42–2.18)



ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; ITT, intention to treat; mCRC, metastatic colorectal cancer; OS, overall survival; VEGF vascular endothelial growth factor.

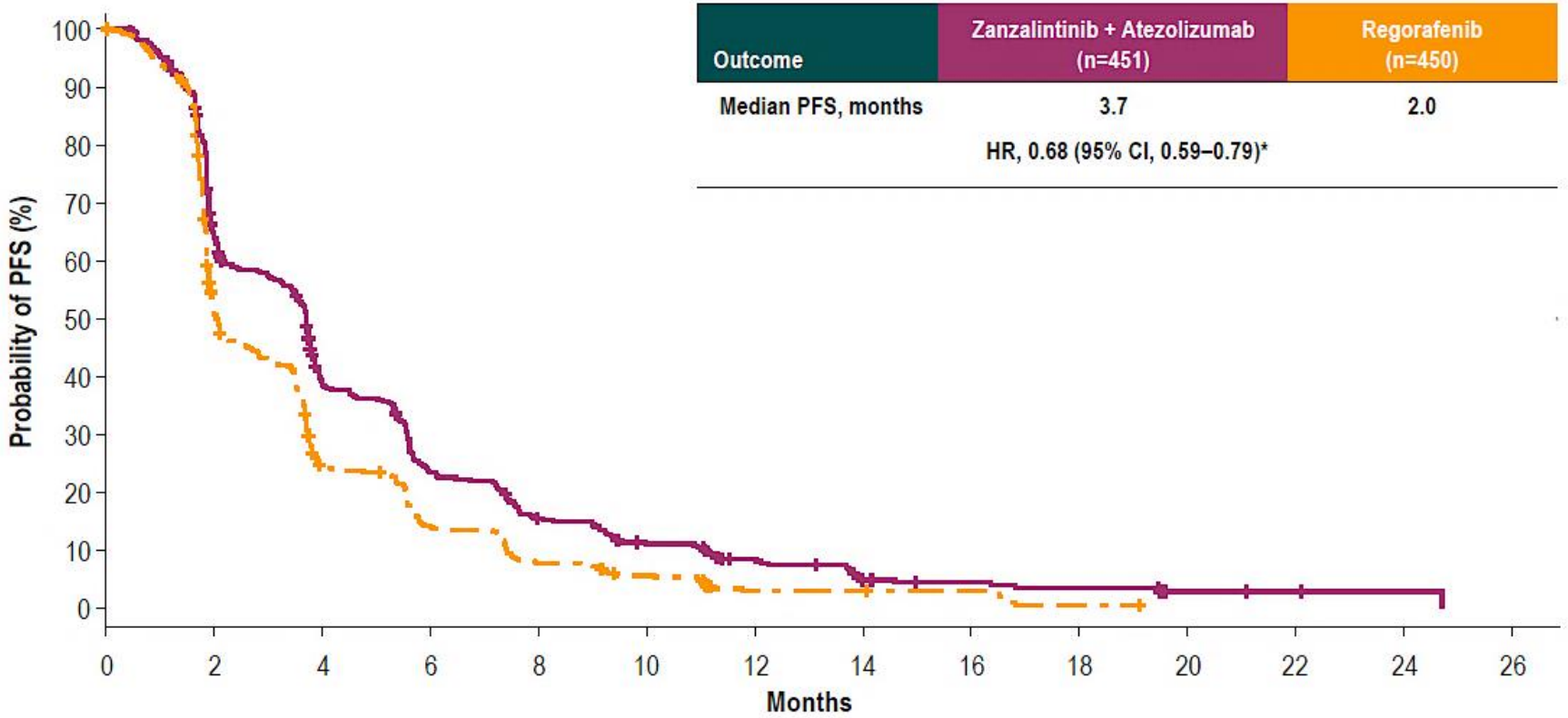
Hecht et al. Lancet 2025; 406: 2360–70.

Trial 4 | STELLAR-303

RESULTS

PFS (ITT Population)

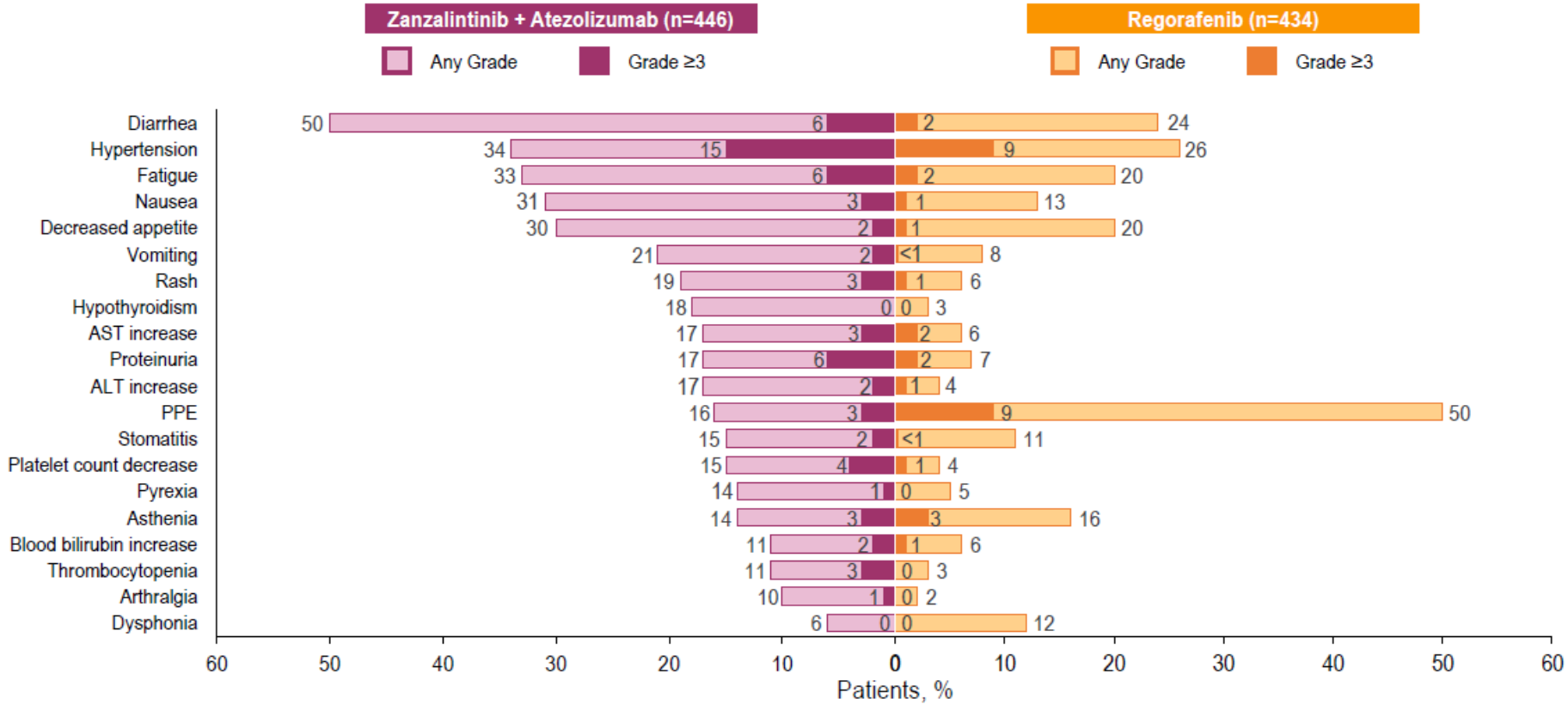
Outcome	Zanzalintinib + Atezolizumab (n=451)	Regorafenib (n=450)
Median PFS, months	3.7	2.0
	HR, 0.68 (95% CI, 0.59–0.79)*	



No. at Risk														
Zanzalintinib + Atezolizumab	451	265	151	89	57	39	25	12	9	7	3	2	1	0
Regorafenib	450	213	97	55	30	20	7	7	6	1	0	0	0	0

Hecht et al. Lancet 2025; 406: 2360–70.

Summary of TRAEs* (Safety Population)



*Occurring in ≥10% of patients in either group; preferred terms of disease progression under study in adverse event database, as per medical review, are excluded. Events are listed by decreasing frequency in the any grade zanzalintinib + atezolizumab group. Adverse events are classified according to the Medical Dictionary for Regulatory Activities, version 28.0. ALT, alanine aminotransferase; AST, aspartate aminotransferase; PPE, palmar-plantar erythrodysesthesia syndrome; TRAE, treatment-related adverse event.

Hecht et al. Lancet 2025; 406: 2360–70.

Trial 4 | STELLAR-303

IMPLICATIONS

1. First IO-based OS benefit in non-MSI-H/dMMR mCRC
2. TKI+ICI approach: TAM/MET/VEGFR + anti-PD-L1
3. Chemo free option for heavily pretreated patients
4. Consistent benefit across subgroups incl. liver mets
5. Head-to-head vs TFD+bev needed (unmet need)

Hecht et al. Lancet 2025; 406: 2360–70.

Year in Review:
Colorectal Cancer

INTRODUCTION: RTP Paper of the Year!

MODULE 1: Checkpoint Inhibitors for Localized MSI-High Tumors

MODULE 2: Circulating Tumor DNA Assays

MODULE 3: Checkpoint Inhibitors for Metastatic Disease

MODULE 4: Other Important Papers

RTP Year in Review 2026

Trial 5 | BREAKWATER mFOLFOX6

BREAKWATER: Study Design

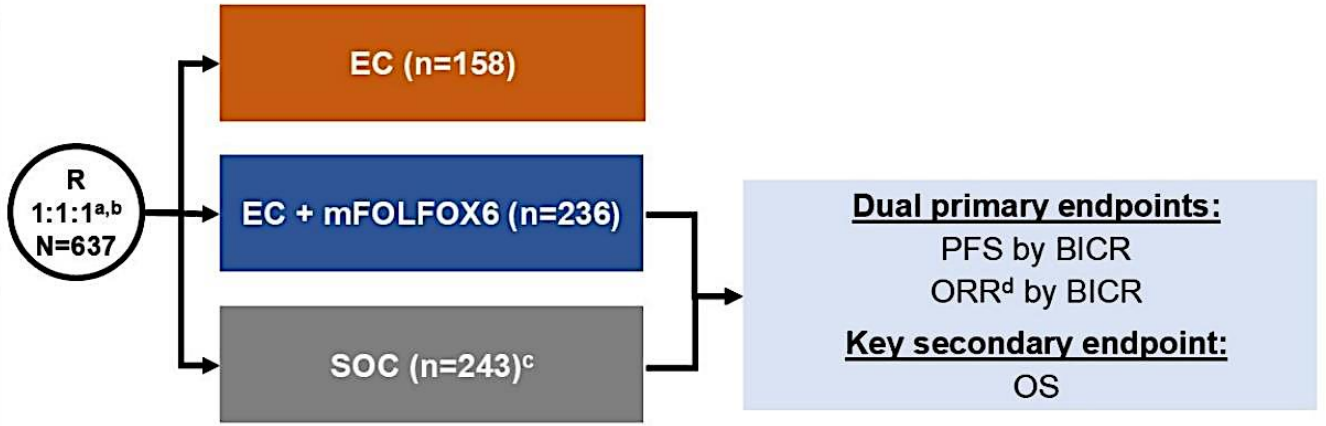
BREAKWATER (NCT04607421) is an open-label, multicenter, phase 3 study in first-line BRAF V600E-mutant mCRC

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



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

We present the primary analysis of PFS by BICR and a second interim analysis of OS in the EC + mFOLFOX6 and SOC arms, the efficacy data in the EC arm, and safety data in all arms

[a]**Following a protocol amendment, enrollment to the EC arm was stopped and patients were randomized 1:1 to the EC + mFOLFOX6 or SOC arms.** [b]**Patients were enrolled between November 16, 2021, and December 22, 2023.** [c]**mFOLFOX6/FOLFOXIRI/CAPOX ± bevacizumab.** [d]**In the first 110 patients in each of the EC + mFOLFOX6 and SOC arms.**

BICR, blinded independent central review; CAPOX, capecitabine/oxaliplatin; dMMR, deficient mismatch repair; EC, encorafenib plus cetuximab; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; FOLFOXIRI, fluorouracil/leucovorin/oxaliplatin/irinotecan; mFOLFOX6, modified fluorouracil/leucovorin/oxaliplatin; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high; RECIST, Response Evaluation Criteria in Solid Tumors.

Elez et al. NEJM 2025;392:2425-2437.

Trial 5 | BREAKWATER mFOLFOX6

IMPLICATIONS

1. Paradigm shift: 1L targeted Tx for BRAF V600E
2. mOS 30.3 mo ≈ BRAF-WT — transformative
3. EC+mFOLFOX6 = new global SOC
4. EC alone (19.5 mo): chemo-ineligible option

Elez et al. NEJM 2025;392:2425-2437.

Trial 6 | BREAKWATER FOLFIRI

BREAKWATER Cohort 3: Study Design

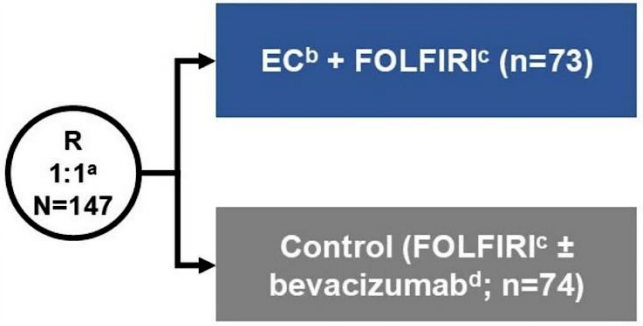
- BREAKWATER (NCT04607421) is an open-label, multicenter, phase 3 study in first line BRAF V600E-mutant mCRC

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 preexisting medical condition)
- Presence of a *RAS* mutation



Stratified by ECOG PS

Primary endpoint:
ORR by BICR[e]

Key secondary endpoint:
PFS by BICR

Other secondary endpoints:
OS, DOR, TTR, safety

Here we present the primary analysis of ORR by BICR (the primary endpoint), an analysis of OS, and safety in the EC + FOLFIRI and control arms

[a]Patients were enrolled between December 28, 2023, and July 1, 2024; enrollment to Cohort 3 started after enrollment to Phase 3 was complete. The planned sample size was approximately 136 patients (68 in each arm). [b]Encorafenib 300 mg orally QD; cetuximab 500 mg/m² IV Q2W. [c]Irinotecan 180 mg/m² IV Q2W; leucovorin 400 mg/m² IV Q2W; and 5-FU 400 mg/m² IV bolus, then 5-FU 2400 mg/m² continuous IV infusion over 46-48 hours Q2W. [d]Per prescribing information. [e]Using a one-sided chi-square test at a significance level of 0.025.

BICR, blinded independent central review; dMMR, deficient mismatch repair; DOR, duration of response; EC, encorafenib plus cetuximab; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; FOLFIRI, fluorouracil/leucovorin/irinotecan; IV, intravenously; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability–high; Q2W, once every 2 weeks; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; TTR, time to response.

Kopetz Proc ASCO GI 2026;Abstract 13

Trial 6 | BREAKWATER FOLFIRI

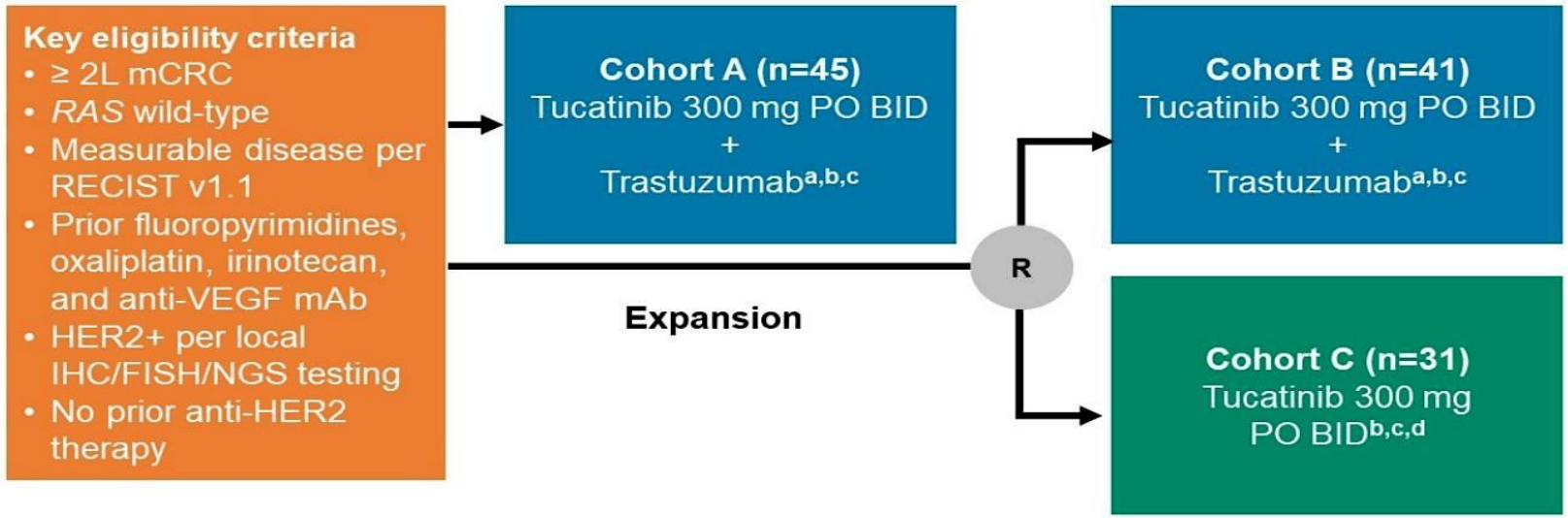
IMPLICATIONS

1. Irinotecan-based alt to EC+mFOLFOX6
2. For oxaliplatin contraindication/intolerance
3. Comparable ORR to FOLFOX arm
4. Awaiting randomized PFS/OS
5. Expands BRAF-targeted options

Kopetz Proc ASCO GI 2026;Abstract 13

Trial 7 | MOUNTAINEER

MOUNTAINEER: Multi-Center, Open-Label, Phase 2 Trial (NCT03043313)



Study Endpoints

Efficacy in Cohorts A+B

- *Primary:* cORR, RECIST v1.1 per BICR
- *Secondary:* DOR and PFS per BICR, and OS

Safety:

- TEAEs

Biomarker Analyses:

- Clinical outcomes by HER2 testing methods

For the final analysis (cutoff date of November 2, 2023), the efficacy and safety endpoints evaluated remained the same. Biomarker analyses, including a long-term responder analysis, were exploratory

[a] 6 mg/kg Q3W (loading dose 8 mg/kg); [b] each treatment cycle is 21 days; [c] Patients remained on therapy until evidence of radiographic or clinical progression or death, unacceptable toxicity, withdrawal of consent, or study closure; [d] Patients were allowed to cross over and receive tucatinib and trastuzumab if they experienced radiographic progression at any time point or if they had not achieved a partial or complete response by week 12.
≥ 2L, second line and later; BICR, blinded independent central review; BID, twice a day; cORR, confirmed objective response rate; DOR, duration of response; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; mAb, monoclonal antibody; mCRC, metastatic colorectal cancer; NGS, next-generation sequencing; OS, overall survival; PFS, progression-free survival; PO, orally; Q3W, every 3 weeks; R, randomization; *RAS*: rat sarcoma virus; RECIST, Response Evaluation Criteria in Solid Tumors; TEAE; treatment-emergent adverse event; VEGF, vascular endothelial growth factor.

Strickler JH et al Nat Commun 2026

Trial 7 | MOUNTAINEER

IMPLICATIONS

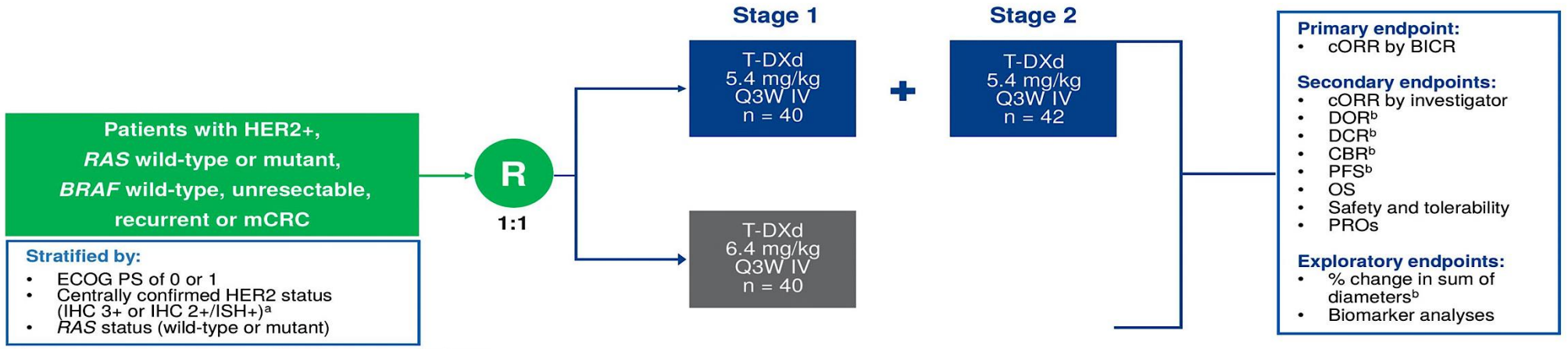
1. First FDA HER2-targeted therapy for mCRC
2. Validates dual HER2 blockade (mAb+TKI)
3. mOS 23.9 mo — exceptional in pretreated
4. MOUNTAINEER-03 ongoing (phase 3)
5. Universal HER2 testing warranted

Strickler et al. Lancet 2023;401:609-619.

Trial 8 | DESTINY-CRC02

DESTINY-CRC02: A Multicenter, Randomized, 2-Stage, 2-Arm, Phase 2 Trial (NCT04744831)

Based in part on the results of DESTINY-CRC02, T-DXd has been approved in several countries for the treatment of patients with previously treated unresectable or metastatic HER2 IHC 3+ solid tumors, including CRC



This study was not powered to statistically compare the 2 arms.
The site staff were blinded to treatment assignment through the roles and permissions document in the interactive response technology system.
Treatment assignments were also unknown to patients, central imaging readers, and the interstitial lung disease adjudication committee.

Objective: To evaluate the efficacy and safety of T-DXd 5.4 mg/kg and 6.4 mg/kg at the final analysis of DESTINY-CRC02 (DCO, December 4, 2024)

Kanwal Raghav, MD, MBSS

[a]HER2 status was assessed using the PATHWAY anti-HER2/neu (4B5) Rabbit Monoclonal Primary Antibody (Roche Diagnostics), available in some regions as the VENTANA HER2 (4B5) Rabbit Monoclonal Primary Antibody RxDx (Roche Diagnostics). [b]By BICR and investigator.
BICR, blinded independent central review; CBR, clinical benefit rate; CRC, colorectal cancer; cORR, confirmed objective response rate; DCO, data cutoff; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; IV, intravenously; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression-free survival; PROs, patient-reported outcomes; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan.

DESTINY-CRC02

BERLIN 2025 ESMO congress

Raghav et al. ESMO 2025;Abstract 737MO

Trial 8 | DESTINY-CRC02

IMPLICATIONS

1. Confirms ADC viable in HER2+ mCRC
2. 5.4 mg/kg: best benefit-risk — selected
3. Active in RAS-mutant HER2+ (vs MOUNTAINEER)
4. Complementary MOA to tras+tucatinib
5. Supports biomarker-driven sequencing

Raghav et al. ESMO 2025;Abstract 737MO

Trial 9 | CodeBreaK 300 OS

CodeBreaK 300 Phase 3 Study Design

Global, randomized, open-label, active-controlled study of sotorasib + panitumumab in mCRC (NCT05198934)

Key eligibility criteria

- ≥ 18 years of age
- *KRAS* G12C–mutated mCRC, identified through central molecular testing
- ≥ 1 prior line of therapy for mCRC; progressed on or after fluoropyrimidine, irinotecan, and oxaliplatin*
- ECOG ≤ 2
- Measurable disease per RECIST 1.1
- No prior $KRAS^{G12C}$ inhibitor†

Stratified by: prior anti-angiogenic therapy (yes / no), **time from diagnosis of mCRC** (≥ 18 mo / < 18 mo), **ECOG status** (0 or 1 / 2)

Randomization 1:1:1 (N = 160)

- **Sotorasib 960 mg daily + panitumumab 6 mg/kg 2QW (n = 53)**
- **Sotorasib 240 mg daily + panitumumab 6 mg/kg 2QW (n = 53)**
- **Investigator's choice: Trifluridine/tipiracil or regorafenib (n = 54)**

Primary endpoint: PFS by BICR (measured by CT / MRI and assessed by RECIST v1.1)

Key secondary endpoints: OS, ORR

OS analysis was performed at 50% maturity and was not powered for statistical significance

*Patients deemed by the investigator not to be candidates for fluoropyrimidine, irinotecan, or oxaliplatin may still be eligible if ≥ 1 prior line of therapy was received for metastatic disease and trifluridine and tipiracil and/or regorafenib were deemed appropriate next line of therapy. †Patients with prior treatment with trifluridine and tipiracil and with regorafenib were excluded, where the investigator's choice would be these agents.

2QW, every 2 weeks; BICR, blinded independent central review; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; KRAS, Kirsten rat sarcoma; mCRC, metastatic colorectal cancer; MRI, magnetic resonance imaging; OS, overall survival; ORR, objective response rate; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

Pietrantonio et al. JCO 2025;43:2147-2154.

Trial 9 | CodeBreaK 300 OS

IMPLICATIONS

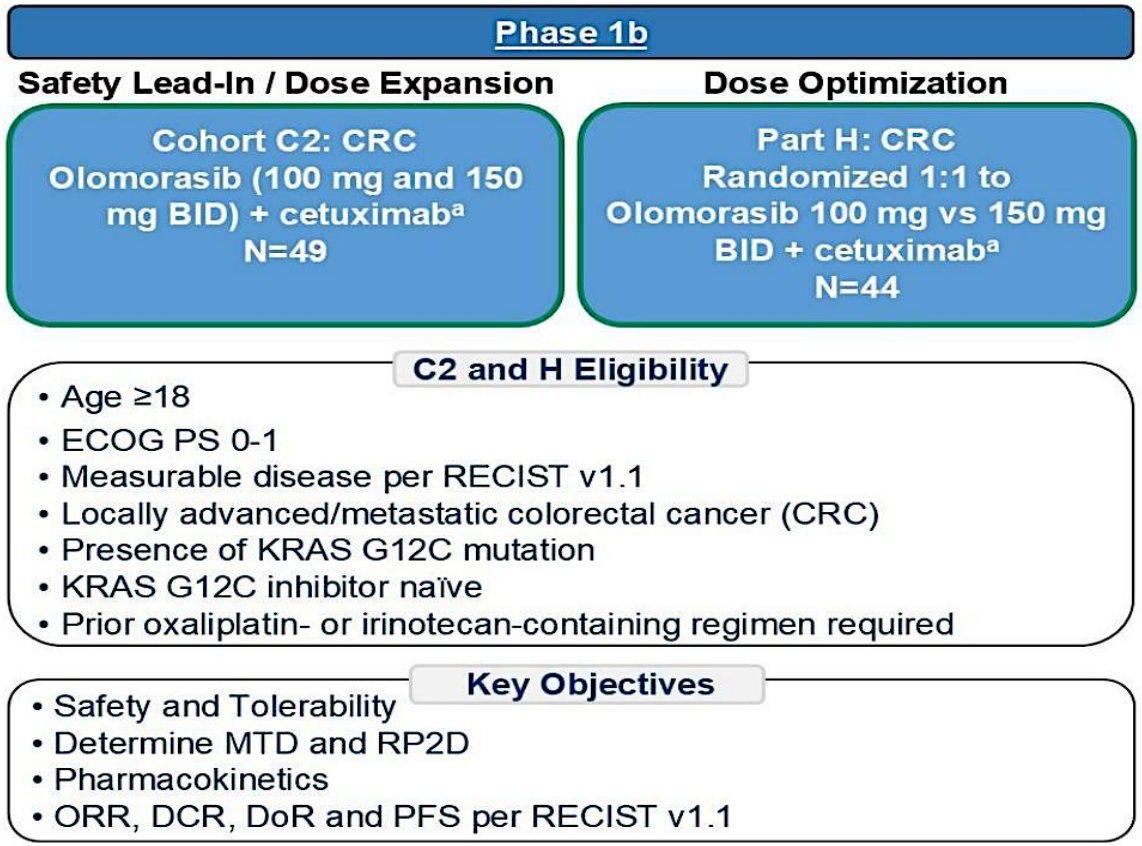
1. First phase 3 G12Ci with PFS benefit in mCRC
2. OS trend supports soto960+pani as SOC
3. Confounded by 28% crossover
4. 30.2% ORR clinically meaningful
5. FDA approved — validates approach

Pietrantonio et al. JCO 2025;43:2147-2154.

Trial 10 | Olomorasib

LOXO-RAS-20001 Study Cohort C2 and Part H Eligibility, Design, Objectives

- Primary objective was to identify the optimal dose of olomorasib (100 or 150 mg BID) to be administered with cetuximab based on pharmacokinetics (PK), safety and efficacy data
- As previously disclosed, PK results of olomorasib (100 and 150 mg BID) in combination with cetuximab were consistent with exposures observed with monotherapy olomorasib (100 and 150 mg BID)[1]



[1]Murciano-Goroff YR. et al. Presented at AACR Annual Meeting, Apr 14-19, 2023. [a]Cetuximab dose - 400 mg/m^2 on C1D1, then 250 mg/m^2 QW. Abbreviations: CRC, Colorectal cancer; MTD, maximum tolerated dose; RP2D, recommended phase 2 dose. NCT04956640

Hollebecque Proc ASCO 2025;Abstract 3507

Trial 10 | Olomorasib

IMPLICATIONS

1. Next-gen G12Ci with superior efficacy potential
2. 47% ORR > CodeBreaK 300 benchmark
3. Room for improvement in G12C therapy
4. Phase 3 randomized data needed
5. Expanding KRAS toolkit

Hollebecque Proc ASCO 2025;Abstract 3507

Trial 11 | MK-1084

KANDLELIT-001 Study Design

Ongoing Open-Label, Phase 1 Dose-Finding Trial

Key Eligibility Criteria: All Arms

- Age ≥18 years
- Histologic or blood-based confirmation of *KRAS* G12C mutation
- ECOG PS 0 or 1
- Measurable disease per RECIST v1.1

Primary endpoints: incidence of DLTs, AEs, and AEs that led to discontinuation

Secondary endpoints

- ORR and DOR per RECIST v1.1 by investigator review
- PK of MK-1084

Tertiary endpoints

- PFS per RECIST v1.1 by investigator review
- OS

Arms 1 and 3: MK-1084 Monotherapy 25-800 mg/d PO[a]

- Locally advanced unresectable or metastatic solid tumor
- ≥1 prior systemic therapy for advanced disease

Arm 2: MK-1084 25-400 mg/d PO[a] + Pembrolizumab[b]

- Metastatic NSCLC with PD-L1 TPS ≥1%
- No indication for EGFR-, ALK-, or ROS1-directed therapy as primary treatment
- No prior therapy for metastatic disease

Arm 4: MK-1084 25-200 mg/d PO[a] + Pembrolizumab[b] + Chemotherapy[c]

- Metastatic NSCLC of any TPS[d]
- No indication for EGFR-, ALK-, or ROS1-directed therapy as primary treatment
- No prior therapy for metastatic disease

Arm 5: MK-1084 25-200 mg/d PO[a] + Cetuximab[e]

- Locally advanced unresectable or metastatic CRC
- 1 or 2 prior line(s) of systemic therapy for advanced disease

Arm 6: MK-1084 25-100 mg/d PO[a] + Cetuximab[e] + mFOLFOX6[f]

- Locally advanced unresectable or metastatic CRC
- 0 or 1 prior line(s) of systemic therapy for advanced disease

[a]Administered QD or BID for the total daily dose indicated. [b]200 mg IV Q3W for ≤35 cycles. [c]Carboplatin AUC 5 mg/mL/min IV Q3W for 4 cycles and pemetrexed 500 mg/m^2 IV Q3W. [d]PD-L1 testing not required for enrollment, but archival or fresh tumor samples must be submitted for each participant. [e]500 mg/m^2 IV Q2W. [f]Oxaliplatin 85 mg/m^2 IV Q2W for ≥3 cycles, leucovorin 400 mg/m^2 IV Q2W for ≥3 cycles, and 5-fluorouracil 400 mg/m^2 IV on days 1 and 15 then 1200 mg/m^2/d x 2 days IV Q2W for ≥3 cycles. ClinicalTrials.gov identifier: NCT05067283.

KANDLELIT ONCOLOGY CLINICAL TRIALS

Lugowska Proc ASCO 2025;Abstract 3508 Slides

Trial 11 | MK-1084

IMPLICATIONS

1. First G12C degrader — paradigm shift
2. 50% ORR+cetux: highest in G12C mCRC
3. May overcome adaptive resistance
4. Early data — needs confirmation
5. Could redefine G12C treatment

Lugowska Proc ASCO 2025;Abstract 3508 Slides

Trial 12 | OrigAMI-1

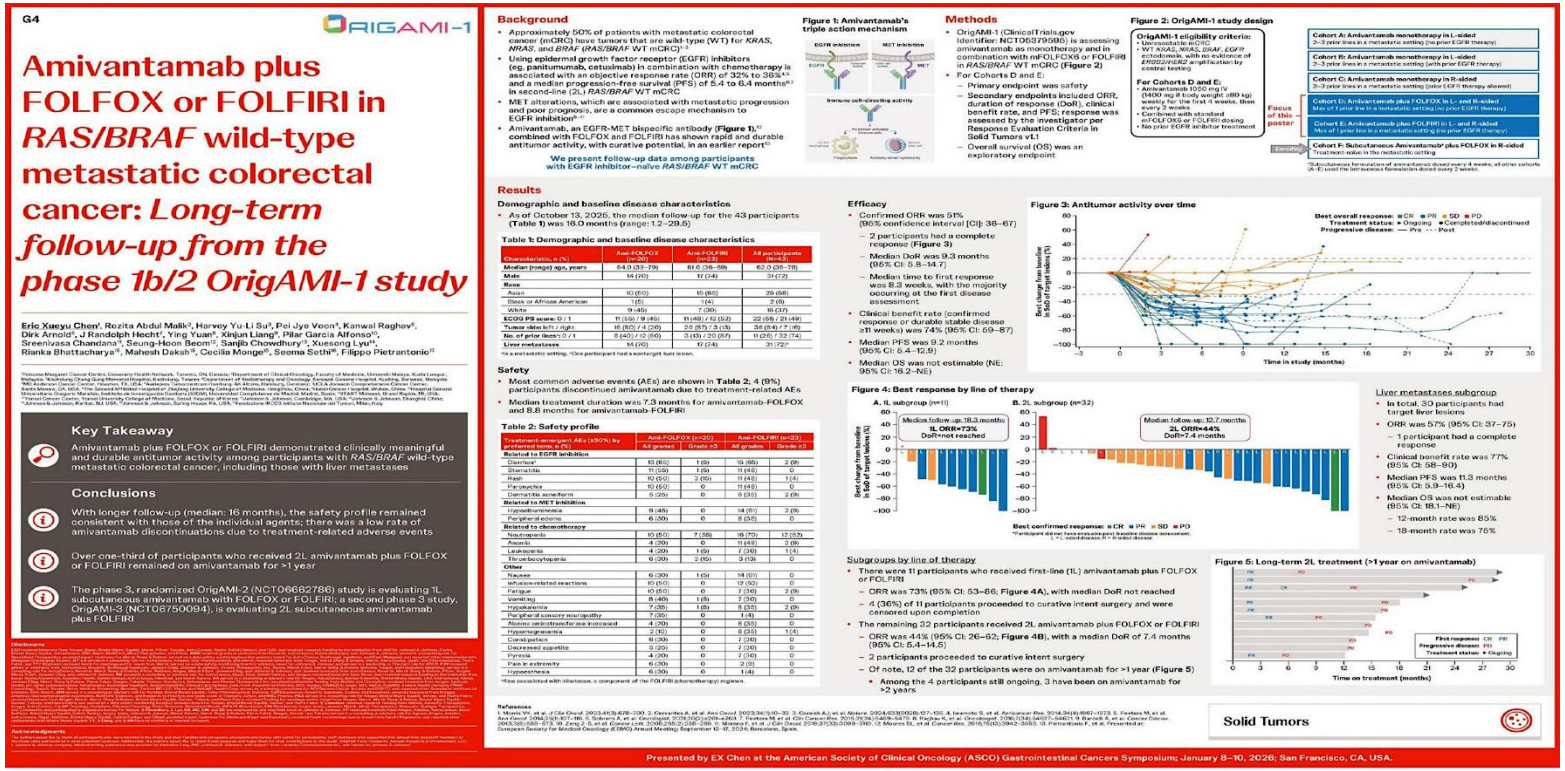
STUDY SCHEMA & BIOMARKERS

Study Design

- Phase 1b/2, open-label (NCT05379595)
- RAS/BRAF WT mCRC, anti-EGFR naïve
- Amivantamab: EGFR-MET bispecific
- Multiple cohorts: mono + chemo combos

Endpoints & Treatment

- Primary: Safety/RP2D (combo); ORR (mono)
- Ami 1050mg + FOLFOX or FOLFIRI
- 1L or 2L (anti-EGFR naïve)
- Phase 3 OrigAMI-2/3 enrolling



Chen EX et al. ASCO GI 2026; Abstract 166

Trial 12 | OrigAMI-1

IMPLICATIONS

1. EGFR-MET bispecific: novel beyond anti-EGFR mAbs
2. 49% ORR competitive with cetux/pani
3. Intrahepatic ORR 53% — unmet need
4. Phase 3 OrigAMI-2/3 pivotal
5. Could shift 1L RAS WT paradigm

Chen EX et al. ASCO GI 2026; Abstract 166

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RTP Year in Review 2026