Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Colorectal Cancer

Friday, May 30, 2025
6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)

Faculty

Andrea Cercek, MD
Arvind Dasari, MD, MS
Pashtoon Kasi, MD, MS
Eric Van Cutsem, MD, PhD

Moderator

J Randolph Hecht, MD

RTP
RESEARCH
TO PRACTICE

Faculty

Andrea Cercek, MD
Section Head, Colorectal Cancer
Co-Director, Center for Young Onset Colorectal and Gastrointestinal Cancers
Attending, Gastrointestinal Oncology Service
Department of Medicine
Memorial Sloan Kettering Cancer Center
New York, New York

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

Pashtoon Kasi, MD, MS
Medical Director of GI Oncology
Endowed Rad Family Chair in Gastrointestinal Oncology
Associate Professor
Department of Medical Oncology and Therapeutics Research
City of Hope Orange County
Irvine, California

Eric Van Cutsem, MD, PhD
Professor of Medicine
Digestive Oncology
University Hospitals Leuven
Leuven, Belgium

Moderator
J Randolph Hecht, MD
Professor of Clinical Medicine
Director, UCLA GI Oncology Program
Carol and Saul Rosenzweig Chair in Cancer Therapies Development
UCLA David Geffen School of Medicine
Santa Monica, California

RTP
RESEARCH TO PRACTICE

Dr Cercek — Disclosures
Faculty

Advisory Boards	3T Biosciences, AbbVie Inc, Agents, Amgen Inc, Daiichi Sankyo Inc, GSK, Janssen Biotech Inc, Merck, Pfizer Inc, Regeneron Pharmaceuticals Inc, Roche Laboratories Inc, Summit Therapeutics, UroGen Pharma
Contracted Research	GSK, Pfizer Inc

Dr Dasari — Disclosures
Faculty

Advisory Committees	Agenus Inc, Bristol Myers Squibb, Exelixis Inc, Illumina, Lantheus, Personalis, Sanofi, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc
Contracted Research	Bristol Myers Squibb, Crinetics Pharmaceuticals, Eisai Inc, Enterome, Guardant Health, Hutchison MediPharma, Natera Inc, NeoGenomics, Personalis, RayzeBio Inc, Taiho Oncology Inc, Xencor

RTP
RESEARCH
TO PRACTICE

Dr Kasi — Disclosures
Faculty

Advisory Committees	Elicio Therapeutics
Consulting Agreements	Agenus Inc, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, Bexion Pharmaceuticals, BostonGene, Daiichi Sankyo Inc, Delcath Systems Inc, Eisai Inc, Exact Sciences Corporation, Foundation Medicine, Guardant Health, Illumina, Lilly, Merck, MSD, Natera Inc, NeoGenomics, QED Therapeutics, Regeneron Pharmaceuticals Inc, SAGA Diagnostics, Seagen Inc, Servier Pharmaceuticals LLC, Taiho Oncology Inc, Tempus, Xilio Therapeutics
Contracted Research	Agenus Inc, Merck, Novartis
Stock Options/Stock — Public Companies	Elicio Therapeutics

Prof Van Cutsem — Disclosures
Faculty

Advisory Committees	AbbVie Inc, Agenus Inc, ALX Oncology, Amgen Inc, Arcus Biosciences, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, BioNTech SE, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Cantargia AB (CANFOUR trial), Daiichi Sankyo Inc, Debiopharm, Eisai Inc, ElmediX, Galapagos NV, GSK, Hookipa Pharma Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Lilly, Merck KGaA, Mirati Therapeutics Inc, MSD, Nordic Pharma, Novartis, Pfizer Inc, Pierre Fabre, Roche Laboratories Inc, Seagen Inc, Servier Pharmaceuticals LLC, Simcere, Taiho Oncology Inc, Takeda Pharmaceutical Company Limited, Terumo Medical Corporation
Nonrelevant Financial Relationships	Bexon Clinical Consulting

Dr Hecht — Disclosures
Moderator

Advisory Committees	Actym Therapeutics, MBQ Pharma, Radical AI, Triumvira Immunologics
Consulting Agreements	BeiGene Ltd, Hexagon Bio, Parabilis Medicines, Revolution Medicines, UroGen Pharma, Xilio Therapeutics
Contracted Research	A2 Bio, Affini-T Therapeutics, Agenus Inc, AstraZeneca Pharmaceuticals LP, Bold Therapeutics, Camurus, CG Invites, Crinetics Pharmaceuticals, Exelixis Inc, Gilead Sciences Inc, Gritstone bio, GSK, IGM Biosciences Inc, Janssen Biotech Inc, Mirati Therapeutics Inc, Pfizer Inc, Regeneron Pharmaceuticals Inc, Revolution Medicines, Tizona Therapeutics Inc, Xilio Therapeutics
Stock Options — Private Companies	Actym Therapeutics, Radical AI, Triumvira Immunologics

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, Alexion Pharmaceuticals, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Arvinas, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, Black Diamond Therapeutics Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Clovis Oncology, Coherus BioSciences, 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, Hologic 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, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Rigel Pharmaceuticals Inc, R-Pharm US, Sanofi, Seagen Inc, Servier Pharmaceuticals LLC, SpringWorks Therapeutics Inc, Stemline Therapeutics Inc, Syndax Pharmaceuticals, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, TerSera Therapeutics LLC, and Tesaro, A GSK Company.

RTP
RESEARCH
TO PRACTICE

Commercial Support

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

Research To Practice CME Planning Committee Members, Staff and Reviewers

Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

This educational activity contains discussion of non-FDA-approved uses of agents and regimens. Please refer to official prescribing information for each product for approved indications.

RTP
RESEARCH
TO PRACTICE

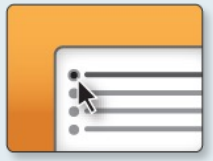
Friday May 30	**Immunotherapy and Antibody–Drug Conjugates in Lung Cancer** 11:15 AM – 12:45 PM CT (12:15 PM – 1:45 PM ET)
	Colorectal Cancer 6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)
	EGFR Mutation–Positive Non–Small Cell Lung Cancer 6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)
Saturday May 31	**Urothelial Bladder Cancer** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Non–Hodgkin Lymphoma 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
	Prostate Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Sunday June 1	**Chronic Lymphocytic Leukemia (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)
	HER2–Positive Gastrointestinal Cancers 7:00 PM – 8:30 PM CT (8:00 PM – 9:30 PM ET)
	Ovarian and Endometrial Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Monday June 2	**Renal Cell Carcinoma (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)
	Multiple Myeloma (Webinar) 6:00 PM – 7:00 PM CT (7:00 PM – 8:00 PM ET)
	Metastatic Breast Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Tuesday June 3	**Soft Tissue Sarcoma and Other Connective Tissue Neoplasms (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)

RTP
RESEARCH TO PRACTICE

Clinicians in the Meeting Room

Networked iPads are available.

Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.



Answer Survey Questions: Complete the pre- and postmeeting surveys.

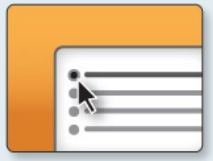
Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.

RTP RESEARCH TO PRACTICE

Clinicians Attending via Zoom

Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.



Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

Get CME Credit: A CME credit link will be provided in the chat room at the conclusion of the program.

RTP
RESEARCH
TO PRACTICE

About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based program. An email will be sent to all attendees when the activity is available.
- To learn more about our education programs, visit our website, **www.ResearchToPractice.com**

RTP RESEARCH TO PRACTICE

Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Colorectal Cancer

Friday, May 30, 2025
6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)

Faculty

Andrea Cercek, MD
Arvind Dasari, MD, MS
Pashtoon Kasi, MD, MS
Eric Van Cutsem, MD, PhD

Moderator

J Randolph Hecht, MD

RTP
RESEARCH
TO PRACTICE

Contributing General Medical Oncologists

Warren S Brenner, MD
Lynn Cancer Institute
Boca Raton, Florida

Gigi Chen, MD
John Muir Health Cancer
Medical Group
Walnut Creek, California

Stephen "Fred" Divers, MD
American Oncology Network
Hot Springs, Arkansas

Victoria Giffi, MD
Meritus Medical Center
Hagerstown, Maryland

Henna Malik, MD
Texas Oncology
Houston, Texas

Shachar Peles, MD
Florida Cancer Specialists
& Research Institute
Lake Worth, Florida

Priya Rudolph, MD, PhD
Georgia Cancer Specialists
Athens, Georgia

Erik Rupard, MD
Penn State Cancer Institute
Hershey, Pennsylvania

Syed F Zafar, MD
Florida Cancer Specialists
& Research Institute
Fort Myers, Florida

Neil Love, MD
Research To Practice
Miami, Florida

RTP
RESEARCH
TO PRACTICE

Agenda

MODULE 1: Role of Circulating Tumor DNA (ctDNA) Evaluation in Nonmetastatic Colorectal Cancer (CRC) — Dr Dasari

MODULE 2: Role of Immune Checkpoint Inhibitors in the Management of Nonmetastatic Microsatellite Instability-High (MSI-H) CRC — Dr Cercek

MODULE 3: Management of Oligometastatic Disease and Hepatic-Only Metastases in CRC; Role of ctDNA Evaluation in Metastatic Disease — Dr Kasi

MODULE 4: Role of Immune Checkpoint Inhibitors in the Management of MSI-H Metastatic CRC (mCRC) — Dr Hecht

MODULE 5: Identification and Care of Patients with mCRC and Actionable Genomic Alterations — Prof Van Cutsem

RTP RESEARCH TO PRACTICE

Agenda

MODULE 1: Role of Circulating Tumor DNA (ctDNA) Evaluation in Nonmetastatic Colorectal Cancer (CRC) — Dr Dasari

MODULE 2: Role of Immune Checkpoint Inhibitors in the Management of Nonmetastatic Microsatellite Instability-High (MSI-H) CRC — Dr Cercek

MODULE 3: Management of Oligometastatic Disease and Hepatic-Only Metastases in CRC; Role of ctDNA Evaluation in Metastatic Disease — Dr Kasi

MODULE 4: Role of Immune Checkpoint Inhibitors in the Management of MSI-H Metastatic CRC (mCRC) — Dr Hecht

MODULE 5: Identification and Care of Patients with mCRC and Actionable Genomic Alterations — Prof Van Cutsem

RTP RESEARCH TO PRACTICE

Role of ctDNA Evaluation in Nonmetastatic Colon Cancer

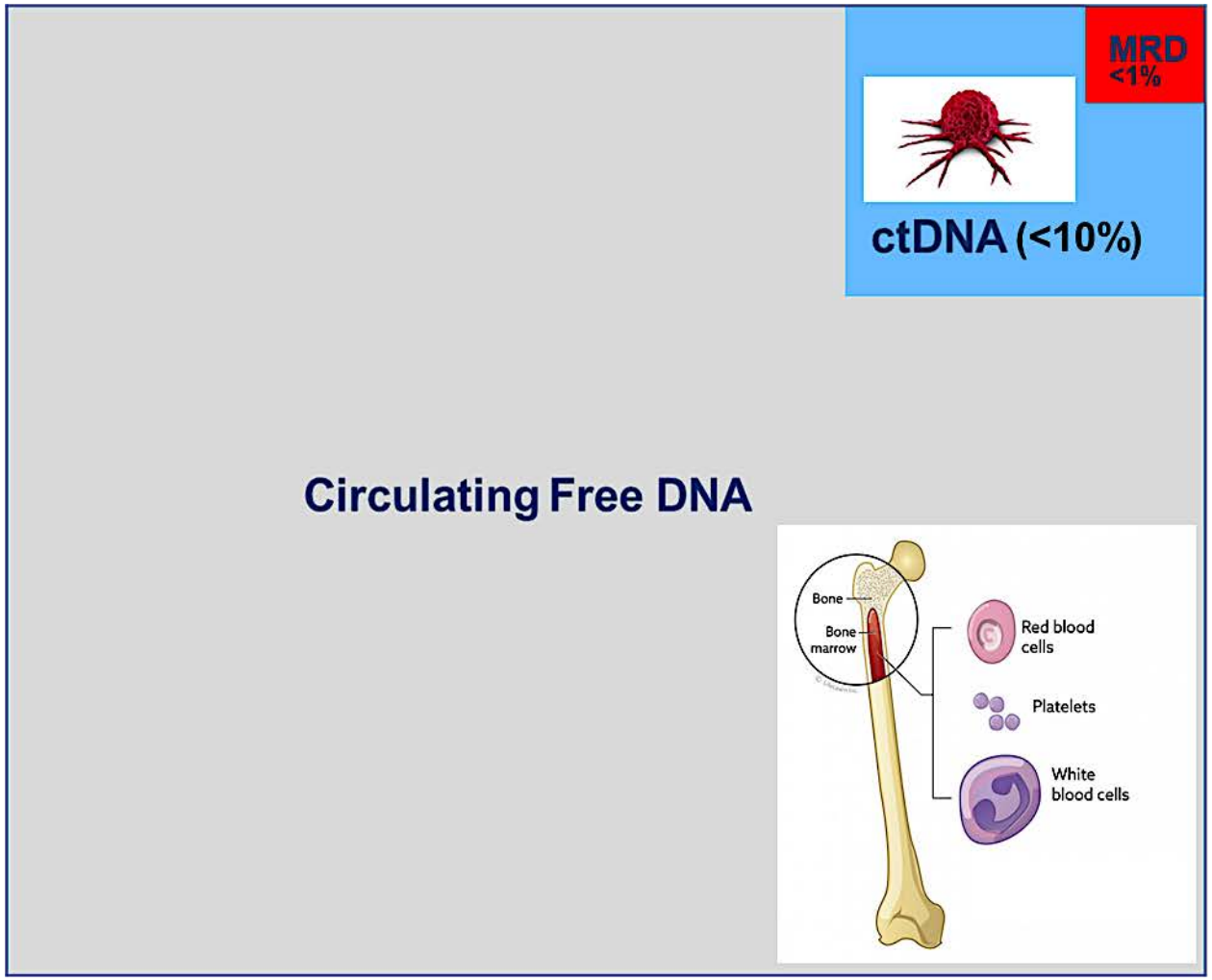
Arvind N. Dasari, MD, MS

Professor

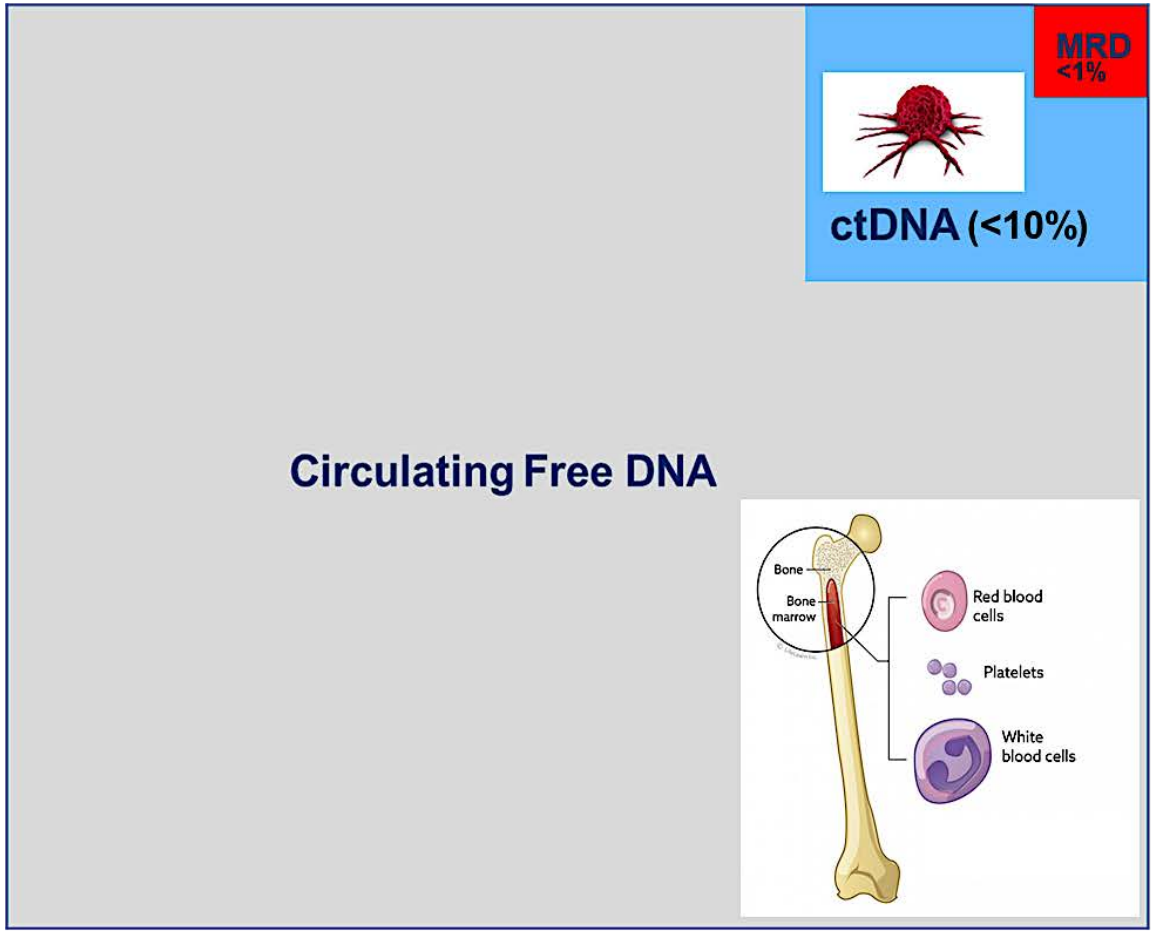
Department of GI Medical Oncology

University of Texas MD Anderson Cancer Center, Houston, TX

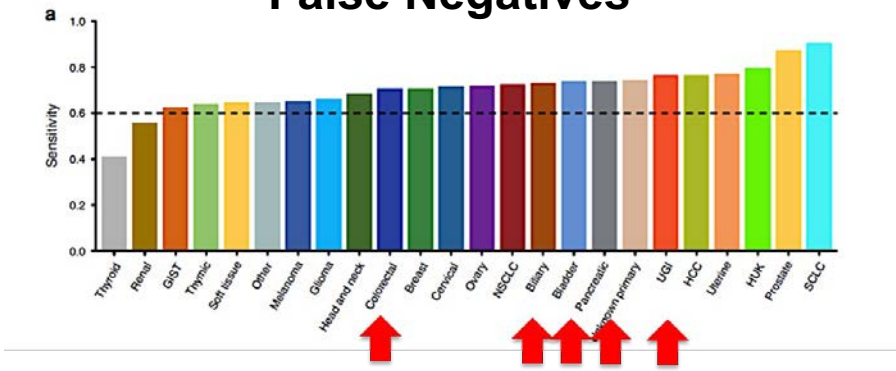
Circulating Tumor (ctDNA) vs Free (cfDNA) DNA



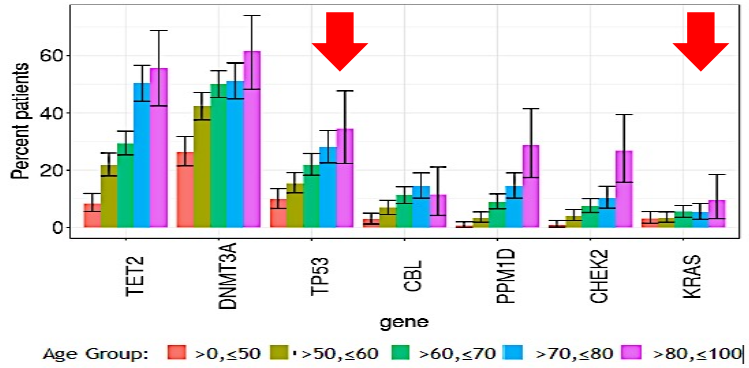
ctDNA vs cfDNA DNA – Implications for MRD



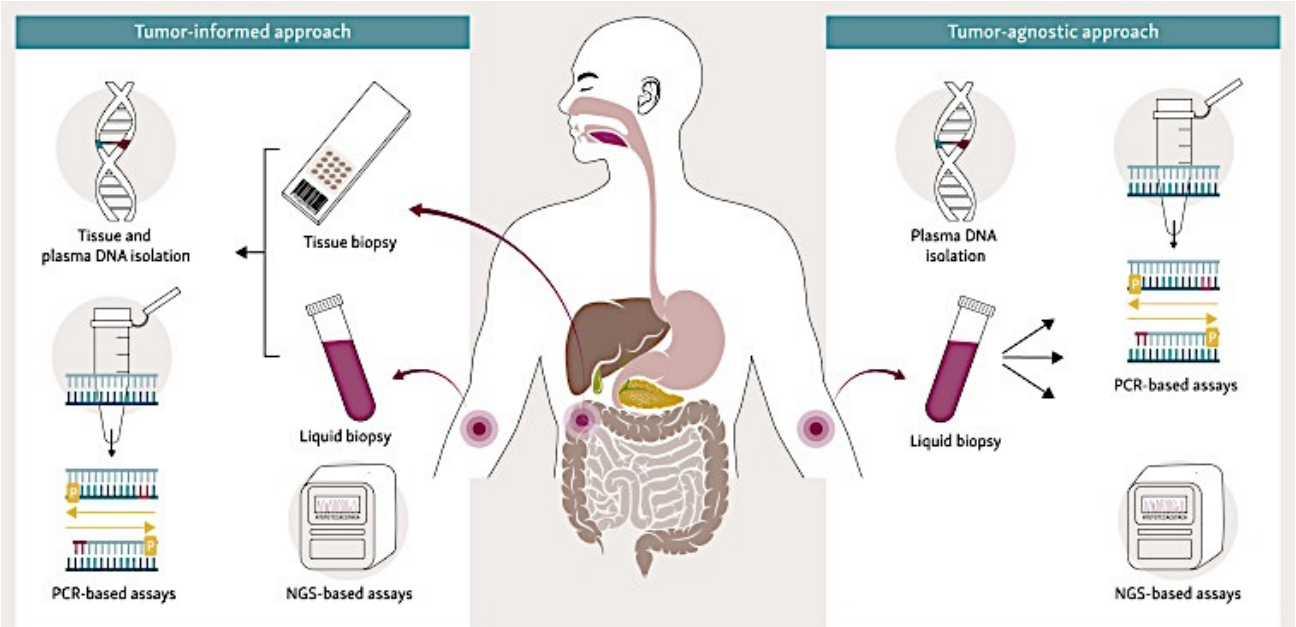
False Negatives



False Positives (CHIP)



MRD Assays: Tumor Informed vs Agnostic

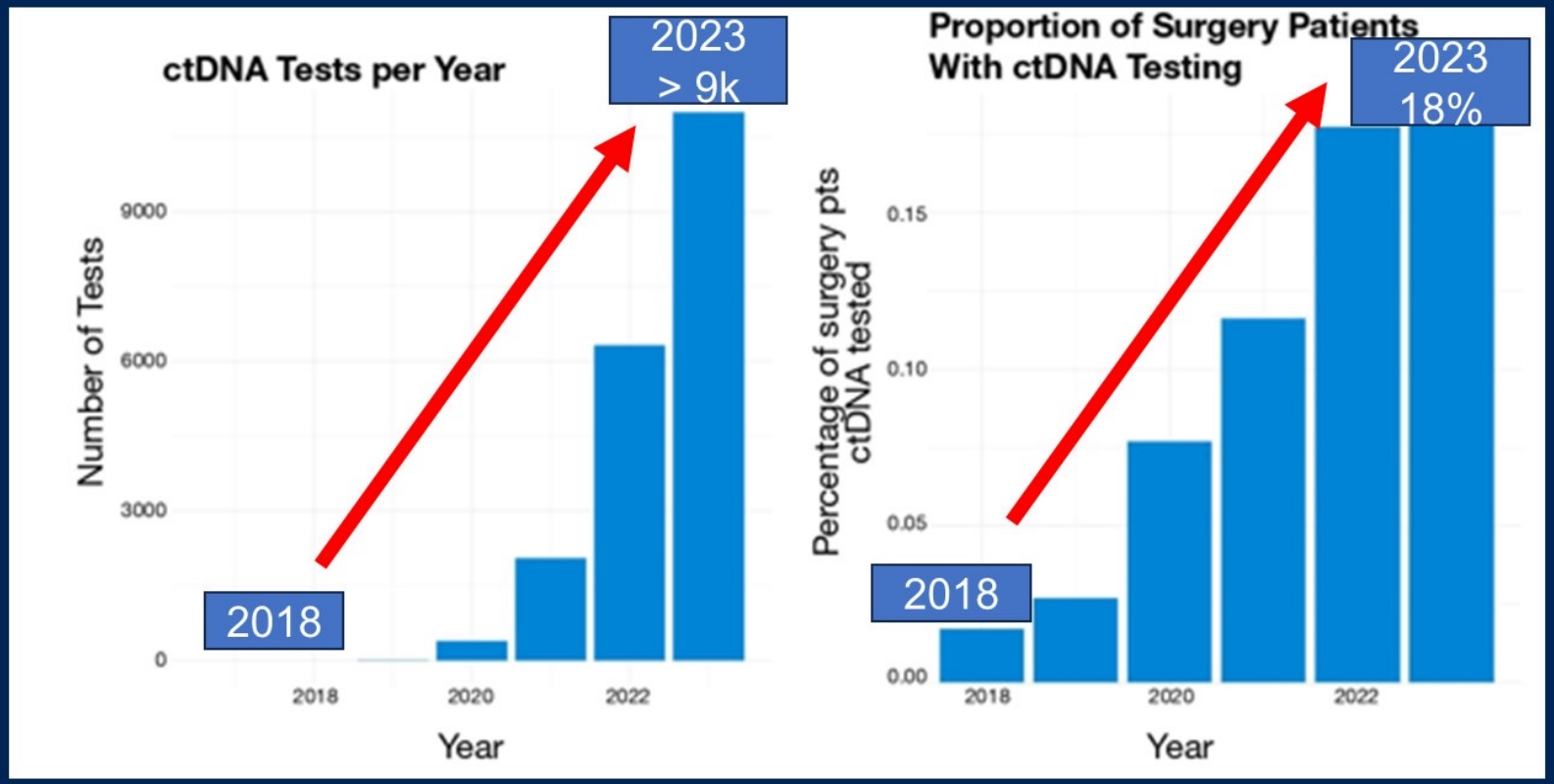


	TUMOR-INFORMED	TUMOR AGNOSTIC
Requires matched tumor tissue?	Yes	No
Turn-around time adequate for adjuvant chemotherapy window?	Yes….	Yes
Gene coverage	Personalized	Extensive panel including most commonly mutated genes
Correction for CHIP confounding?	Yes	Yes…..

Taieb et al.

Where Are We Today - Rapid Clinical Uptake

1st MRD assay for CRC included in CMS coverage in 2020



Fidyk et al, J Clin Oncol 42, 2024 (suppl 16; abstr 3610)

Observational Studies & What We Know

1. MRD is VERY strongly prognostic for recurrence

	BESPOKE CRC	GALAXY	INTERCEPT
n	627	2860	1140
Stage	II-IV	II-III	II-IV
HR for DFS	12.1	10.5	22.6

Kasi et al, J Clin Oncol 42, 2024 (suppl 3; abstr 9)
Kotani et al, Nat Med. 2023 Jan;29(1):127-134
Nakamura et al, Nat Med. 2024 Nov;30(11):3272-3283
Maddalena et al, J Clin Oncol 42, 2024 (suppl 3; abstr 27)
Maddalena et al, unpublished data

Observational Studies & What We Know

1. MRD is VERY strongly prognostic for recurrence

	BESPOKE CRC	GALAXY	INTERCEPT
n	627	2860	1140
Stage	II-IV	II-III	II-IV
HR for DFS	12.1	10.5	22.6

2. MRD-ve: Recurrence low irrespective of adjuvant therapy

	BESPOKE CRC	GALAXY	INTERCEPT
n	530	2860	532
2-year DFS (%)			
With ACT	93.7	89.1	85.6
Without ACT	90.4	90	83.8

Kasi et al, J Clin Oncol 42, 2024 (suppl 3; abstr 9)
Kotani et al, Nat Med. 2023 Jan;29(1):127-134
Nakamura et al, Nat Med. 2024 Nov;30(11):3272-3283
Maddalena et al, J Clin Oncol 42, 2024 (suppl 3; abstr 27)
Maddalena et al, unpublished data

Observational Studies & What We Know

1. MRD is VERY strongly prognostic for recurrence

	BESPOKE CRC	GALAXY	INTERCEPT
n	627	2860	1140
Stage	II-IV	II-III	II-IV
HR for DFS	12.1	10.5	22.6

2. MRD-ve: Recurrence low irrespective of adjuvant therapy

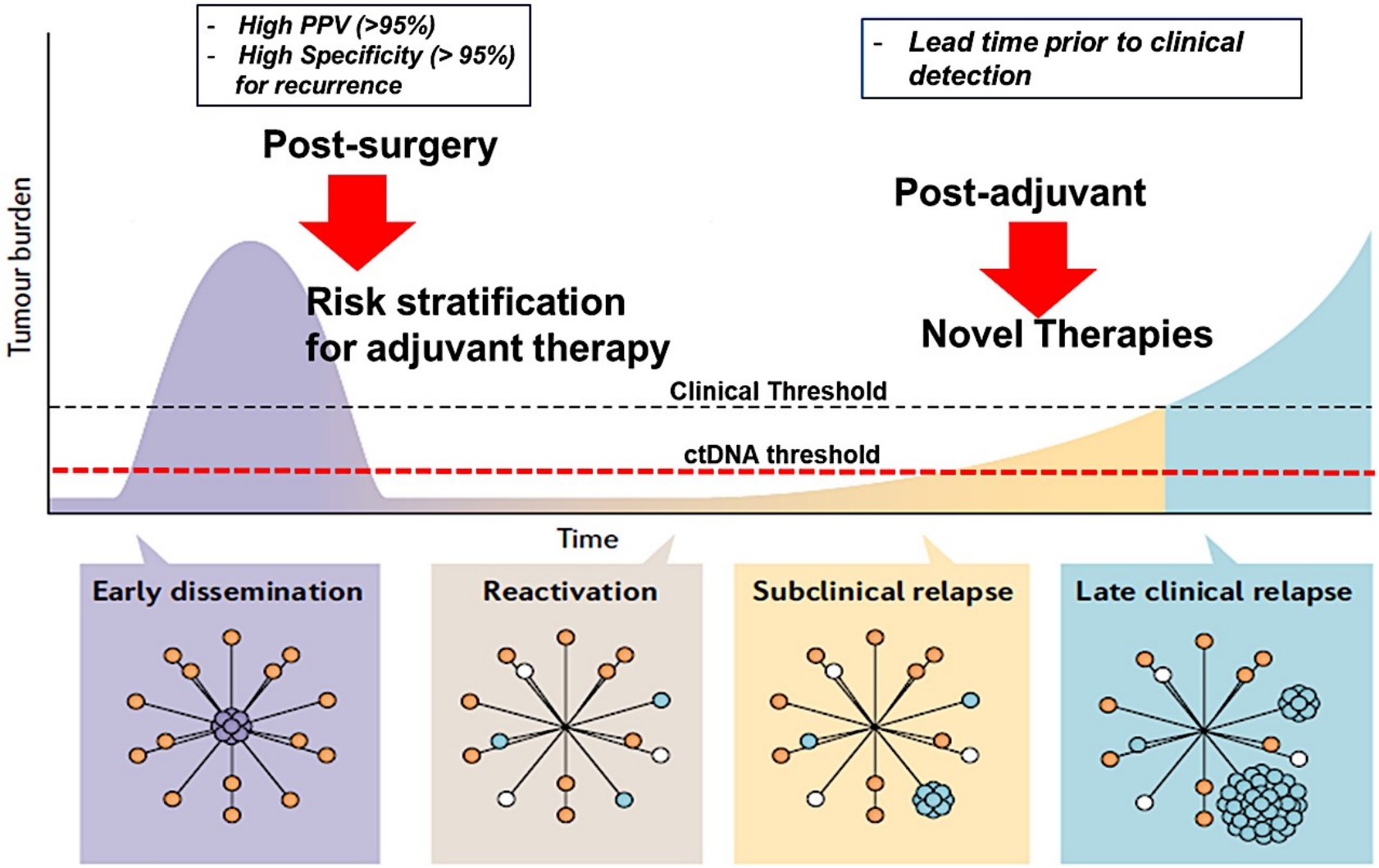
	BESPOKE CRC	GALAXY
n	530	2860
2-year DFS (%)		
With ACT	93.7	89.1
Without ACT	90.4	90

3. MRD+ve: Recurrence high even with adjuvant therapy

	BESPOKE CRC	GALAXY	INTERCEPT
n	96	192	532
2-year DFS (%)			
With ACT	42.4	35.8	12.8
Without ACT	12.5	2.8	2.6

Kasi et al, J Clin Oncol 42, 2024 (suppl 3; abstr 9)
Kotani et al, Nat Med. 2023 Jan;29(1):127-134
Nakamura et al, Nat Med. 2024 Nov;30(11):3272-3283
Maddalena et al, J Clin Oncol 42, 2024 (suppl 3; abstr 27)
Maddalena et al, unpublished data

MRD Timepoints & Applications: Surveillance



Reinert et al, JAMA Onc, 2019

Key ctDNA Clinical Trials (Stage II)

	Australia	France	US/Canada	Germany/Austria/ Sweden	Denmark
Name	DYNAMIC	Circulate.fr / PRODIGE70	COBRA	CIRCULATE/AIO-KRK-0217	IMPROVE-IT2*
Assay	Safe-SeqS	Methylation probes for WIF1 & NPY	Guardant LUNAR	Dresden NGS	German platform
Methodology	**Escalate**	**Escalate**	**Escalate**	**Escalate**	**Escalate**
Escalate to:	Chemo	Chemo	FOLFOX x 6m	Chemo	PET surveillance
Sample size	455	2640 screen	635	3609 stage II (4812 screen)	254
Phase	II	III	II/III	III	II
Trial PI	Jeanne Tie, MBChB, FRACP, MD	Julien Taieb, MD, PhD	Van Morris, MD	Gunnar Folprecht, MD	Claus L Andersen, PhD

DYNAMIC Study Design

Stage II Colon Cancer

- R0 resection
- ECOG 0 – 2
- Staging CT within 8 weeks
- Provision of adequate tumor tissue within 4 weeks post-op
- No synchronous colorectal cancer

Tumor-Informed ctDNA Analysis
(Targeted CRC panel)

W4 — R 2:1 — W7

(N = 455)

ctDNA-Guided Management

- **ctDNA-Positive → Adjuvant Chemo**
  (oxaliplatin-based or single agent FP)
- **ctDNA-Negative → Observation**

ctDNA-Positive = Positive result at week 4 and/or 7

Standard Management

Adjuvant treatment decisions based on conventional clinico-pathologic criteria

Follow-Up

Until recurrence

- CEA: 3-monthly for 24M, then 6-monthly to 5 years
- CT C/A/P: 6-monthly for 24M, then at 36M

Post-recurrence

- Survival: 6-monthly to 5 years

Endpoints	
Primary: RFS at 2 years (non-inferiority margin 8.5%)	**Secondary:** RFS by ctDNA status, EoT ctDNA clearance
Key secondary: Proportion receiving adjuvant chemo, OS	**Exploratory:** Post-op ctDNA levels

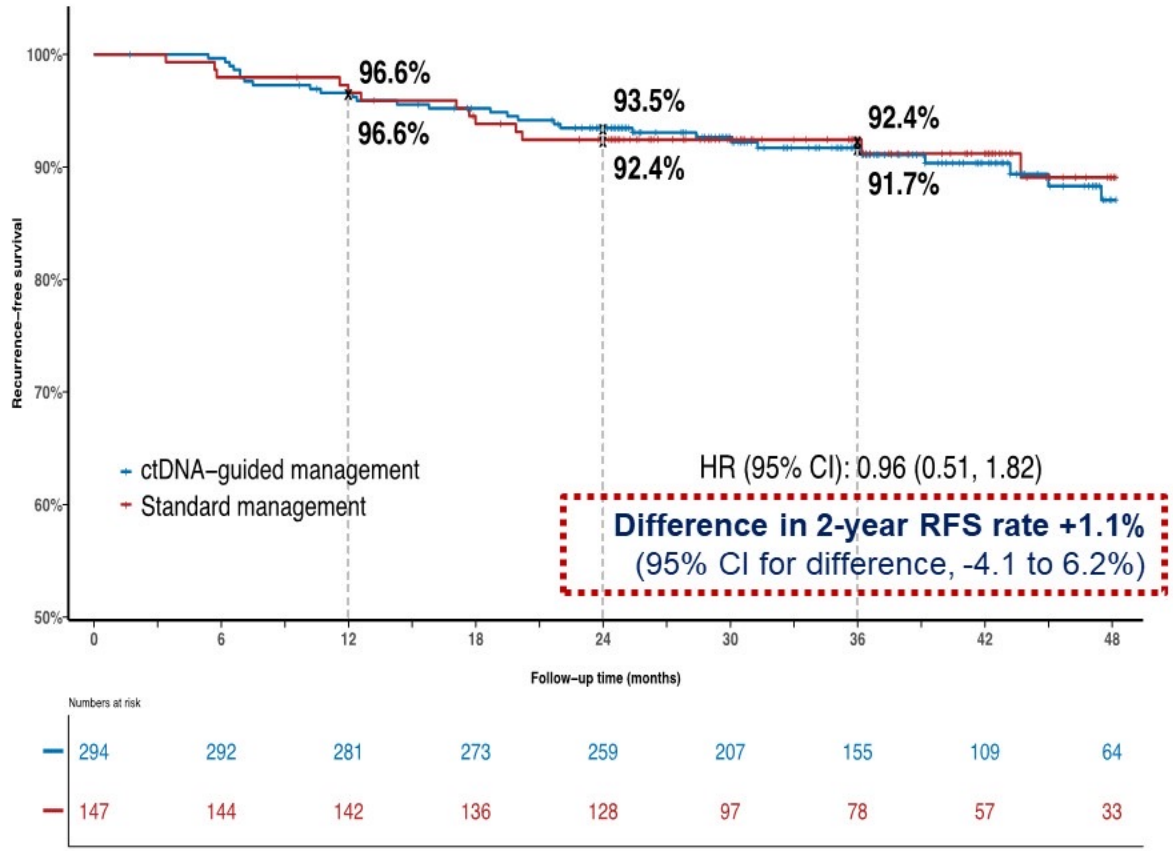
ctDNA-Guided Adjuvant Treatment in Stage II Colon Cancer

NEJM, June 2022

Treatment delivery: ctDNA-guided approach significantly reduced chemotherapy use

Treatment Information	ctDNA-Guided N = 294	Standard Management N = 147	P-value
Adjuvant Chemotherapy received, n	45 **(15%)**	41 **(28%)**	0.0017
Chemotherapy regimen, n			
Oxaliplatin-based doublet	28/45 **(62%)**	4/41 **(10%)**	
Single agent FP	17/45 **(38%)**	37/41 **(90%)**	<.0001
Time from surgery to commencing chemotherapy, median (IQR), days	83 (76, 89)	53 (49, 61)	<.0001
Treatment duration, median (IQR), weeks	24 (19, 24)	24 (21, 24)	0.9318

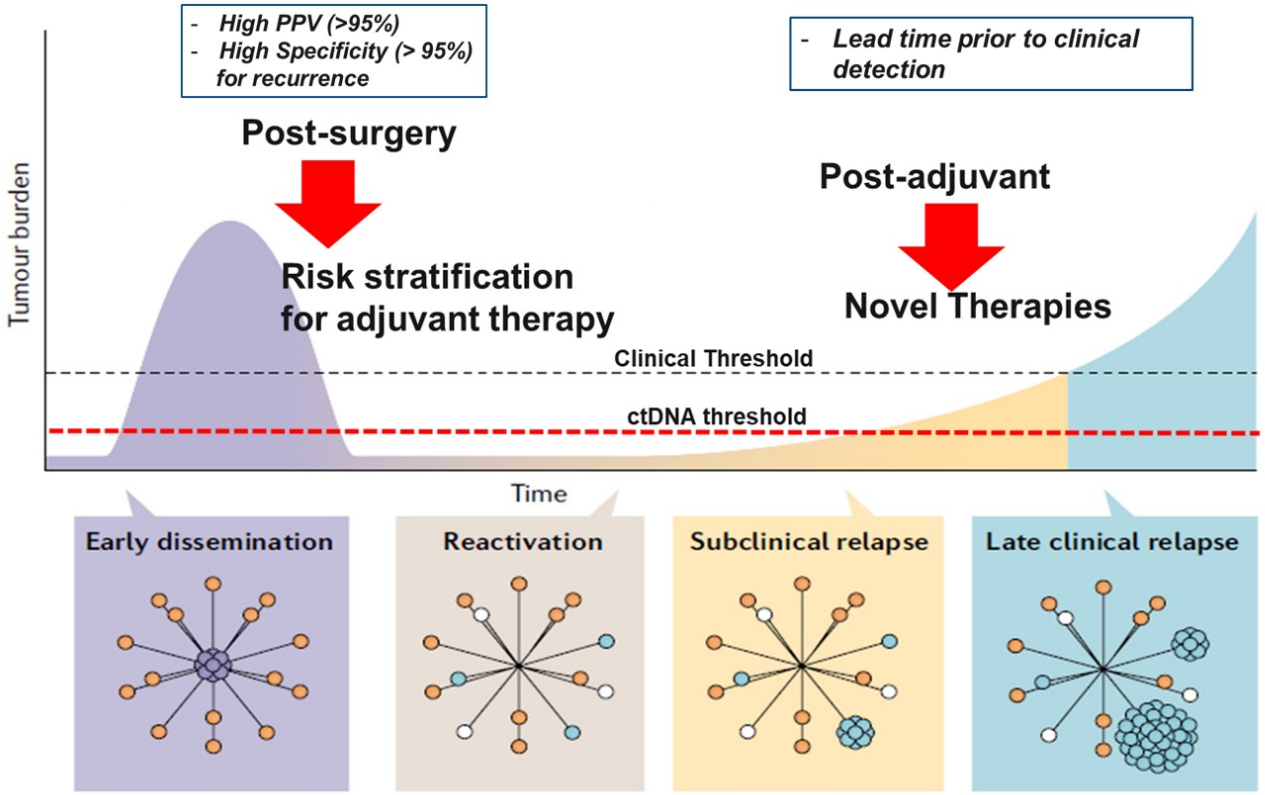
Primary RFS analysis: ctDNA-guided approach non-inferior to standard management

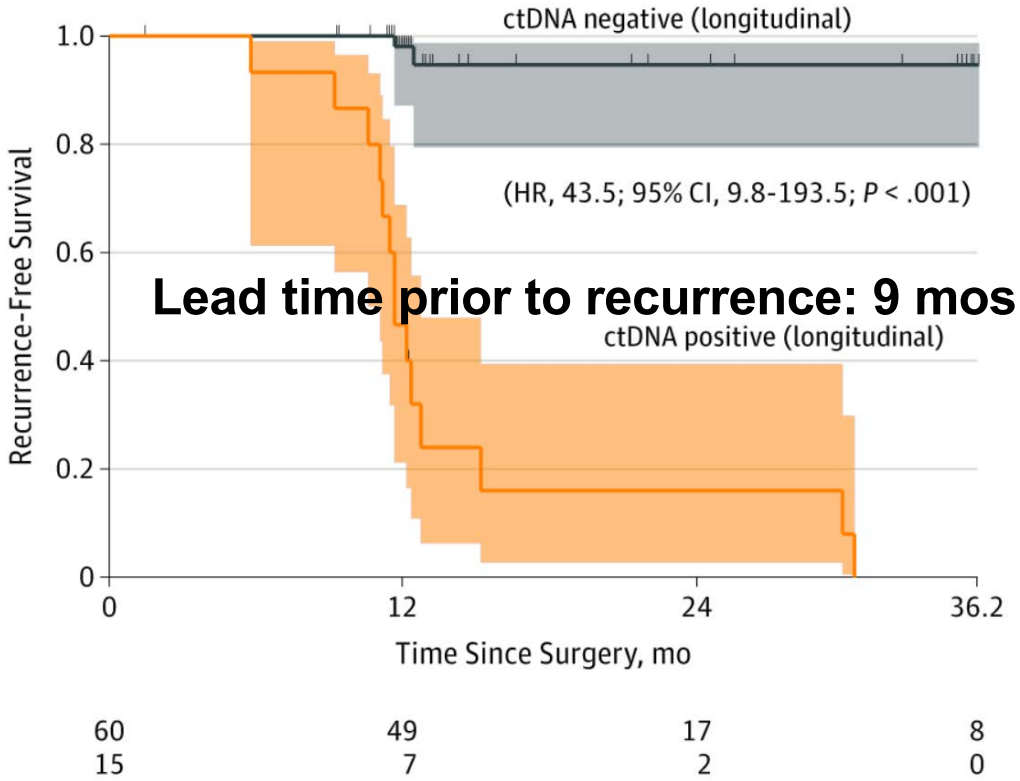


Key ctDNA Clinical Trials (Stage III)

		Japan	US	Italy
Name	DYNAMIC III	CIRCULATE-Japan	NRG GI-008 (CIRCULATE-US)	PEGASUS*
Assay	Safe-Seq S	**Signatera, serial**	**Signatera, serial**	**LUNAR-1, serial**
Methodology	**Escalate / De-escalate**	**Escalate / De-escalate**	**Escalate / De-escalate**	**Escalate / De-escalate**
Escalate to	Higher intensity from pre-assay choice	FTD/TPI (ALTAIR Trial)	FOLFIRINOX	CAPOX / FOLFIRI
De-escalate to	Lower intensity from pre-assay choice	Surveillance (VEGA Trial)	Surveillance	Capecitabine
Sample size	961	1240 (VEGA) 240 (ALTAIR)	1912	135
Phase	II/III	III	II/III	II
Trial PI	Jeanne Tie, MBChB, FRACP, MD	Yoshiaki Nakamura, MD Hiroya Taniguchi, MD Daisuke Kotani, MD Takayuki Yoshino, MD, PhD	Arvind Dasari, MD Christopher Lieu, MD	Silvia Marsoni, MD

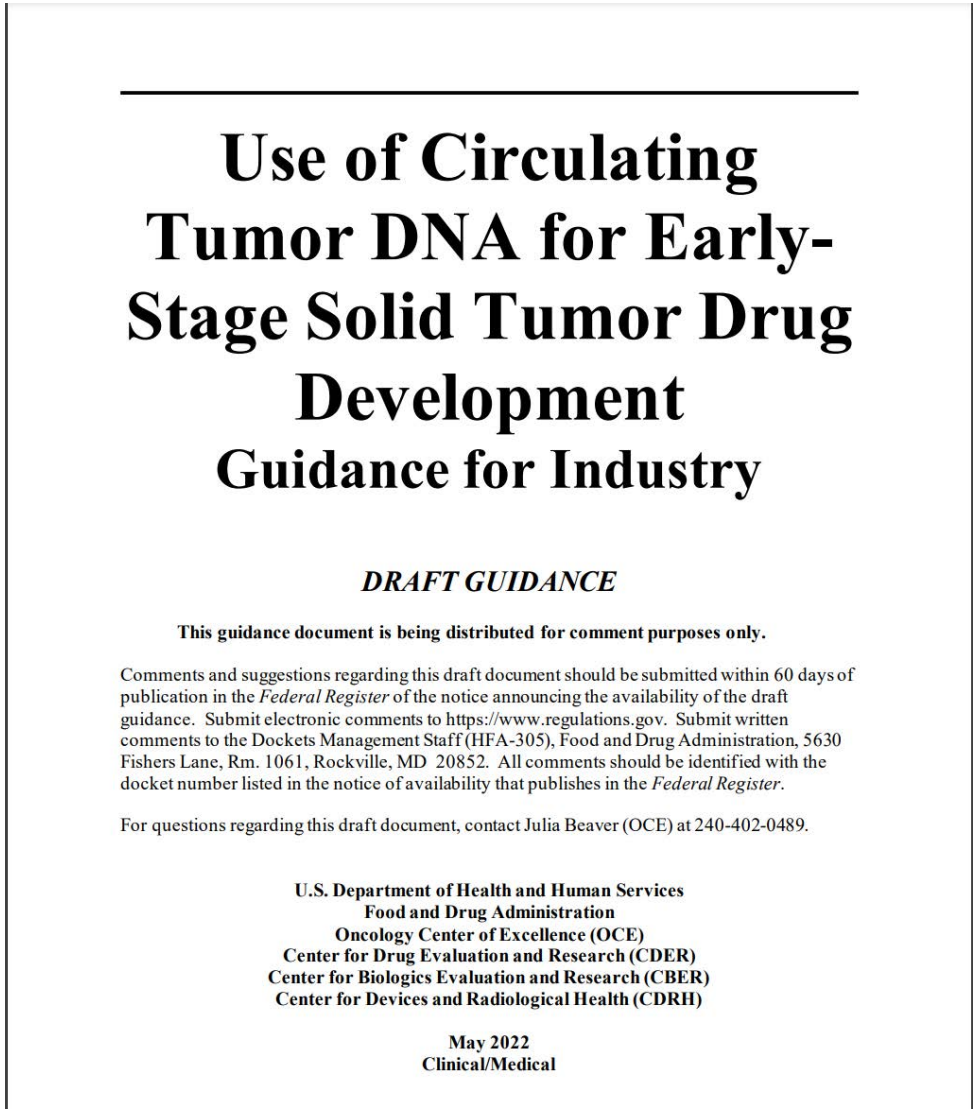
MRD Timepoints & Applications: Surveillance





Reinert et al, JAMA Onc, 2019

FDA Draft Guidance



Use of Circulating Tumor DNA for Early-Stage Solid Tumor Drug Development

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Julia Beaver (OCE) at 240-402-0489.

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

May 2022
Clinical/Medical

Key Takeaways (for MRD):

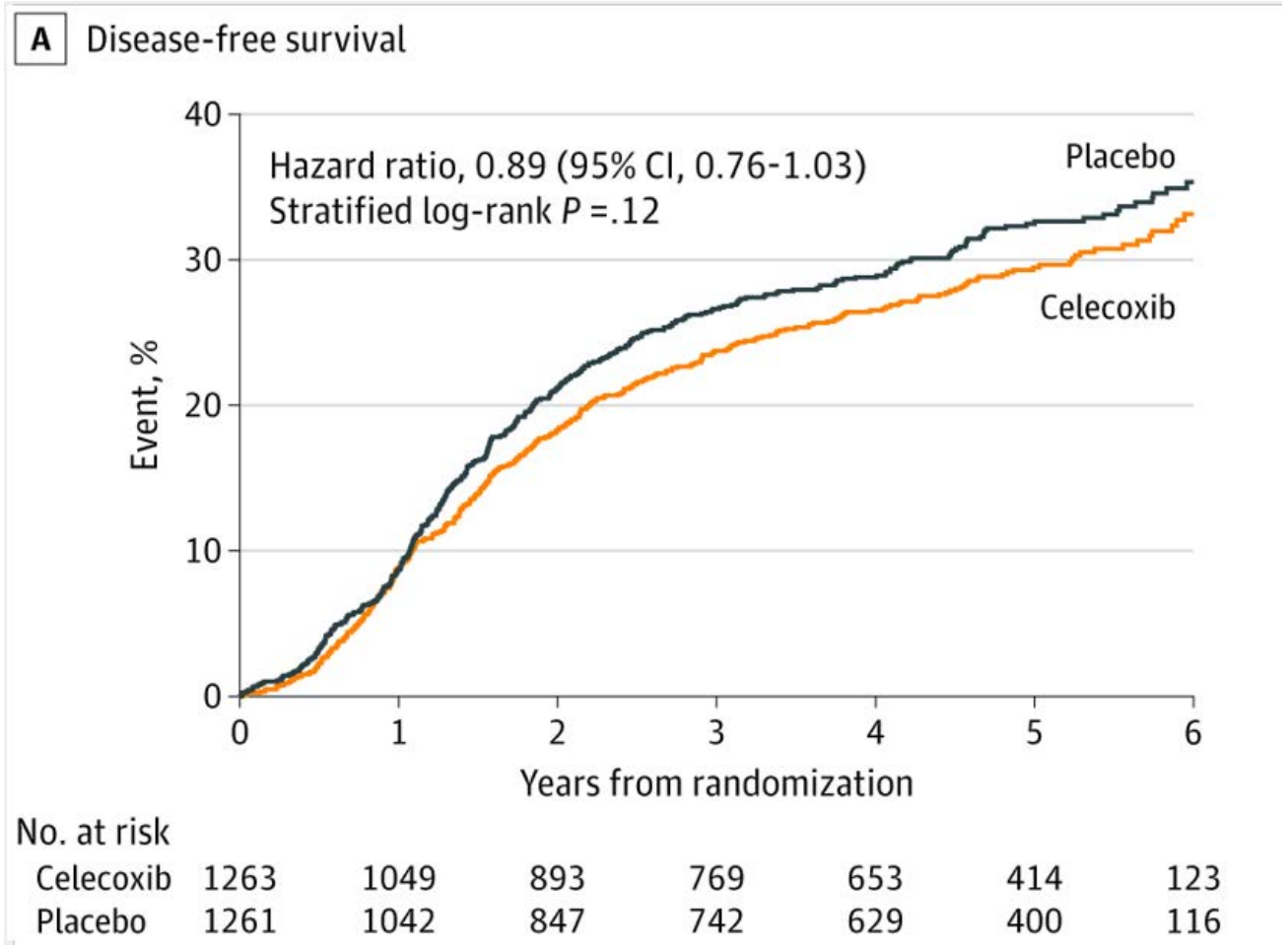
- ctDNA testing after surgery or (neo)adjuvant therapy **could determine study eligibility** of a biomarker positive population.

- ctDNA **could be used in early phase clinical trials to aid in signal finding of drug activity** and to potentially aid sponsors in their drug development plans.

- **Further data (meta-analysis) are required to support the use of ctDNA** as an endpoint reasonably likely **to predict long term outcome** (DFS/EFS/OS).

- **MRD panels** can utilize tumor-informed methods, tumor-naïve methods, or a smaller panel of candidate genes **each with its own strengths and limitations.**

CALGB 80702 Trial: Effect of Celecoxib Added to Adjuvant Therapy: Initial Analysis (All Patients)

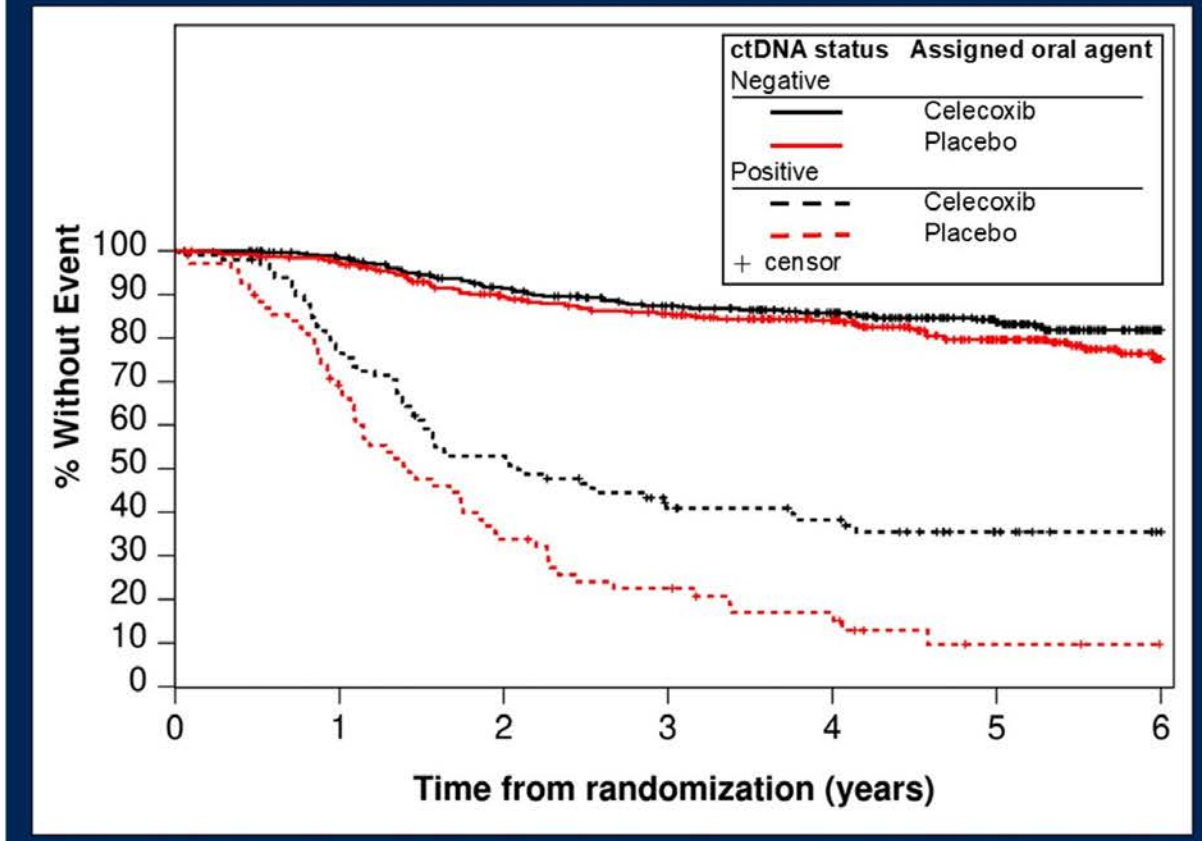


HR = 0.89 (95% CI, 0.76 – 1.03)

Meyerhardt et al, JAMA 2021

CALGB 80702 Study Re-Analysis According to ctDNA Status

Disease-free survival by ctDNA status and celecoxib use



Assigned Oral Agent by ctDNA status	Events / Total	Hazard Ratio (95% CI)[1]	3 Year Survival Estimate (95% CI)[2]	P-value
Negative				0.1293[4]
Celecoxib	58/375	0.76 (0.54-1.08)	87.4 (84.0-91.0%)	
Placebo	73/392	Reference	85.6 (82.0-89.4%)	
Positive				0.0013[4]
Celecoxib	61/99	0.55 (0.39-0.80)	41.0 (32.2-52.2%)	
Placebo	57/74	Reference	22.6 (14.3-35.5%)	
Interaction P-value: 0.1359[3]				

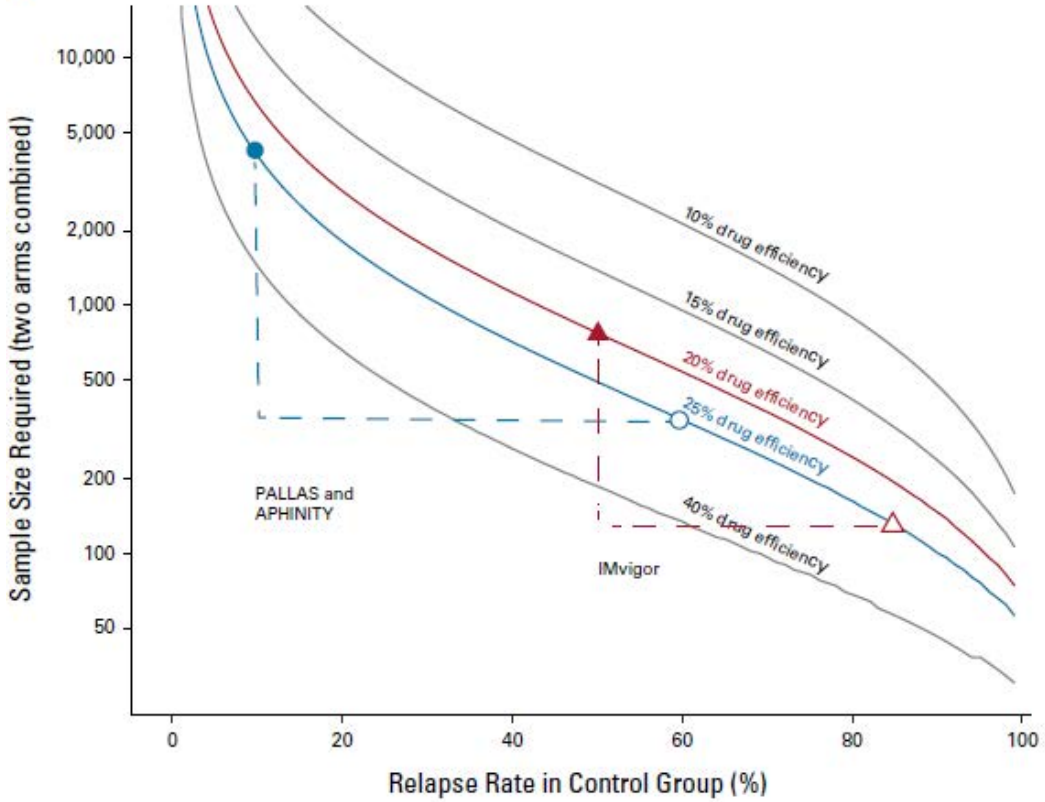
[1] Unadjusted Cox model, [2] Kaplan-Meier method, [3] Likelihood-ratio test, [4] Log-rank test

Immunotherapy in ctDNA+ MSI-H Patients

- ***MSI-H patients (any tumor type) after resection and adjuvant therapy screened for MRD***
- ***22 / 174 (12.6%) were MRD+***
- ***13 / 22 (59%) treated with pembrolizumab x 6 mos***
- ***11 / 13 (85%) with ctDNA clearance at 6 mos; 5 / 13 (38%) with recurrence***

Janjigian et al, Proceedings of the American Association for Cancer Research Annual Meeting 2025; Part 2 (Late-Breaking, Clinical Trial, and Invited Abstracts); 2025 Apr 25-30; Chicago, IL. Philadelphia (PA): AACR; Cancer Res 2025;85(8_Suppl_2):Abstract nr CT002

MRD and Trial Sample Size



C adjuvant trial

Enrollment reduced by > 8-fold

~75% cost reduction

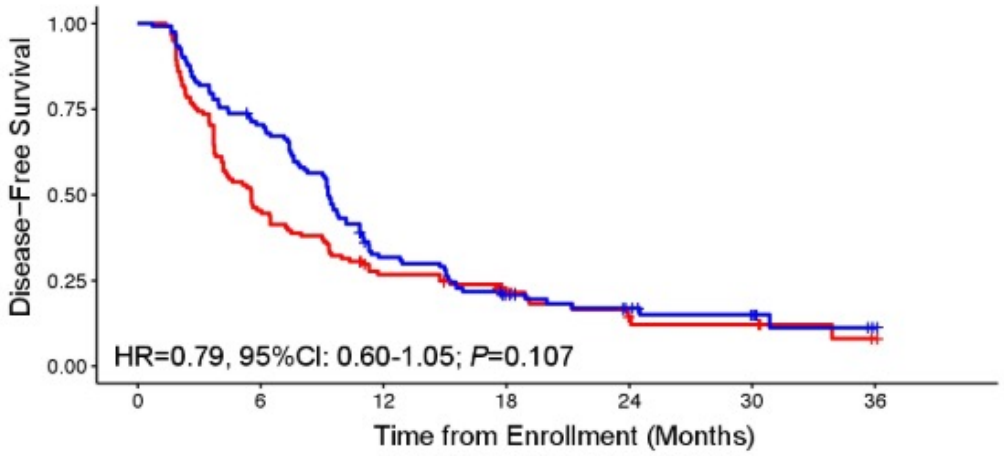
~3X ARR in ctDNA-positive enriched patient population

Enrollment Strategy	Percent of All-Comers Enrolled	Event Rate Among Patients	Sample Size (needed)	Total Screened	Total Costs ($k)	ARR
No enrichment	100	0.27	1,660	1,660	70,392	27% × 25% = 6.8%
ctDNA enriched	19	0.75	199	1,047	16,919	75% × 25% = 18.8%

Kasi et al. JCO PO 2022

ALTAIR Study Results

A



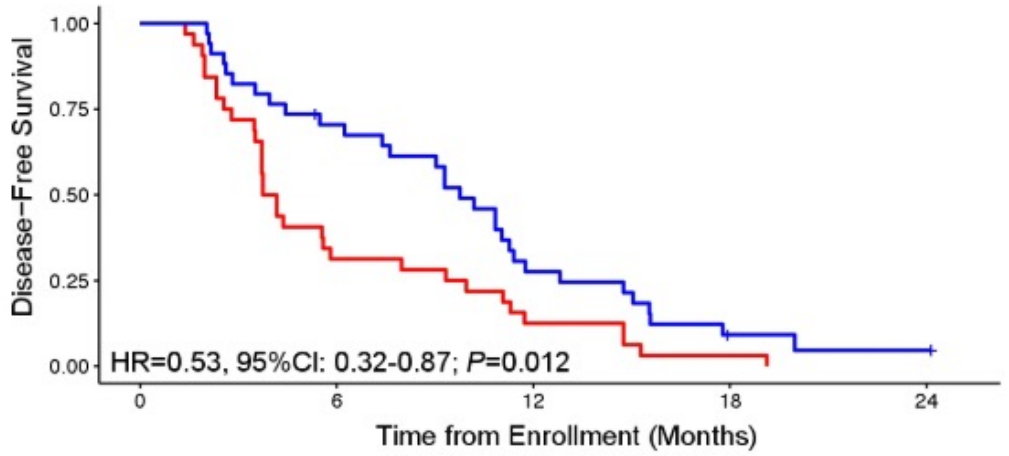
Number at risk

FTD/TPI	122	85	35	19	11	6	1
Placebo	121	55	28	16	6	5	1

Treatment status	FTD/TPI	Placebo
Events %	81.15 (99/122)	81.82 (99/121)
6M-DFS %	70.5 (61.5-77.7)	45.5 (36.42–54)
12M-DFS %	31.8 (23.6–40.2)	26.8 (19.16–35)
18M-DFS %	20.8 (13.9–28.7)	21.5 (14.43–29.6)
24M-DFS %	16.9 (10.4–24.8)	14.5 (7.85–23.1)
mDFS (mo)	9.30 (7.92–10.84)	5.55 (4.17–7.33)

DFS analysis stratified by Stage (Stage II or Lower, Stage III or M1) and ctDNA status 1mo post-surgery (Positive vs Negative/Unmeasured)

B



Number at risk

FTD/TPI	34	23	9	2	1
Placebo	32	10	4	1	0

Treatment status	FTD/TPI	Placebo
Events %	94.12 (31/34)	100 (32/32)
6M-DFS %	70.47 (52.05–82.9)	31.25 (16.38–47.3)
12M-DFS %	27.57 (13.79–43.3)	12.5 (3.95–26.2)
18M-DFS %	9.19 (.236–21.9)	3.12 (0.24–13.7)
24M-DFS %	4.60 (0.43–17.5)	NR
mDFS (mo)	9.76 (7.62–11.76)	3.96 (3.71–7.98)

Enrollment ctDNA timepoint MTM/mL
Stage IV patients vs non-Stage IV: 0.68 vs 0.32, *P* = 0.024

Bando et al GI ASCO 2025

Conclusions

- ***ctDNA is a powerful tool in management of cancer patients; assays continue to improve***
- ***Extensive ongoing work for ctDNA as a marker for minimal residual disease and to determine intensity of adjuvant therapy***
- ***True MRD patients can be successfully enrolled onto trials during surveillance***

Case Presentation: 70-year-old woman with T3N1 right-sided colon cancer declines adjuvant chemotherapy

Dr Warren S Brenner (Boca Raton, Florida)

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

Outside of a clinical trial, what is the current role of ctDNA testing in Stage III CRC? Would you currently be comfortable de-escalating adjuvant chemotherapy on the basis of negative ctDNA results? What about forgoing adjuvant chemotherapy altogether for a patient who is hesitant to receive it?

Outside of a clinical trial, what is the current role of ctDNA testing in Stage II CRC? Would you currently be comfortable forgoing adjuvant chemotherapy on the basis of negative ctDNA results? What about using a more intensive adjuvant chemotherapy regimen on the basis of positive results?

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

How do you interpret the recently presented results from the CALGB/SWOG 80702 trial? Are there any situations in which you are currently offering celecoxib as a component of adjuvant therapy?

Case Presentation: 65-year-old woman with Stage IIIB colon cancer receives reduced cycles of adjuvant FOLFOX due to intolerance

Dr Shachar Peles (Lake Worth, Florida)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

What would you recommend for this patient at this point?

How often should ctDNA be ordered in the surveillance setting?

What would you have recommended if this patient's ctDNA had become positive without evidence of peritoneal disease on PET? Would you currently initiate systemic therapy on the basis of ctDNA results alone, in the absence of evidence of recurrent disease on imaging? Is there a particular level of ctDNA that you would be looking for to reinitiate treatment?

Agenda

MODULE 1: Role of Circulating Tumor DNA (ctDNA) Evaluation in Nonmetastatic Colorectal Cancer (CRC) — Dr Dasari

MODULE 2: Role of Immune Checkpoint Inhibitors in the Management of Nonmetastatic Microsatellite Instability-High (MSI-H) CRC — Dr Cercek

MODULE 3: Management of Oligometastatic Disease and Hepatic-Only Metastases in CRC; Role of ctDNA Evaluation in Metastatic Disease — Dr Kasi

MODULE 4: Role of Immune Checkpoint Inhibitors in the Management of MSI-H Metastatic CRC (mCRC) — Dr Hecht

MODULE 5: Identification and Care of Patients with mCRC and Actionable Genomic Alterations — Prof Van Cutsem

RTP RESEARCH TO PRACTICE

Immunotherapy in Early Stage Colorectal Cancer

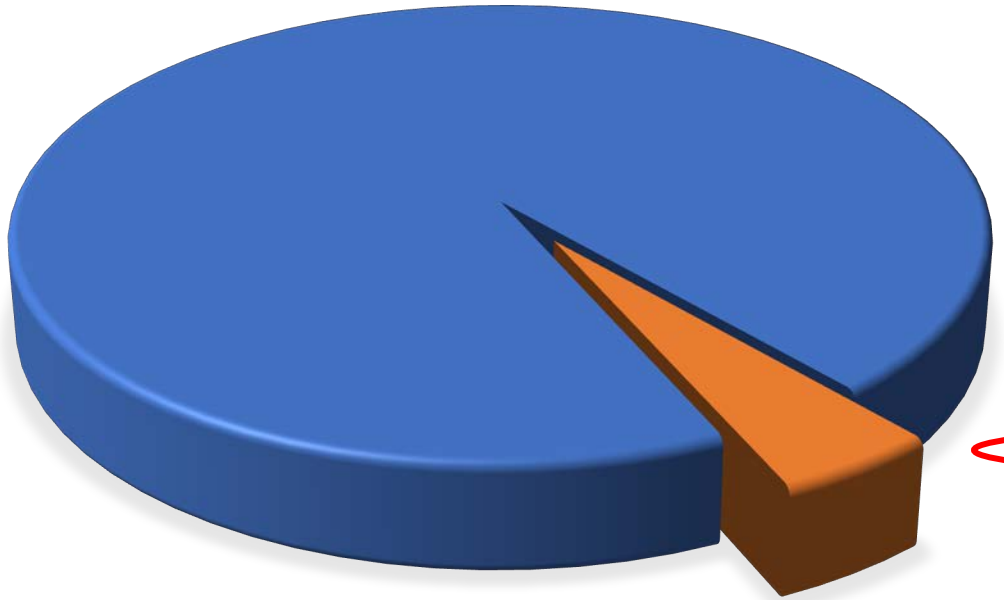
May 30, 2025

Andrea Cercek, MD
Attending
Ford Family Chair
Section Head Colorectal Cancer
Co-Director Center for Young Onset Colorectal and Gastrointestinal Cancers
Memorial Sloan Kettering Cancer Center
New York, New York

Outline

- Neoadjuvant ICB
  - dMMR rectal cancer
  - dMMR colon cancer
- Adjuvant ICB
  - dMMR colon cancer
- Neoadjuvant ICB
  - pMMR colon cancer
  - pMMR rectal cancer

Rectal Cancer: Mismatch repair deficient (dMMR/MSI)



About 5-10% of all rectal cancers

Less sensitive to chemotherapy

Rectal cancer treated with total neoadjuvant therapy chemotherapy and chemoRT followed by TME

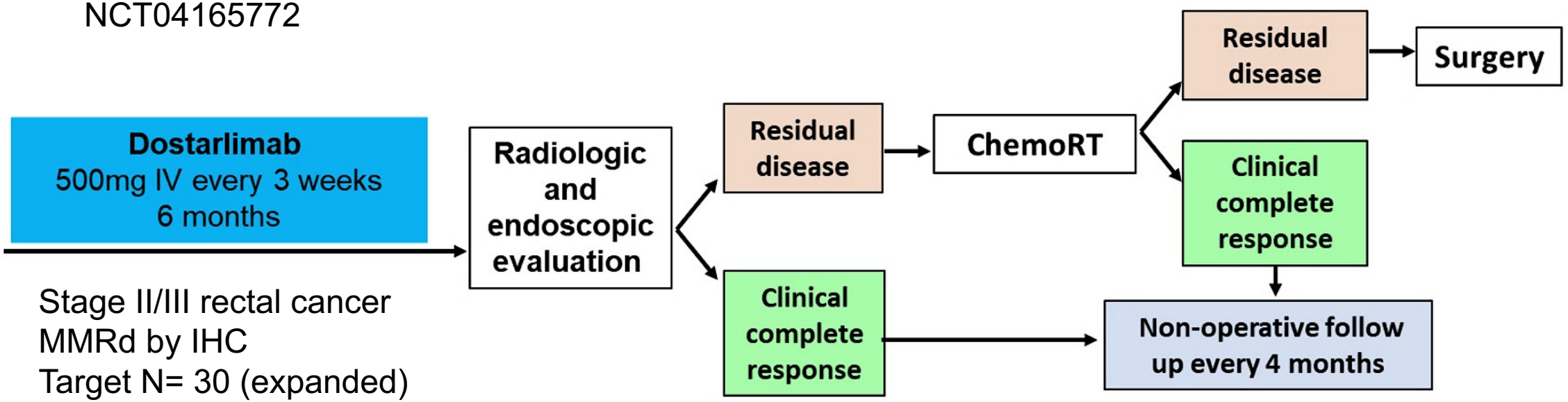
Outcome	No. of patients (%) dMMR	pMMR
FOLFOX as initial treatment	*n = 21*	*n = 63*
Progression of disease	6 (29)	0
Response or stable disease	15 (71)	63 (100)
Chemoradiation as initial treatment	*n = 16*	*n = 48*
Progression of disease	0	0
Complete pathologic response	2 (13)	8 (17)

dMMR/MSI mCRC sensitive to ICB in metastatic disease

Cercek, et al CCR 2020 Le, et al NEJM 2015

Neoadjuvant PD1 blockade in dMMR locally advanced rectal cancer

NCT04165772



Stage II/III rectal cancer
MMRd by IHC
Target N= 30 (expanded)

Primary Endpoints:

- ORR after completion of PD-1 alone or in combination with chemoRT
- pCR or sustained cCR for 12 mo after completion of PD1 alone or in combination with chemoRT

Sample Collection: ctDNA, biopsy, imaging
Baseline, 6 weeks, 3 mo, 6 mo and q4 mo during NOM

Cercek, et al. NEJM 2022

Initial Results

Primary Objective

- Overall response rate of PD-1 blockade

Presented initial data June 2022
14 consecutive patients with clinical complete response (cCR) to dostarlimab alone

Clinical trial is ongoing (NCT04165772)

PD-1 blockade incorporated into NCCN guidelines for locally advanced dMMR rectal cancer May 2023

Cercek et al, NEJM 2022; Cercek ASCO 2022; NCCN guidelines 2024

Study Objectives

Primary Objectives

- Overall response rate of PD-1 blockade with or without chemoradiation
- Clinical complete response (cCR) rate at 12 months after PD-1 blockade

Secondary Objective

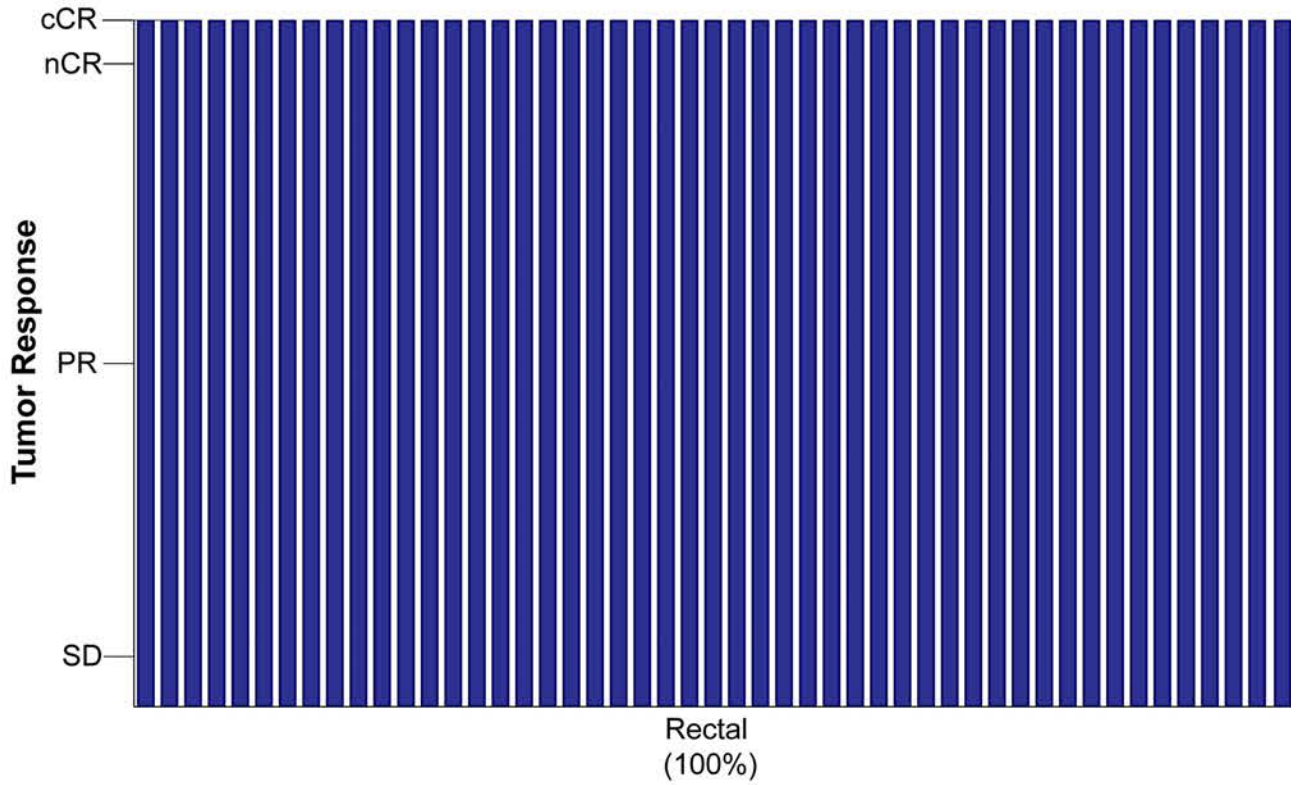
- Safety and tolerability

Cohort 1 – Rectal Cancers – Response and Surgical Management

Cohort 1 Rectal
n = 49

Clinical Complete Response
n = 49

Non-Operative Management
n = 49

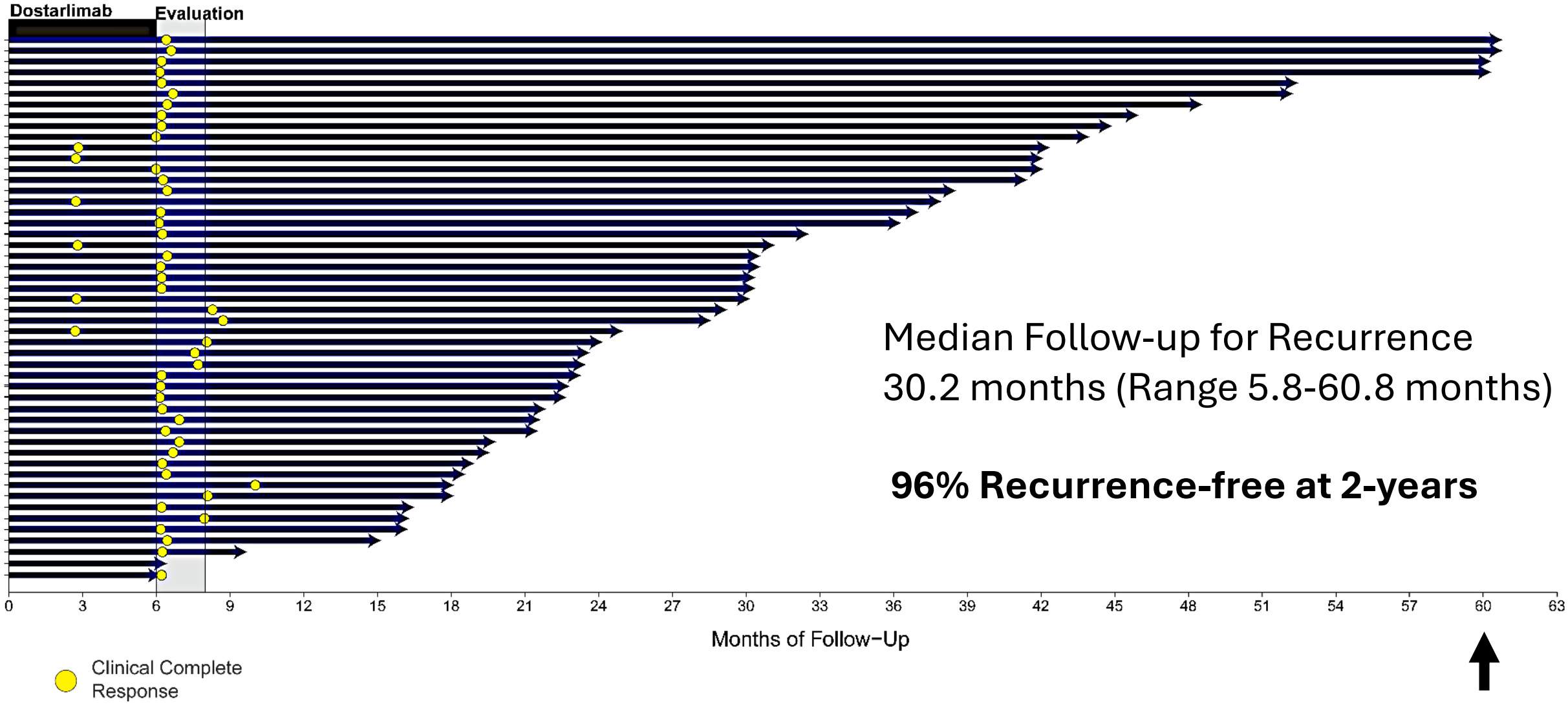


Rectal cancers achieved 100% clinical complete responses

Cercek, Diaz NEJM 2025

Cohort 1 – Rectal Cancers – Durability of Response

n=50



Median Follow-up for Recurrence
30.2 months (Range 5.8-60.8 months)

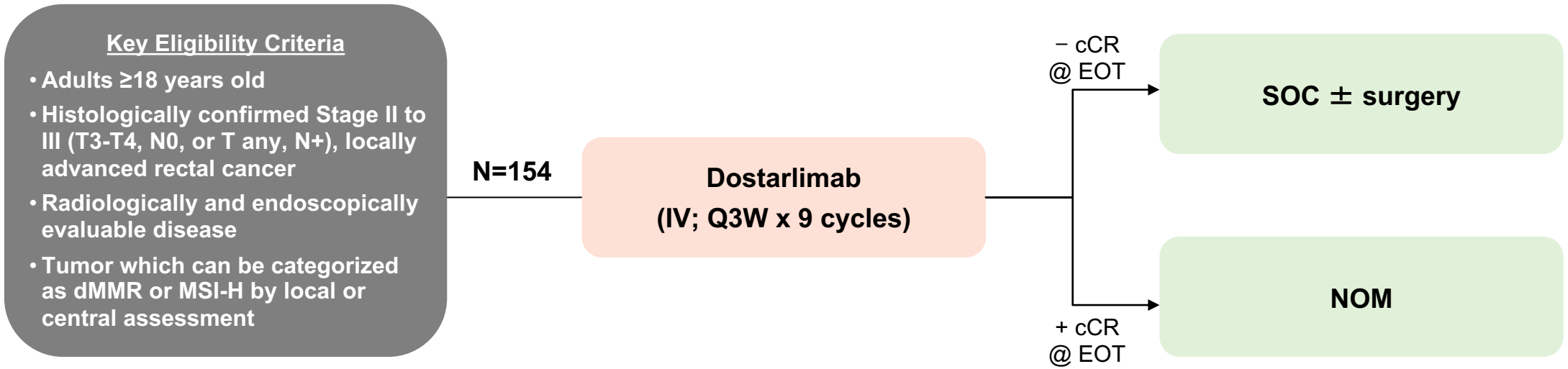
96% Recurrence-free at 2-years

5-years

Cercek, Diaz NEJM 2025

AZUR-1: A Phase 2 Study of Dostarlimab in Patients With Untreated dMMR/MSI-H Locally Advanced Rectal Cancer

Study design[1,2]



1 Primary endpoint:

- Proportion who sustain cCR for 12 months (cCR12) by ICR

2 Secondary endpoints:

- cCR24 and cCR36 by ICR
- cCR12 by INV
- 3-year EFS by INV
- DSS (overall and 5-year)
- Organ preservation rate
- OS (overall and 5-year)
- ORR by ICR and INV
- Safety (AE, AELD, SAE, irAE)
- PK parameters

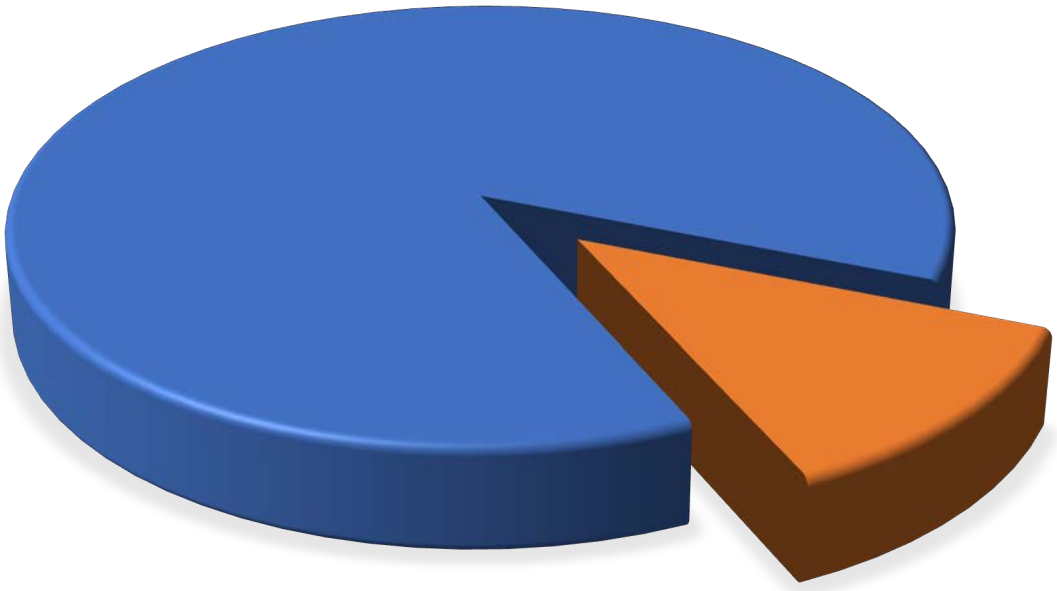
AE, adverse event; AELD, adverse event leading to discontinuation; cCR, clinical complete response; DFS, disease-free survival; dMMR, deficient mismatch repair; EFS, event-free survival; EOT, end of treatment; ICR, ndependent central review; INV, investigator assessment; irAE, immune-related adverse event; IV, intravenous; MSI-H, microsatellite instability-high; NOM, non-operative management; ORR, objective response rate; OS, overall survival; Q3W, every 3 weeks; SAE, serious adverse event; SOC, standard of care.

1. ClinicalTrials.gov (NCT05723562). Accessed May 27, 2025. Available at: https://clinicaltrials.gov/ct2/show/ NCT05723562. 2. Cercek A, et al. *J Clin Oncol*. 2023;41(suppl_16):TPS3639.

Conclusions

- 100% clinical complete response in all 49 patients who completed dostarlimab
- Clinical complete responses are durable
- Low grade AEs
- AZUR1 Global confirmatory study of dostarlimab in dMMR rectal cancer has completed accrual
- All locally advanced rectal tumors should have MMR testing

Colon Cancer: Mismatch repair deficient (dMMR/MSI)



About 10-15% of all early stage colon tumors

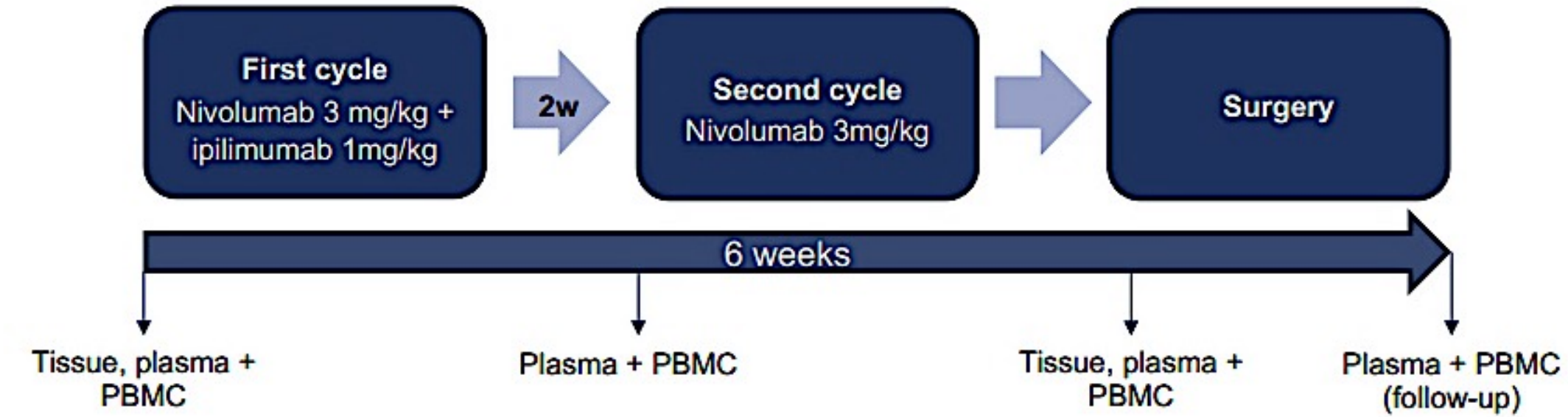
Standard treatment includes resection + adjuvant chemotherapy

Tumor agnostic approval for ICB MMRd solid tumors in advanced disease

Le, et al NEJM 2015

NICHE-2 study design

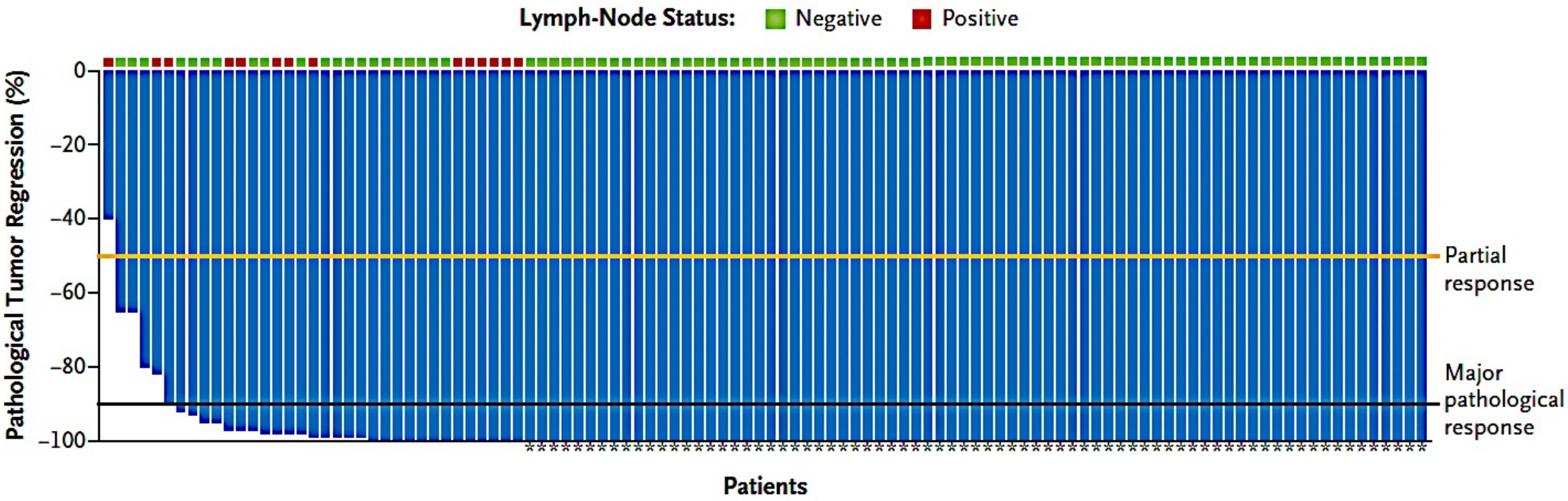
- Investigator-initiated, non-randomized multicenter* study



*6 participating hospitals in the Netherlands
PBMC = peripheral blood mononuclear cells

Chalabi M, et al. ESMO 2022

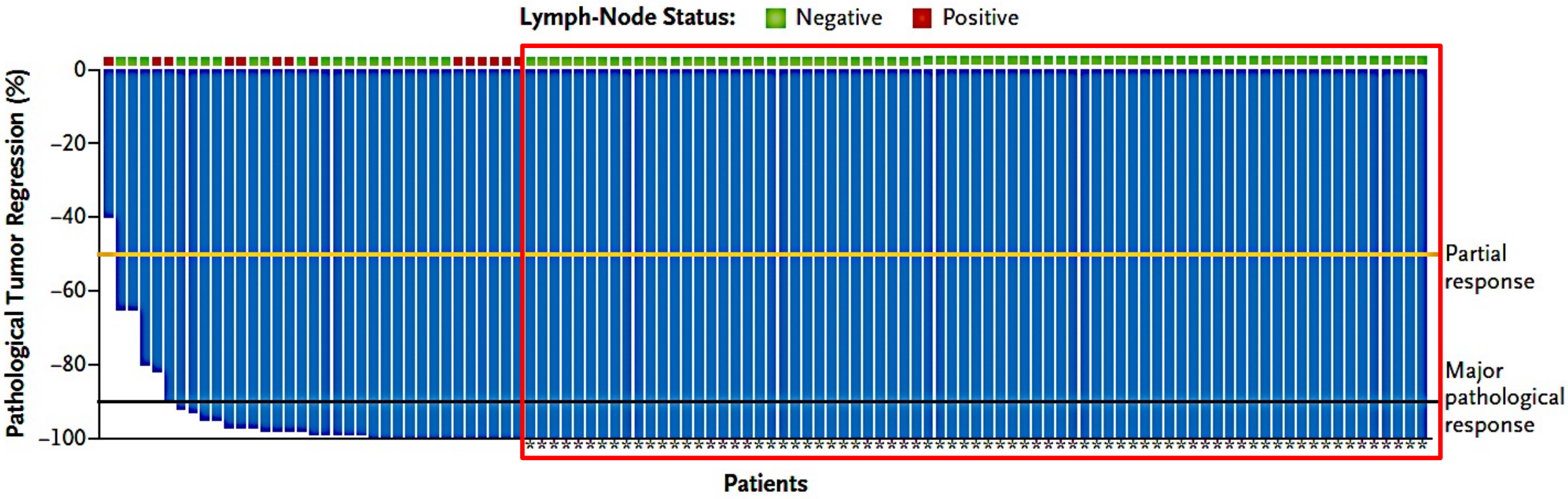
NICHE 2: Results



68% pCR

Chalabi NEJM 2024

NICHE 2: Results

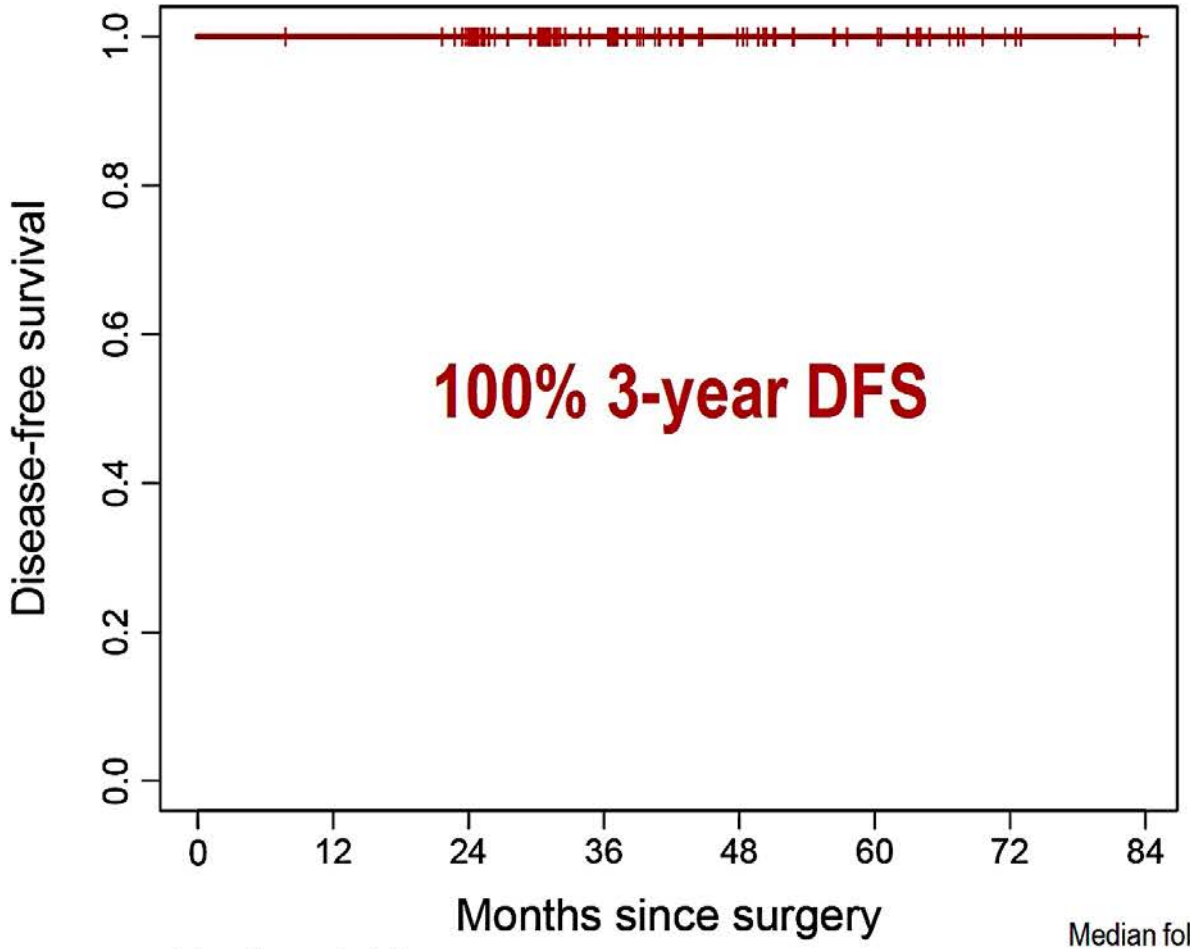


68% pCR

AEs: Grade 3 or 4 events in 5 patients

Chalabi NEJM 2024

NICHE-2: Results

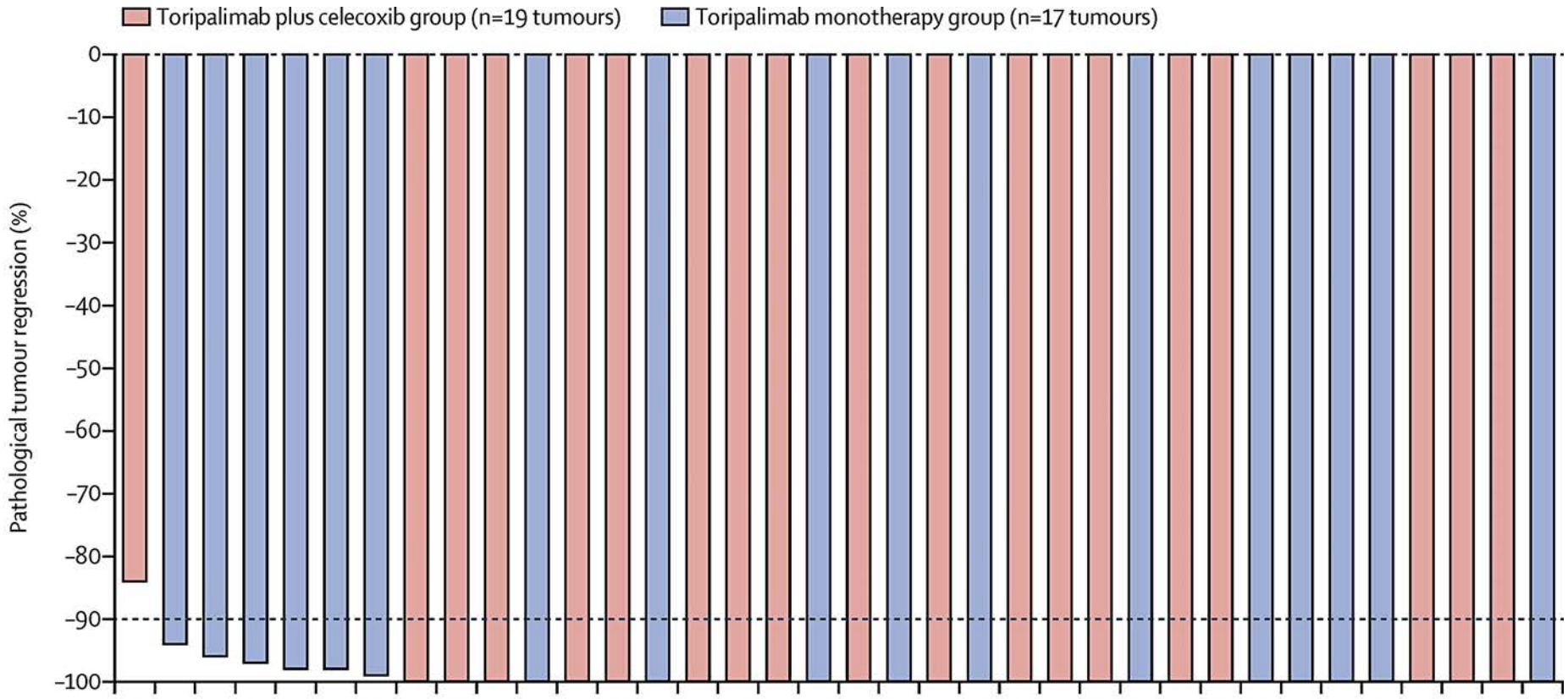


Median follow-up after surgery: 36.6 months (7.8 - 83.4)

BARCELONA 2024 ESMO congress

Data cut-off: 11 September 2024

Neoadjuvant PD-1 blockade with toripalimab, with or without celecoxib, in mismatch repair-deficient or microsatellite instability-high, locally advanced, colorectal cancer (PICC): a single-centre, parallel-group, non-comparative, randomised, phase 2 trial



Treatment: Toripalimab (anti PD1) for 3 months with or without celecoxib

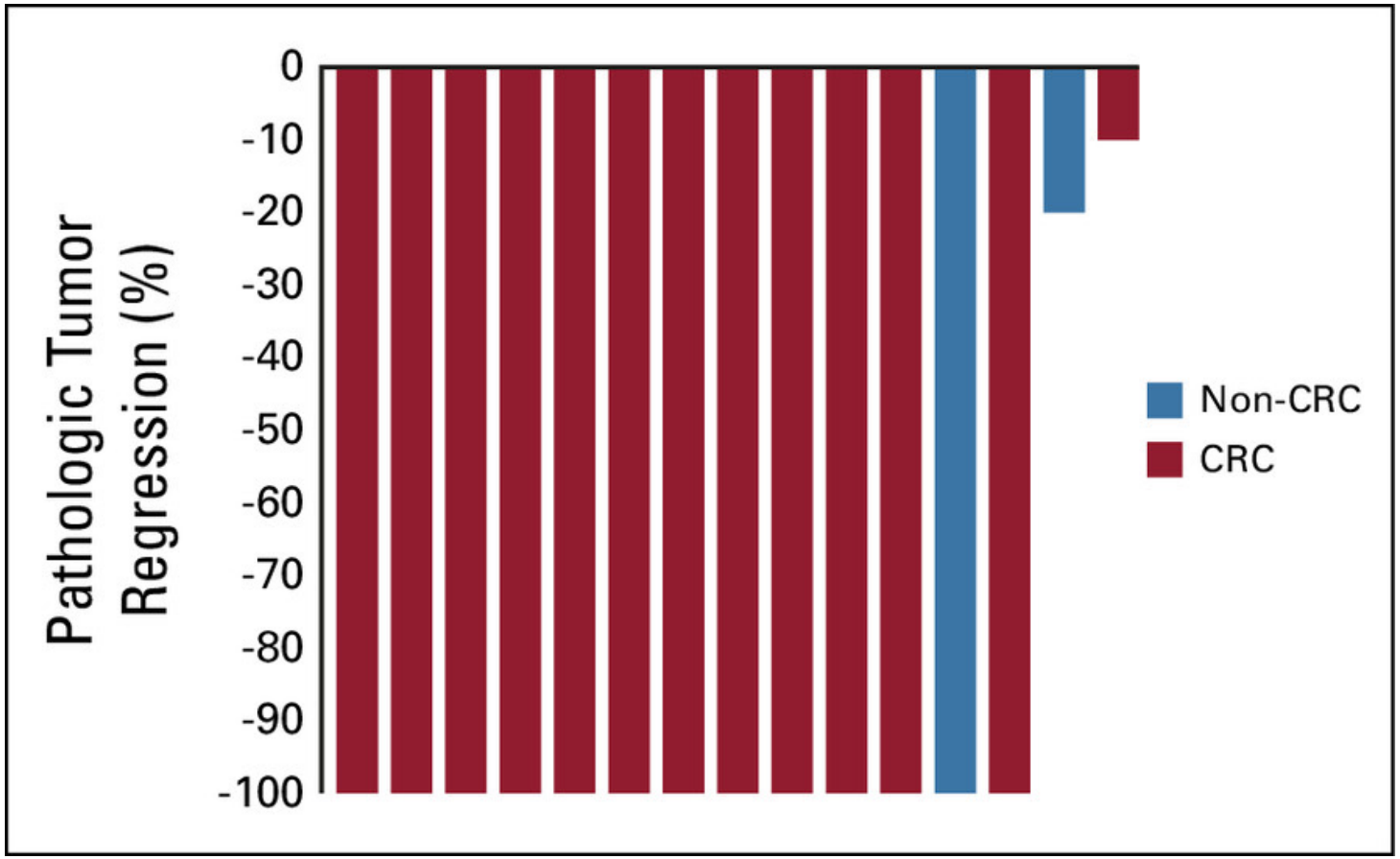
Hu et al, The Lancet Gastroenterol Hepatol 2022

Phase II study of neoadjuvant pembrolizumab in localized unresectable MSI solid tumors

Included 19 MSI colon cancer patients

17 underwent surgery

pCR 65%



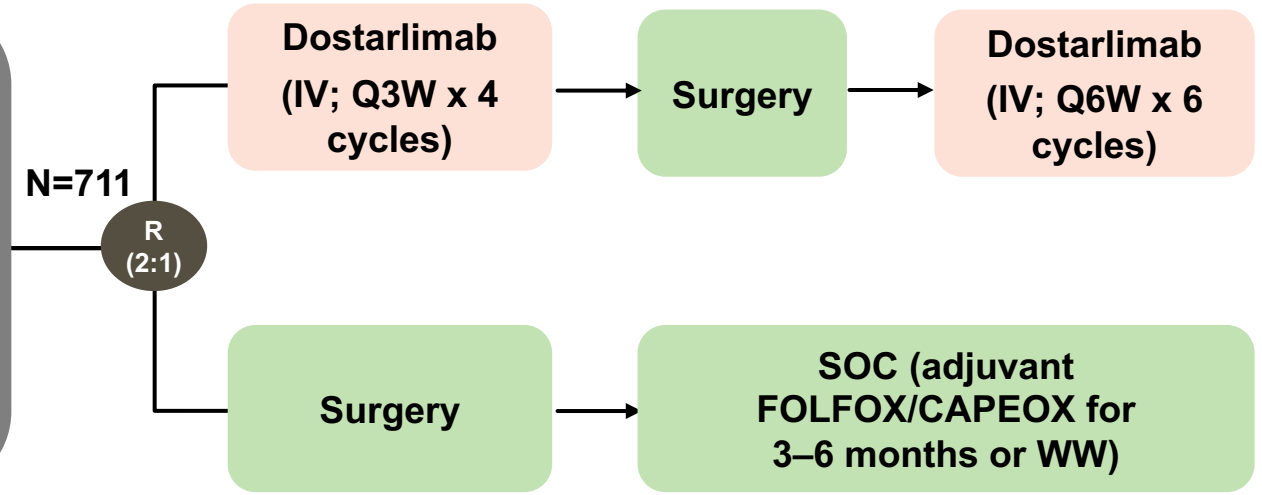
Ludford et al JCO 2023

AZUR-2: A Phase 3 Study of Perioperative Dostarlimab in Patients With Untreated T4N0 or Stage III dMMR/MSI-H Resectable Colon Cancer

Study design[1,2]

Key Eligibility Criteria

- Adults ≥18 years old
- Untreated pathologically confirmed colon adenocarcinoma
- Resectable colon adenocarcinoma defined as clinically T4N0 or Stage III
- Radiologically evaluable disease
- Tumour demonstrating either dMMR or MSI-H status



1 Primary endpoint:

- EFS up to 5 years (BICR)

2 Secondary endpoints:

- OS
- Participants with pathological response
- EFS (by LA)
- Participants with treatment-emergent AEs, SAEs, imAEs, AEs leading to death or discontinuation
- PK parameters
- Participants with anti-drug antibodies

AE,adverse event; BICR, blinded independent central review; dMMR, deficient mismatch repair; EFS, event free survival; imAE, immune-mediated adverse event; IV, intravenous; LA, local assessment; MSI-H, microsatellite instability-high; OS, overall survival; QxW, every x weeks; SAE, serious adverse event; SOC, standard of care; WW, watch and wait.

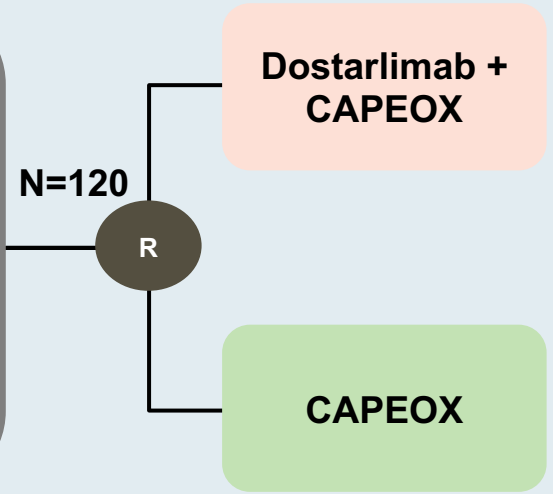
1. ClinicalTrials.gov (NCT05855200). Accessed May 27, 2025. Available at: https://clinicaltrials.gov/ct2/show/NCT05855200. 2. Starling N, et al. *J Clin Oncol* 2024;42 (suppl_3):TPS240

Phase II AZUR-4 Trial: Neoadjuvant Dostarlimab with CAPEOX versus CAPEOX for Previously Untreated MMRp/MSS Colon Cancer

Study design[1]

Key Eligibility Criteria

- Adults ≥18 years old
- Untreated pathologically confirmed colon adenocarcinoma
- Resectable colon adenocarcinoma defined as clinically T4N0 or Stage III
- Radiologically evaluable disease
- Tumour demonstrating either MMRp or MSS/MSI-L status



1 Primary endpoints:

- mPR
- AEs
- SAEs
- imAEs

2 Secondary endpoint:

- Response rate

First patient dosed March 1, 2025

Poster Presentation at ASCO 2025 (TPS3649)

AE = adverse event; imAE = immune-mediated adverse event; MMRp = mismatch repair-proficient; mPR = major pathological response rate; MSI-L = microsatellite instability-low; MSS = microsatellite stable; SAE = serious adverse event

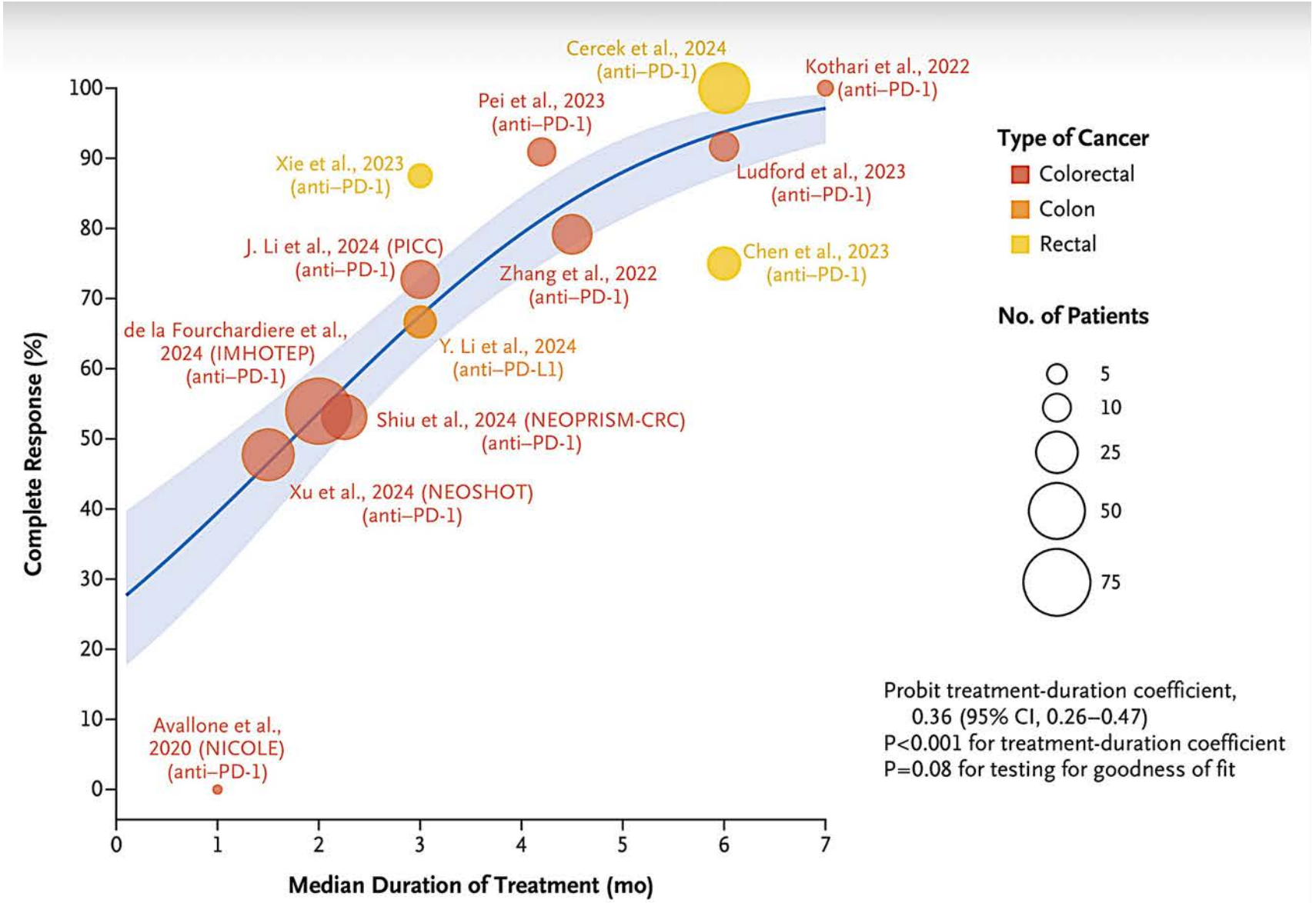
1. clinicaltrials.gov. NCT06567782. Accessed May 2025.

RTP RESEARCH TO PRACTICE

Neoadjuvant Immunotherapy in MSI-H Colon Cancer

- Significant tumor regression, 67-75% complete pathologic response
- Duration of immunotherapy was variable 1-6 mo

Duration of Neoadjuvant Immunotherapy and Incidence of Complete Response among Patients with MMRd Colorectal Cancer



Rousseau, White, Cercek, Diaz NEJM 2025

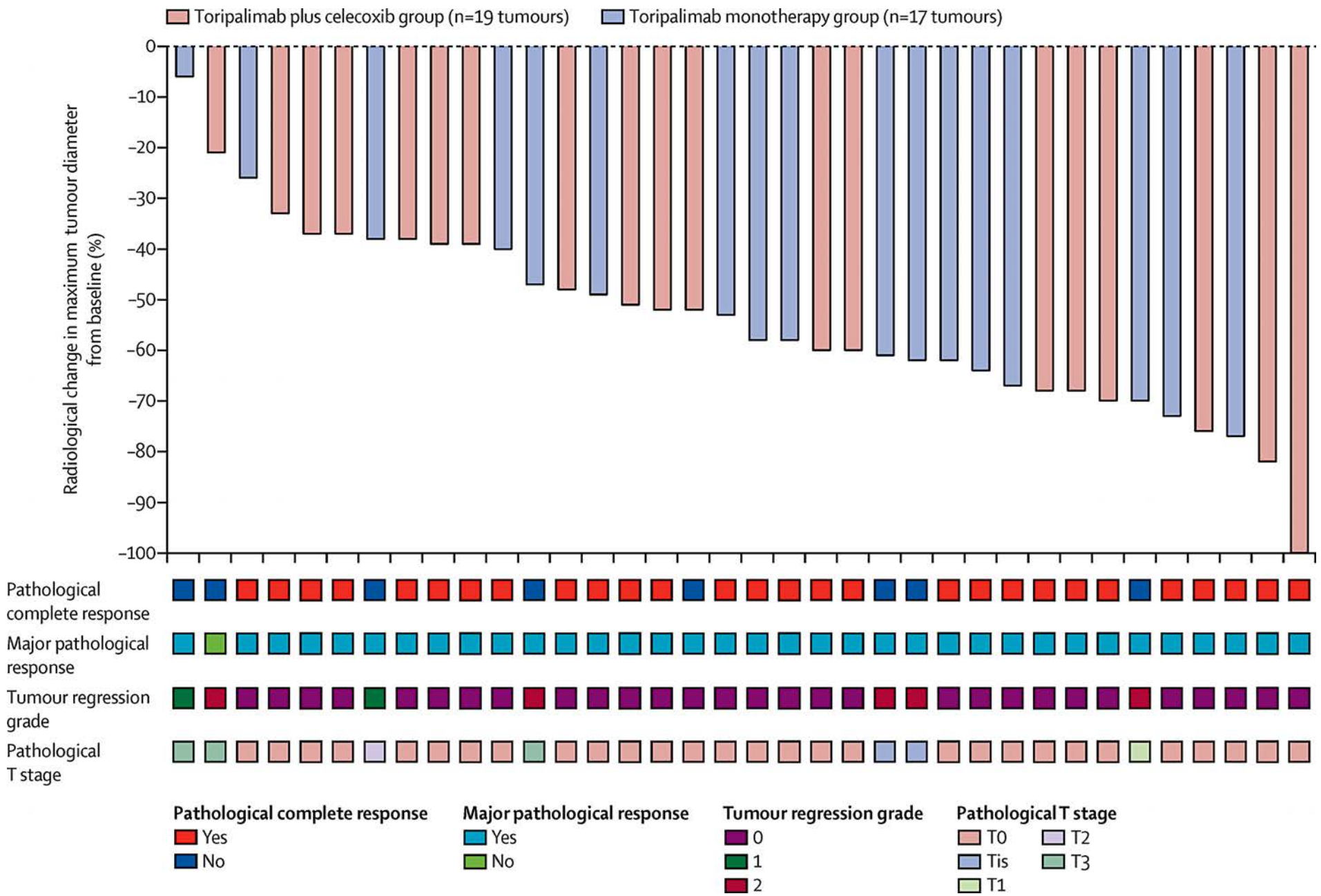
Neoadjuvant Immunotherapy in MSI-H Colon Cancer

Organ preservation?

In rectal cancer MRI and endoscopic evaluation correlate with cCR assessment

In colon cancer assessment of cCR is challenging

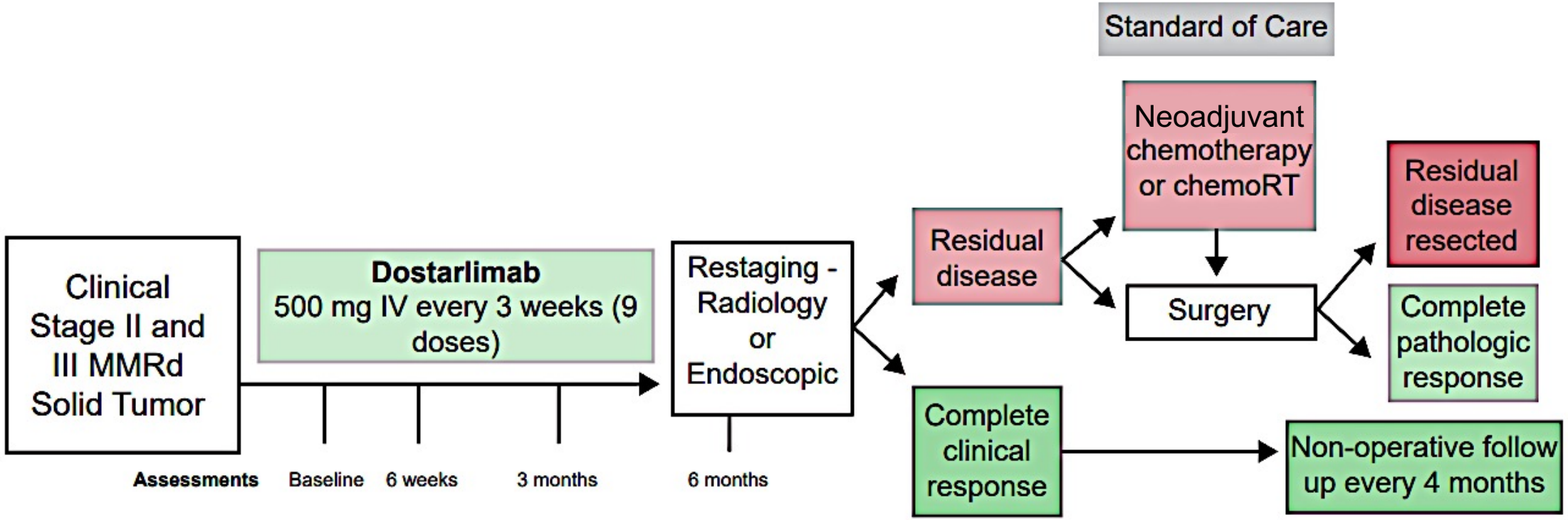
In metastatic setting resected lesions reported pCR up to 60%



Hu et al, The Lancet Gastroenterol Hepatol 2022

Neoadjuvant PD1 blockade in dMMR locally advanced solid tumors

NCT04165772



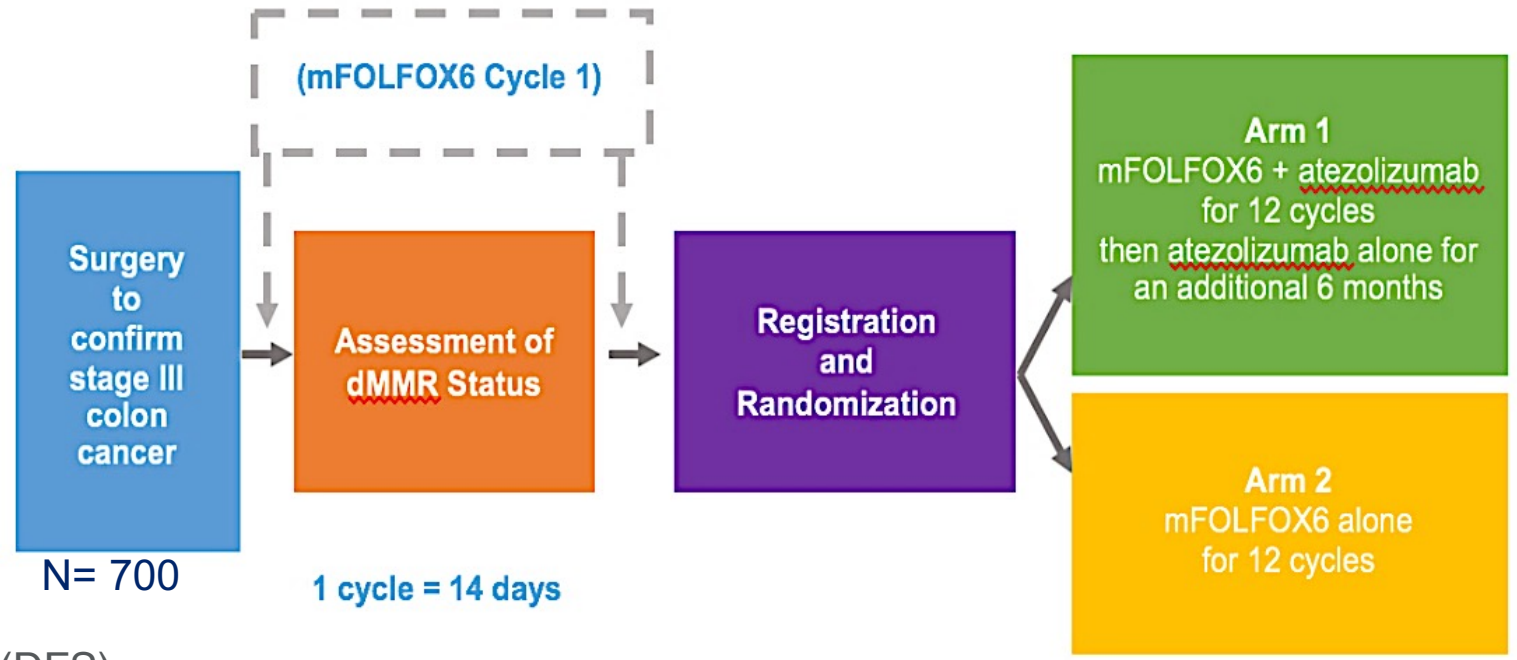
Ongoing Neoadjuvant Trials

NCT Number	Class of ICB agent(s)	ICB agent	Setting	Additional Agents	Response Endpoint	Microsatellite status of Included Tumors	Phase
NCT03926338	PD-1	Toripalimab	Neoadjuvant	COX2(Celecoxib)	pCR	MSI	I/II
NCT05371197	PD-1	Envafolimab	Neoadjuvant	-	pCR	MSI	II
NCT05197322 NEOPRISM-CRC	PD-1	Pembrolizumab	Neoadjuvant	-	pCR	MSI	II
NCT04165772	PD-1	Dostarlimab	Neoadjuvant	-	cCR	MSI	II
NCT03026140	PD-1, CTLA-4, IL-8, Anti-LAG3	Ipilimumab +Nivolumab +/- celecoxib, Nivolumab + BMS-986253, Nivolumab+ Relatlimab	Neoadjuvant	COX2 (Celecoxib)	pCR	MSS/MSI	II

Adjuvant therapy for dMMR colon cancer

ATOMIC Alliance A021502

NCT02912559



The primary objective:

- Disease-free survival (DFS)

Secondary objectives:

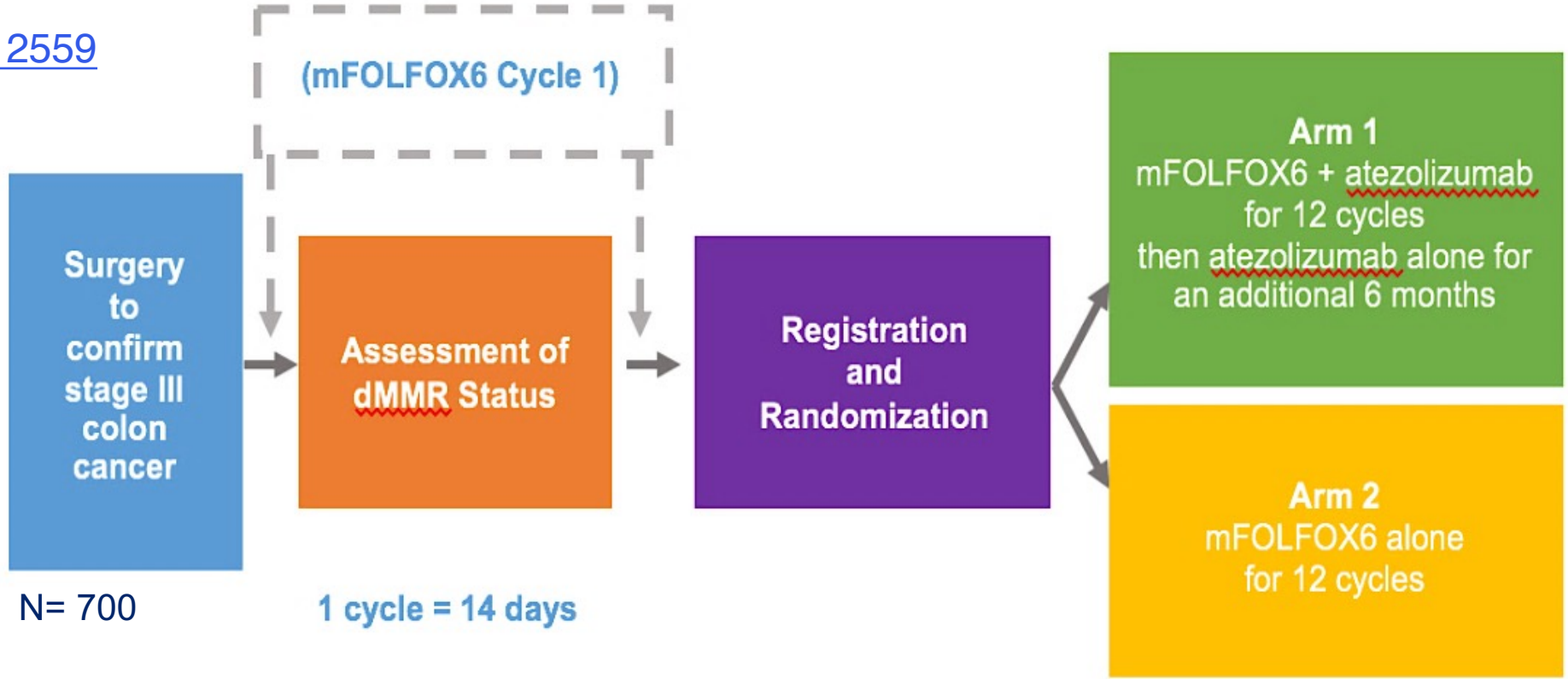
- Overall survival (OS)
- Adverse events (AE) profile and safety of each treatment arm

Quality of life objective:

- To determine the impact of the addition of atezolizumab to FOLFOX on patient-reported neuropathy, health-related quality of life (QOL), and functional domains of health-related QOL.

ATOMIC Alliance A021502

NCT02912559



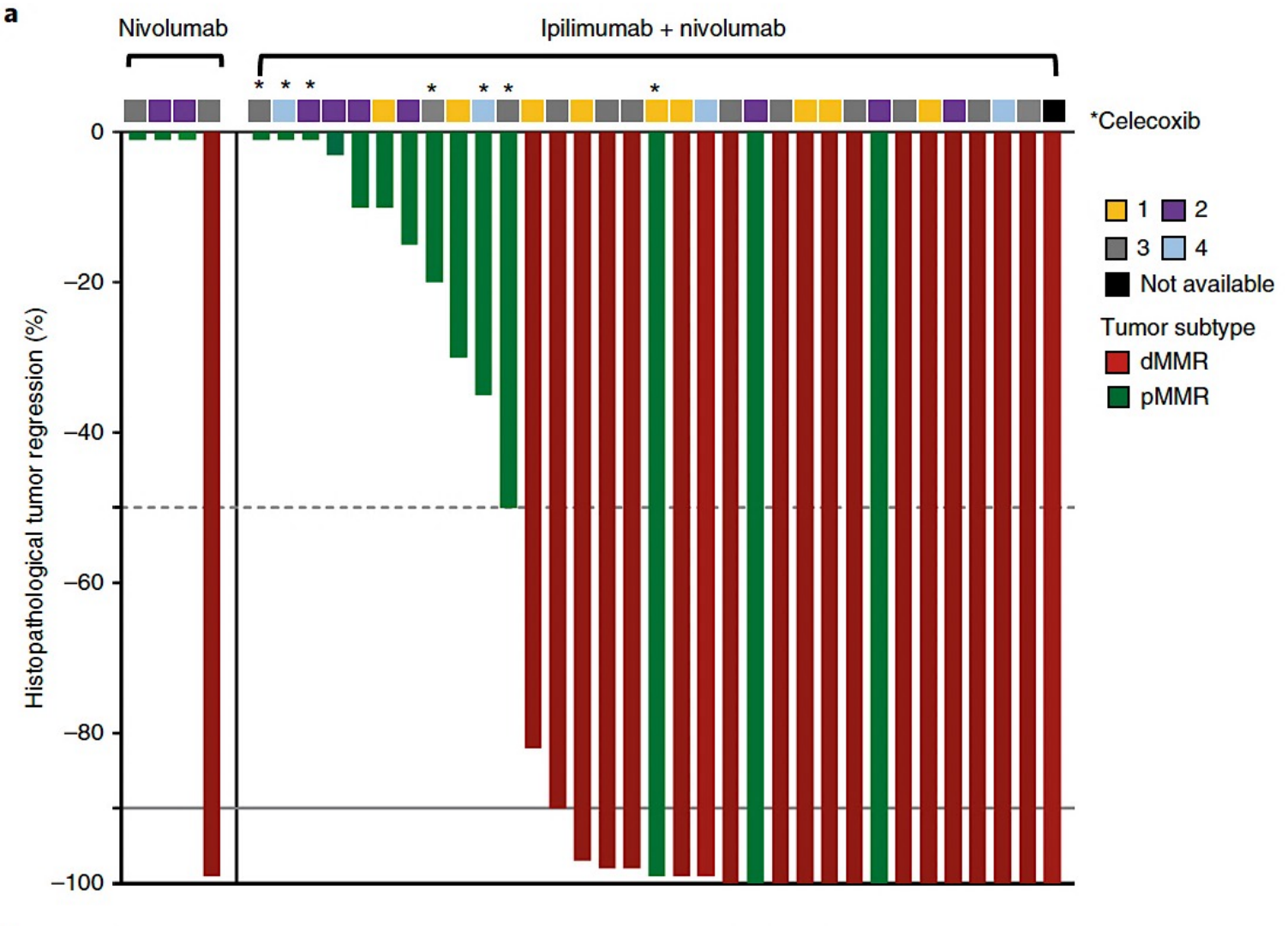
LBA1 Plenary Session on Sunday June 1, 2025!

Is there a role for immunotherapy in pMMR colon and rectal cancer?

Neoadjuvant Ipi/Nivo in MSS colon cancer: NICHE 1

MSS early stage colon
Ipi x1
Nivo X2
Resection w/in 6 weeks

7/31 patients with >50% pathologic response

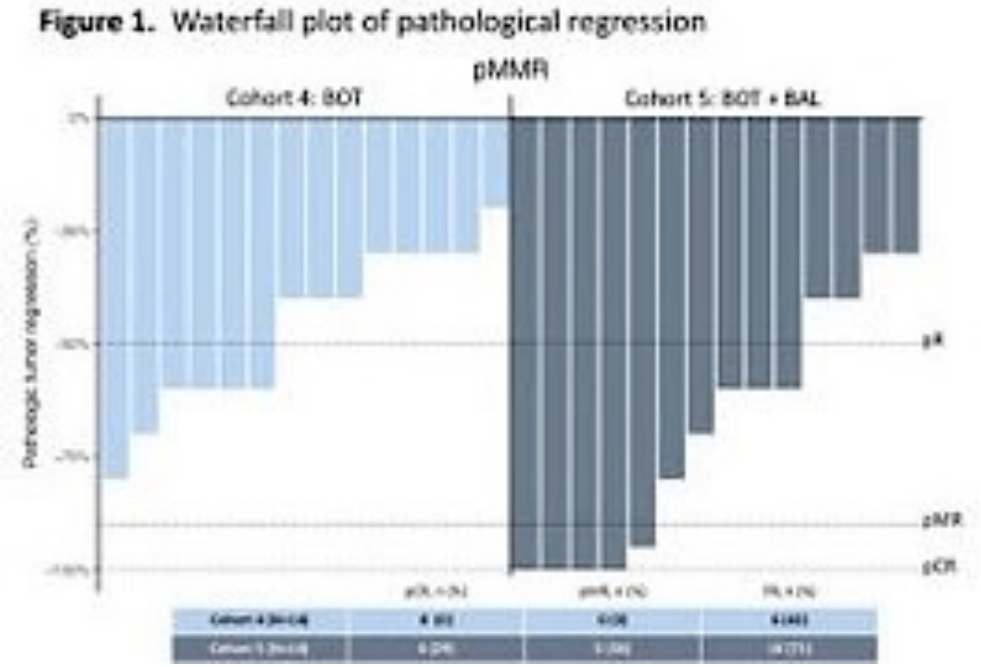


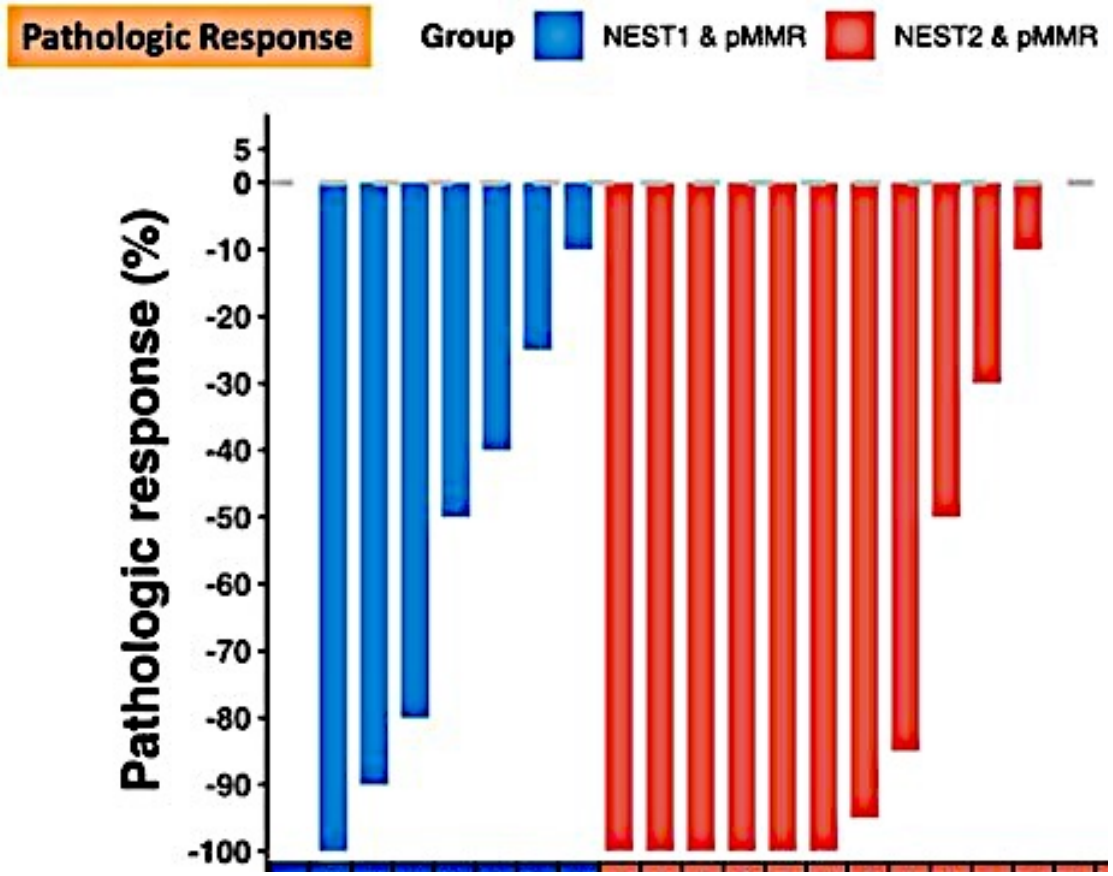
Chalabi et al Nature Med 2020; SITC 2023

Ongoing studies evaluating combination PD1/anti CTLA4 in pMMR early stage CRC

- NEST
- UNICORN
- NEOASIS

Primary endpoint pCR





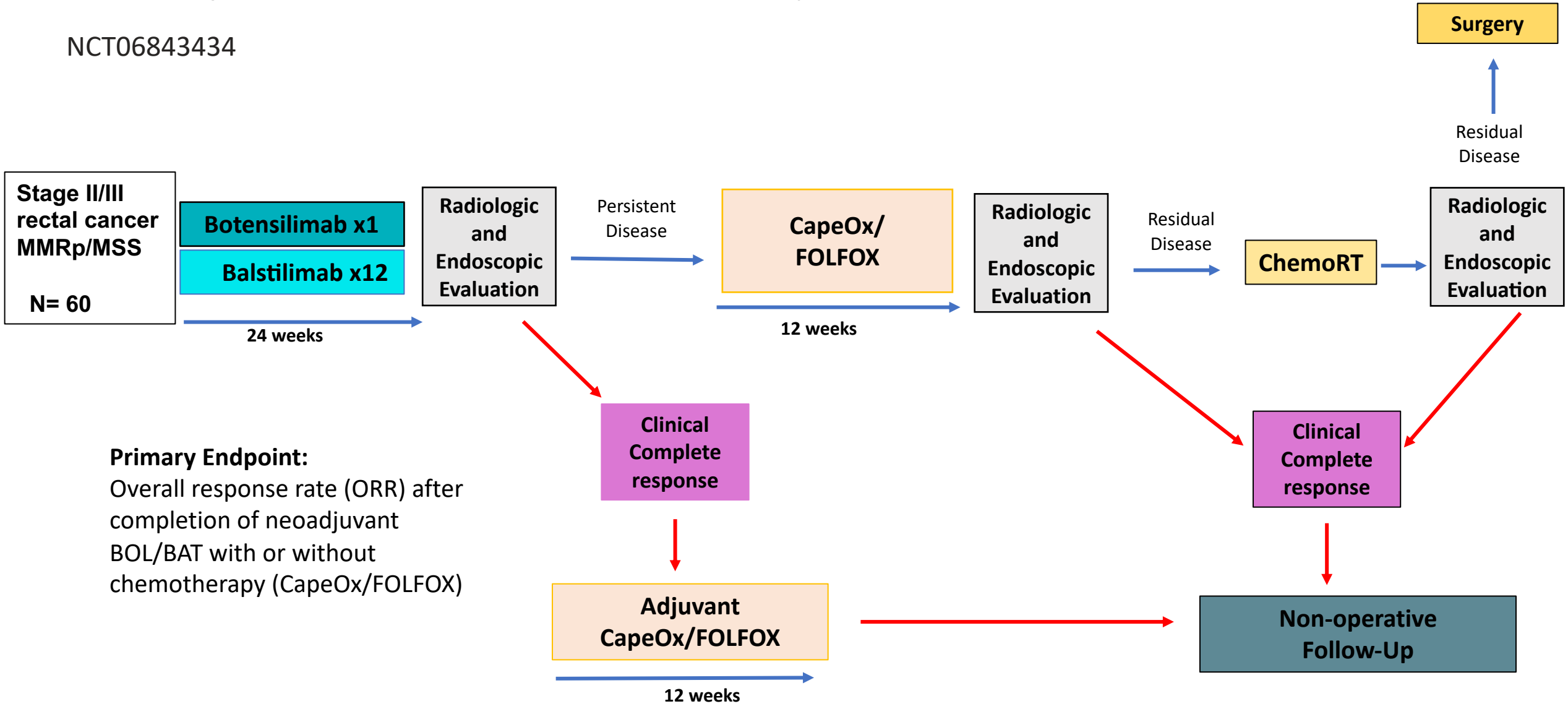
Kasi et al. ASCO GI 2025

Trials incorporating ICB to neoadjuvant therapy in rectal cancer

Study	Design	Eligibility	N	Median FU	Treatment Schedule	Primary Endpoint
Voltage-A NCT02948348	Phase I/II: single arm	cT3-T4 or N+, <= 12cm from AV	44 (39 MMRp and 5 MMRdI)	MMRp: 33 months MMRd: 17 months	LCCRT + Nivolumab x5 + surgery	pCR (30% in MSS)
NRG-GI002 NCT02921256	Phase II: RCT	cT3-T4 or N+, <= 5cm from AV	185	3.5 years	FOLFOX x6 + LCCRT + surgery	
					FOLFOX x6 + LCCRT/ Pembrolizumab + surgery	NAR (negative) Benefit in OS in P arm (not DFS)
PANDORA NCT04083365	Phase II: single arm	cT3-T4 or N+	55	22.2 months	LCCRT + Durvalumab x3 + surgery	pCR 34.5%
Union NCT04928807	Phase III: RCT	cT3-T4 or N+, <= 10 cm from AV	231	9.7 months	LCCRT + CAPOX x2 + surgery	pCR 15.3
					SCRT + CAPOX/ Camrelizumab x2 + surgery	39.8
TARZAN NCT04017455	Phase II: single arm	<=T3ab N0-1 distal-mid rectal	44	23 months	SCRT + Atezolizumab/ bevacizumab x3	nCR 45% (42% organ preservation)
Averectal NCT03503630	Phase II: single arm	cT3b-T4 or N+	40	44 months	SCRT + mFOLFOX6/ Avelumab x6 + surgery	pCR 37.5%

Neoadjuvant PD1/CTLA4 in MMRp/MSS Rectal Cancer

NCT06843434



Primary Endpoint:
Overall response rate (ORR) after completion of neoadjuvant BOL/BAT with or without chemotherapy (CapeOx/FOLFOX)

Conclusion

- Studies highlight the clinical impact of biomarker driven therapy in early-stage disease
- In colon cancer organ preservation should be pursued
- Duration of therapy is unclear and inconsistent
- Longer duration would likely yield higher responses in colon cancer
- Radiographic determination of clinical complete response is challenging in colon cancer
- Improved assessment of complete response; ctDNA, novel imaging?

Case Presentation: 68-year-old man with T3N1 MSI-H rectal cancer receives neoadjuvant dostarlimab

Dr Henna Malik (Houston, Texas)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Should all patients with localized/locally advanced CRC undergo MSI/MMR testing? Which patients with MSI-high/MMR-deficient disease should be offered neoadjuvant therapy with an immune checkpoint inhibitor?

When administering neoadjuvant dostarlimab to patients with MSI-high/MMR-deficient locally advanced rectal cancer, how long should it be continued? Should it be continued in the adjuvant setting for patients who have residual disease at surgery?

QUESTIONS FOR THE FACULTY

For a patient with MSI-high/MMR-deficient locally advanced rectal cancer with a significant response to neoadjuvant dostarlimab, is it acceptable to proceed directly to surgery without chemoradiation therapy?

For which patients with MSI-high/MMR-deficient locally advanced rectal cancer with a significant response to neoadjuvant dostarlimab is it acceptable to forgo surgery altogether? How long do you continue the dostarlimab for these patients, and would it be beneficial to monitor them using ctDNA?

Case Presentation: 38-year-old woman diagnosed with Lynch syndrome and dMMR Stage IIA colon cancer undergoes resection

Dr Erik Rupard (Hershey, Pennsylvania)

QUESTIONS FOR THE FACULTY

What adjuvant therapy, if any, would you have recommended in this woman's case? Given her young age and MSI-high status, is there a role for adjuvant immunotherapy?

At this point, would you consider monitoring her using ctDNA?

Given this patient's family history, would you recommend genetic testing and risk-reducing surgery for her siblings? Have any of your patients with Lynch syndrome developed breast cancer? How do you counsel your patients with Lynch syndrome, particularly those who are younger, about the risk of breast cancer?

Agenda

MODULE 1: Role of Circulating Tumor DNA (ctDNA) Evaluation in Nonmetastatic Colorectal Cancer (CRC) — Dr Dasari

MODULE 2: Role of Immune Checkpoint Inhibitors in the Management of Nonmetastatic Microsatellite Instability-High (MSI-H) CRC — Dr Cercek

MODULE 3: Management of Oligometastatic Disease and Hepatic-Only Metastases in CRC; Role of ctDNA Evaluation in Metastatic Disease — Dr Kasi

MODULE 4: Role of Immune Checkpoint Inhibitors in the Management of MSI-H Metastatic CRC (mCRC) — Dr Hecht

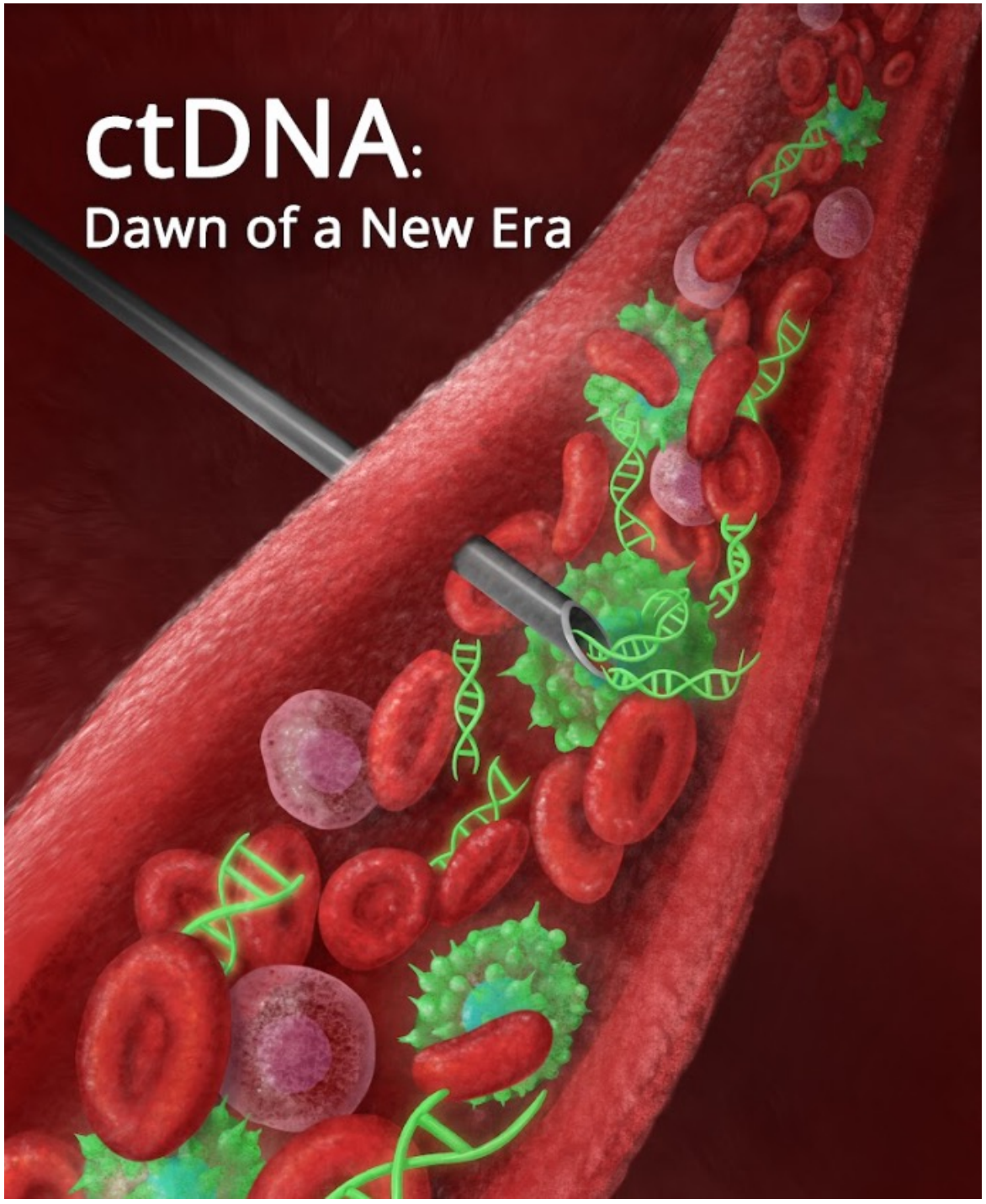
MODULE 5: Identification and Care of Patients with mCRC and Actionable Genomic Alterations — Prof Van Cutsem

RTP RESEARCH TO PRACTICE

Management of “Oligo”-metastatic disease and Hepatic-only metastases in CRC; role of ctDNA Evaluation in metastatic disease

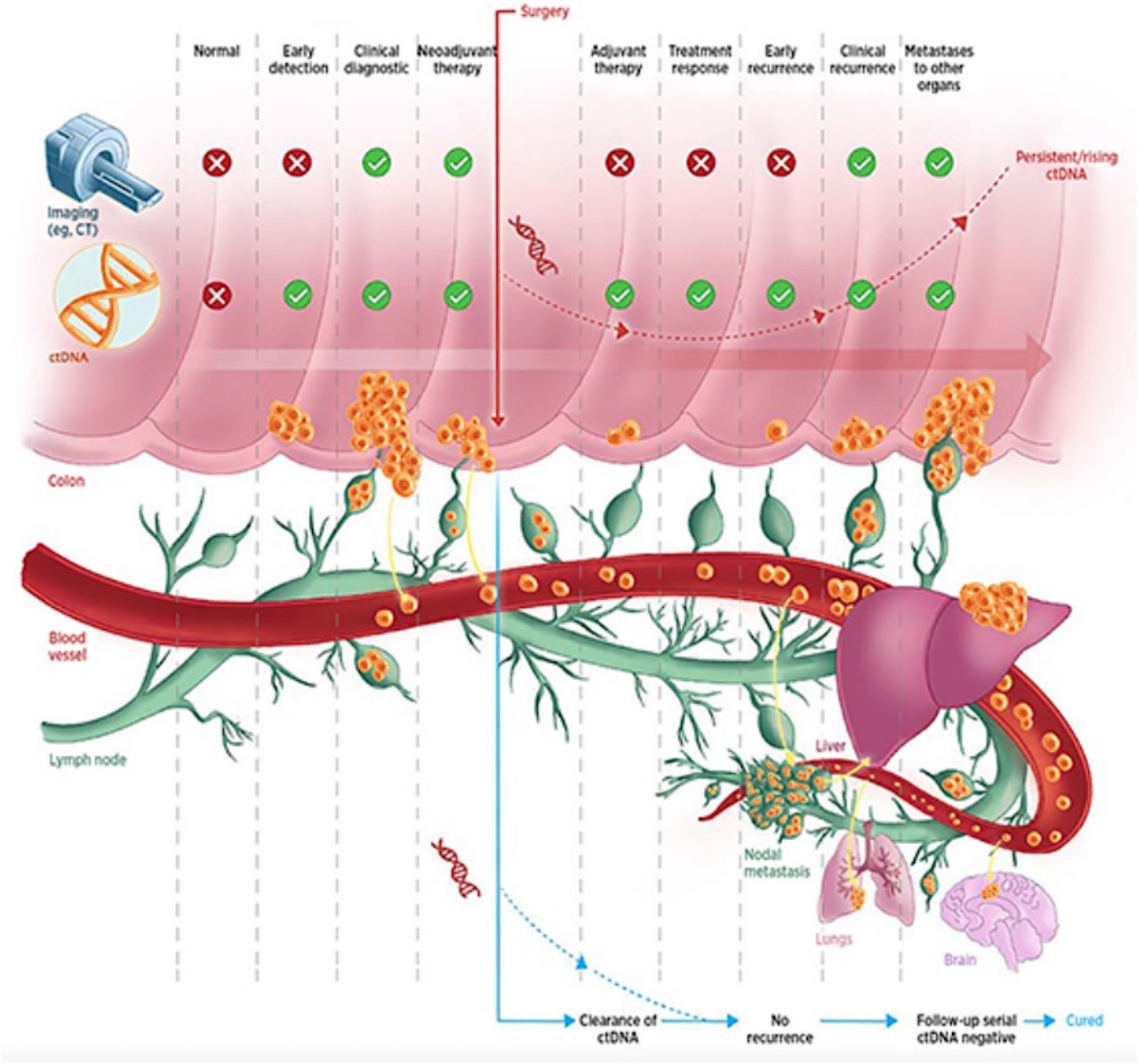
Pashtoon Kasi, MD, MS

Medical Director of GI Oncology,
City of Hope Orange County.
Rad Family Chair in Gastrointestinal Oncology
kasi@coh.org
X: @pashtoonkasi



Goals and objectives

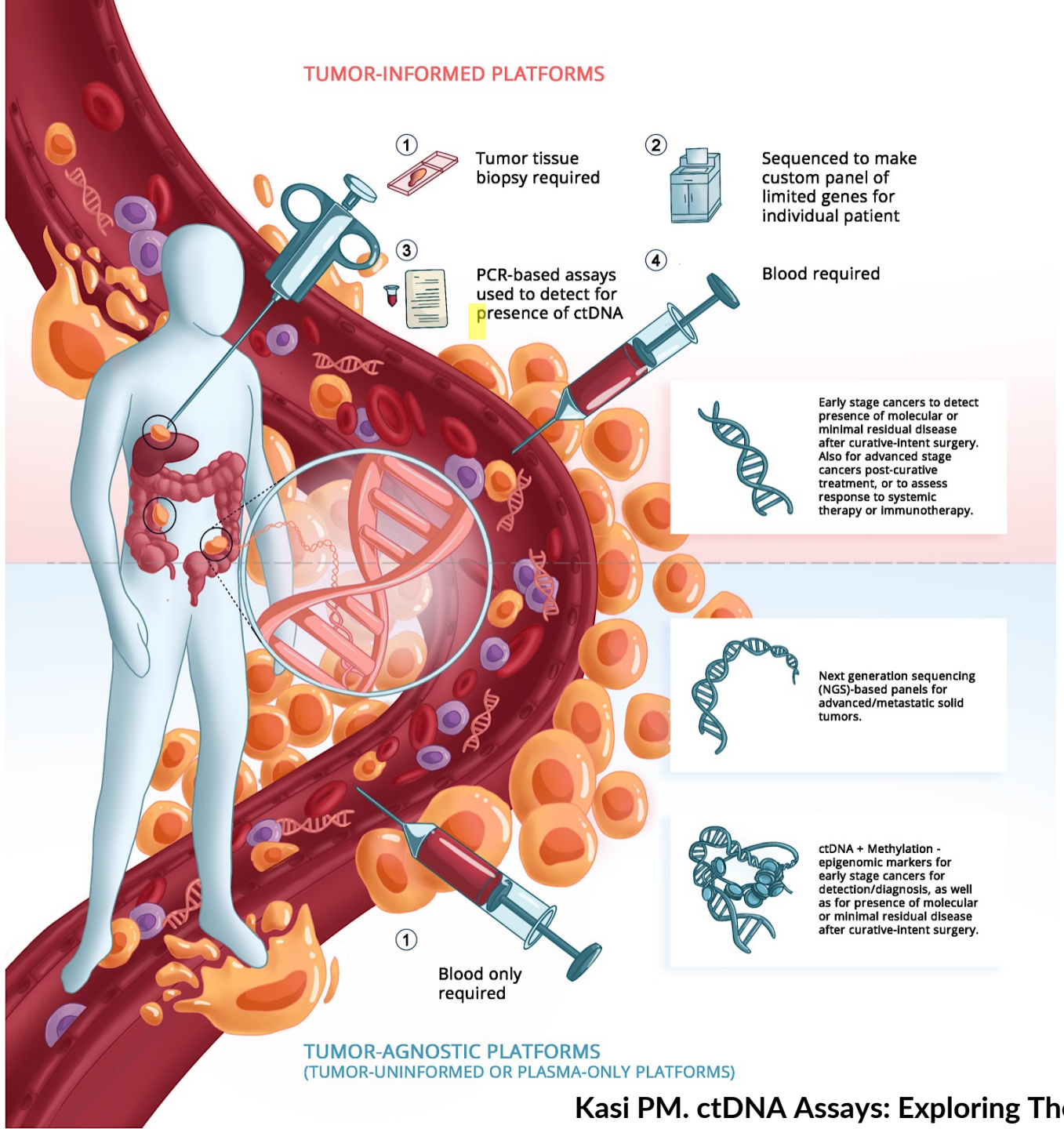
- Clinical trial database guiding the management of **oligometastatic disease** and **hepatic-only** metastases in CRC.
- Predictive impact of **ctDNA** status noted in published datasets evaluating its use in oligometastatic CRC.
- Published data supporting the use of **ctDNA testing to monitor for response** in patients with mCRC receiving systemic therapy.
- Role of ctDNA testing to detect **acquired resistance mechanisms** and clonal evolution in patients with mCRC.



- Diagnosis
- Minimal Residual Disease
- Treatment Response
- Acquired Resistance

ASCO Daily News®

Kasi PM. ctDNA Assays: Exploring Their Clinical Use in Oncology Care. January 2022. ASCO Daily News.



Tumor-informed Platforms Versus Tumor-agnostic (tumor-uninformed or plasma-only) Platforms

ASCO Daily News®

Kasi PM. ctDNA Assays: Exploring Their Clinical Use in Oncology Care. January 2022. ASCO Daily News.

Units of Measurement

VAF%

- Variant Allele Fraction

VAF represents the percentage of sequencing reads that support a specific variant allele relative to the total number of reads at that genomic locus

MTM

- Mean Tumor Molecules/ml

Absolute measurement

Focuses on the number of target molecules in a given volume

PPM

- Parts per million

Relative measurement

Focuses on the ratio of ctDNA molecules containing MRD targets out of the total cfDNA molecules measured (ctDNA + normal cfDNA)

1.67 parts per million (PPM) = 1.67 × 10^{-6} tumor fraction = 0.000167% VAF

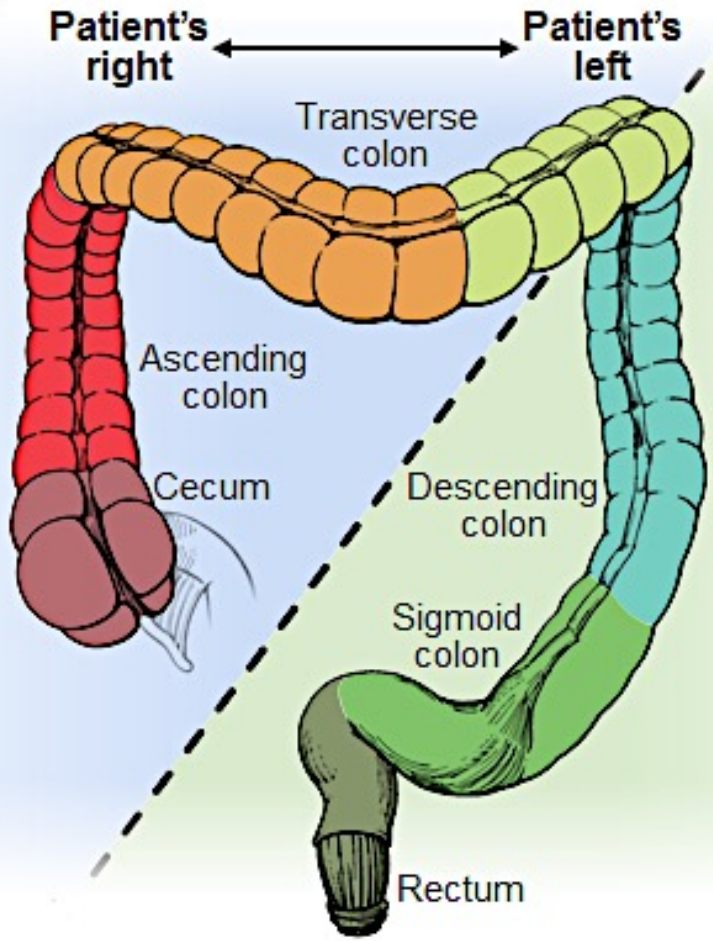
RIGHT vs. LEFT

MIDGUT DERIVATIVE

- ↑ females
- ↑ sessile serrated lesions
- ↑ mucinous tumors

Overall WORSE prognosis

- ↑ CIMP-high
- ↑ BRAF
- ↑ MSI-high
- ↑ CMS-1-MSI immune tumors
- ↑ CMS-3-metabolic tumors (↑ KRAS)



HINDGUT DERIVATIVE

- ↑ males

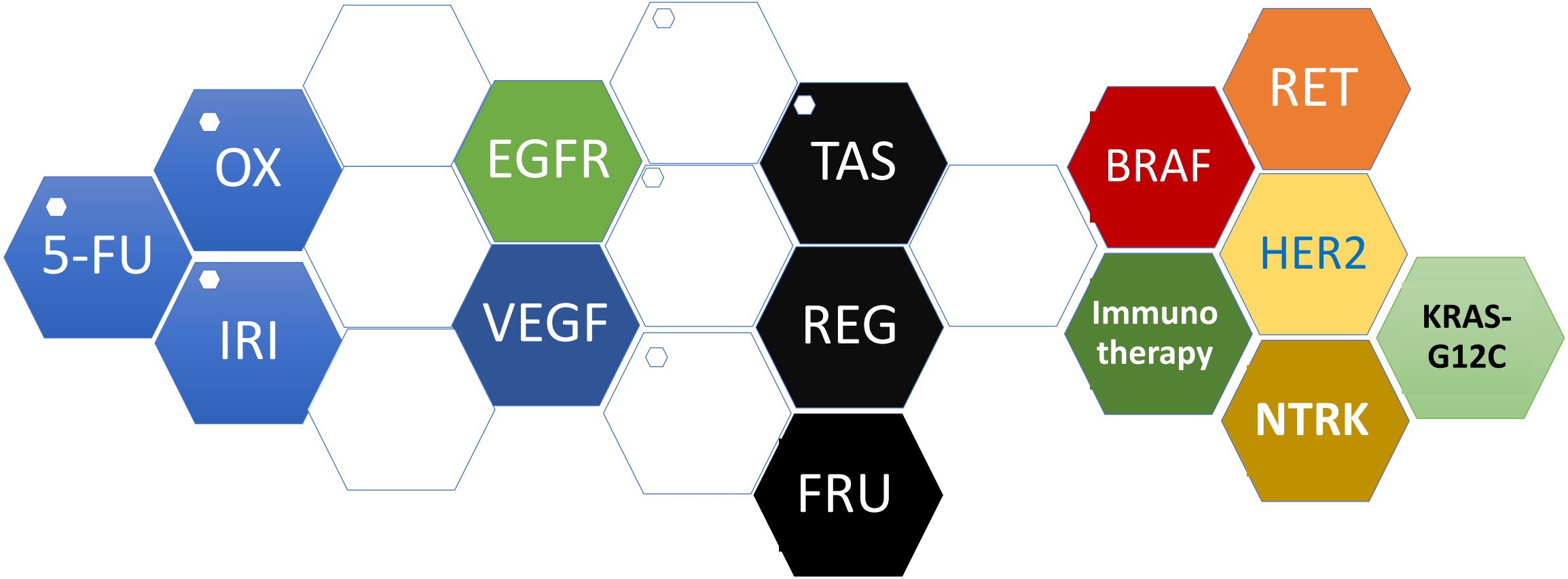
Overall BETTER prognosis

- ↑ CMS-4-MSI mesenchymal
- ↑ CMS-2-canonical distally
- ↑ TP53
- ↑ APC

X: @pashtoonkasi

Kasi PM et al. Colorectal Cancer. Lancet Oct 2019.

Treatment options for patients with mCRC



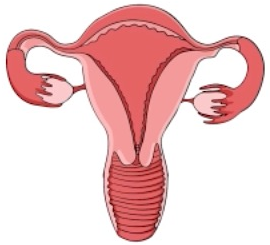
X: @pashtoonkasi

Kasi PM et al. Colorectal Cancer. Lancet Oct 2019.

Opportunities for Precision Medicine are Missed Up to 30% of the Time

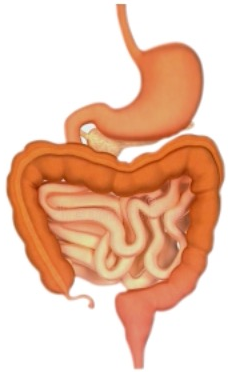
Frequency of tissue insufficiency

OVARIAN CANCER [1]



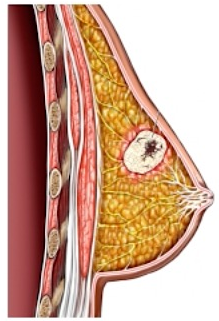
~10%

GI CANCERS [1-2]



~10%

BREAST CANCER [1-3]

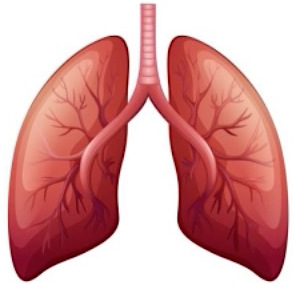


~20%

BILIARY TRACT CANCERS [4]

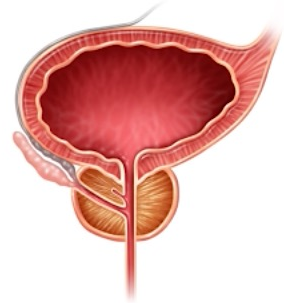
~25%

NSCLC [5-6]



~30%

PROSTATE CANCER [7]



~30%

GI = gastrointestinal, NSCLC = non-small cell lung cancer

1. Zehir A, Benayed R, Shan RH, et al. *Nat Med*. 2017;23(6):703-713; 2. Nakamura Y, Taniguchi H, Ikeda M, et al. *Nat Med*. 2020;26(12):1859-1846; 3. Meric-Bernstam F, Brusco L, Shaw K, et al. *J Clin Oncol*. 2015;33(25):2753-2762; 4. Lamarca A, Kapacee Z, Breeze M, et al. *J Clin Med*. 2020;9(9):2854; 5. Hagemann IS, Devarakonda S, Lockwood CM, et al. *Cancer*. 2015;121(4):631-639; 6. Aggarwal C, Thompson JC, Black TA, et al. *JAMA Oncol*. 2019;5(2):173-180; 7. Hussain M, Corcoran C, Sibilla C, et al. *Clin Cancer Res*. 2022;28(8):1518-1530.

1st line Anti-EGFR therapy selection

- **Selection** of the patient for anti-EGFR – tissue
  - LEFT
  - RAS-wildtype
  - BRAF-wildtype
  - HER2-negative
- Role for **liquid biopsies (YES)**

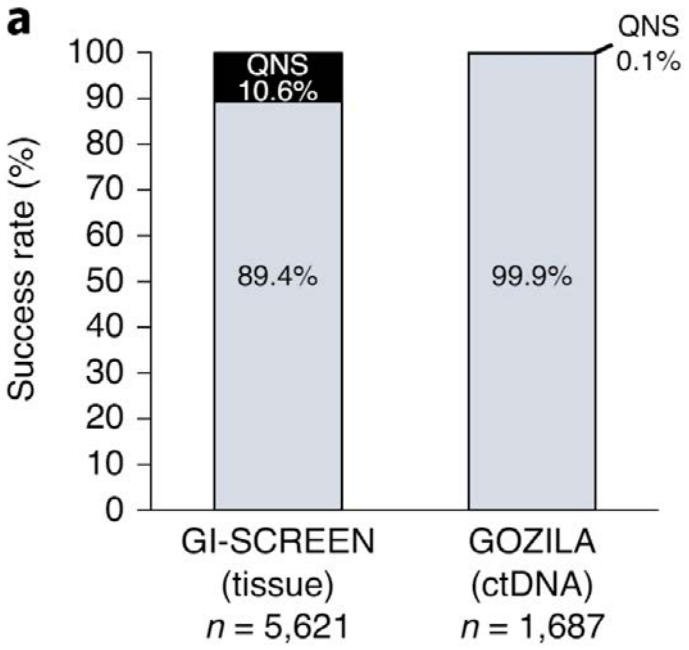
	Anti-EGFR OS (months)	Anti-VEGF OS (months)
NCDB	**42.9**	27.5
CALGB 80405	**39.3**	32.6
PEAK	**43.4**	32.0
FIRE-3	**38.3**	28.0
PARADIGM	**37.9**	34.7
PARADIGM (ctDNA hyper-selected)	**42.1**	35.5

Shitara K et al.
Negative hyperselection of patients with RAS wild-type metastatic colorectal cancer for panitumumab: A biomarker study of the phase III PARADIGM trial.
DOI: 10.1200/JCO.2023.41.4_suppl.11 Journal of Clinical Oncology 41, no. 4_suppl (February 01, 2023)

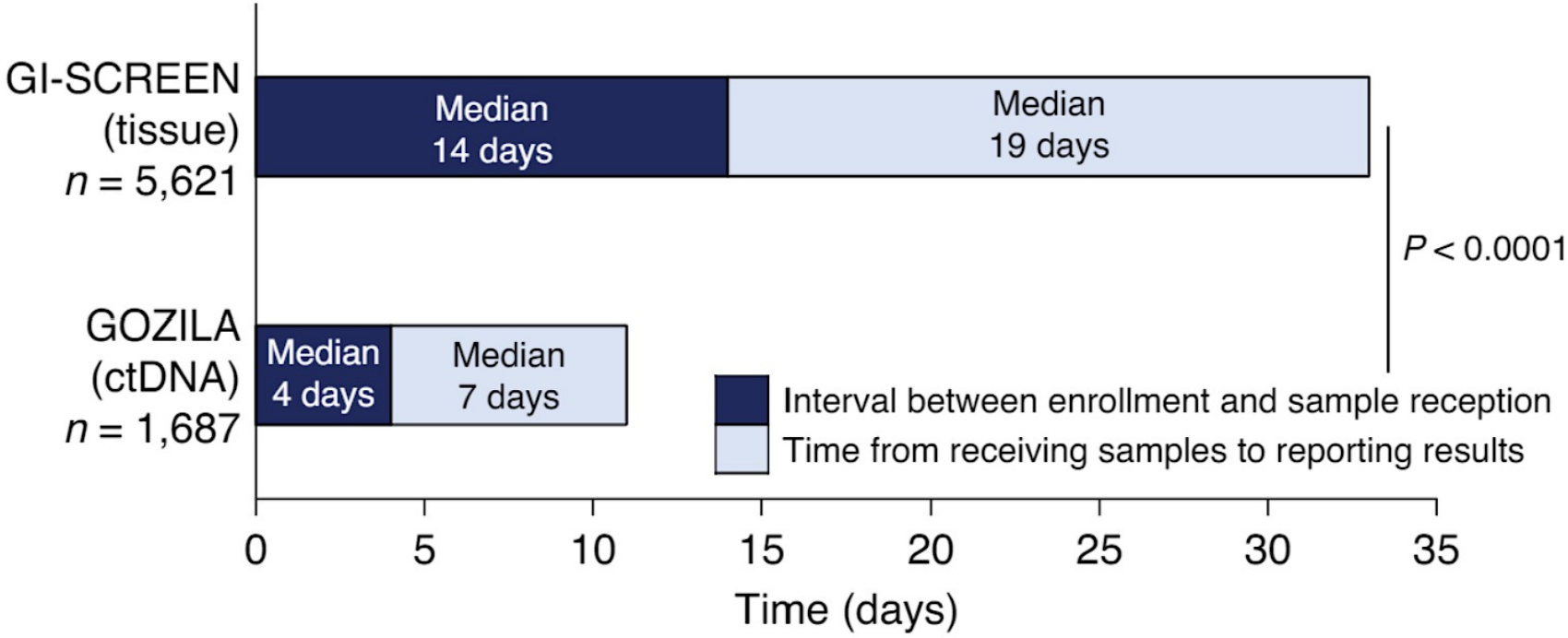
Potential Advantages of Using ctDNA Assays to Assess Actionable Mutations

- Analysis of trial enrollment of patients with advanced GI cancers using ctDNA sequencing (GOZILA, n = 1687) vs tumor tissue sequencing (GI-SCREEN, n = 5621)

Quantity Not Sufficient



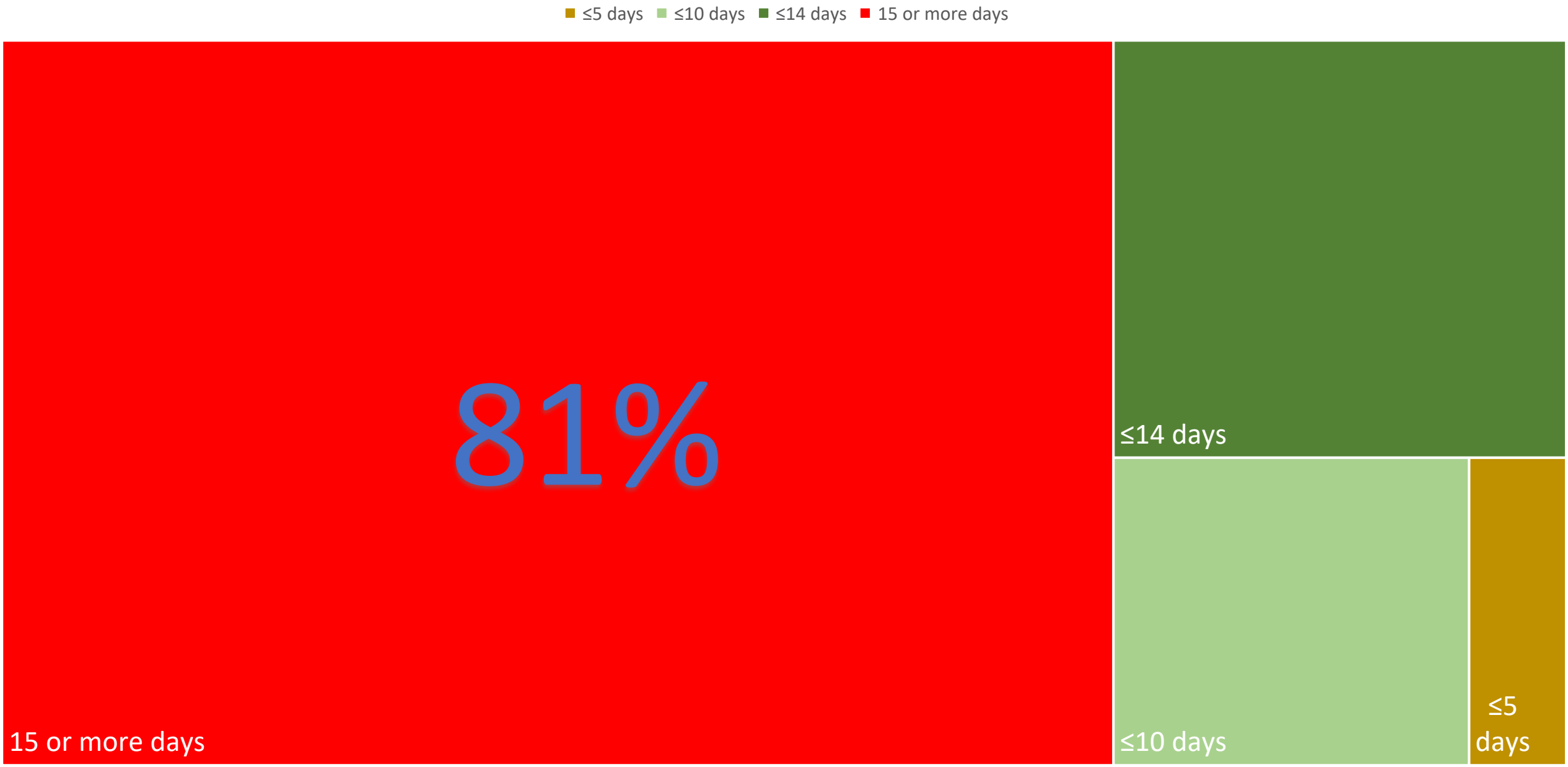
Turnaround time



Turnaround time

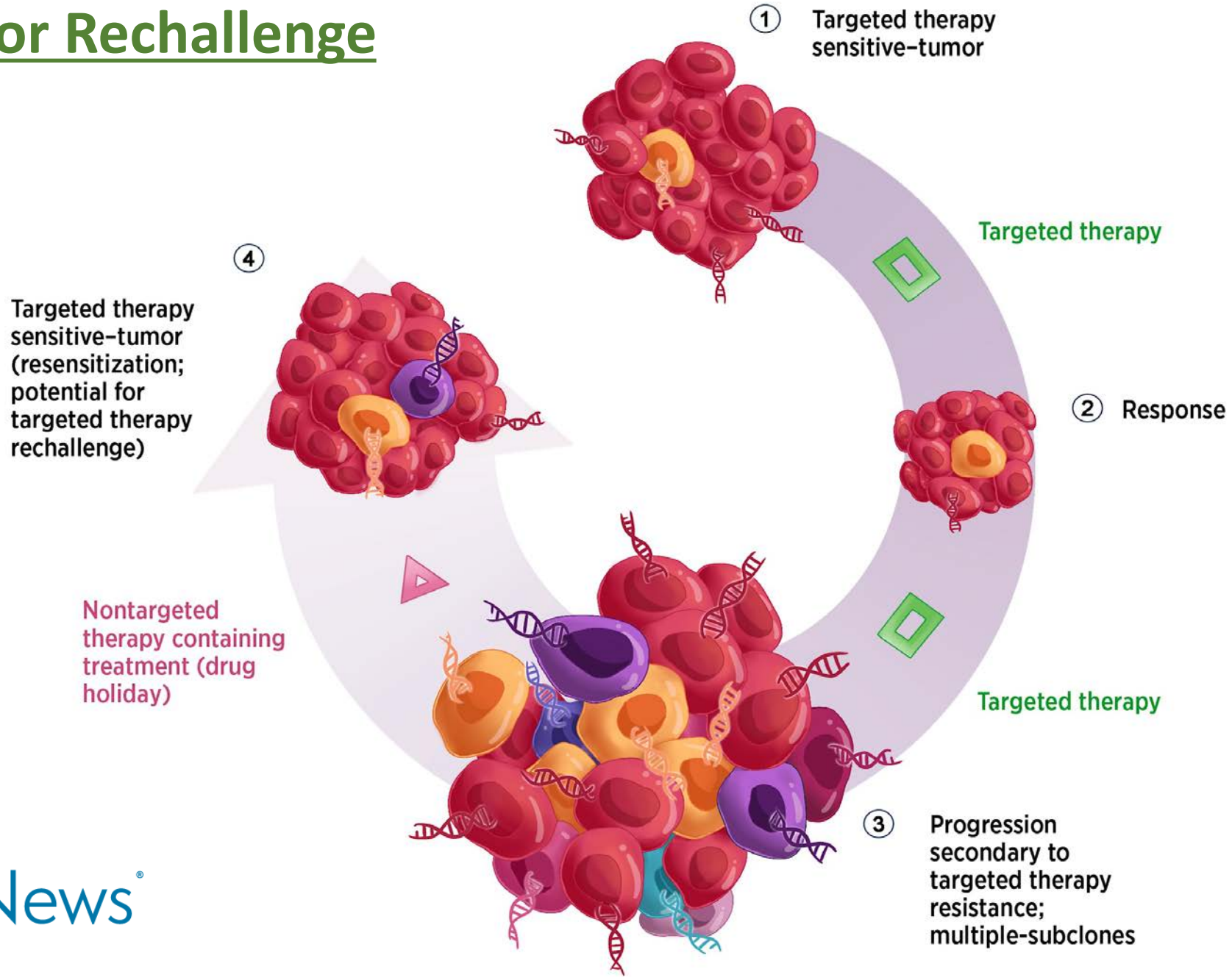
Nakamura. Nat Med. 2020;26:1859.

RAS-testing and turnaround times



Sangaré L, Delli-Zotti K, Florea A, Rehn M, Benson AB, Lowe KA. An evaluation of *RAS* testing among metastatic colorectal cancer patients in the USA. Future Oncol. 2021 May;17(13):1653-1663. PMID: 33629919.

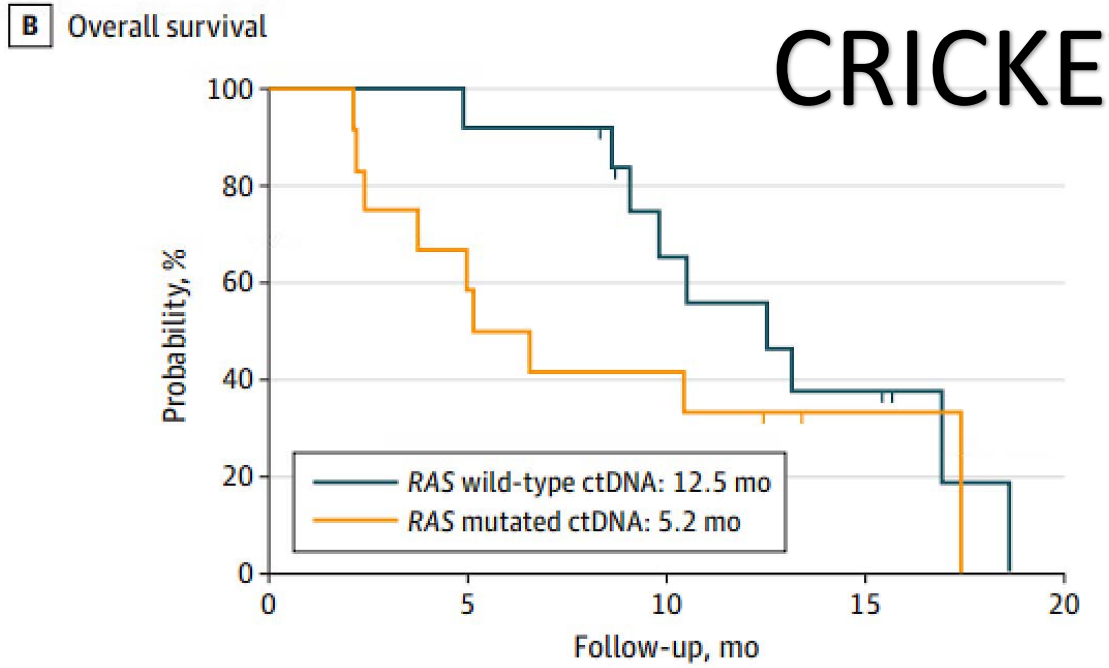
Resensitization or Rechallenge



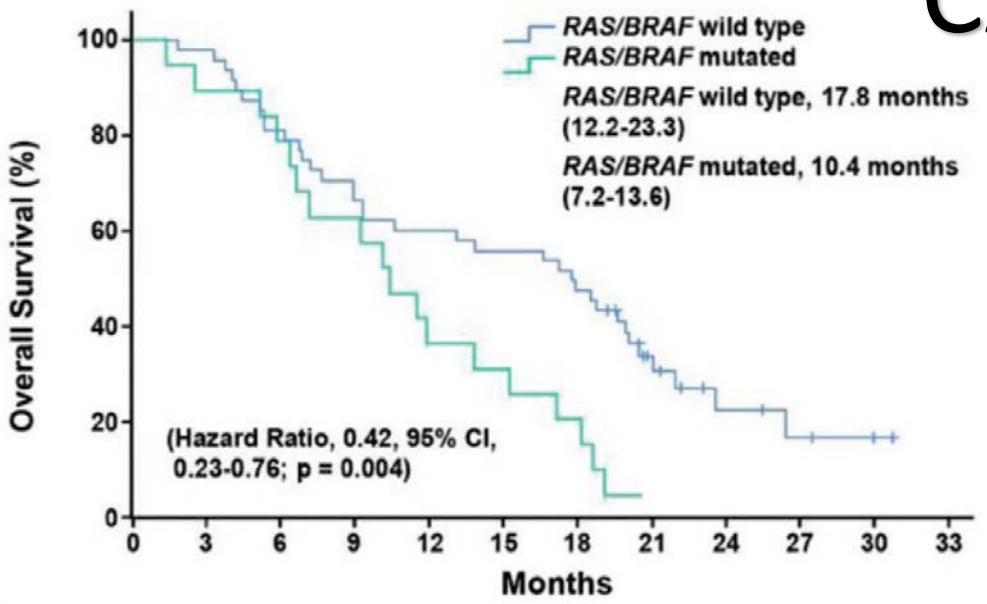
ASCO Daily News®

Kasi PM. ctDNA Assays: Exploring Their Clinical Use in Oncology Care. January 2022. ASCO Daily News.

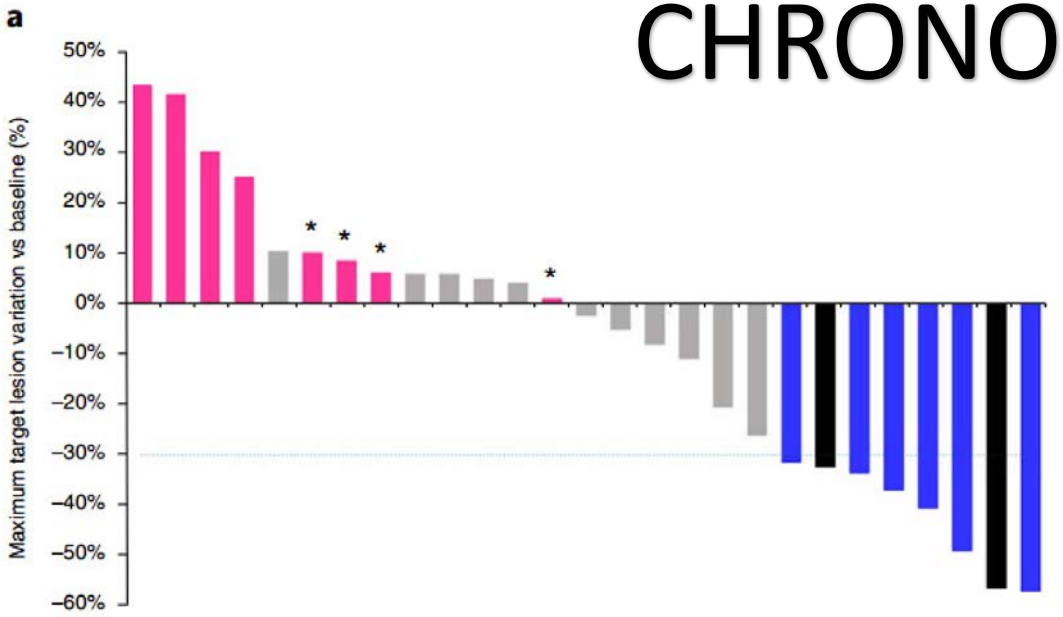
CRICKET



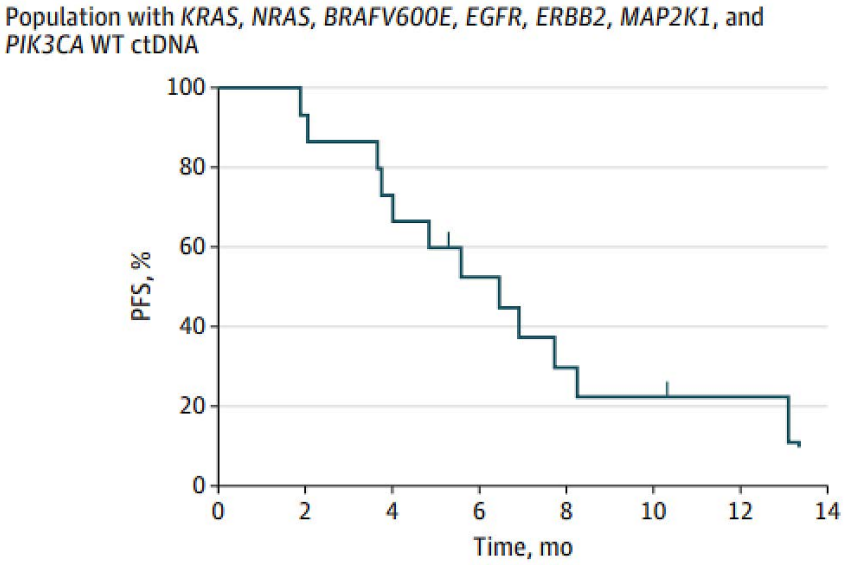
CAVE



CHRONOS



VELO



Ciardiello D. Anti-EGFR Rechallenge in Patients With Refractory ctDNA RAS/BRAF wt Metastatic Colorectal Cancer: A Nonrandomized Controlled Trial. JAMA Netw Open. 2024 Apr 1;7(4):e245635.

ctDNA as a rapid surrogate of tumor response

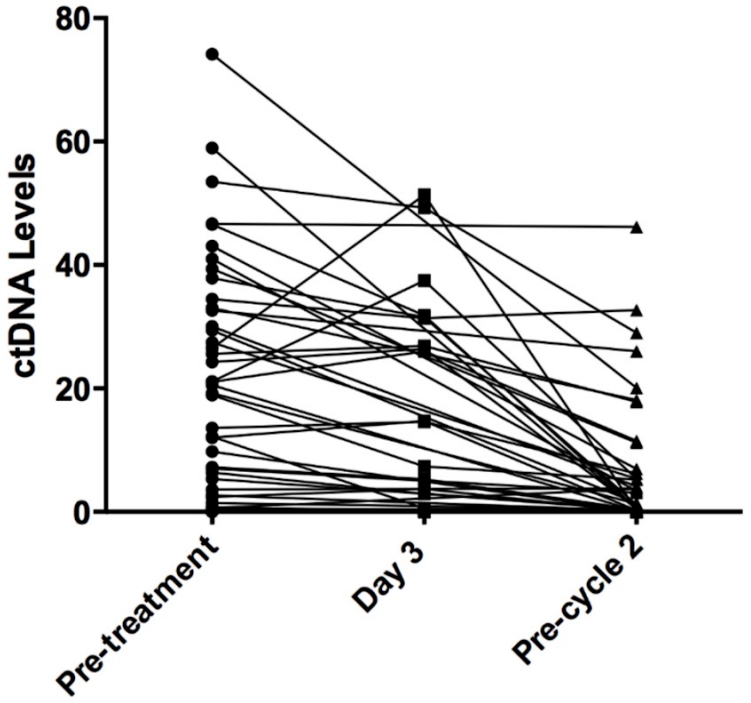
Half-life of ctDNA in circulation is measured in minutes/hours

Protein markers (CEA) may have half-life of days, with post-treatment spikes

Similar findings also seen in urinary ctDNA.

Husain et al CCR ‘17

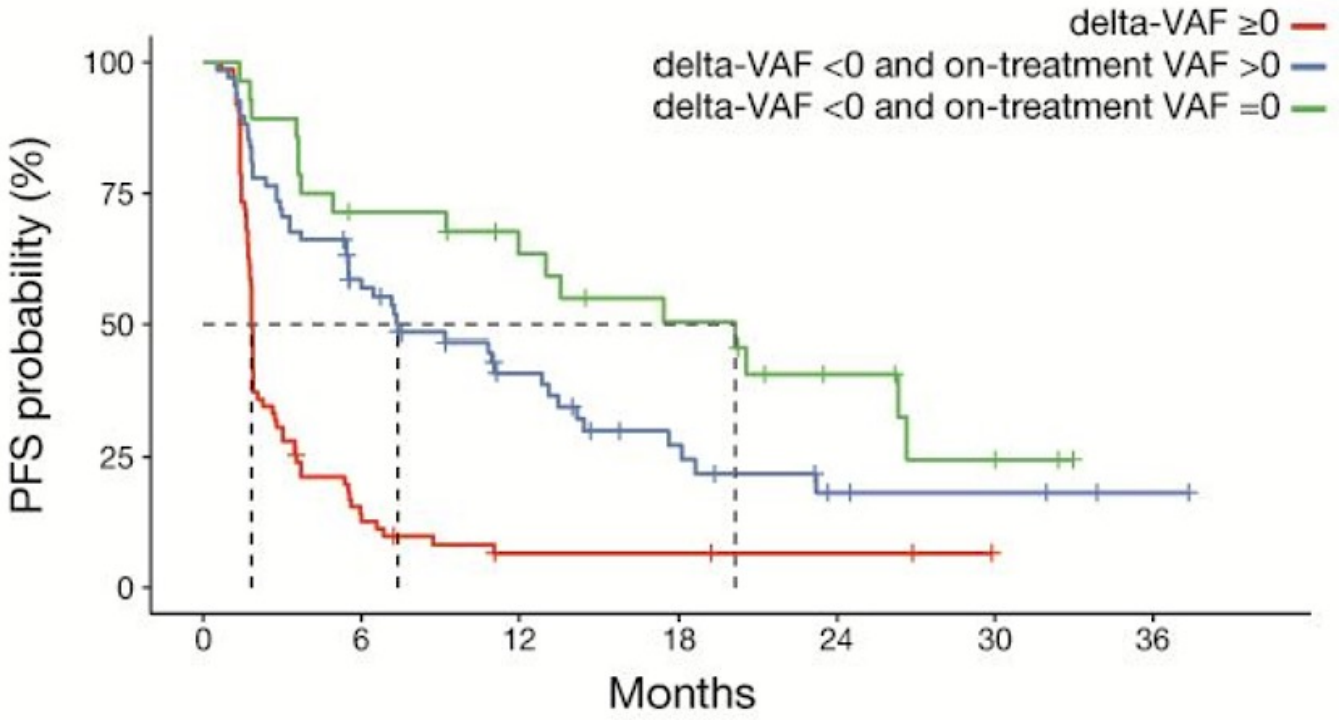
ctDNA levels fall >90% in 2 weeks in responding CRC patients

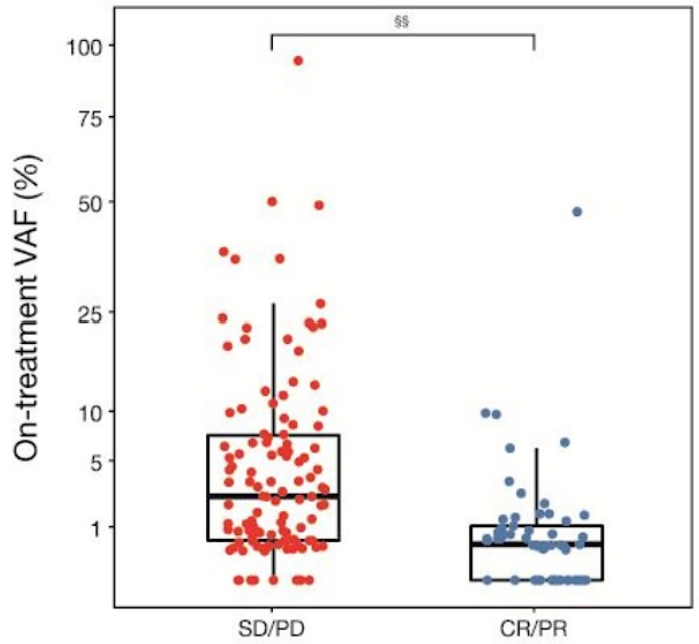


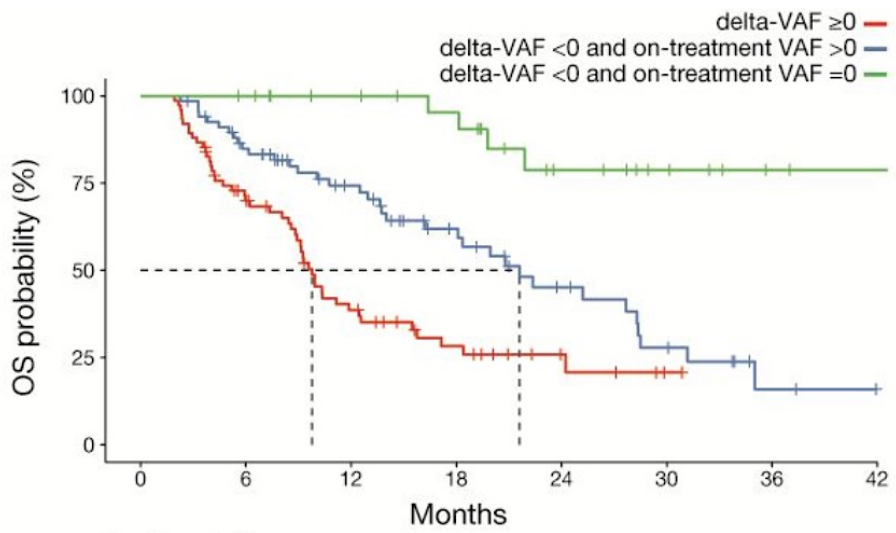
Tie et al Annals Oncology ‘15

CANCER DISCOVERY

August 14, 2020

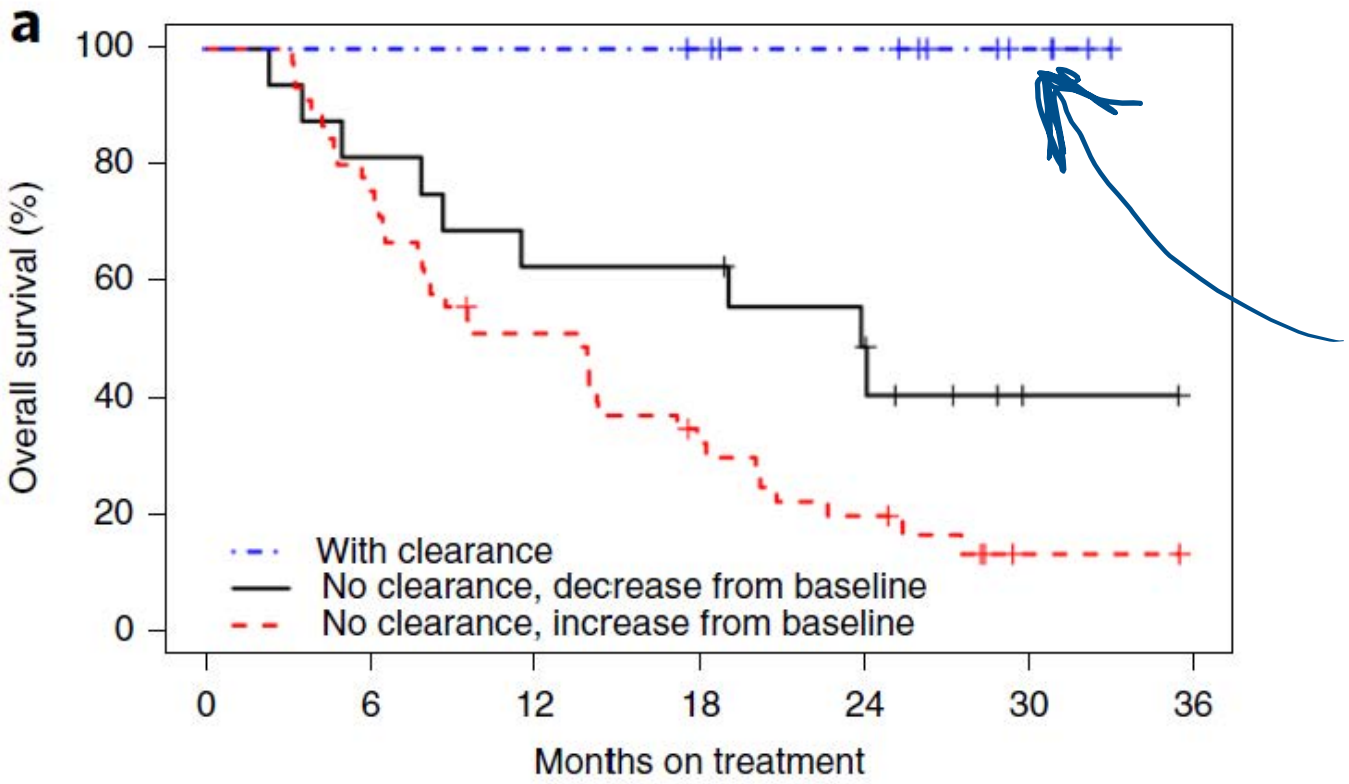


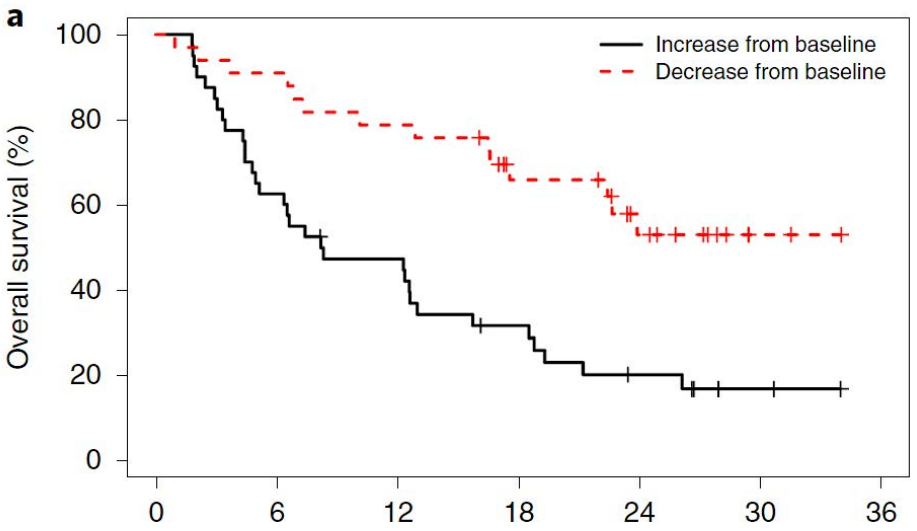


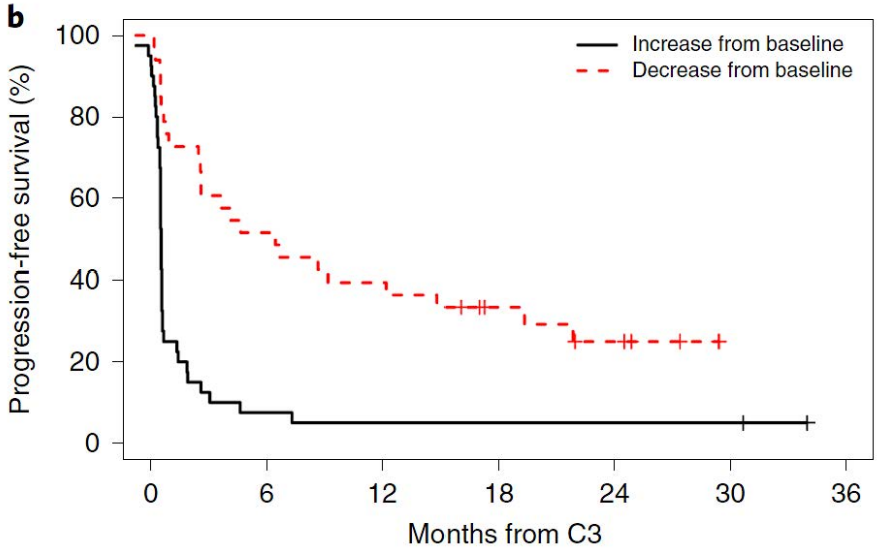


nature cancer

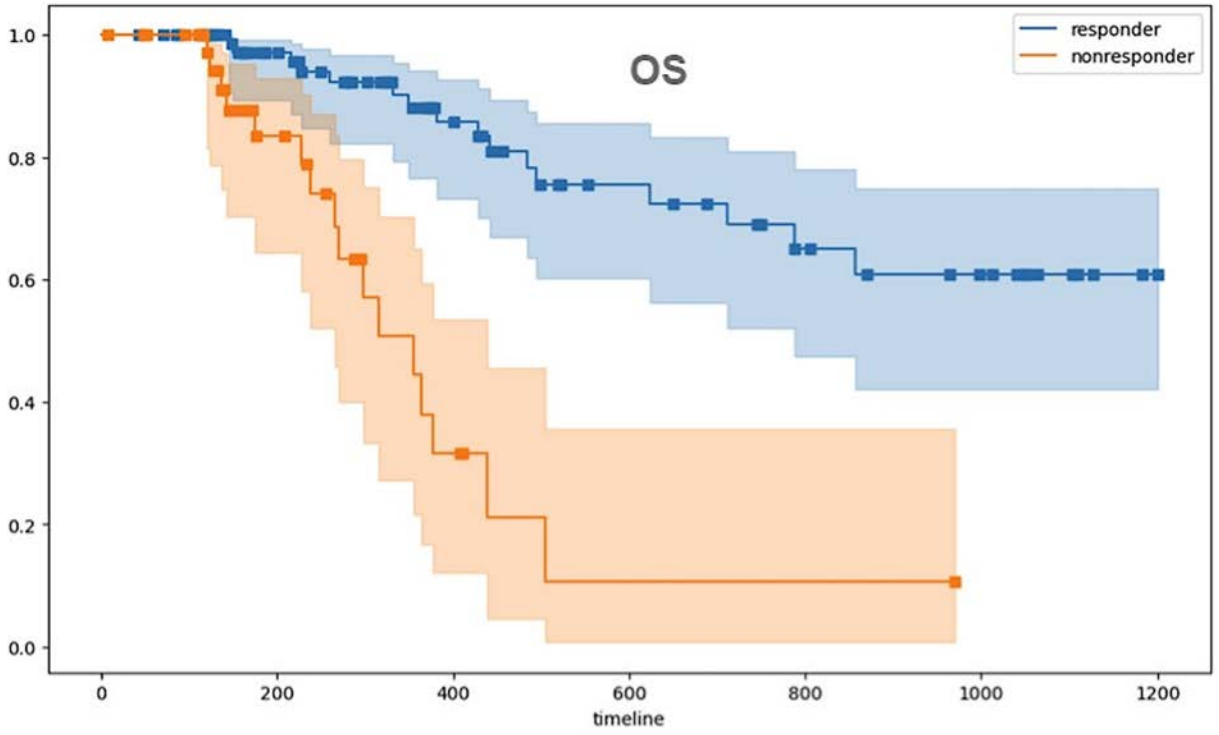
03 August 2020







ctDNA response assessment and survival



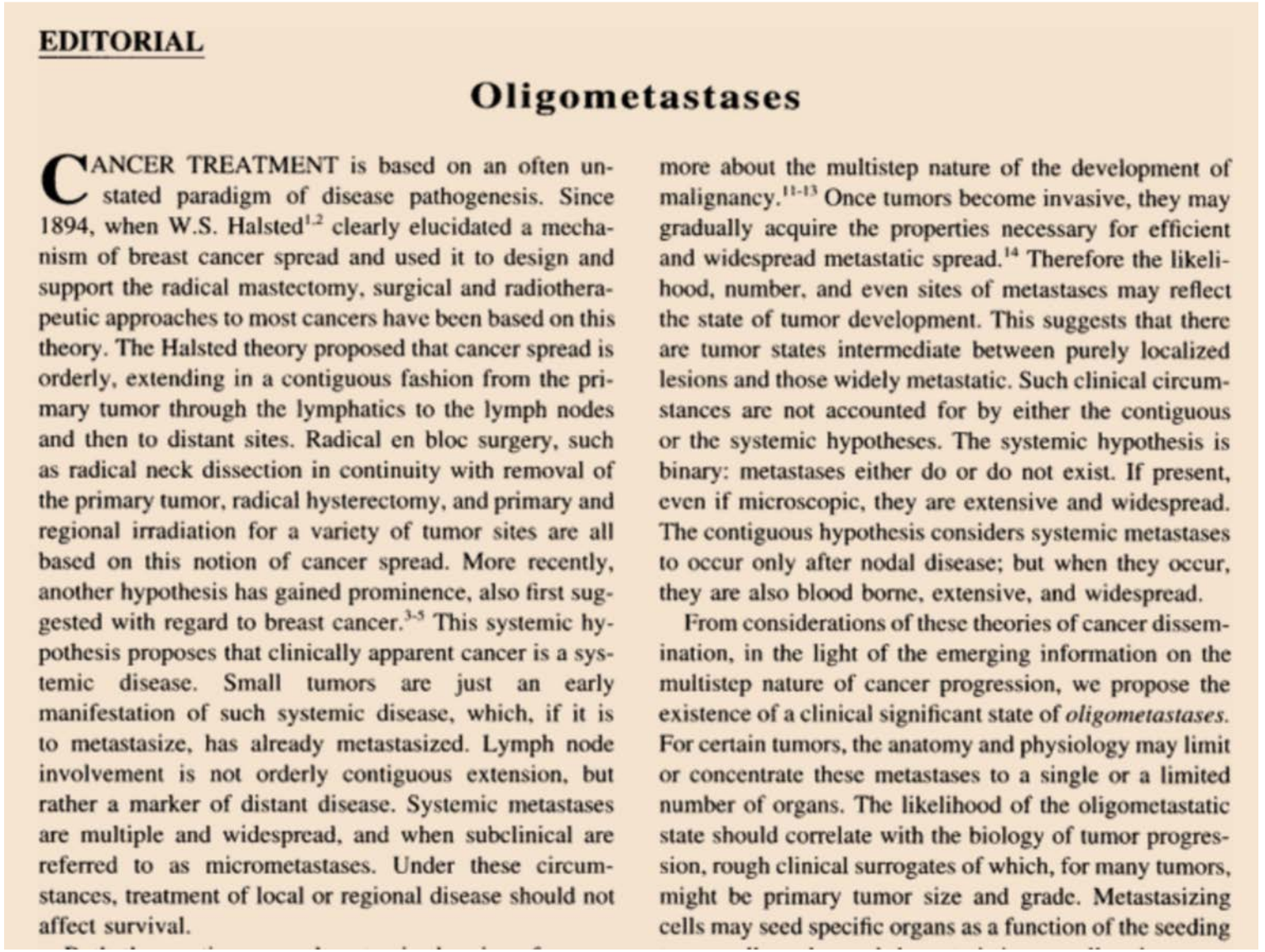
Clinical outcome	Cohort	MR category	Median in months [CI]
OS	Chemotherapy	non-responder	11.8 [8.7-14.6]
		responder	**NR [26.3-NR]**
	All regimens	non-responder	17.8 [10.5-23.4]
		responder	**NR [23.7-NR]**
TTNT	Chemotherapy	non-responder	5.8 [4.0-7.5]
		responder	**10.3 [7.3-NR]**
	All regimens	non-responder	6.1 [4.5-7.6]
		responder	10.1 [8.2-16.1]

Kasi PM, ASCO GI, 2023. J Clin Oncol 41, 2023 (suppl 4; abstr 246).

Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

"Oligo"-metastases

Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol*. 1995;13(1):8-10.



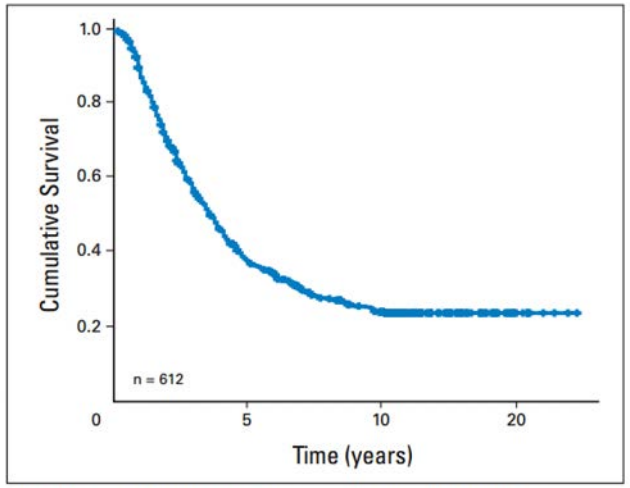
EDITORIAL

Oligometastases

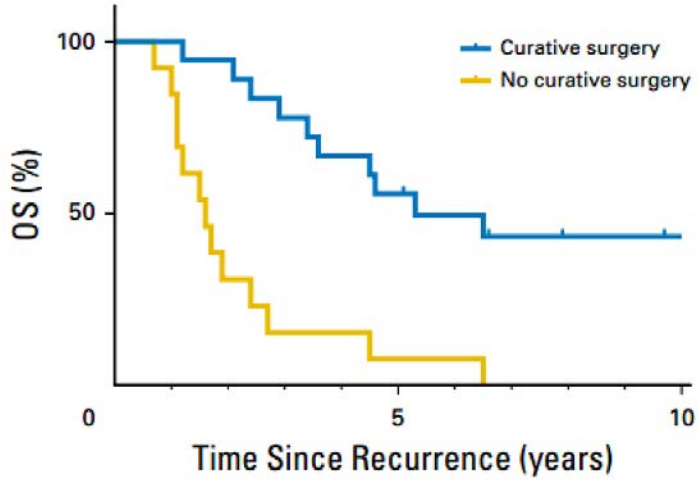
CANCER TREATMENT is based on an often unstated paradigm of disease pathogenesis. Since 1894, when W.S. Halsted[1,2] clearly elucidated a mechanism of breast cancer spread and used it to design and support the radical mastectomy, surgical and radiotherapeutic approaches to most cancers have been based on this theory. The Halsted theory proposed that cancer spread is orderly, extending in a contiguous fashion from the primary tumor through the lymphatics to the lymph nodes and then to distant sites. Radical en bloc surgery, such as radical neck dissection in continuity with removal of the primary tumor, radical hysterectomy, and primary and regional irradiation for a variety of tumor sites are all based on this notion of cancer spread. More recently, another hypothesis has gained prominence, also first suggested with regard to breast cancer.[3-5] This systemic hypothesis proposes that clinically apparent cancer is a systemic disease. Small tumors are just an early manifestation of such systemic disease, which, if it is to metastasize, has already metastasized. Lymph node involvement is not orderly contiguous extension, but rather a marker of distant disease. Systemic metastases are multiple and widespread, and when subclinical are referred to as micrometastases. Under these circumstances, treatment of local or regional disease should not affect survival.

more about the multistep nature of the development of malignancy.[11-13] Once tumors become invasive, they may gradually acquire the properties necessary for efficient and widespread metastatic spread.[14] Therefore the likelihood, number, and even sites of metastases may reflect the state of tumor development. This suggests that there are tumor states intermediate between purely localized lesions and those widely metastatic. Such clinical circumstances are not accounted for by either the contiguous or the systemic hypotheses. The systemic hypothesis is binary: metastases either do or do not exist. If present, even if microscopic, they are extensive and widespread. The contiguous hypothesis considers systemic metastases to occur only after nodal disease; but when they occur, they are also blood borne, extensive, and widespread.

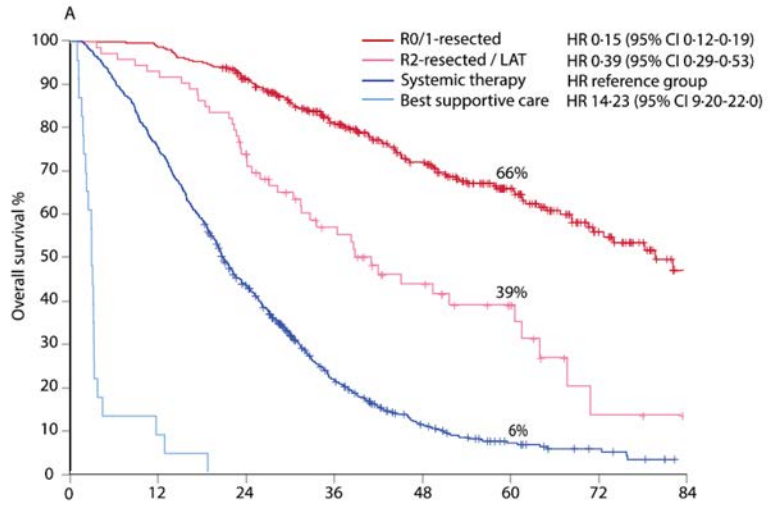
From considerations of these theories of cancer dissemination, in the light of the emerging information on the multistep nature of cancer progression, we propose the existence of a clinical significant state of *oligometastases*. For certain tumors, the anatomy and physiology may limit or concentrate these metastases to a single or a limited number of organs. The likelihood of the oligometastatic state should correlate with the biology of tumor progression, rough clinical surrogates of which, for many tumors, might be primary tumor size and grade. Metastasizing cells may seed specific organs as a function of the seeding



JCO 2007



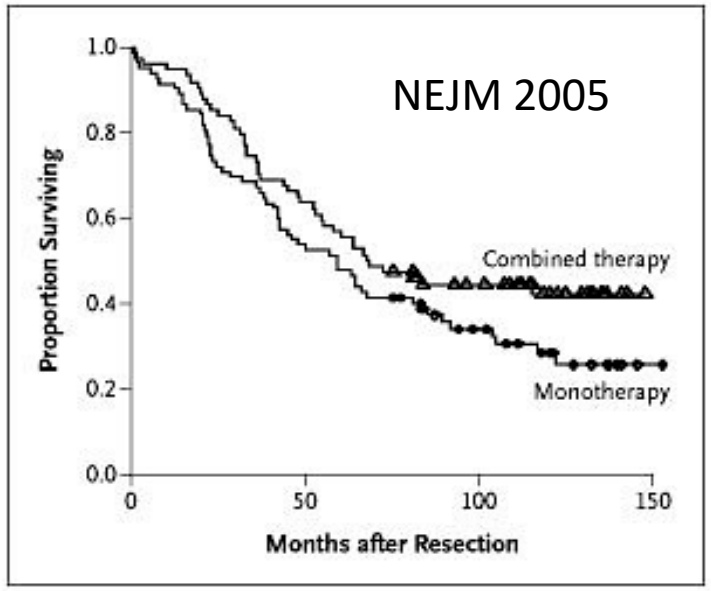
JCO 2017

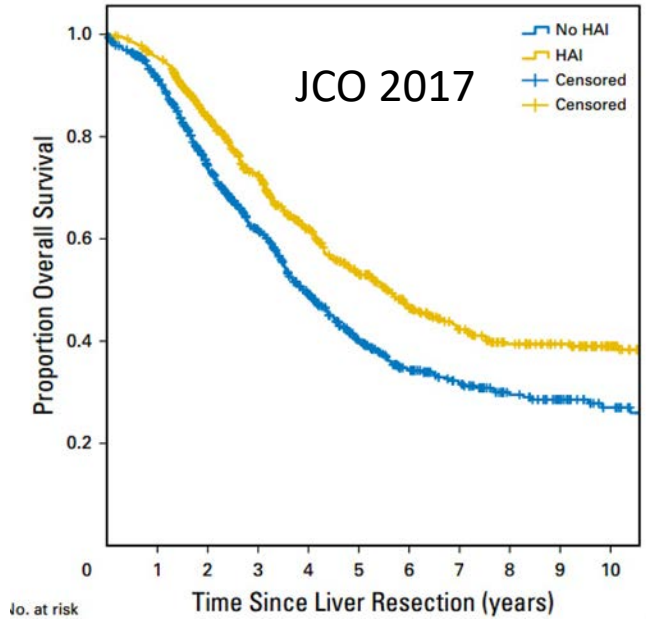


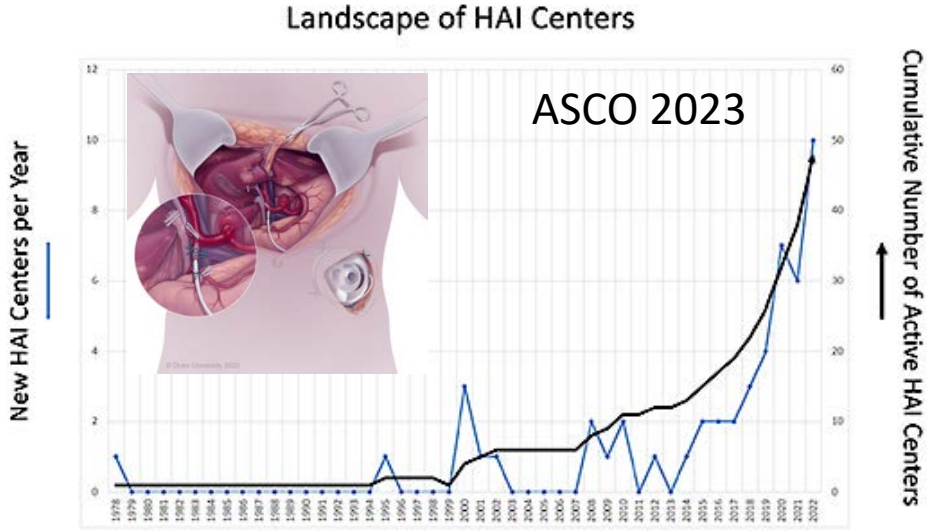
Lancet Reg Health Eur 2021

Surgery

Surgery + HAI (adjuvant)

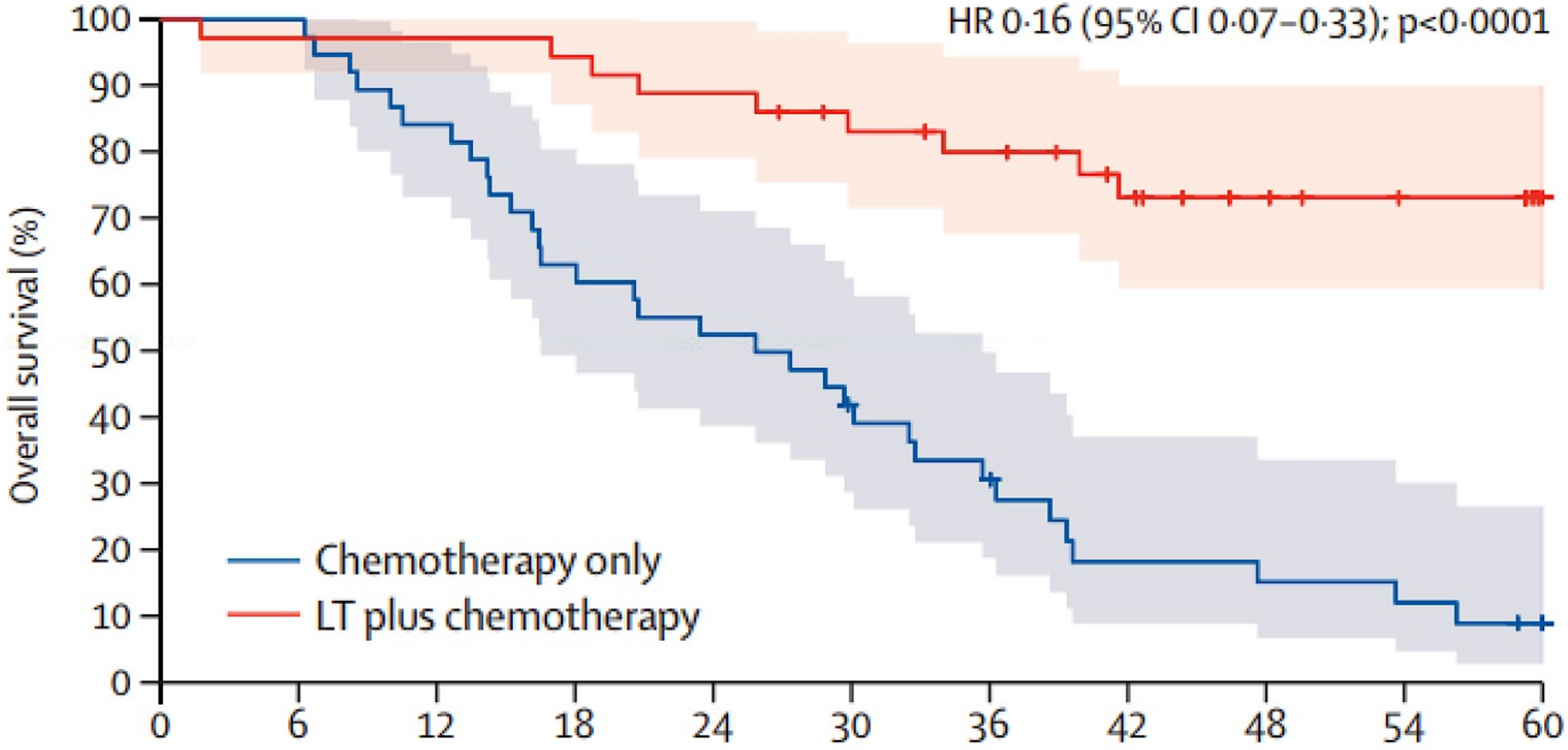






EA2222 - A Randomized Phase III Study of Systemic Therapy With or Without Hepatic Arterial Infusion for Unresectable Colorectal Liver Metastases: The PUMP Trial. PI: Dr. Michael Lidsky

TransMet Trial: Liver transplantation

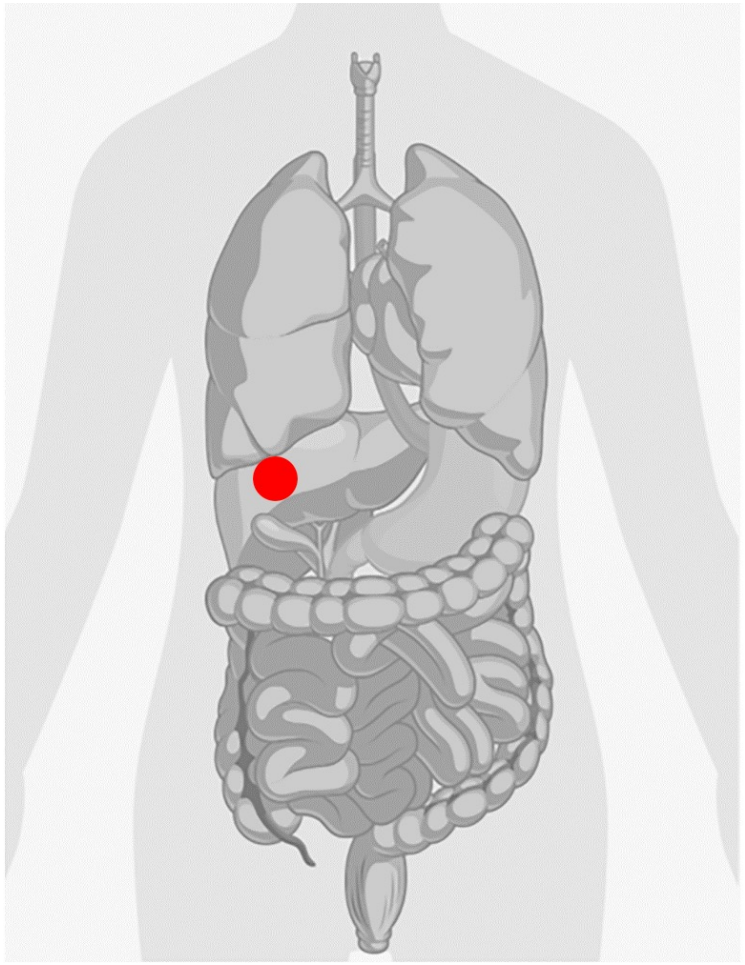


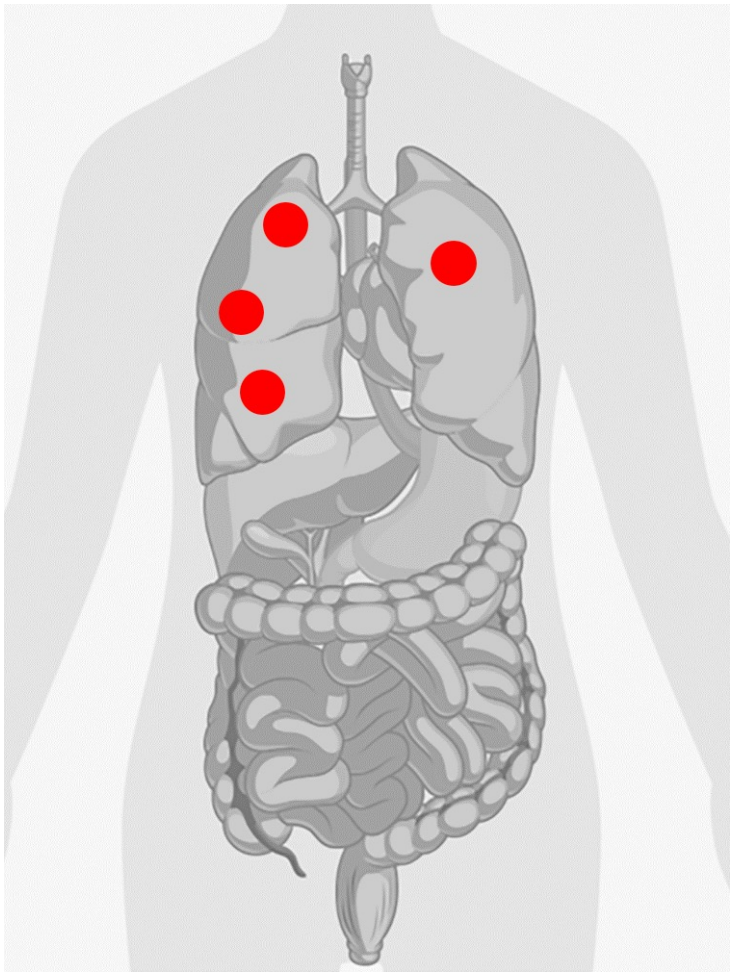
73%

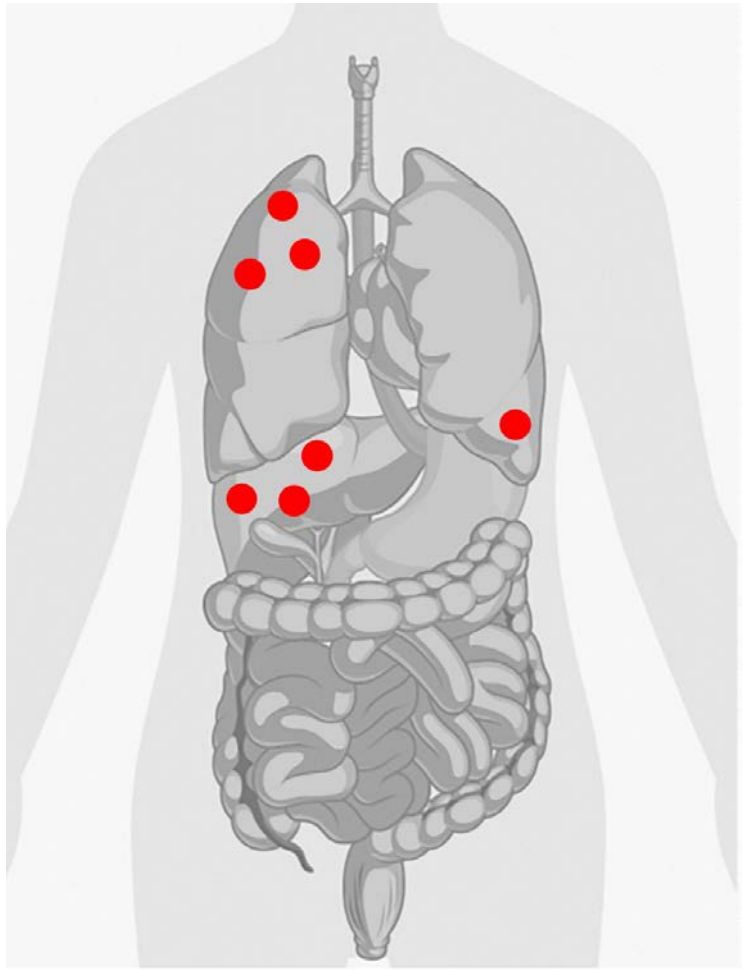
9.3%

Liver transplantation plus chemotherapy versus chemotherapy alone in patients with permanently unresectable colorectal liver metastases (TransMet): results from a multicentre, open-label, prospective, randomised controlled trial. Lancet. 2024 Sep 21;404(10458):1107-1118.

“Oligo”-metastatic



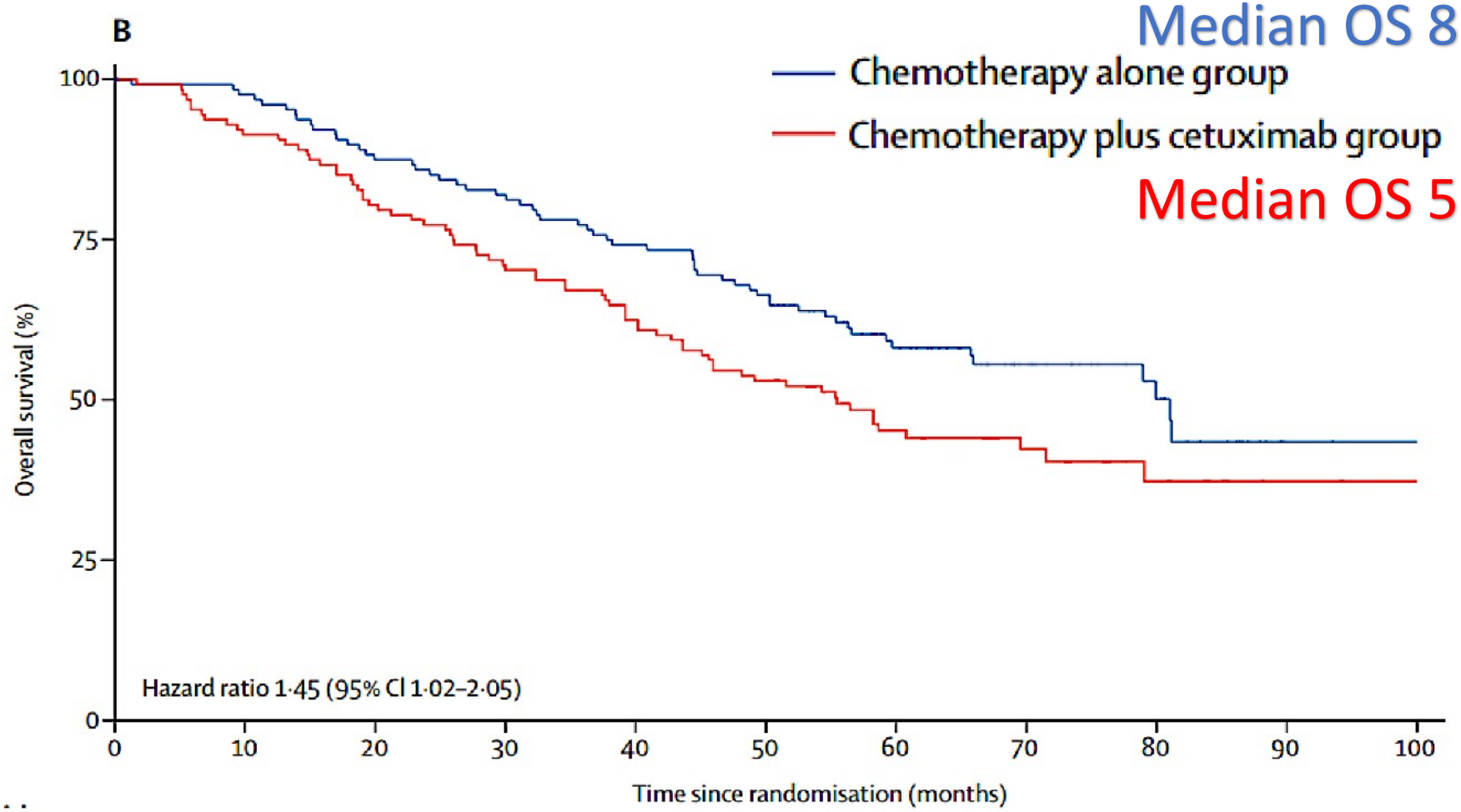




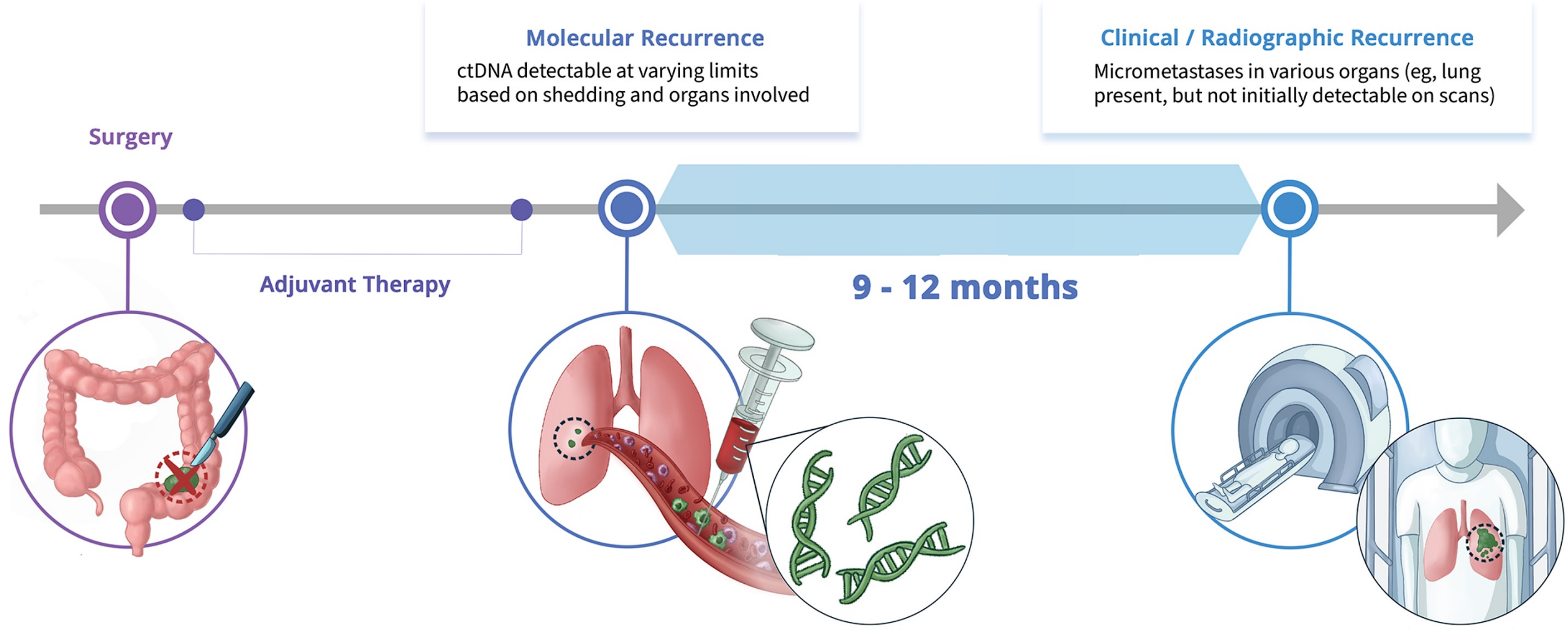
A Pragmatic Randomized Phase III Trial Evaluating Total Ablative Therapy for Patients with Limited Metastatic Colorectal Cancer: Evaluating Radiation, Ablation, and Surgery (ERASur Trial) A022101/NRG-GI009. PI: Dr. Eric Miller.

Systemic chemotherapy with or without cetuximab in patients with **resectable** colorectal liver metastasis - New EPOC Trial

Median OS 81.0 months



Bridgewater JA. Systemic chemotherapy with or without cetuximab in patients with **resectable** colorectal liver metastasis (New EPOC): long-term results of a multicentre, randomised, controlled, phase 3 trial. *Lancet Oncol*. 2020;21(3):398-411.



"Adjuvant-plus"

ASCO Daily News®

Kasi PM. Utility and Debate of Liquid Biopsy Assays in Surveillance Setting. March 2023. ASCO Daily News.

ASCO Daily News®

Kinetics of Liquid Biopsies in Predicting Response to Immunotherapy

October 1, 2020

Pashtoon M. Kasi, MD, MS

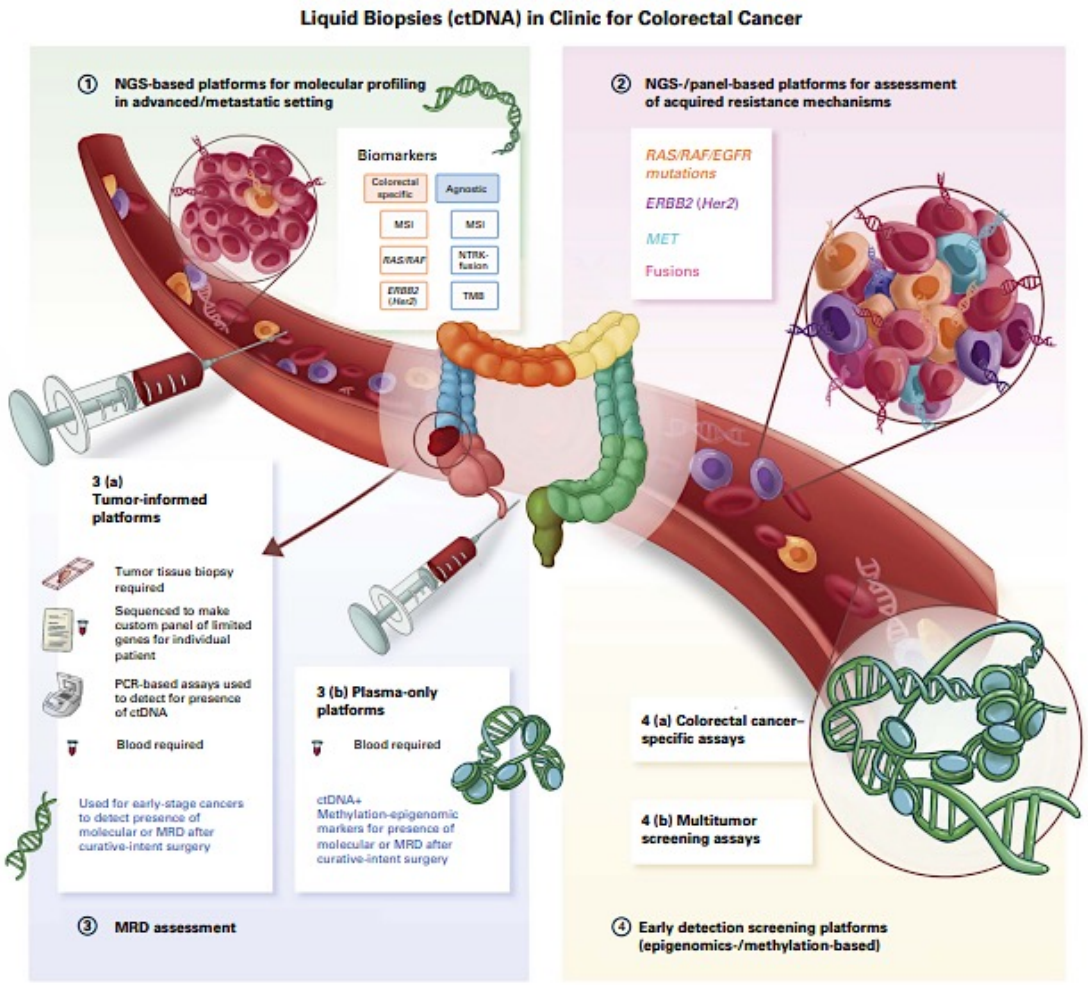
X: @pashtoonkasi

SPECIAL SERIES: PRECISION MEDICINE AND IMMUNOTHERAPY IN GI MALIGNANCIES

Using Circulating Tumor DNA in Colorectal Cancer: Current and Evolving Practices

Midhun Malla, MD, MS[1]; Jonathan M. Loree, MD, MS[2]; Pashtoon Murtaza Kasi, MD, MS[3]; and Aparna Raj Parikh, MD[4]

Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal



Malla M, Loree JM, Kasi PM, Parikh AR. Using Circulating Tumor DNA in Colorectal Cancer: Current and Evolving Practices. *J Clin Oncol*. 2022;40(24):2846-2857. doi:10.1200/JCO.21.02615

Case Presentation: 51-year-old man with colon cancer and recurrence of a single hepatic metastasis undergoes liver resection

Dr Syed F Zafar (Fort Myers, Florida)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

What adjuvant treatment, if any, would you recommend for this patient?

In your opinion, how effective is ctDNA monitoring in patients who have undergone curative-intent resection of oligometastatic CRC?

Can patients with negative ctDNA after resection of oligometastatic CRC safely forgo adjuvant treatment? How would you approach surveillance for these patients?

Case Presentation: 44-year-old man with recurrent MSI-H colon cancer and peritoneal carcinomatosis declines chemotherapy and receives pembrolizumab

Dr Gigi Chen (Walnut Creek, California)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

In your opinion, how effective is ctDNA testing to monitor for response in patients with mCRC receiving systemic therapy?

How would you interpret the slight increase in ctDNA in this patient's case? Would it prompt you to switch therapy in the absence of disease progression on imaging?

What therapy would you recommend next for this patient?

Agenda

MODULE 1: Role of Circulating Tumor DNA (ctDNA) Evaluation in Nonmetastatic Colorectal Cancer (CRC) — Dr Dasari

MODULE 2: Role of Immune Checkpoint Inhibitors in the Management of Nonmetastatic Microsatellite Instability-High (MSI-H) CRC — Dr Cercek

MODULE 3: Management of Oligometastatic Disease and Hepatic-Only Metastases in CRC; Role of ctDNA Evaluation in Metastatic Disease — Dr Kasi

MODULE 4: Role of Immune Checkpoint Inhibitors in the Management of MSI-H Metastatic CRC (mCRC) — Dr Hecht

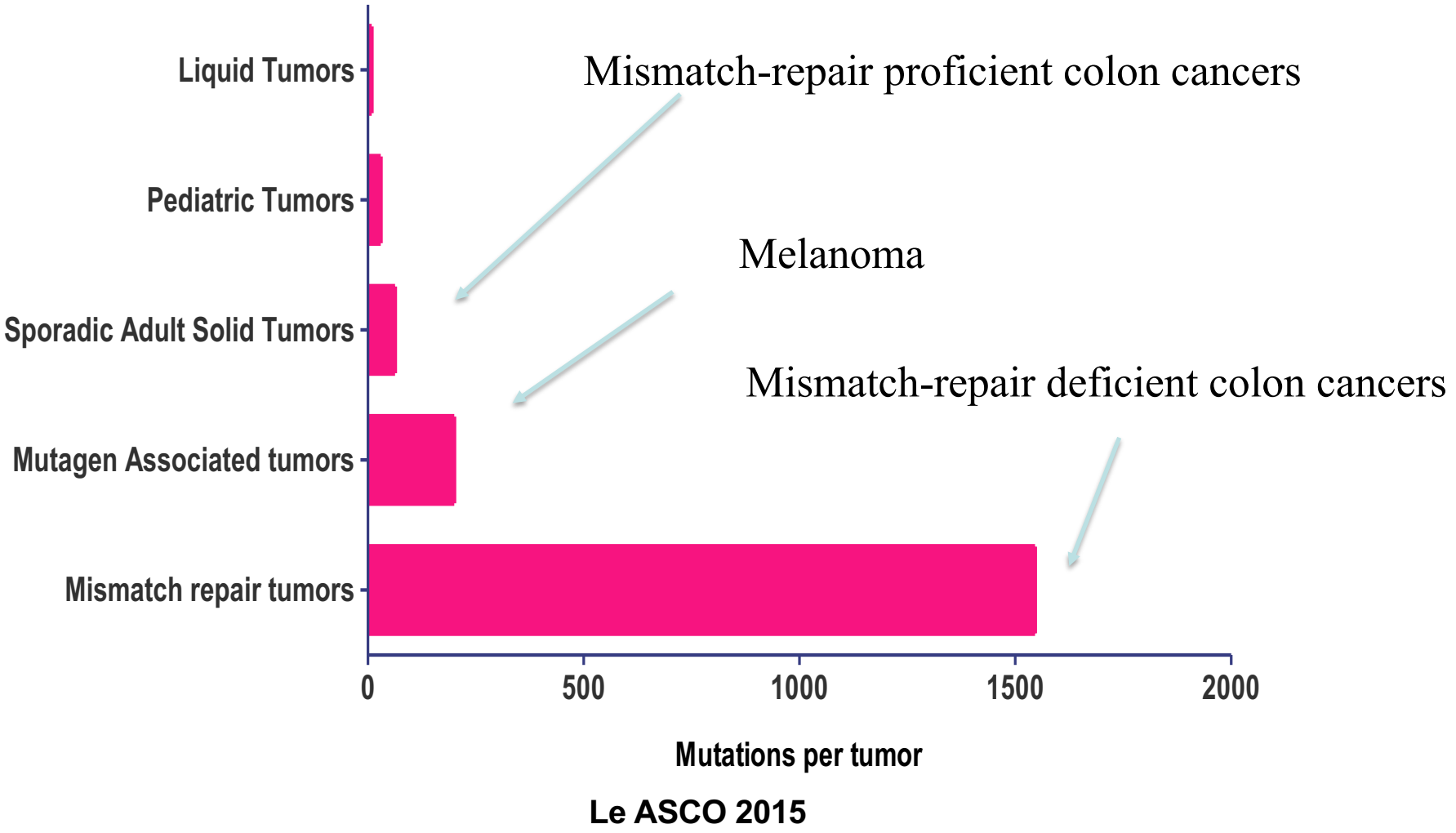
MODULE 5: Identification and Care of Patients with mCRC and Actionable Genomic Alterations — Prof Van Cutsem

RTP RESEARCH TO PRACTICE

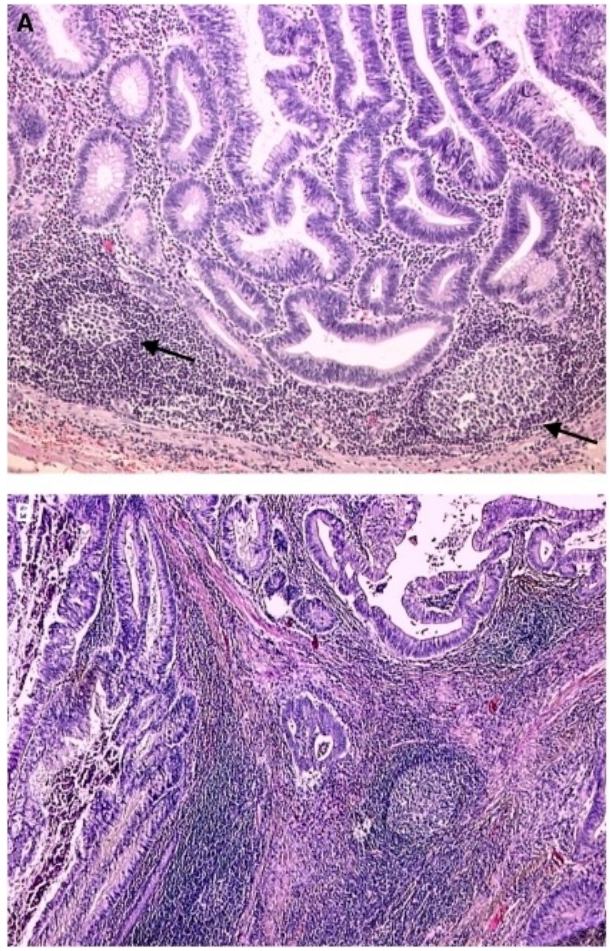
J. Randolph Hecht, MD
Director, UCLA GI Oncology Program

Role of Immune Checkpoint Inhibitors in the Management of MSI-High mCRC

Background: Mutations per tumor



Le ASCO 2015



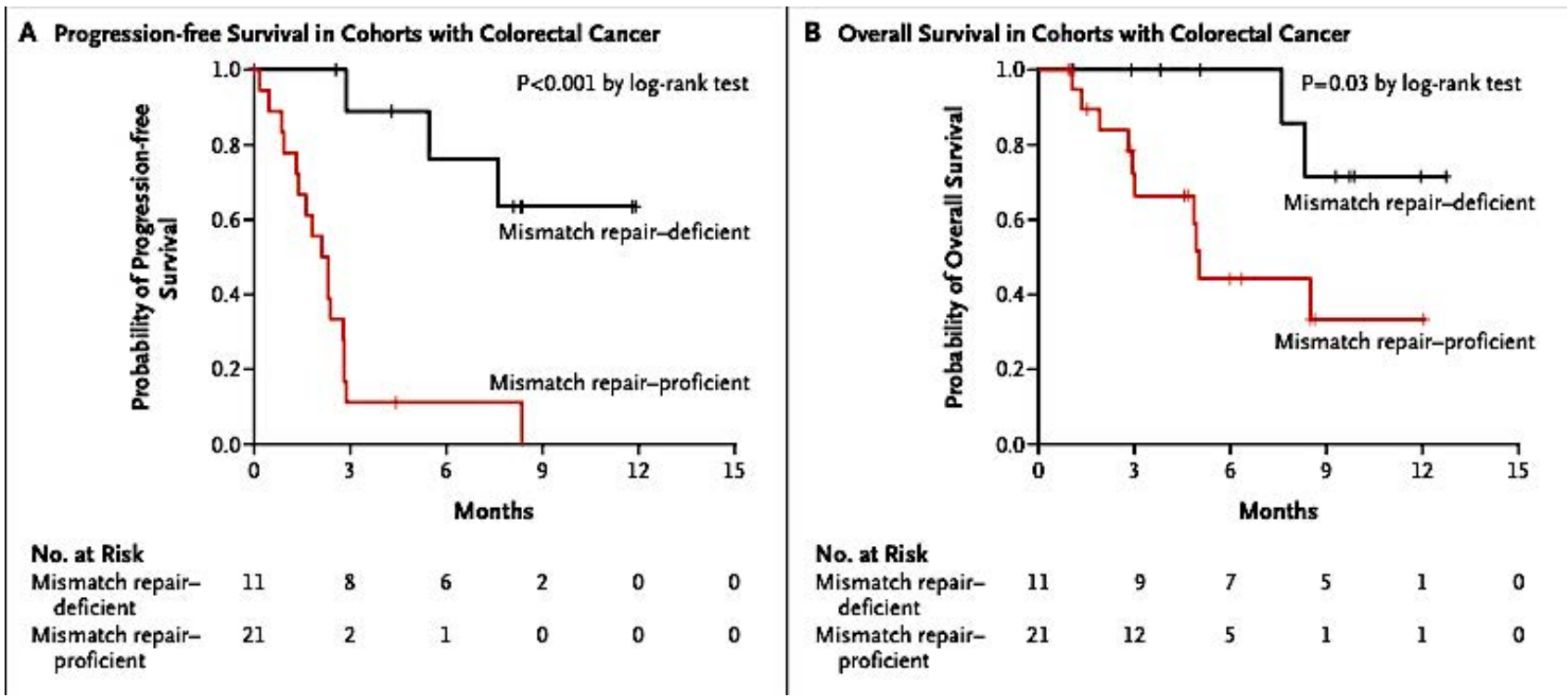
Buckowitz BJC 2005

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring,



Le NEJM 2015

CPI Previously Treated MSI mCRC

- CheckMate 142
- KEYNOTE-164
- NIPICOL
- CheckMate 8HW nivo/ipi vs nivo (~47%)

KEYNOTE-164 Pembro in 2+L

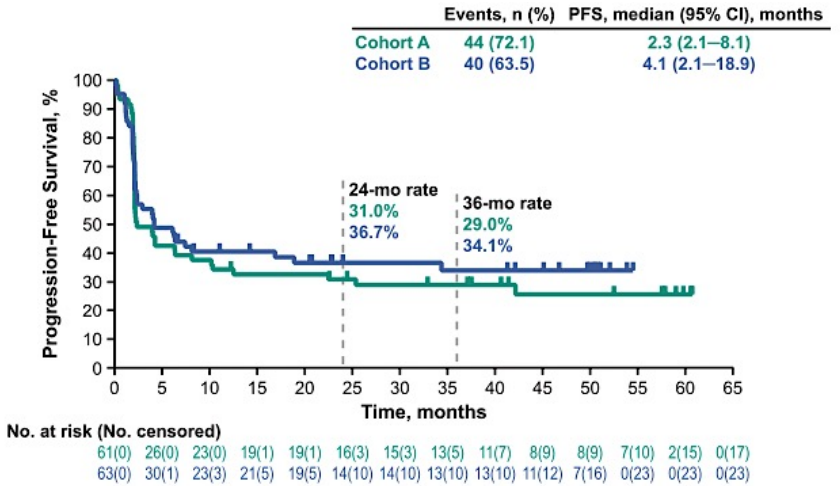


Fig. 2. PFS assessed per RECIST v1.1 by BICR for patients with MSI-H/dMMR locally advanced unresectable or metastatic colorectal cancer in cohorts A and B. CI, confidence interval; dMMR, mismatch repair deficient; MSI-H, microsatellite instability–high; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1.

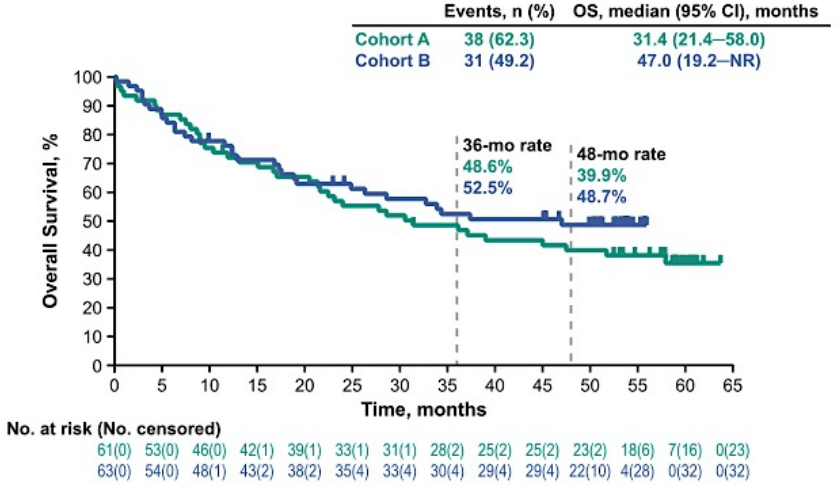


Fig. 3. OS in patients with MSI-H/dMMR locally advanced unresectable or metastatic colorectal cancer in cohorts A and B. CI, confidence interval; dMMR, mismatch repair deficient; MSI-H, microsatellite instability–high; NR, not reached; OS, overall survival.

Le EJC 2023

CheckMate 142 Nivo/Ipi Salvage Cohort

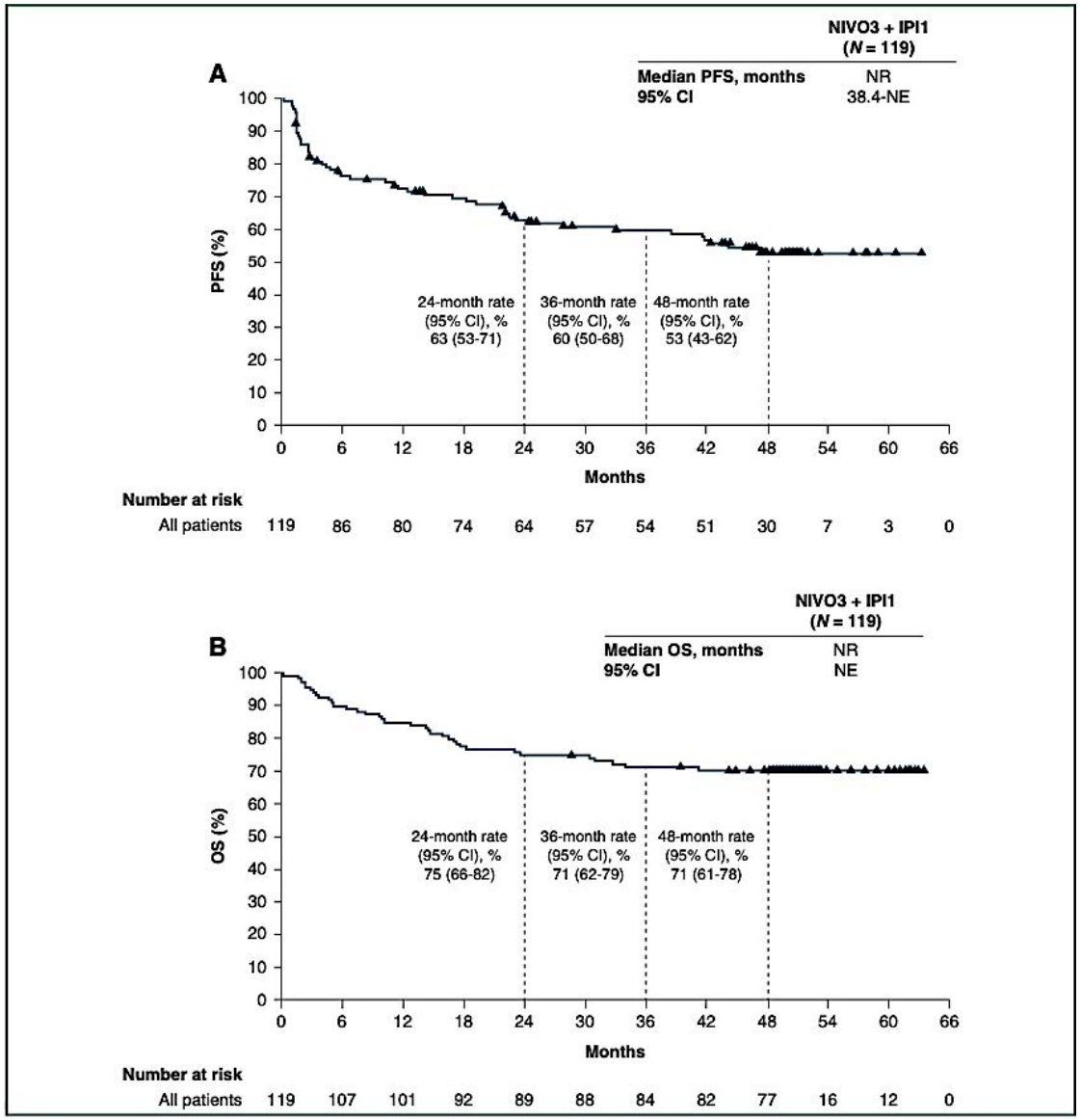
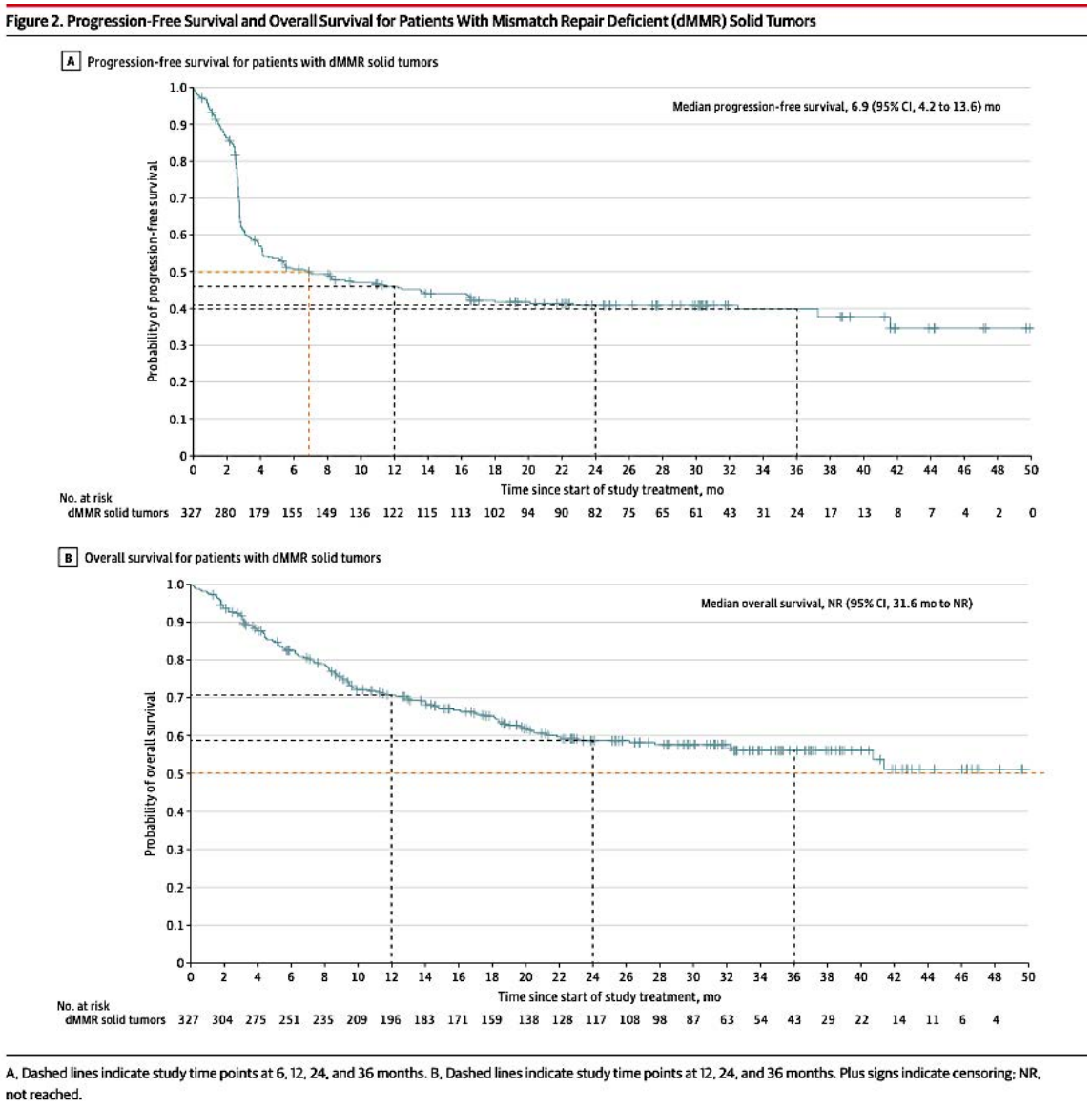


Figure 2. Kaplan-Meier plots of survival. (A) PFS as per investigator assessment and (B) OS in all patients.
CI, confidence interval; IPI1, ipilimumab 1 mg/kg; mo, months; NE, not estimable; NIVO3, nivolumab 3 mg/kg; NR, not reached; OS, overall survival; PFS, progression-free survival.

André Ann Oncol 2022

Other CPIs

- Dostarlimab
  - GARNET mPFS mCRC 8.4 mOS NR
  - FDA Approval all dMMR
- Others (tislelizumab, serplulimab, etc.) similar



André JAMA Network Open 2023

First-line MSI-H mCRC

- KEYNOTE-177 pembro vs chemo Ph III
- CheckMate 142 Nivo/Ipi 1st Line
- CheckMate 8HW
  - Nivo/Ipi vs chemo
  - Nivo/Ipi vs Nivo (~53%)

KEYNOTE-177 Pembro 1st line vs Chemo

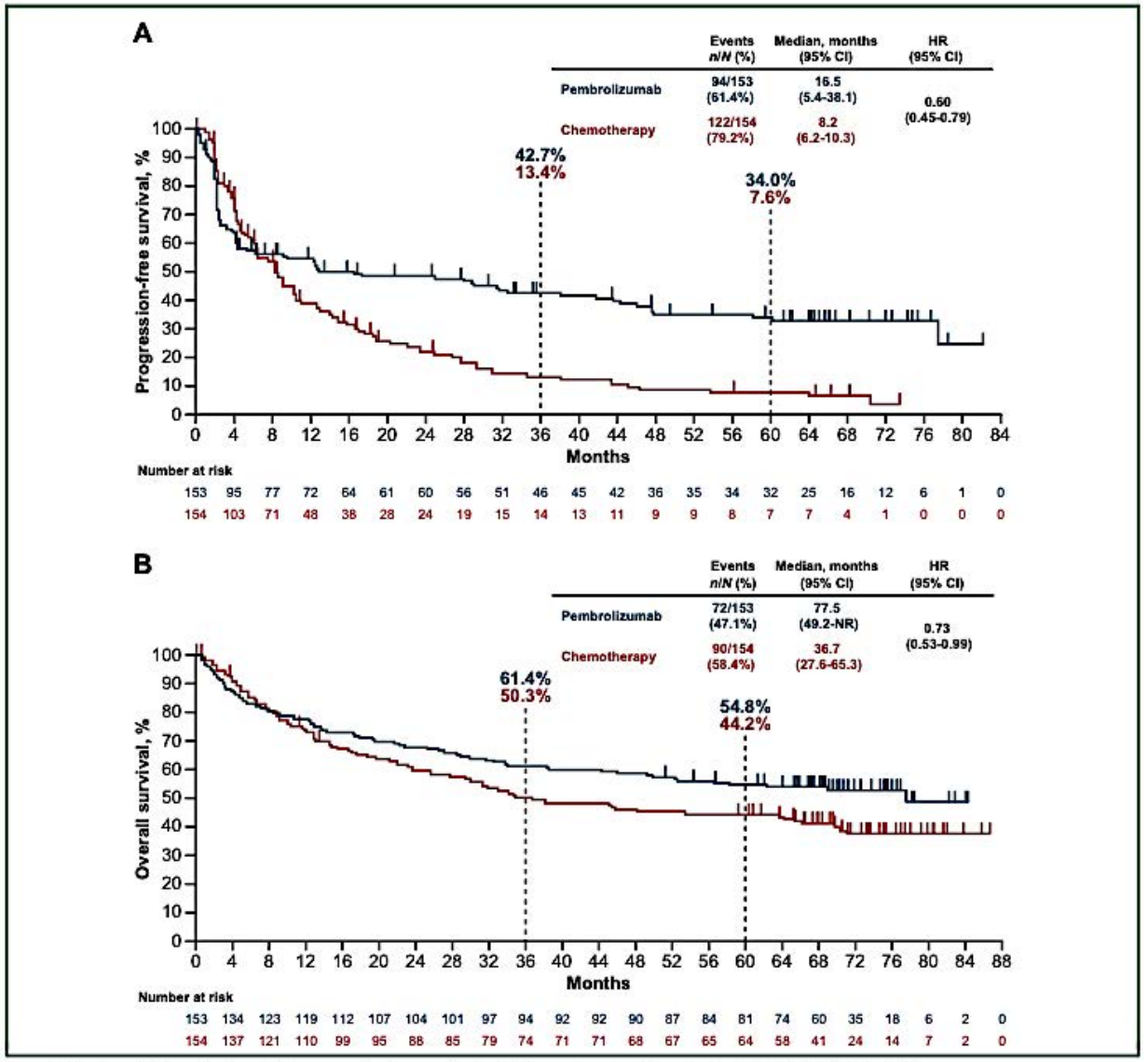


Figure 1. Kaplan–Meier estimates of (A) progression-free survival and (B) overall survival in patients with MSI-H/dMMR mCRC.
CI, confidence interval; dMMR, mismatch repair-deficient; HR, hazard ratio; mCRC, metastatic colorectal carcinoma; MSI-H, microsatellite instability-high; NR, not reached.

André Ann Oncol 2025

CheckMate 142 Nivo/Ipi 1st Line Cohort

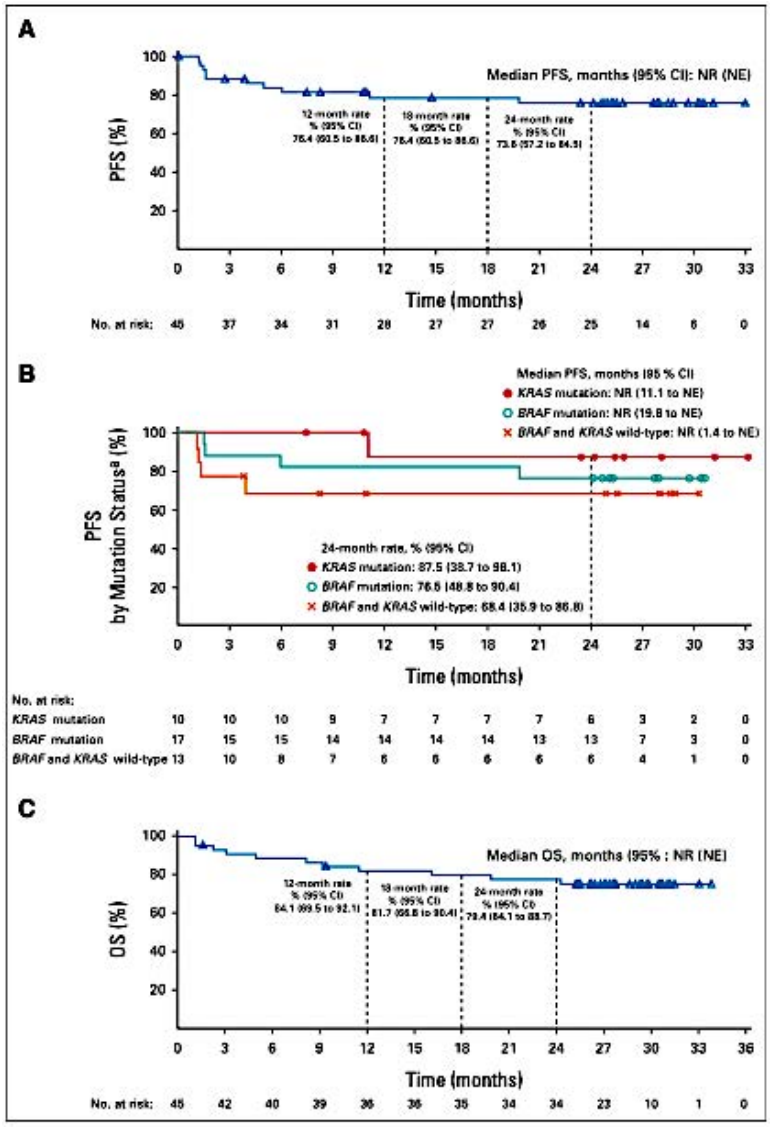


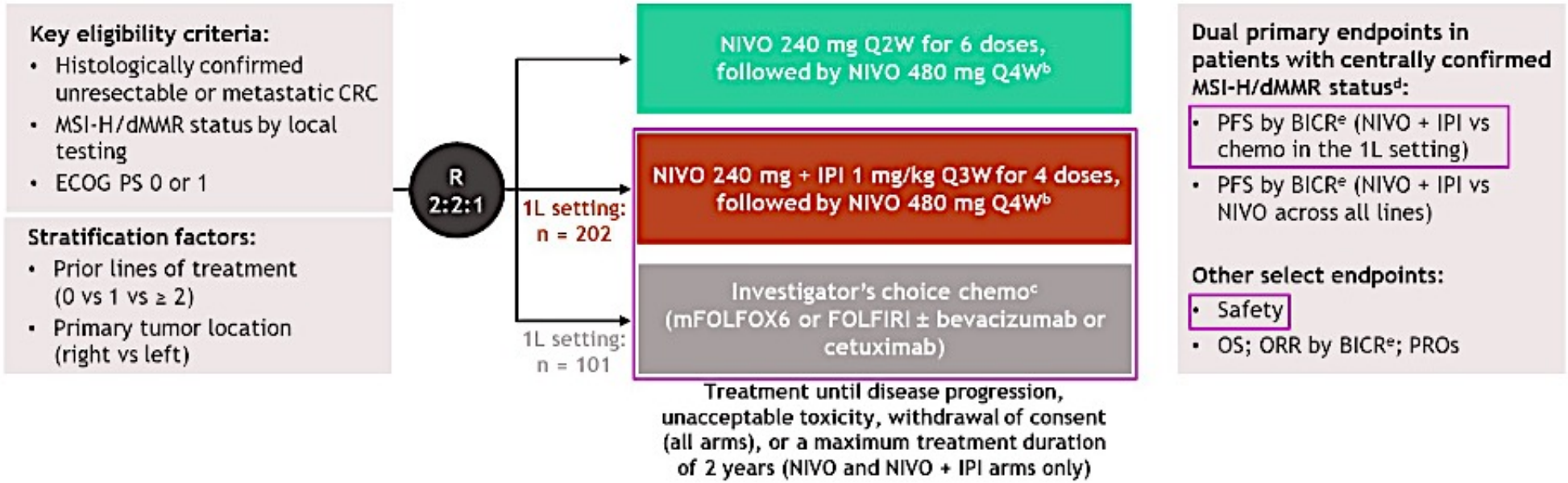
FIG 2. Kaplan-Meier estimate of (A) PFS per investigator assessment, (B) PFS per investigator assessment by mutation status, and (C) OS in all patients with a minimum follow-up of 24.2 months. [a]Excluded five patients with unknown mutation status. *BRAF*, V-Raf murine sarcoma viral oncogene homolog B1; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; NE, not estimable; NR, not reached; OS, overall survival; PFS, progression-free survival.

Lenz JCO 2021

CheckMate 8HW vs Chemo

CheckMate 8HW study design

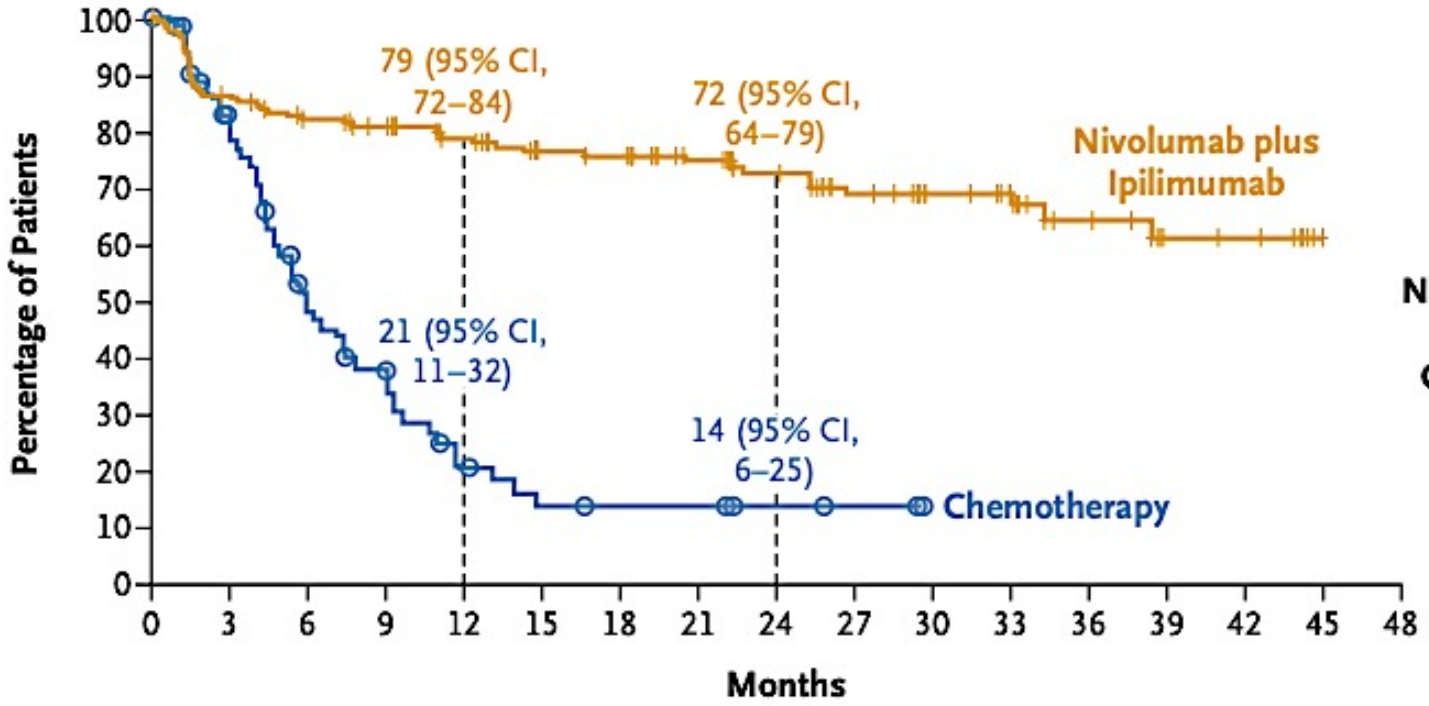
- CheckMate 8HW is a randomized, multicenter, open-label phase 3 study[a]



- At data cutoff (October 12, 2023), the median follow-up[f] was 24.3 months

CheckMate 8HW vs Chemo

A Progression-free Survival in Patients with Centrally Confirmed MSI-H or dMMR Metastatic Colorectal Cancer



	No. of Events/ No. of Patients	Median Progression-free Survival (95% CI)
		mo
Nivolumab plus Ipilimumab	48/171	NR (38.4–NE)
Chemotherapy	52/84	5.9 (4.4–7.8)

Adjusted difference in restricted mean survival time at 24 mo, 10.6 mo (95% CI, 8.4–12.9)
P<0.001 with the use of a two-sided stratified log-rank test

No. at Risk																	
Nivolumab plus ipilimumab	171	144	132	122	108	95	92	77	64	53	42	37	22	10	9	1	0
Chemotherapy	84	53	29	20	10	6	5	5	3	2	0	0	0	0	0	0	0

André NEJM 2024

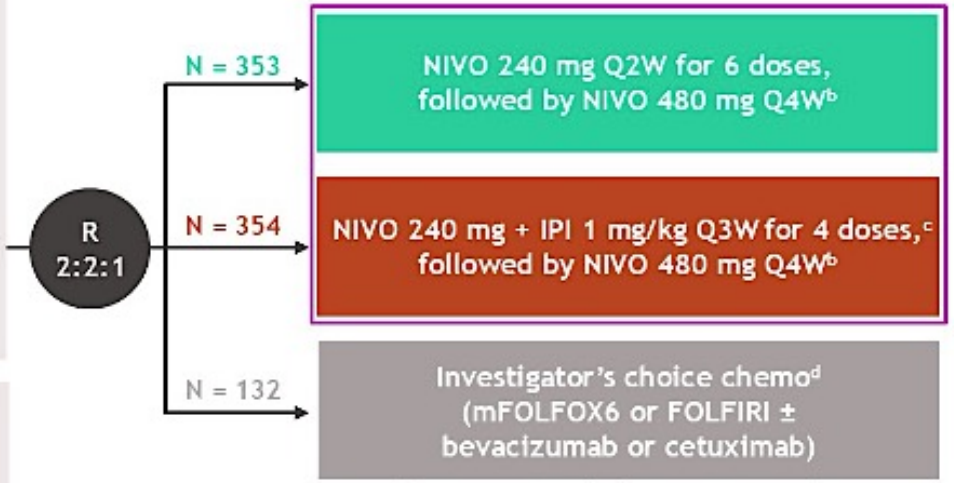
CheckMate 8HW Nivo vs Nivo/Ipi

Study design

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

Key eligibility criteria:
- Histologically confirmed unresectable or metastatic CRC
- MSI-H/dMMR status by local testing
- Immunotherapy-naive
- 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)

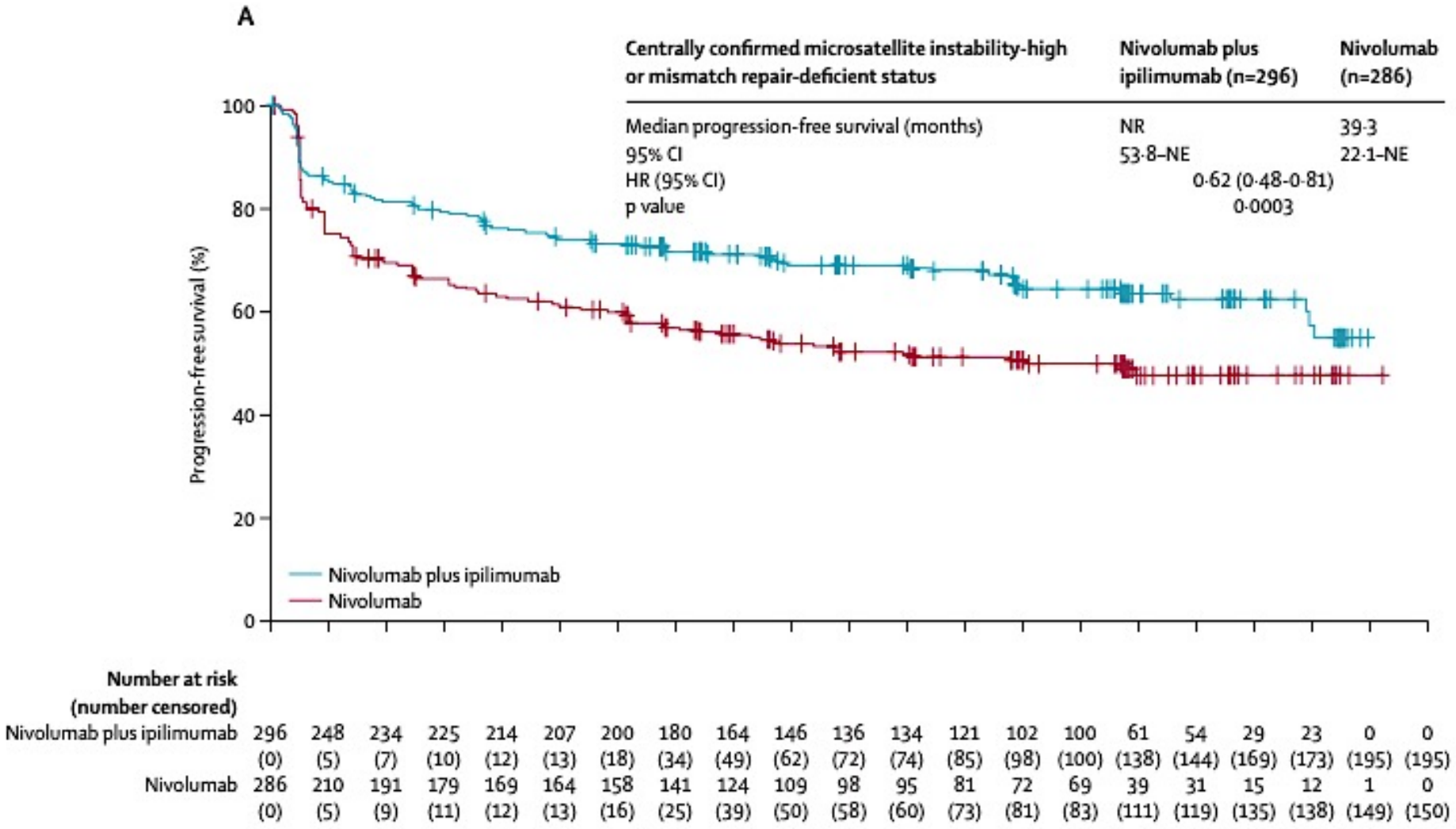
Dual primary endpoints in patients with centrally confirmed MSI-H/dMMR status[e]:
- PFS by BICR[f] (NIVO + IPI vs chemo in the 1L setting)
- PFS by BICR[f] (NIVO + IPI vs NIVO across all lines)

Other select endpoints:
- Safety
- ORR by BICR[f] (NIVO + IPI vs NIVO across all lines)
- HRQoL
- OS

- At data cutoff (August 28, 2024), the median follow-up[g] was 47.0 months (range, 16.7-60.5)

André ASCO GI 2015

CheckMate 8HW Nivo vs Nivo/Ipi PFS



André Lancet 2025

Update ASCO 2025

Nivolumab (NIVO) plus ipilimumab (IPI) vs chemotherapy (chemo) or NIVO monotherapy for microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): Expanded analyses from CheckMate 8HW.

Conclusions:

NIVO + IPI demonstrated sustained clinical benefit vs chemo (1L) and NIVO (all lines) despite use of subsequent therapy, as shown by improved PFS2 in pts with centrally confirmed MSI-H/dMMR mCRC. No new safety signals were observed. These results support NIVO + IPI as a standard of care treatment for MSI-H/dMMR mCRC.

Centrally confirmed MSI-H/dMMR (1L)	**NIVO + IPI (n = 171)**	**Chemo (n = 84)**
Median PFS (95% CI), mo	54.1 (54.1–NE)	5.9 (4.4–7.8)
HR (95% CI)	0.21 (0.14–0.31)	
Median PFS2 (95% CI), mo	NR (NE–NE)	30.3 (15.2–NE)
HR (95% CI)	0.28 (0.18–0.44)	
Centrally confirmed MSI-H/dMMR (all lines)	**NIVO + IPI (n = 296)**	**NIVO (n = 286)**
Median PFS (95% CI), mo	NR (53.8–NE)	39.3 (22.1–NE)
HR (95% CI)	0.62 (0.48-0.81); *P* = 0.0003	
Median PFS2 (95% CI), mo	NR (NE–NE)	NR (NE–NE)
HR (95% CI)	0.57 (0.42–0.78)	

NE, not evaluable; NR, not reached.

Lenz, et al.

CPI in Metastatic MSI-H CRC

- Nivo/Ipi improves PFS in MSI-H mCRC
- Single agent is acceptable
- What about toxicity?

CPI Toxicities

- What are the AEs?
- How do we manage?
- Do IRAEs and treatment reduce efficacy?
- Can we reduce exposure?
  - Does every patient need combination therapy?
  - How long do patients need to be treated?

IRAEs

- Skin
- Colitis
- Hepatitis
- Pneumonitis
- Endocrine
  - thyroid, adrenal, pituitary-hypophysitis, DM
- Musculoskeletal
- Neurologic
- Renal
- CV
- Hematologic
- Ocular

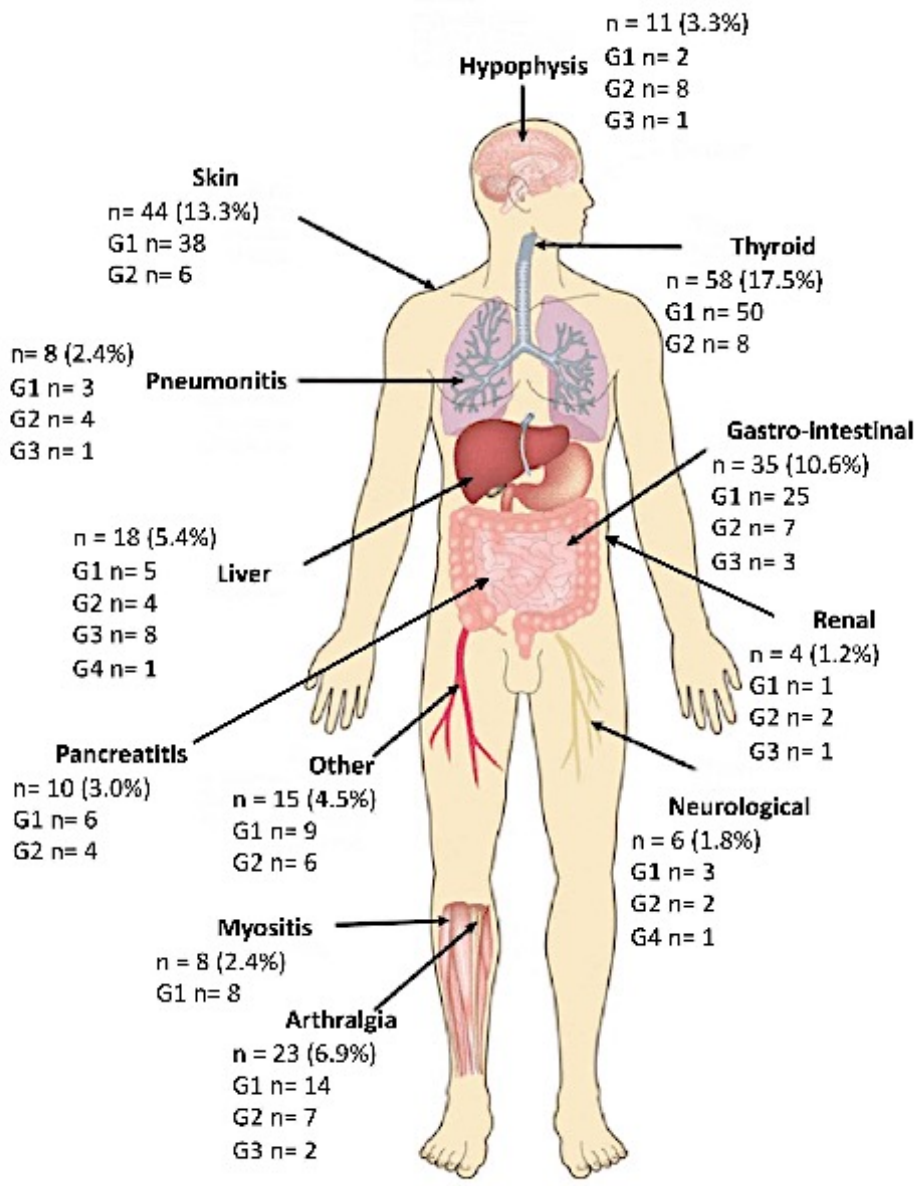


Figure 1 Summary of incidence and severity of immune-related adverse events recorded in the study population.

Nasca JITC 2023

Timeline IRAEs mCRC

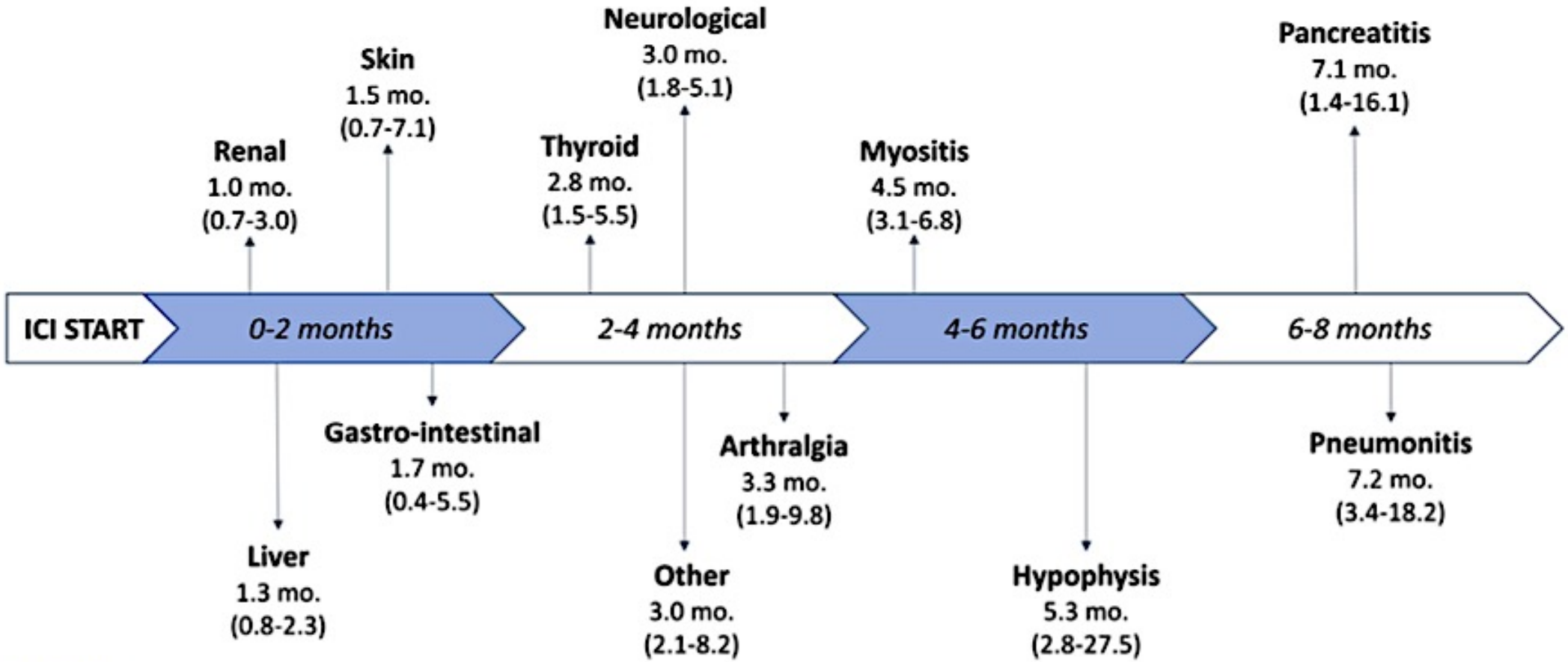


Figure 2 Timeline with median onset-timing (in months, mo.) (IQR) of the different organ-specific irAEs. ICI, immune checkpoint inhibitor; irAEs, immune-related adverse events.

Nasca JITC 2023

IRAEs ASCO(/NCCN/SITC) Guidelines

- Patient and family caregivers should receive timely and up-to-date education about immunotherapies, their mechanism of action, and the clinical profile of possible irAEs before initiating therapy and throughout treatment and survivorship.
- There should be a high level of suspicion that new symptoms are treatment-related.
- In general, ICPi therapy should be continued with close monitoring for grade 1 toxicities, except for some neurologic, hematologic, and cardiac toxicities.
- Consider holding ICPis for most grade 2 toxicities and resume when symptoms and/or laboratory values revert $\leq$ grade 1. Corticosteroids (initial dose of 0.5-1 mg/kg/d of prednisone or equivalent) may be administered.
- Hold ICPis for grade 3 toxicities and initiate high-dose corticosteroids (prednisone 1-2 mg/kg/d or equivalent). Corticosteroids should be tapered over the course of at least 4-6 weeks. If symptoms do not improve with 48-72 hours of high-dose steroid, infliximab may be offered for some toxicities.
- When symptoms and/or laboratory values revert $\leq$ grade 1, rechallenging with ICPis may be offered; however, caution is advised, especially in those patients with early-onset irAEs. Dose adjustments are not recommended. Rechallenge with PD-1/PD-L1 monotherapy may be offered in patients with toxicity from combined therapy with a CTLA-4 antagonist once recovered to $\leq$ grade 1.
- In general, grade 4 toxicities warrant permanent discontinuation of ICPis, except for endocrinopathies that have been controlled by hormone replacement.

Schneider JCO 2021

Do IRAEs and Treatment Reduce Efficacy?

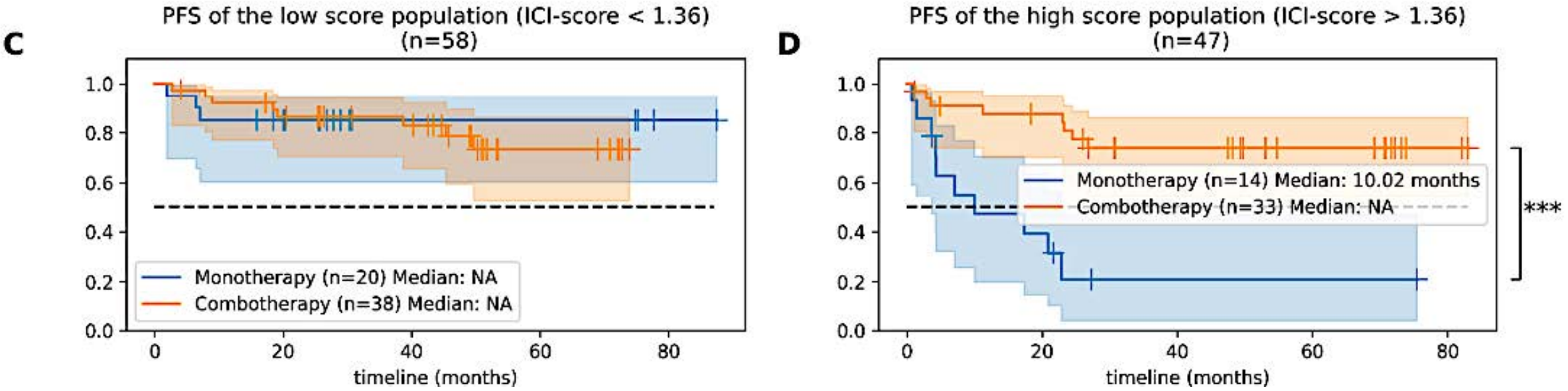
- IRAEs and outcomes
  - For mCRC HR PFS 1.27 OS 0.89 Nasca JITC 2023

- Treatment and outcomes PD-1+ CTLA-4
  - Corticosteroid peak dose for adverse events was associated with impaired survival across multiple tumor types, whereas cumulative dose was not. Verheijeden JCO 2024

Do All Patients Need Dual CPIs Up Front?

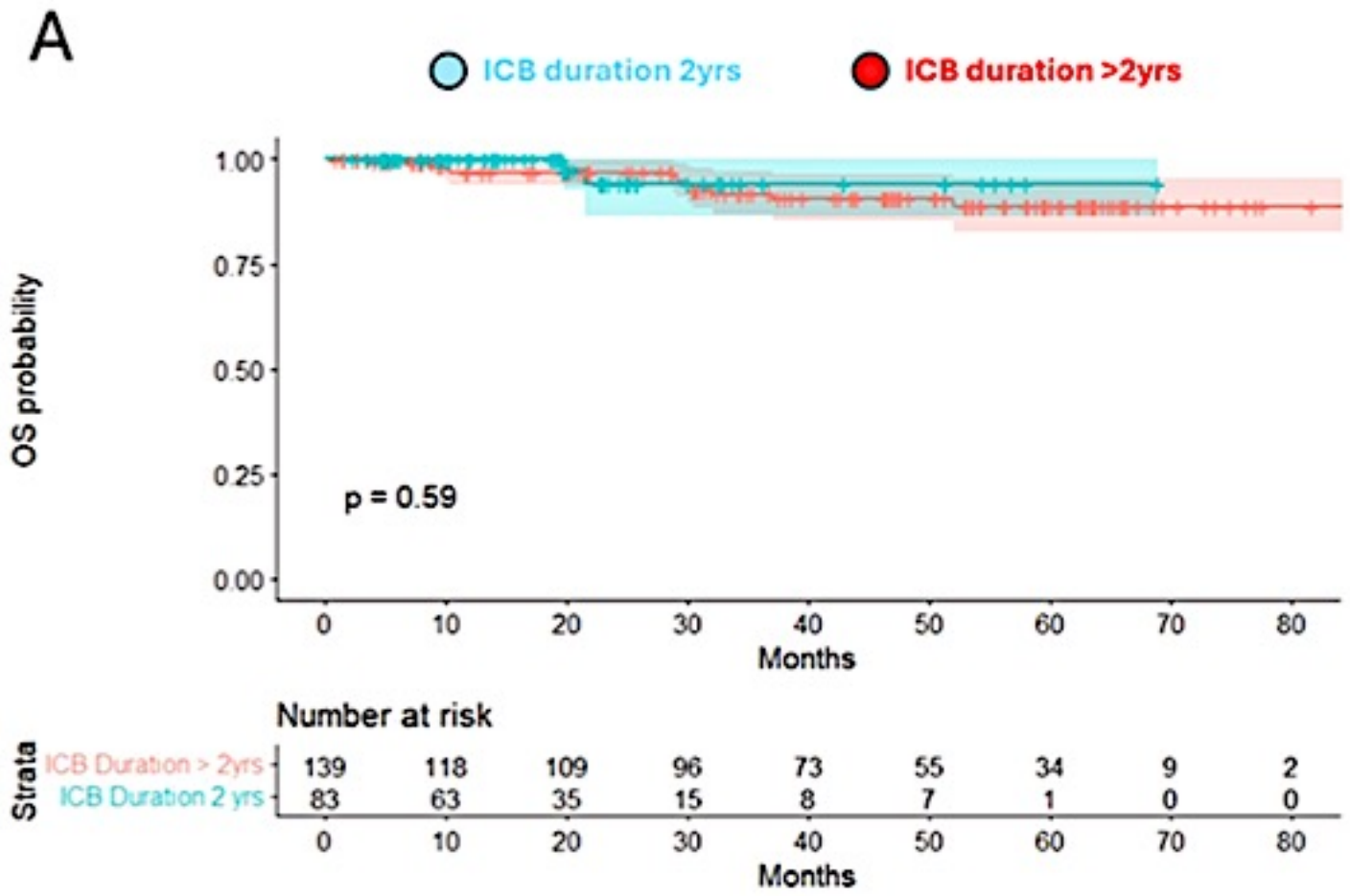
- Potential predictive factors
  - Disease burden
  - Location: liver vs peritoneal
  - Comorbidities, ECOG
  - Radiology Barbé EJC 2024
  - Molecular Gallois CCR 2023
  - Can we salvage?
    - Case reports: Das 2020, Kasi 2022, Krekeler 2023

Barbé HR 5.68 p <0.001



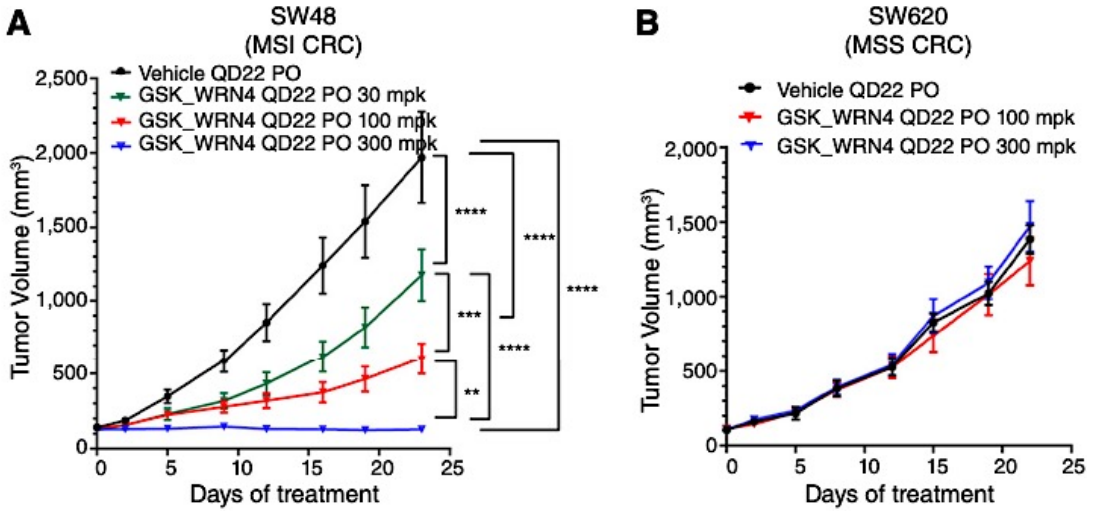
How Long To Treat?

- Unclear advantage over 2 years in melanoma and NSCLC
- mCRC 2 years = > 2 years
  - Margalit EJC 2024



Summary

- Identification of MSI in metastatic CRC is critical in determining appropriate therapy
- CPIs are the standard 1st line therapy for MSI-H mCRC
- Nivo/ipi > nivo or chemotherapy
- Toxicity is real but not that much more
- IRAE management is critical in caring for these patients
- Future research
  - Identification of patients who don't need a CTLA-4
  - Better IRAE management
  - Patients who progress?
    - Other IO agents (CPI, cell therapy)
    - WRN helicase inhibitors (Chan Nature 2019)
      - R075898831, HRO761



Picco Cancer Disc 2024

Case Presentation: 81-year-old woman with MSI-H recurrent mCRC receives pembrolizumab and has a complete response

Dr Stephen “Fred” Divers (Hot Springs, Arkansas)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

How frequently have you encountered patients with MSI-high, BRAF-mutant mCRC? How do you generally sequence immune checkpoint inhibitors and BRAF-targeted therapy for these patients? Are there any situations in which you would start with BRAF-targeted therapy?

For a patient with MSI-high, BRAF-mutant mCRC who experienced disease progression on first-line pembrolizumab, what would you recommend next — the BREAKWATER strategy of FOLFOX/encorafenib/cetuximab or encorafenib/EGFR antibody? Would patient age/fitness have any bearing on your decision?

Case Presentation: 85-year-old woman with recurrent dMMR, BRAF V600E-mutant mCRC with disease progression on FOLFOX

Dr Warren S Brenner (Boca Raton, Florida)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

How do you decide between single-agent pembrolizumab and nivolumab/ipilimumab for patients with newly diagnosed MSI-high mCRC?

How would you indirectly compare the global efficacy and tolerability of nivolumab/ipilimumab to that of anti-PD-1 monotherapy in this setting?

How do you think through the use of immune checkpoint inhibitors for your patients with autoimmune disease or a history of transplant? Does your approach vary in the localized versus metastatic setting?

RTP
RESEARCH
TO PRACTICE

Agenda

MODULE 1: Role of Circulating Tumor DNA (ctDNA) Evaluation in Nonmetastatic Colorectal Cancer (CRC) — Dr Dasari

MODULE 2: Role of Immune Checkpoint Inhibitors in the Management of Nonmetastatic Microsatellite Instability-High (MSI-H) CRC — Dr Cercek

MODULE 3: Management of Oligometastatic Disease and Hepatic-Only Metastases in CRC; Role of ctDNA Evaluation in Metastatic Disease — Dr Kasi

MODULE 4: Role of Immune Checkpoint Inhibitors in the Management of MSI-H Metastatic CRC (mCRC) — Dr Hecht

MODULE 5: Identification and Care of Patients with mCRC and Actionable Genomic Alterations — Prof Van Cutsem

RTP RESEARCH TO PRACTICE

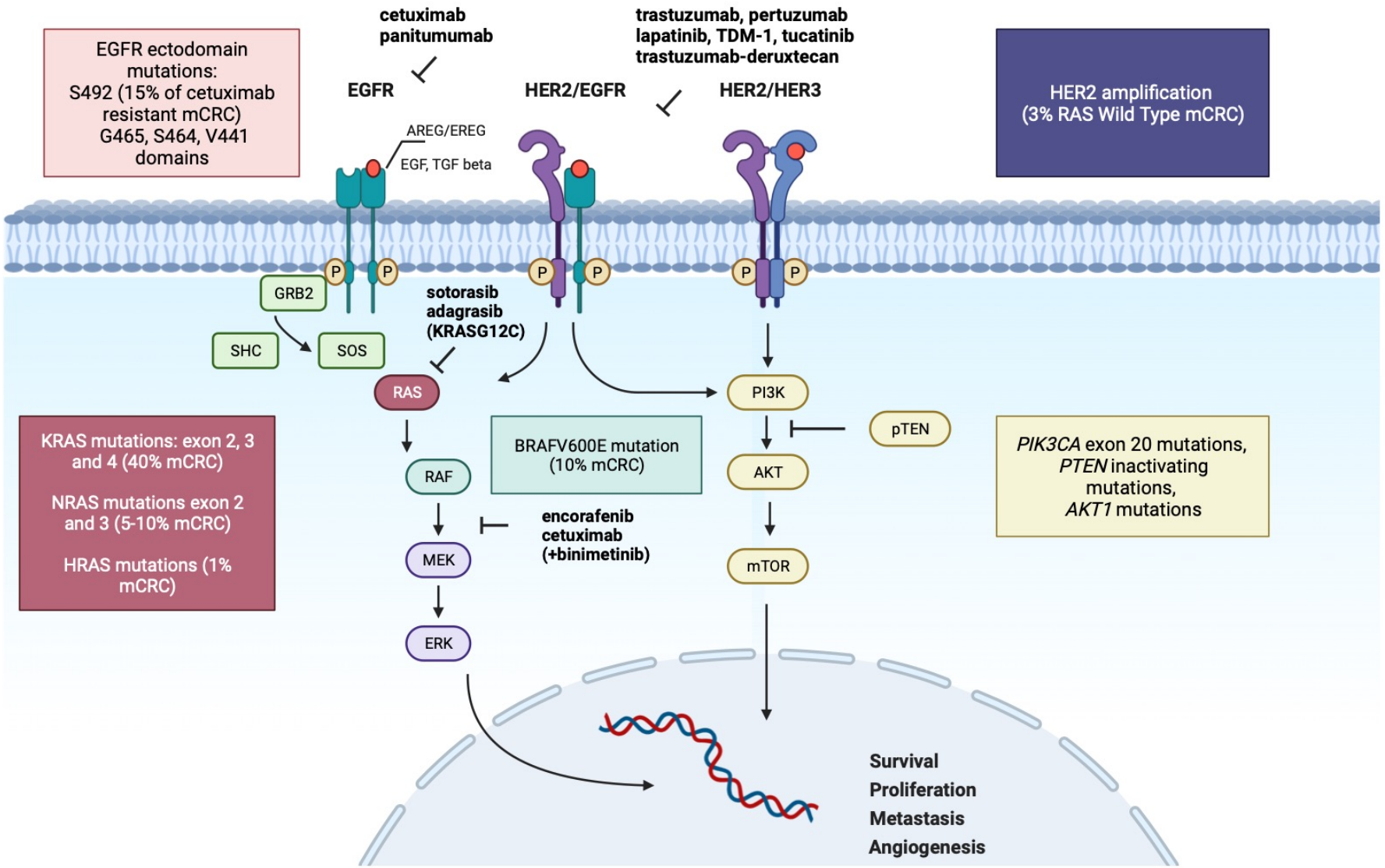
UZ LEUVEN

Identification and Management of Patients with mCRC and Actionable Genomic Alterations

Prof Eric Van Cutsem, MD, PhD
Digestive Oncology
Leuven, Belgium
Eric.VanCutsem@kuleuven.be

Herestraat 49
B - 3000 Leuven
www.uzleuven.be
tel. +32 16 33 22 11
UNIVERSITY HOSPITALS LEUVEN

Targeting the EGFR signaling pathway in mCRC



Napolitano S et al., The Lancet Gastroenterology and Hepatology 2024

Frontline BRAF V600E Phase III RCT

BREAKWATER Study Schema

Safety Lead-in

- Patients with *BRAF* V600E mutant, MSS/pMMR mCRC with 0 -1 prior regimens in the metastatic setting

Encorafenib + Cetuximab + mFOLFOX6
N=30
Encorafenib + Cetuximab + FOLFIRI
N=30

Doses:
Encorafenib- 300 mg PO QD
Cetuximab- 500 mg/m^2 IV Q2W
FOLFOX- full doses IV Q2W
FOLFIRI- full doses IV Q2W

ENDPOINTS

- Incidence of DLTs, Adverse events, dose modifications/discontinuations due to AEs
- PK including drug-drug interactions

Phase 3

- Patients with *BRAF* V600E mutant, MSS/pMMR mCRC and no prior systemic therapy in the metastatic setting

Randomize 1:1:1*

Arm A**
Encorafenib + Cetuximab
N=290

Arm B**
Encorafenib + Cetuximab + FOLFOX or FOLFIRI$^{\beta}$
N=290

Control Arm §
Physicians Choice: FOLFOX, FOLFIRI, FOLFOXIRI, CAPOX, all +/- anti-VEGF antibody
N=290

1° ENDPOINTS

- PFS (BICR) Arm A v. Control
  AND
- PFS (BICR) Arm B v. Control

(BICR-blinded independent central review)

KEY 2° ENDPOINTS

- OS Arm A v. Control
  AND
- OS Arm B v. Control

*Stratified by: ECOG PS 0 v. 1, Region US/Canada v. Europe v. ROW

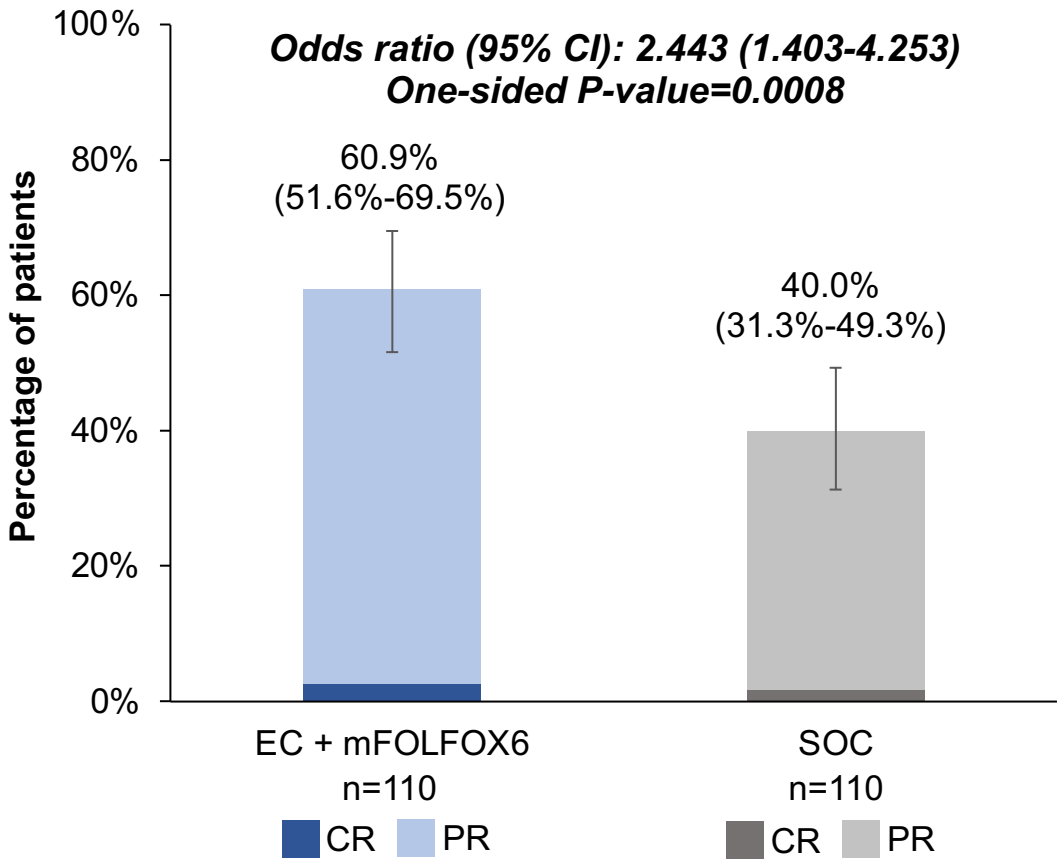
**Same dosing as SLI; $^{\beta}$FOLFOX or FOLFIRI based on SLI results; § No crossover

FOLFOX: Folinic acid (leucovorin), Fluorouracil (5-FU)- infusional, Oxaliplatin
FOLFIRI: Folinic acid (leucovorin), Fluorouracil (5-FU)- infusional, Irinotecan,
CAPOX: Capecitabine, Oxaliplatin
FOLFOXIRI: Folinic acid (leucovorin), Fluorouracil (5-FU), Oxaliplatin, Irinotecan

ClinicalTrials.gov Identifier: NCT04607421

Overview of Response by BICR

Confirmed ORR by BICR



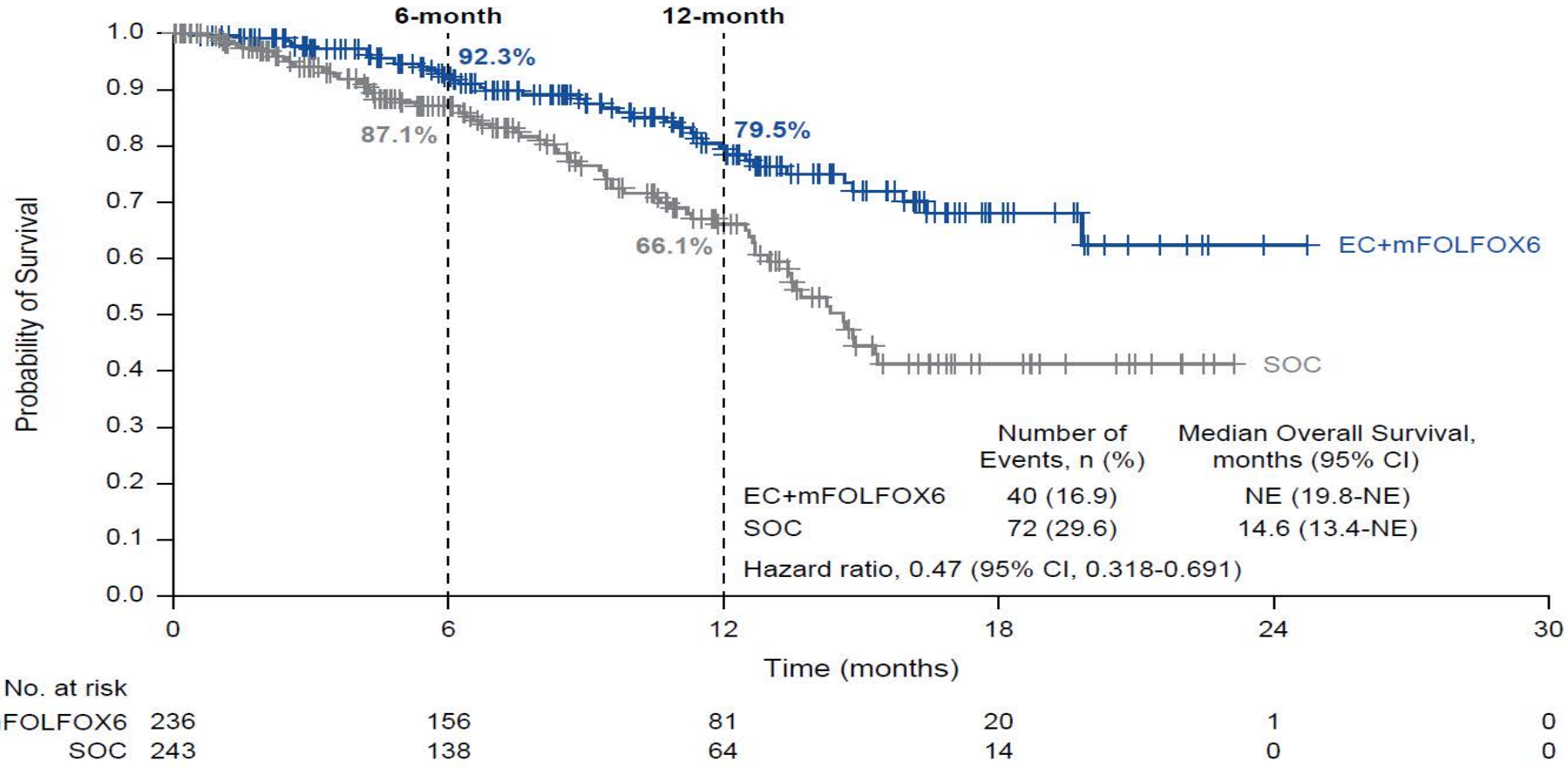
Confirmed Best Overall Response, TTR, and DOR by BICR

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

Data cutoff: December 22, 2023.

BICR, blinded independent central review; CR, complete response; DOR, duration of response; EC, encorafenib plus cetuximab; mFOLFOX6, modified fluorouracil/leucovorin/oxaliplatin; NE, not estimable; PD, progressive disease; PR, partial response; SD, stable disease; SOC, standard of care; TTR, time to response.

Interim Overall Survival[a]



Data cutoff: December 22, 2023.

[a]OS was formally tested in all randomized patients following the prespecified plan with one-sided alpha of 0.000000083, calculated as a portion of the nominal one-sided alpha of 0.001 based on the observed number of deaths, upon achieving statistical significance in the dual primary endpoint of ORR. Statistical significance was not achieved at this analysis; however, follow-up is ongoing, with planned additional interim and final analyses.

EC, encorafenib plus cetuximab; mFOLFOX6, modified fluorouracil/leucovorin/oxaliplatin; NE, not estimable; SOC, standard of care.

BRAF targeted treatment in first line mCRC

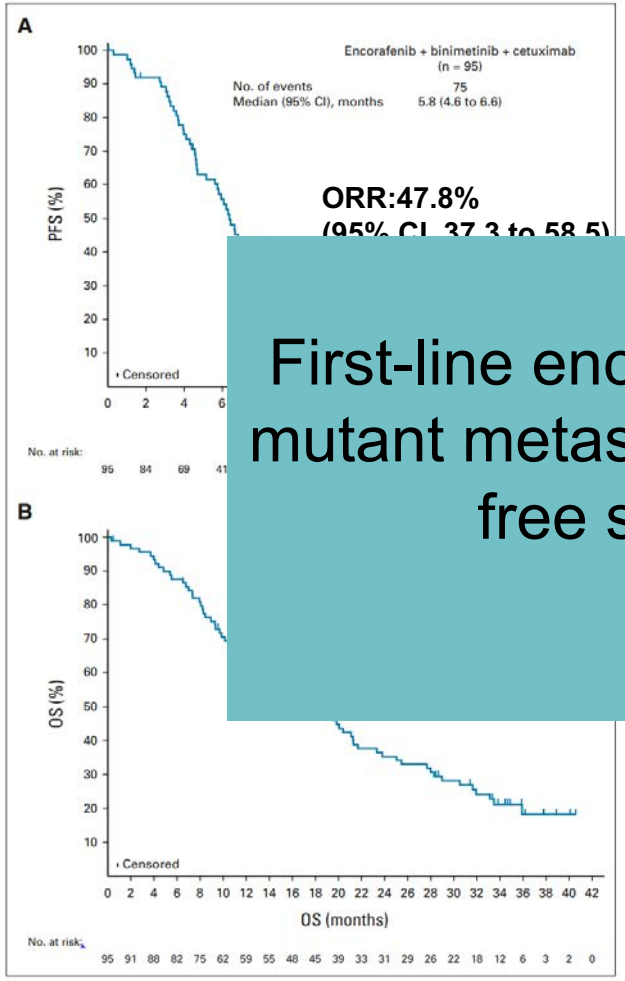


FIG 2. Kaplan-Meier plots of (A) PFS and (B) OS in the full analysis set (n = 95). FAS, full analysis set; OS, overall survival; PFS, progression-free survival.

ORR:47.8%
(95% CI, 37.3 to 58.5)

Table 2 | Confirmed objective response rate, time to treatment and duration of response by blinded independent central review

	EC+mFOLFOX6 (*n*=110)	SOC (*n*=110)
Confirmed best overall response, *n* (%)		
Estimated median duration of response (range), months	13.9 (8.5–NE)	11.1 (6.7–12.7)
Patients with a duration of response of ≥6 months, *n* (%)	46 (68.7)	15 (34.1)
Patients with a duration of response of ≥12 months, *n* (%)	15 (22.4)	5 (11.4)

CI, confidence interval; EC+mFOLFOX6, encorafenib and cetuximab plus oxaliplatin, leucovorin and 5-FU; NE, not estimable. [a]Defined as complete response or partial response according to RECIST 1.1 recorded from the date of randomization until the date of the first documentation of progression of disease, death or start of subsequent anticancer therapy; both complete response and partial response must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met. [b]Asymptotic CI used.

nature medicine

Article https://doi.org/10.1038/s41591-024-03443-3

Encorafenib, cetuximab and chemotherapy in BRAF-mutant colorectal cancer: a randomized phase 3 trial

Cathy Eng[4],
[10],
song Zhang[12] &

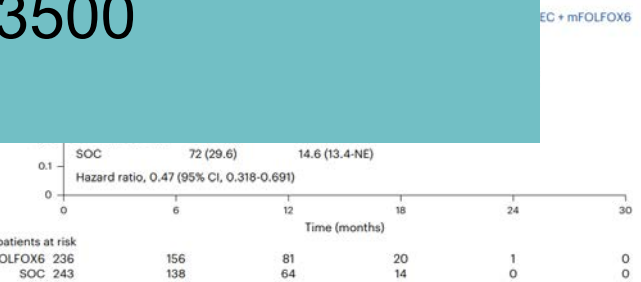


Fig. 3 | Overall survival. Hazard ratio repeated CI: 0.166–1.322.

UPDATE at ASCO 2025 – May 31

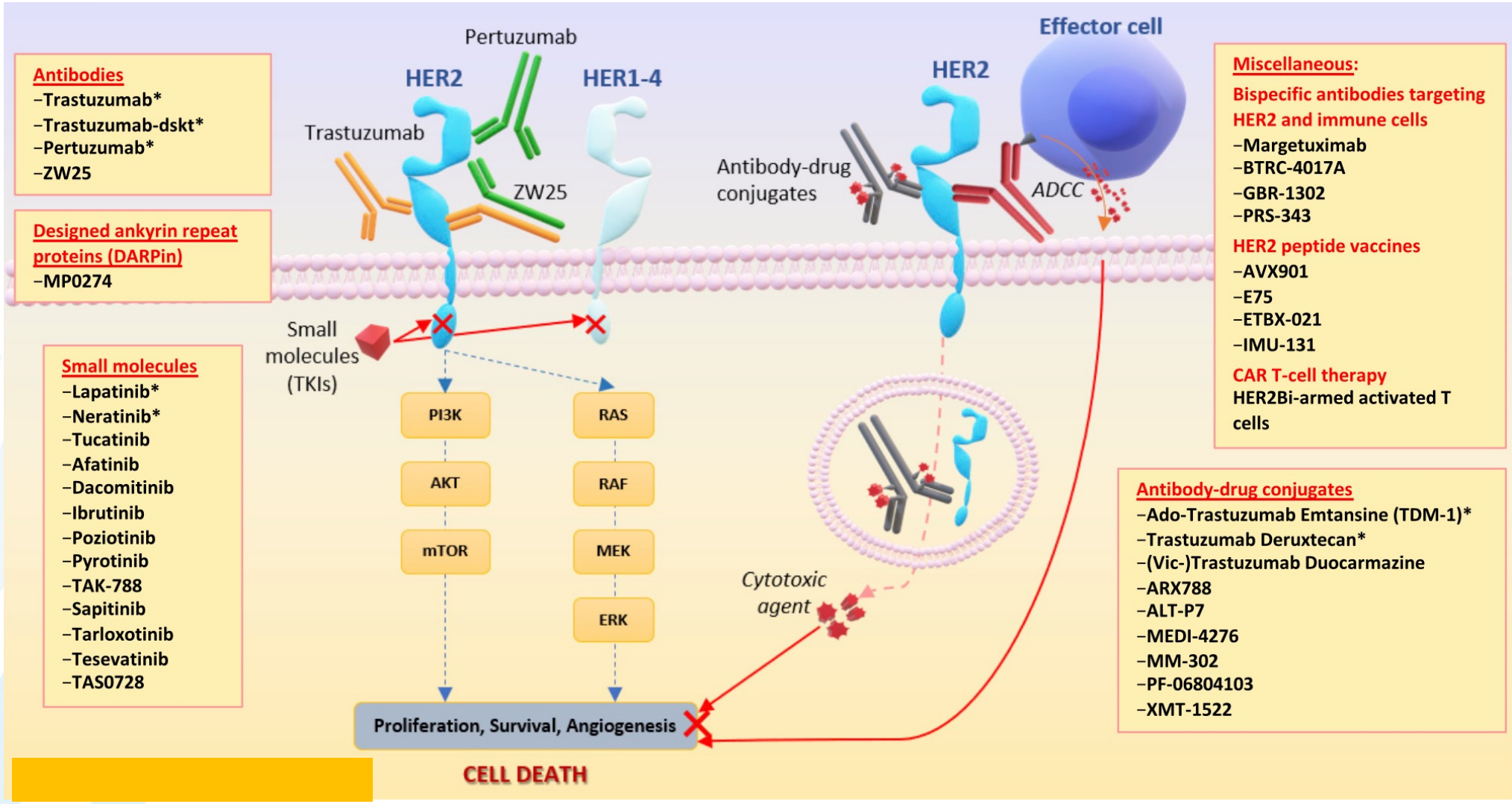
First-line encorafenib + cetuximab + mFOLFOX6 in BRAF V600E-mutant metastatic colorectal cancer (BREAKWATER): Progression-free survival and updated overall survival analyses.

Elez E…. Van Cutsem E et al, LBA 3500

Anchor study:
Van Cutsem E… et al, JCO 2023

Breakwater study:
Kopetz S, Yoshino T, Van Cutsem E, et al, Nature Medicine 2025

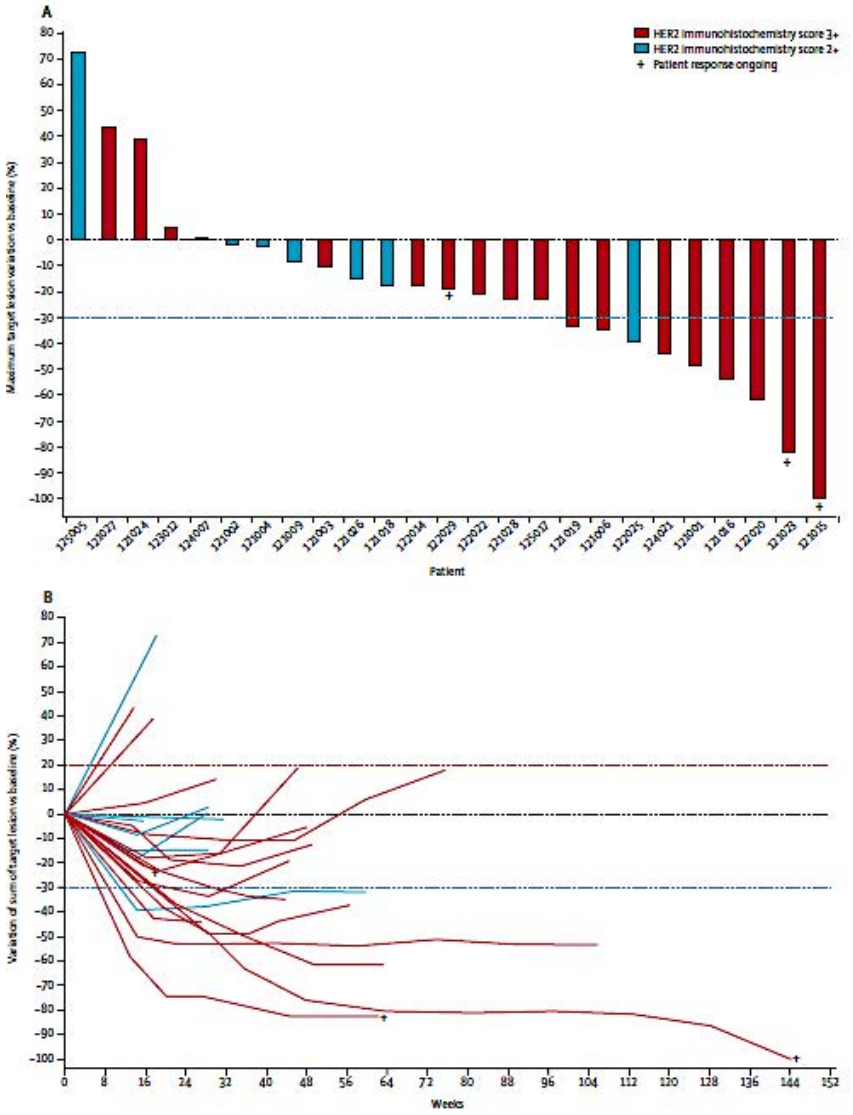
Novel anti-HER2 Strategies for GI Tumors



Siena S. et al Cancer Cell 2020

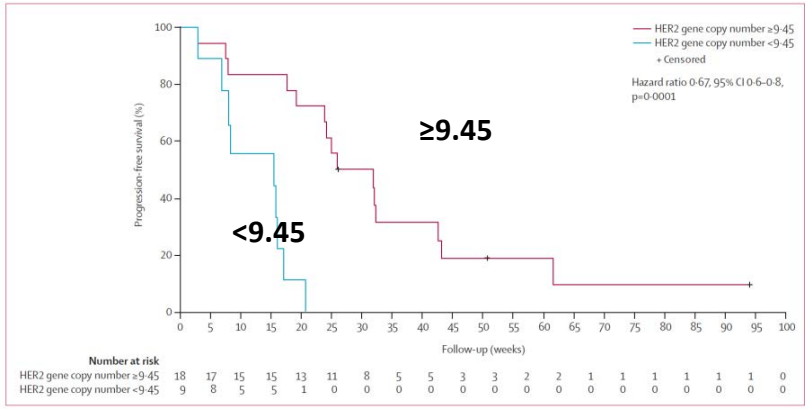
HER2-targeted therapy in mCRC: HERACLES-A

	Patients given trastuzumab and lapatinib (n=27)
Age (years)	62 (50–68)
Sex	
Men	23 (85%)
Women	4 (15%)
ECOG performance status 0–1	27 (100%)
HER2 expression by immunohistochemistry score	
3+	20 (74%)
2+	7 (26%)
Site of primary tumour	
Rectum	7 (26%)
Colon	20 (74%)
Proximal*	4 (20%)
Distal†	16 (80%)
Metastatic disease in multiple sites	26 (96%)
Number of previous lines of therapy	5 (4–6)
Patients with ≥4 previous lines of therapy	20 (74%)
Previous anti-angiogenesis treatment	20 (74%)
Previous therapy with panitumumab or cetuximab	27 (100%)
Patients eligible to be assessed for sensitivity to panitumumab or cetuximab‡	15 (56%)
Previous response to panitumumab or cetuximab	0
Time on previous treatment (total; months)§	20 (16–24)
By primary site	
Proximal	15 (13–19)
Distal	19 (15–24)
Rectum	23 (20–25)



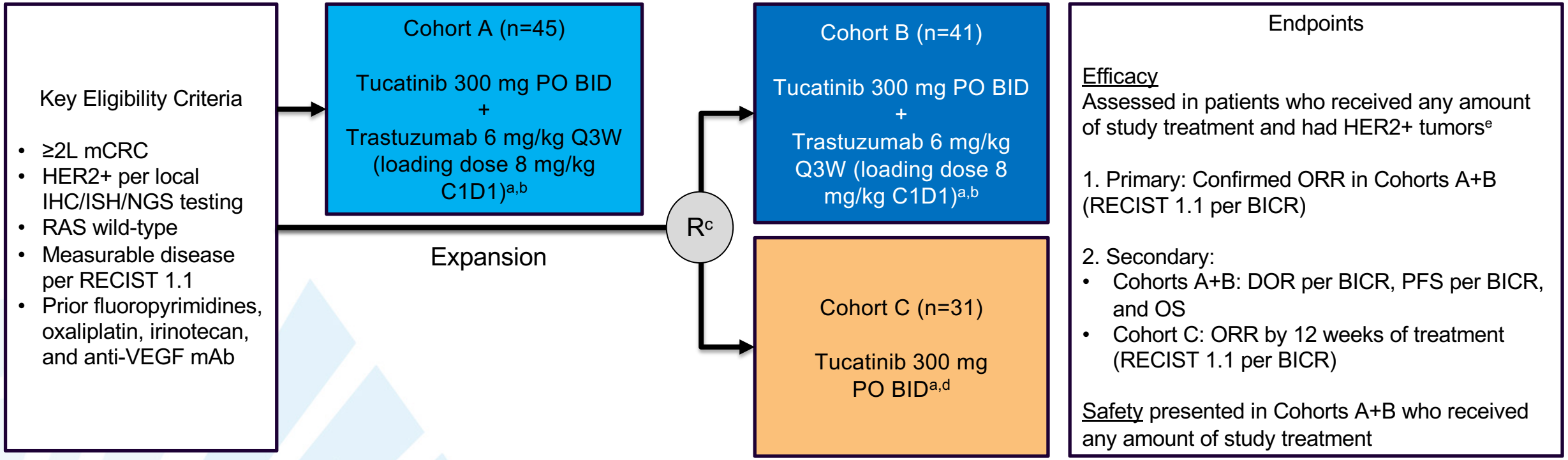
Complete response	1 (4%, −3 to 11)
Partial response	7 (26%, 9 to 43)
Objective response	8 (30%, 14 to 50)
Disease control†	16 (59%, 39 to 78)
Duration of response (weeks)	38 (24 to 94+)

PFS according to HER2 GCN



Sartore-Bianchi A … Siena S, Lancet Oncol 2016

MOUNTAINEER: Global, Open-Label, Phase 2 Trial of Tucatinib and Trastuzumab in HER2+ mCRC



MOUNTAINEER began as a US Investigator-Sponsored Trial and initially consisted of a single cohort (Cohort A) and was expanded globally to include patients randomised to receive tucatinib + trastuzumab (Cohort B) or tucatinib monotherapy (Cohort C)

Data cut-off for current analysis, March 28, 2022

a Each treatment cycle is 21 days; b Patients remained on therapy until evidence of radiographic or clinical progression, unacceptable toxicity, withdrawal of consent, or study closure; c Stratification: Left sided tumor primary vs other; 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 PR or CR by week 12; e Patients had HER2+ tumors as defined by one or more protocol required local tests: IHC 3+ (n=46), amplification by ISH (n=36), or amplification by NGS (n=69)

https://clinicaltrials.gov/ct2/show/NCT03043313

Strickler JH…Van Cutsem E et al. Lancet Oncol. 2023

MOUNTAINEER: Global, Open-Label, Phase 2 Trial of Tucatinib and Trastuzumab in HER2+ mCRC

	Tucatinib plus trastuzumab (cohorts A and B; n=84)
Confirmed objective response rate (95% CI)*	38·1% (27·7–49·3)
Complete response†	3 (4%)
Partial response†	29 (35%)
Stable disease†‡	28 (33%)
Progressive disease†	22 (26%)
Not available§	2 (2%)
Disease control rate (post hoc)¶	60 (71%)
Median duration of response, months (IQR)	12·4 (8·3–25·5)

Data are n (%) unless specified otherwise. Percentages might not total 100 due to rounding. *Confirmed disease response and progression were assessed according to Response Evaluation Criteria in Solid Tumours, version 1.1, by blinded independent central review. †Best overall response. ‡Includes stable disease and non-complete response or non-progressive disease. §Includes patients with no post-baseline response assessment and patients whose disease assessments are not evaluable. ¶Defined as the sum of the complete response, partial response, and stable disease.

Table 2: **Response to treatment in patients treated with tucatinib plus trastuzumab (n=84)**

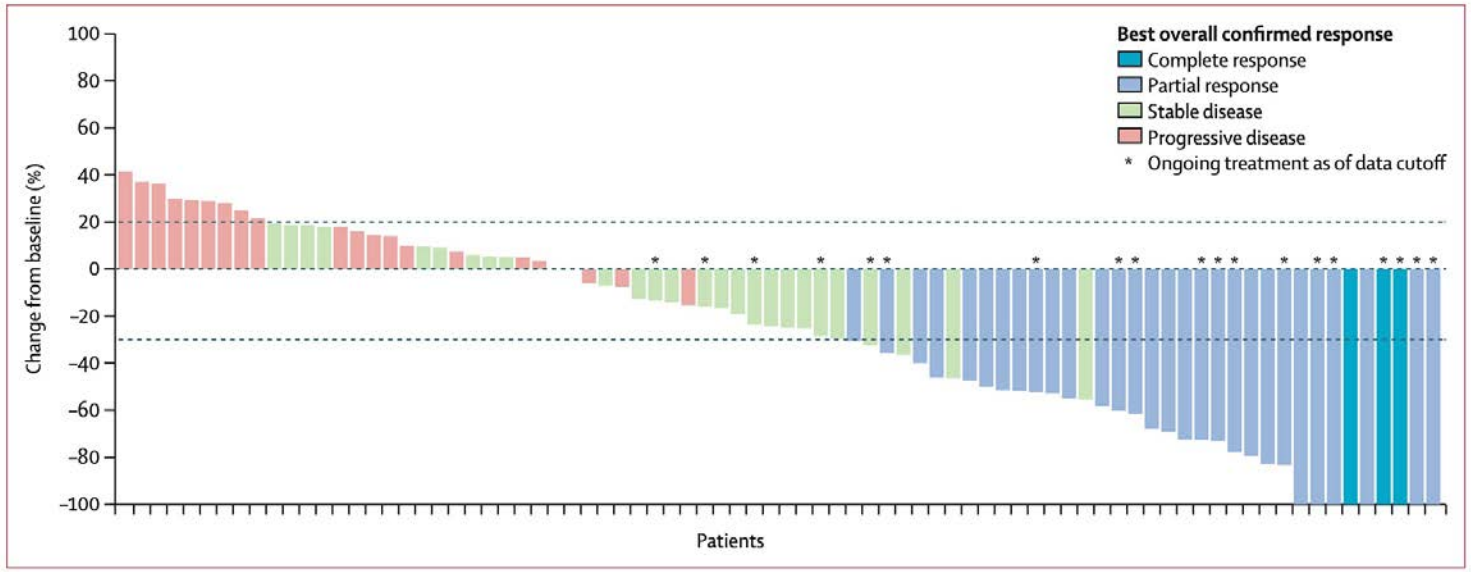


Figure 2: **Anti-tumour activity in patients treated with tucatinib plus trastuzumab with available baseline and post-baseline lesion measurements (n=80)**
Shown are the maximum percentage changes in the sum of the diameters of target lesions per blinded independent central review for all patients treated with combination therapy who had baseline and post-baseline target lesion measurements. Four patients who did not have these measurements were excluded. Six patients had 100% reductions and a best overall confirmed response of partial response due to non-target lesions that had not completely resolved. Similarly, four patients with greater than 30% reduction were classified as having stable disease on the basis of failure to confirm the response due to progression. The upper dashed horizontal line indicates a 20% increase in tumour size, and the lower dashed line indicates a 30% decrease in tumour size (corresponding to the RECIST definitions for progressive disease and partial response).

Post-hoc subgroup analysis by HER2 status according to immunohistochemistry: confirmed ORR by BICR were

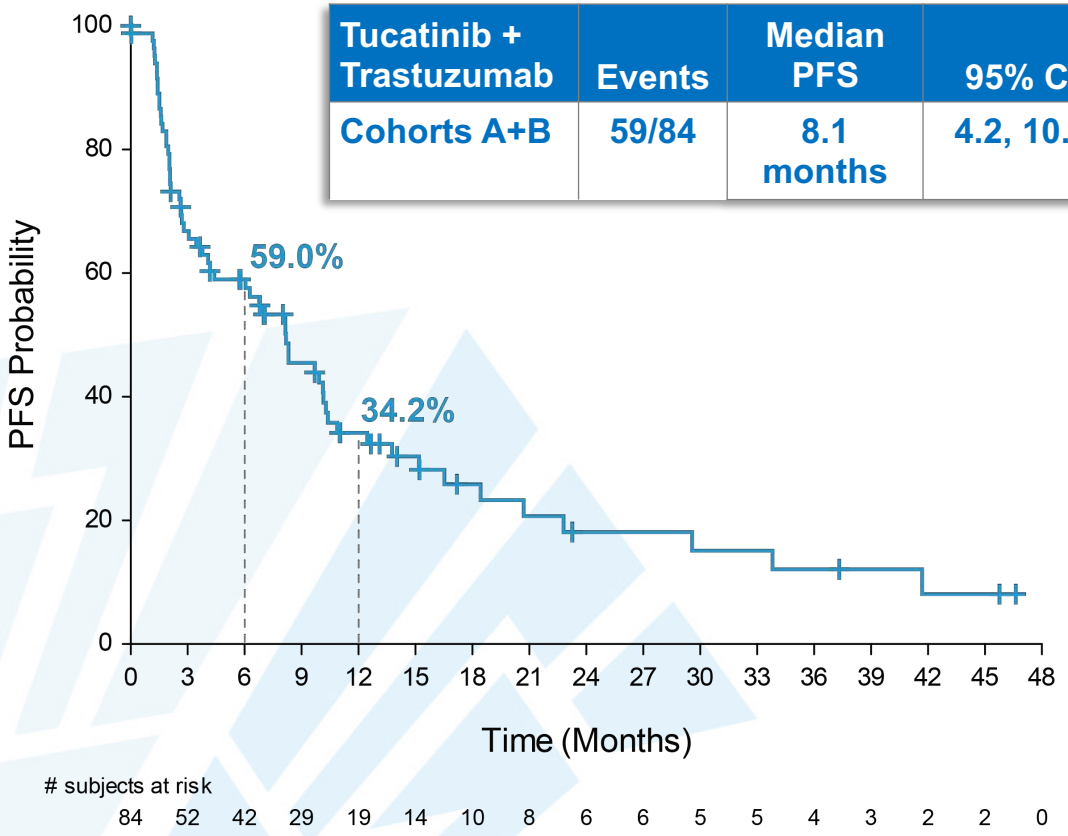
- ✓ **46·7% (95% CI 31·7–62·1; 21 of 45 patients) in those with IHC 3+ tumours,**
- ✓ **20·0% (4·3–48·1; three of 15 patients) in those with IHC 2+ and in-situ hybridisation-positive tumours**
- ✓ **10·0% (0·3–44·5; one of ten patients) in those with HER2-negative tumours**

Strickler JH…Van Cutsem E et al. *Lancet Oncol.* 2023; Strickler JH… Van Cutsem E et al. ASCO 2024; Abstract 3509.

MOUNTAINEER: Global, Open-Label, Phase 2 Trial of Tucatinib and Trastuzumab in HER2+ mCRC

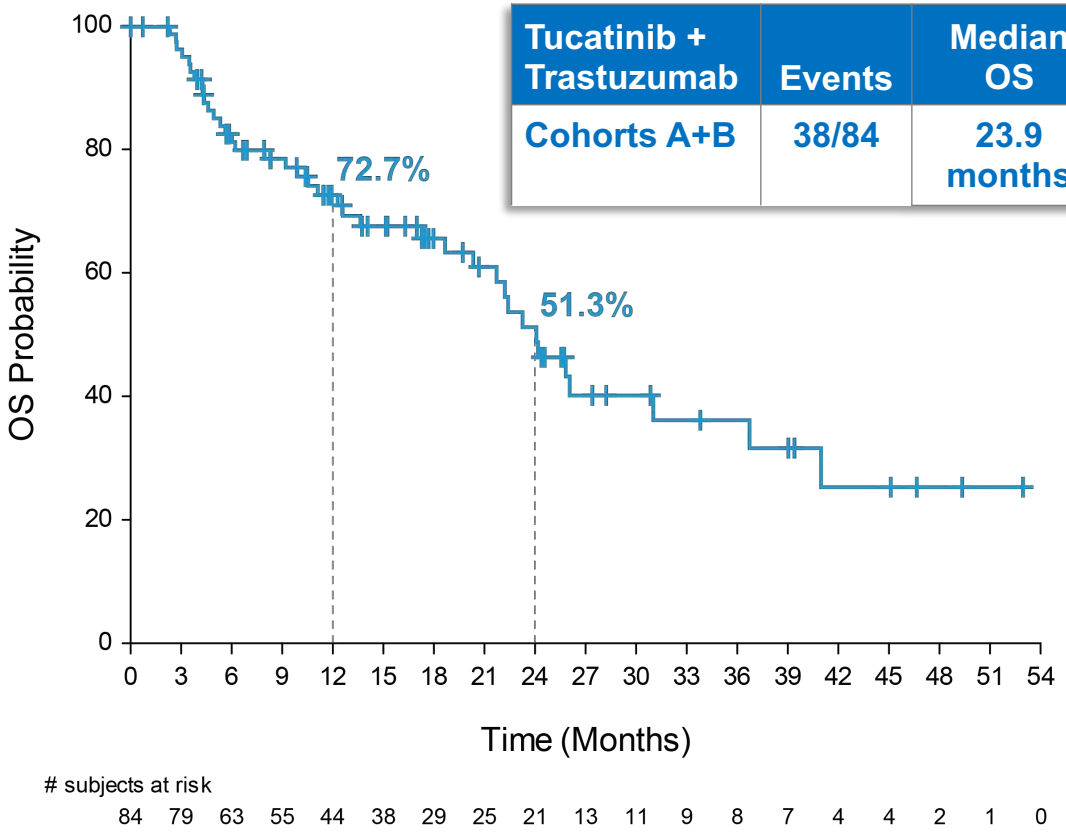
Progression-free Survival per BICR

Tucatinib + Trastuzumab	Events	Median PFS	95% CI
Cohorts A+B	59/84	8.1 months	4.2, 10.2



Overall Survival

Tucatinib + Trastuzumab	Events	Median OS	95% CI
Cohorts A+B	38/84	23.9 months	18.7, 28.3



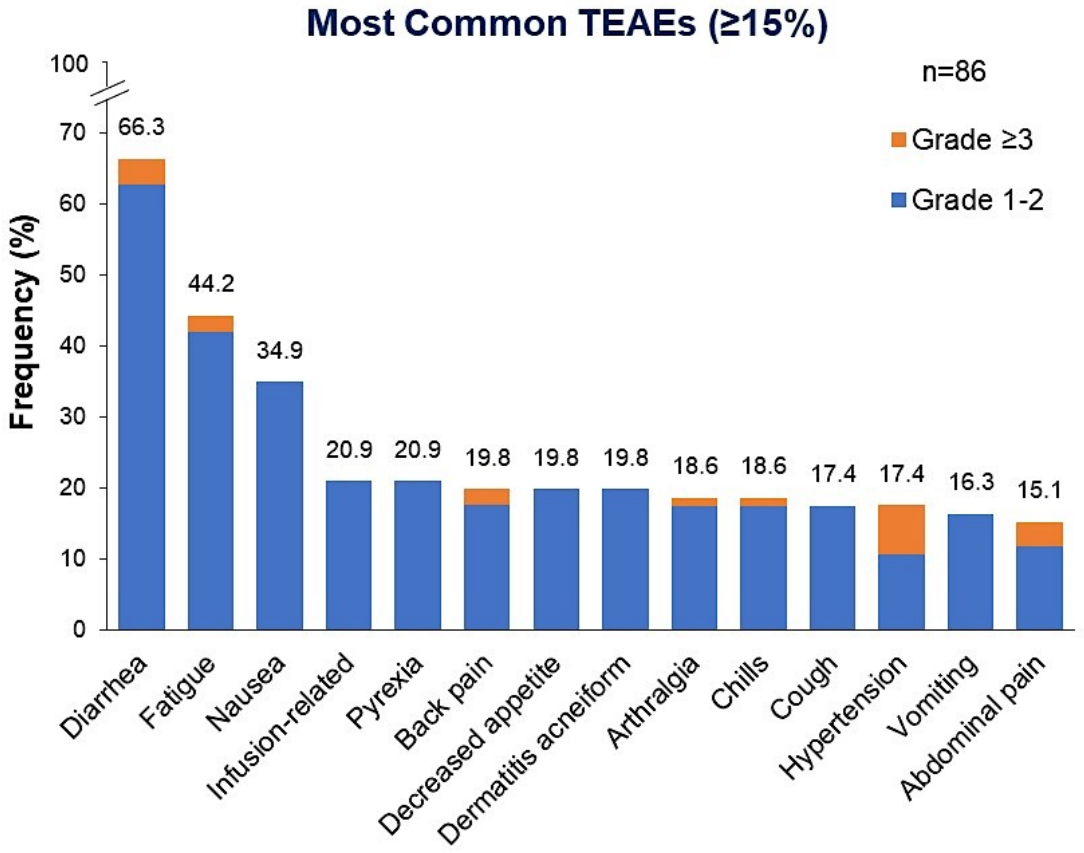
Median follow-up for Cohorts A+B in final analysis was 32.4 months.

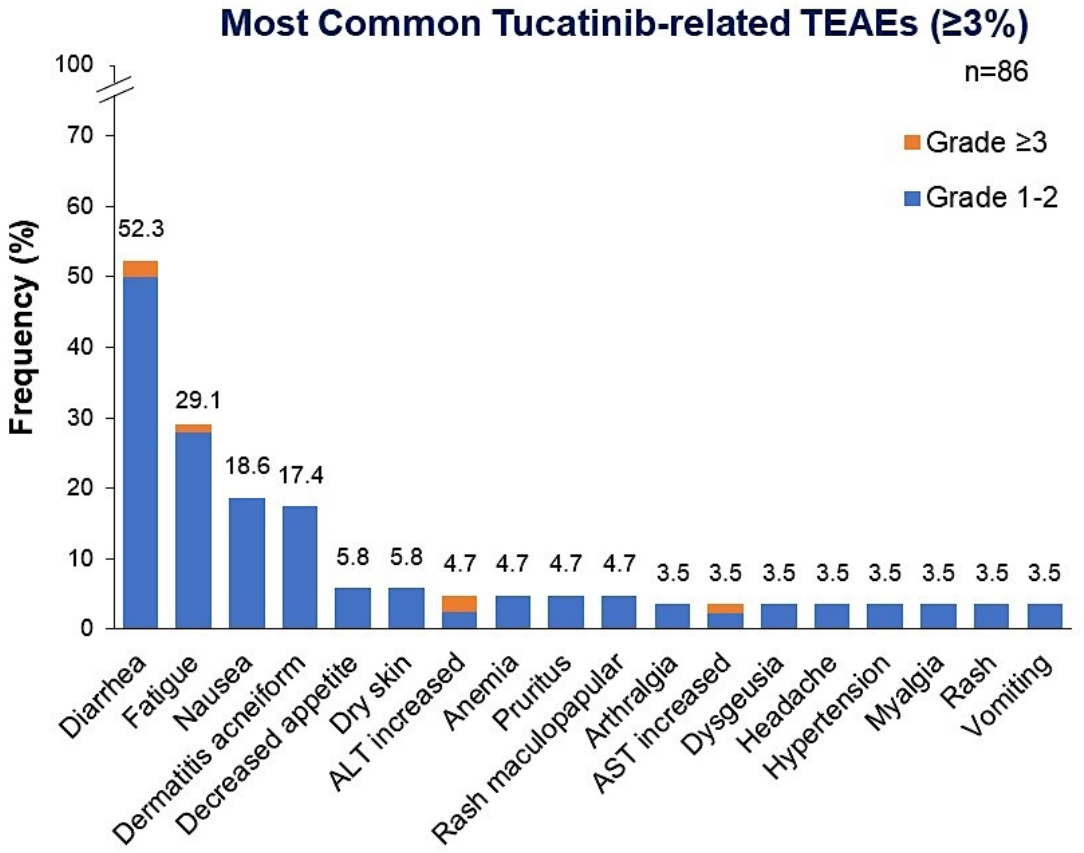
BICR, blinded independent central review; IQR, interquartile range; OS, overall survival; PFS, progression-free survival.

Data cutoff: 28 Mar 2022

Strickler JH…Van Cutsem E et al. *Lancet Oncol.* 2023; Strickler JH…Van Cutsem E et al. ASCO 2024; Abstract 3509.

Most Common TEAEs for Tucatinib + Trastuzumab





AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

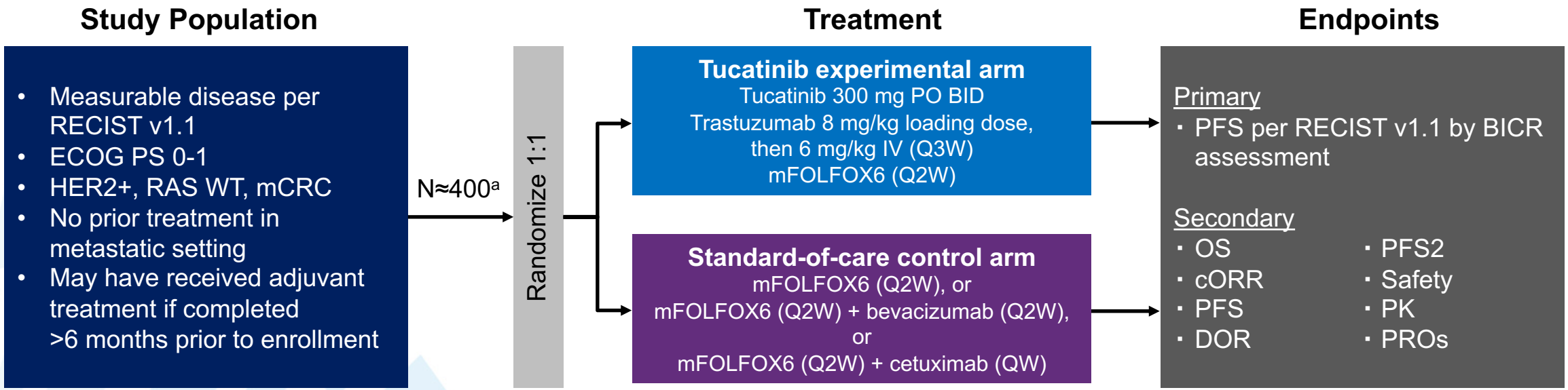
- Most common tucatinib-related AEs: diarrhoea (52.3%), fatigue (29.1%), nausea (18.6%), and dermatitis acneiform (17.4%)
  - Grade ≥3 tucatinib-related AEs (≥3%): alanine aminotransferase increase (2.3%) and diarrhoea (2.3%)

Data cutoff: 28 Mar 2022

Strickler JH…Van Cutsem E et al. *Lancet Oncol.* 2023; Strickler JH…Van Cutsem E et al. ASCO 2024; Abstract 3509.

MOUNTAINEER-03 trial in first line mCRC

- MOUNTAINEER-03 (NCT05253651) is a global, open-label, randomized, phase 3 study of tucatinib with trastuzumab and mFOLFOX6 versus standard of care for the first-line treatment of HER2+ and *RAS* wild-type mCRC



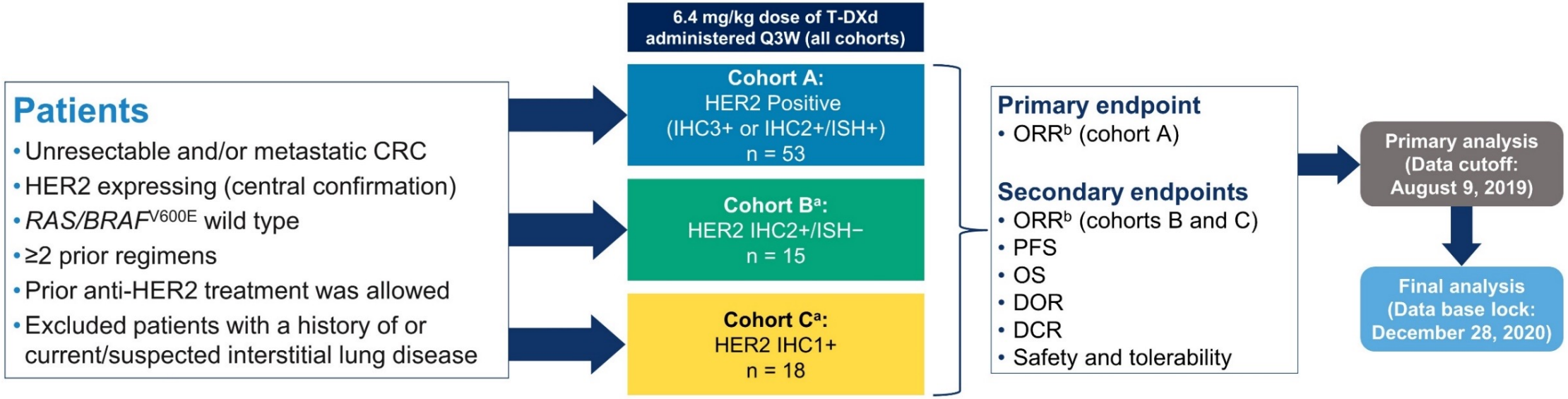
a Stratification by both primary tumor location (left-sided versus all other) and liver metastases (presence or absence)

BICR, blinded independent central review; BID, twice a day; cORR, confirmed objective response rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HER2, human epidermal growth factor receptor 2; IV, intravenously; mCRC, metastatic colorectal cancer; mFOLFOX6, modified 5-fluorouracil, leucovorin, and oxaliplatin; OS, overall survival; PFS, progression-free survival; PFS2, time from randomization to disease progression on next-line treatment or death from any cause; PK, pharmacokinetics; PO, by mouth; PROs, patient-reported outcomes; Q, each; RAS, rat sarcoma virus; RECIST, Response Evaluation Criteria in Solid Tumors; W, week; WT, wild-type.

Strickler J ....Van Cutsem E et al, Future Oncol 2024

DESTINY-CRC01 Study Design

An open-label, multicenter, phase 2 study (NCT03384940)



Primary analysis of cohort A[1]

- Results yielded promising antitumor activity and a manageable safety profile
- The median follow-up was 27.1 weeks at data cutoff

Patient disposition at final analysis[c]

- No patients remain on treatment
- At the end of the study, median follow-up was 62.4 weeks for cohort A, 27.0 weeks for cohort B and 16.9 weeks for cohort C

CRC, colorectal cancer; DCR, disease control rate; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; q3w, every three weeks; RECIST, Response Evaluation Criteria in Solid Tumors; T-DXd, trastuzumab deruxtecan.

[a]A futility monitoring analysis was done after ≥20 patients in Cohort A had 12 weeks of follow-up to inform opening of Cohorts B and C. [b]ORR was based on RECIST version 1.1 in all cohorts. [c]Data presented are from the full analysis set.

1. Siena S et al. *Lancet Oncol*. 2021;S1470-2045(21)00086-3.

Siena S et al, Lancet Oncol 2021
Yoshino T et al, Nat Comm 2023

DESTINY-CRC01 trial

Table 3 | Key efficacy endpoints

	HER2 IHC 3 + or IHC 2 + /ISH + Cohort A *n* = 53	HER2 IHC 2 + /ISH − Cohort B *n* = 15	HER2 IHC 1 + Cohort C *n* = 18
Confirmed ORR by ICR	24 (45.3) [95% CI, 31.6–59.6]	0 [95% CI, 0.0–21.8]	0 [95% CI, 0.0–18.5]
Complete response	0	0	0
Partial response	24 (45.3)	0	0
Stable disease	20 (37.7)	9 (60.0)	4 (22.2)
Progressive disease	5 (9.4)	5 (33.3)	10 (55.6)
Not evaluable[a]	4 (7.5)	1 (6.7)	4 (22.2)
DCR	83.0 (70.2–91.9)	60.0 (32.3–83.7)	22.2 (6.4–47.6)
Median DoR, months	7.0 (5.8–9.5)	NE (NE–NE)	NE (NE–NE)
Median treatment duration, months	5.1 (3.9–7.6)	2.1 (1.4–2.6)	1.4 (1.3–1.5)

Data are presented as *n* (%), % (95% CI), or medians (95% CI).
DCR disease control rate, *DoR* duration of response, *ICR* independent central review, *IHC* immunohistochemistry, *ISH* in situ hybridization, *NE* not evaluable, *ORR* objective response rate.
[a]Patients were missing postbaseline scans.

Yoshino T et al, Nat Comm 2023

DESTINY-CRC01 trial: analysis according to IHC of HER2

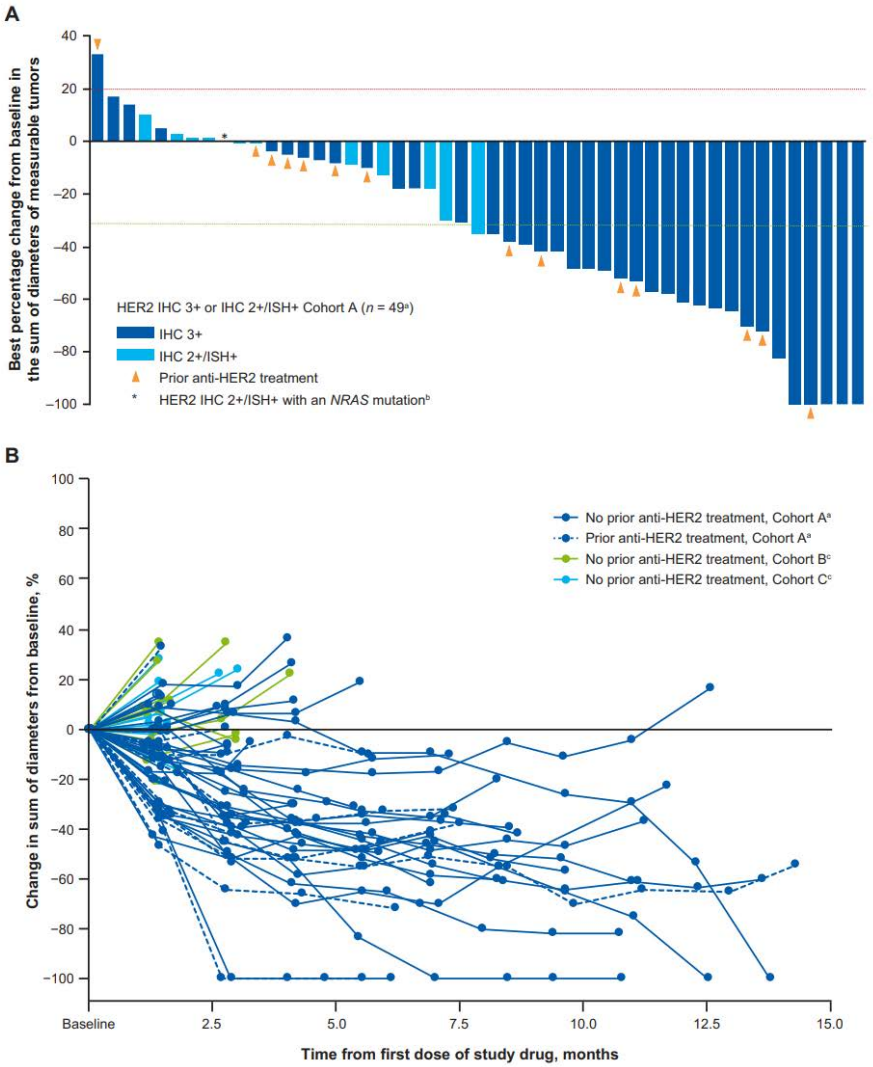


Fig. 1 | Antitumor activity of trastuzumab deruxtecan. A Waterfall plot showing the greatest percentage change from baseline in the sum of diameters of measurable tumors in patients with HER2-positive mCRC (cohort A). Each bar represents a patient. The line at 20% indicates progressive disease. The line at −30% indicates partial response. **B** Spider plot showing change over time from baseline in the sum of diameters of measurable tumors in cohorts A, B, and C. [a]Four patients from the full analysis set were excluded; 1 patient had no measurable target lesion and 3 patients had no postbaseline data. [b]By local assessment. [c]One patient from cohort B and 5 patients from cohort C had missing postbaseline data. HER2 human epidermal growth factor receptor 2, IHC immunohistochemistry, ISH in situ hybridization.

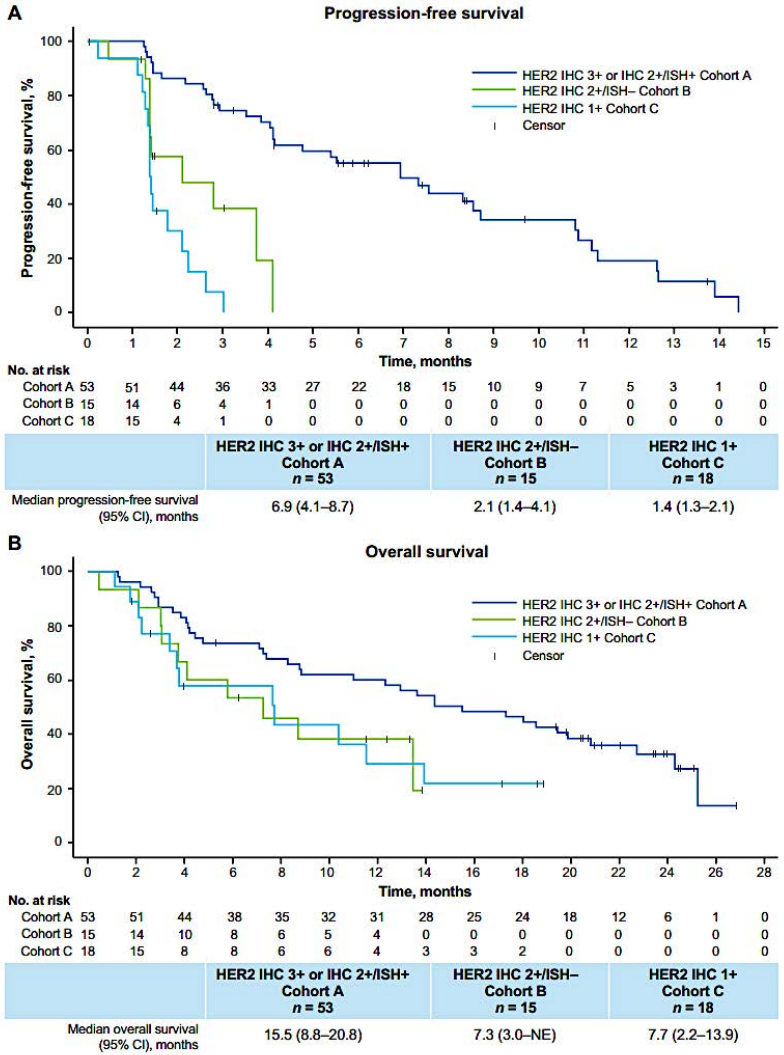


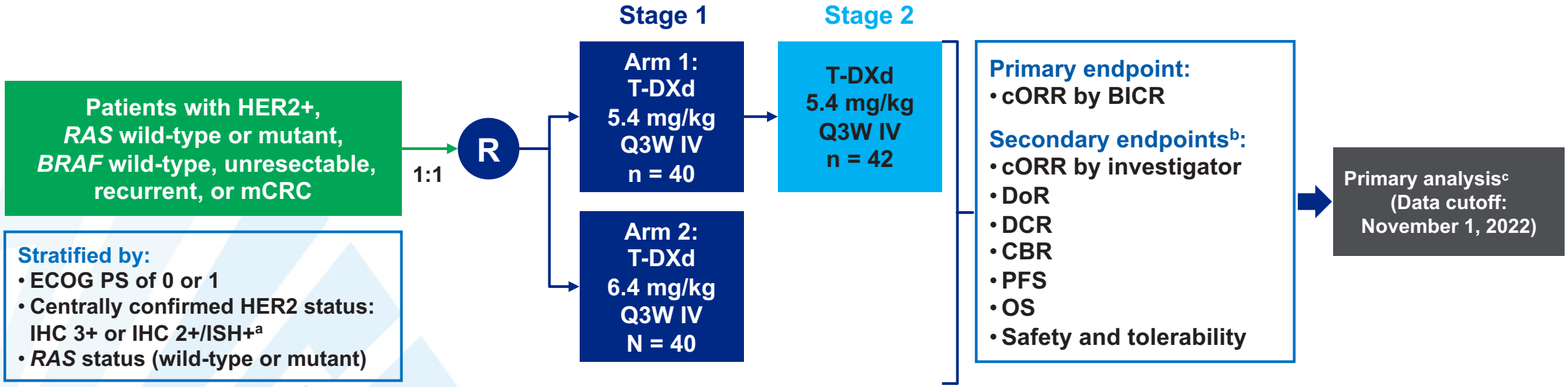
Fig. 2 | Progression-free survival and overall survival in patients with HER2-positive and HER2-low mCRC receiving trastuzumab deruxtecan. Kaplan–Meier curves representing (**A**) progression-free survival and (**B**) overall survival. Marks indicate where data were censored. HER2 human epidermal growth factor receptor 2, IHC immunohistochemistry, ISH in situ hybridization, NE not evaluable.

Yoshino T et al, Nat Comm 2023

DESTINY-CRC02 Study Design

A randomized, blinded, 2-stage, 2-arm, multicenter, global, phase 2 study (NCT04744831)

- Stage 1 (randomized) was followed by Stage 2 (nonrandomized), which enrolled an additional 42 patients



This study was not powered to statistically compare the two arms.

BICR, blinded independent central review; *BRAF*, v-raf murine sarcoma viral oncogene homolog B1; CBR, clinical benefit rate; cORR, confirmed objective response rate; 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; Q3W, every 3 weeks; R, randomization; *RAS*, rat sarcoma; T-DXd, trastuzumab deruxtecan.
Both investigators and patients were blind to treatments.
[a]HER2 status was assessed with the Roche VENTANA HER2 Dual ISH DNA probe cocktail assay (IUO). [b]Exploratory endpoints included best percent change in the sum of diameters of measurable tumors based on BICR and investigator. [c]Primary analysis occurred ≥6 months after the last patient had been enrolled or when all patients discontinued from the study, whichever was earlier.

Raghav K... Yoshino T. Lancet Oncol 2024.

DESTINY-CRC02: efficacy results

	T-DXd 5.4 mg/kg Q3W			T-DXd 6.4 mg/kg Q3W
	Stage 1 n = 40	**Stage 2 n = 42**	**Total N = 82**	**Stage 1 N = 40**
cORR, n (%) [95% CI]	**18 (45.0) [29.3-61.5]**	**13 (31.0) [17.6-47.1]**	**31 (37.8) [27.3-49.2]**	**11 (27.5) [14.6-43.9]**
CR	0	0	0	0
PR	18 (45.0)	13 (31.0)	31 (37.8)	11 (27.5)
SD	20 (50.0)	20 (47.6)	40 (48.8)	23 (57.5)
PD	2 (5.0)	6 (14.3)	8 (9.8)	4 (10.0)
NE	0	3 (7.1)	3 (3.7)	2 (5.0)
Confirmed DCR, n (%) [95% CI]	38 (95.0) [83.1-99.4]	33 (78.6) [63.2-89.7]	71 (86.6) [77.3-93.1]	34 (85.0) [70.2-94.3]
Median DoR, mo (95% CI)	8.1 (4.2-NE)	4.6 (4.1-7.0)	5.5 (4.2-8.1)	5.5 (3.7-NE)
Median follow-up, mo (range)	10.6 (2.9-17.1)	7.7 (0.5-10.3)	8.9 (0.5-17.1)	10.3 (0.7-16.4)
Median treatment duration, mo (range)	5.5 (1.4-13.2)	4.8 (0.7-10.8)	5.5 (0.7-13.2)	4.9 (0.7-13.8)
Median total dose, mg/kg (range)	39.6 (10.5-96.8)	37.4 (5.4-81.3)	37.8 (5.4-96.8)	40.8 (6.4-128.4)
Median number of cycles initiated (range)	8.0 (2-19)	7.0 (1-15)	7.0 (1-19)	7.0 (1-20)

cORR, confirmed objective response rate; CR, complete response; DCR, disease control rate; DoR, duration of response; mo, month; NE, not evaluable; PD, progressive disease; PR, partial response; Q3W, every 3 weeks; SD, stable disease; T-DXd, trastuzumab deruxtecan.

Raghav K... Yoshino T. Lancet Oncol 2024.

DESTINY-CRC01 and DESTINY-CRC02: adverse events

	Trastuzumab deruxtecan 5·4 mg/kg group (n=83*)				Trastuzumab deruxtecan 6·4 mg/kg group (n=39)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any drug-related treatment-emergent adverse events	42 (51%)	29 (35%)	4 (5%)	1 (1%)	18 (46%)	13 (33%)	6 (15%)	0
Nausea	39 (47%)	6 (7%)	0	0	22 (56%)	0	0	0
Alopecia	18 (22%)	NA	NA	NA	11 (28%)	NA	NA	NA
Decreased appetite	16 (19%)	2 (2%)	0	0	6 (15%)	0	0	0
Diarrhoea	14 (17%)	2 (2%)	0	0	8 (21%)	0	0	0
Asthenia	14 (17%)	2 (2%)	0	0	3 (8%)	2 (5%)	0	0
Fatigue	12 (14%)	4 (5%)	0	0	7 (18%)	0	0	0
Platelet count decreased	11 (13%)	3 (4%)	1 (1%)	0	7 (18%)	2 (5%)	2 (5%)	0
Anaemia	11 (13%)	6 (7%)	0	0	6 (15%)	8 (21%)	0	0
Vomiting	11 (13%)	3 (4%)	0	0	3 (8%)	0	0	0
Stomatitis	9 (11%)	0	0	0	5 (13%)	1 (3%)	0	0
Constipation	9 (11%)	0	0	0	1 (3%)	0	0	0
Aspartate aminotransferase increased	7 (8%)	0	0	0	5 (13%)	0	0	0
Neutropenia	6 (7%)	1 (1%)	0	0	0	1 (3%)	0	0
Neutrophil count decreased	5 (6%)	11 (13%)	2 (2%)	0	6 (15%)	6 (15%)	4 (10%)	0
White blood cell count decreased	4 (5%)	5 (6%)	0	0	2 (5%)	4 (10%)	0	0
Pneumonitis	4 (5%)	0	0	0	4 (10%)	0	0	0
Malaise	3 (4%)	1 (1%)	0	0	4 (10%)	0	0	0
Epistaxis	3 (4%)	1 (1%)	0	0	2 (5%)	0	0	0
Lymphocyte count decreased	3 (4%)	0	0	0	1 (3%)	1 (3%)	1 (3%)	0
Thrombocytopenia	3 (4%)	0	0	0	1 (3%)	0	1 (3%)	0
Hypoalbuminaemia	1 (1%)	1 (1%)	0	0	0	0	0	0
Candida infection	0	1 (1%)	0	0	0	0	0	0
Pneumonia bacterial infection	0	1 (1%)	0	0	0	0	0	0
Dizziness	0	1 (1%)	0	0	0	0	0	0
Febrile neutropenia	0	1 (1%)	0	0	0	0	1 (3%)	0
Pancytopenia	0	0	1 (1%)	0	0	0	0	0
Sepsis	0	0	1 (1%)	0	0	0	0	0
Hepatic failure	0	0	0	1 (1%)	0	1 (3%)	0	0
Hypokalaemia	0	0	0	0	0	2 (5%)	0	0
Hepatic encephalopathy	0	0	0	0	0	0	1 (3%)	0

Data are n (%). Data are from the total population treated with trastuzumab deruxtecan (safety analysis set). For treatment-emergent adverse events of grade 1 or 2, any occurring in ≥10% of patients are reported here. All grade 3, 4, and 5 events are reported. NA=not applicable. *One patient randomly assigned to receive trastuzumab deruxtecan 6·4 mg/kg was mistakenly given trastuzumab deruxtecan 5·4 mg/kg and counted in the 5·4 mg/kg group safety analysis set.

Table 3: **Drug-related treatment-emergent adverse events**

Adjudicated drug-related interstitial lung disease or pneumonitis

- **Destiny CRC-02: n=7 (8%) in 5.4 mg/kg**
  n=5 (13%) in 6.4 mg/kg
  all grade 1 or 2

- **Destiny CRC-01:**

Table 6 | Drug-related adjudicated interstitial lung disease/ pneumonitis events

	HER2 IHC 3 + or IHC 2 + /ISH + Cohort A *n* = 53	HER2 IHC 2 + / ISH − Cohort B *n* = 15	HER2 IHC 1 + Cohort C *n* = 18	All Patients *N* = 86
Grade 1	0	0	0	0
Grade 2	2 (3.8)	2 (13.3)	0	4 (4.7)
Grade 3	0	0	1 (5.6)	1 (1.2)
Grade 4	0	0	0	0
Grade 5	2 (3.8)	1 (6.7)	0	3 (3.5)
Any grade/ total	4 (7.5)	3 (20.0)	1 (5.6)	8 (9.3)[a]

Data are presented as *n* (%).
HER2 human epidermal growth factor receptor 2, *IHC* immunohistochemistry, *ILD* interstitial lung disease, *ISH* in situ hybridization.
[a]ILD grades are the highest/most severe grade recorded in a patient.

Yoshino T et al, Nat Comm 2023
Siena S et al, Nat Comm 2024

Targeting KRAS^{G12C}: Codebreak 300
Sotorasib + panitumumab

Key eligibility

- mCRC with KRAS^{G12C} mutation
- Failed or experienced diseases recurrence on ≥1 prior therapy that must include fluoropyrimidine, irinotecan and oxaliplatin
- Measurable disease as per RECIST v.1.1
- ECOG PS ≤2

R1:1

N≈153

- **Sotorasib 960 mg once daily + panitumumab**
- **Sotorasib 240 mg once daily + panitumumab**
- **Trifluridine with tipiracil or regorafenib**

Primary endpoint: PFS
Secondary endpoints: OS, ORR

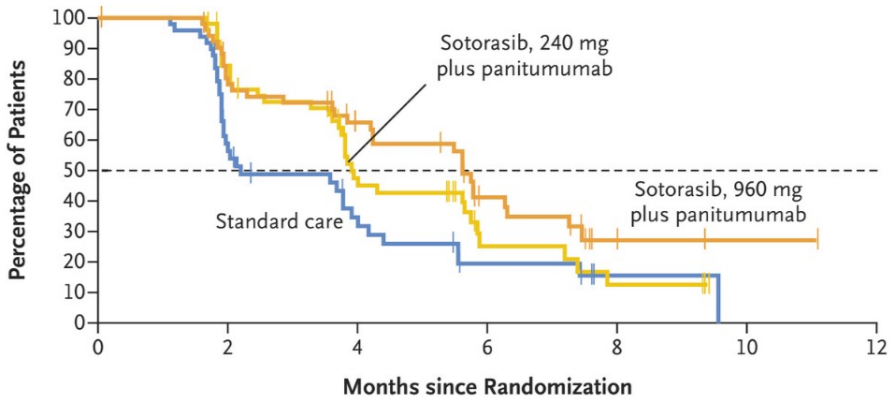
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 7, 2023 VOL. 389 NO. 23

Sotorasib plus Panitumumab in Refractory Colorectal Cancer with Mutated *KRAS* G12C

M.G. Fakih, L. Salvatore, T. Esaki, D.P. Modest, D.P. Lopez-Bravo, J. Taieb, M.V. Karamouzis, E. Ruiz-Garcia, T.-W. Kim, Y. Kuboki, F. Meriggi, D. Cunningham, K.-H. Yeh, E. Chan, J. Chao, Y. Saportas, Q. Tran, C. Cremolini, and F. Pietrantonio

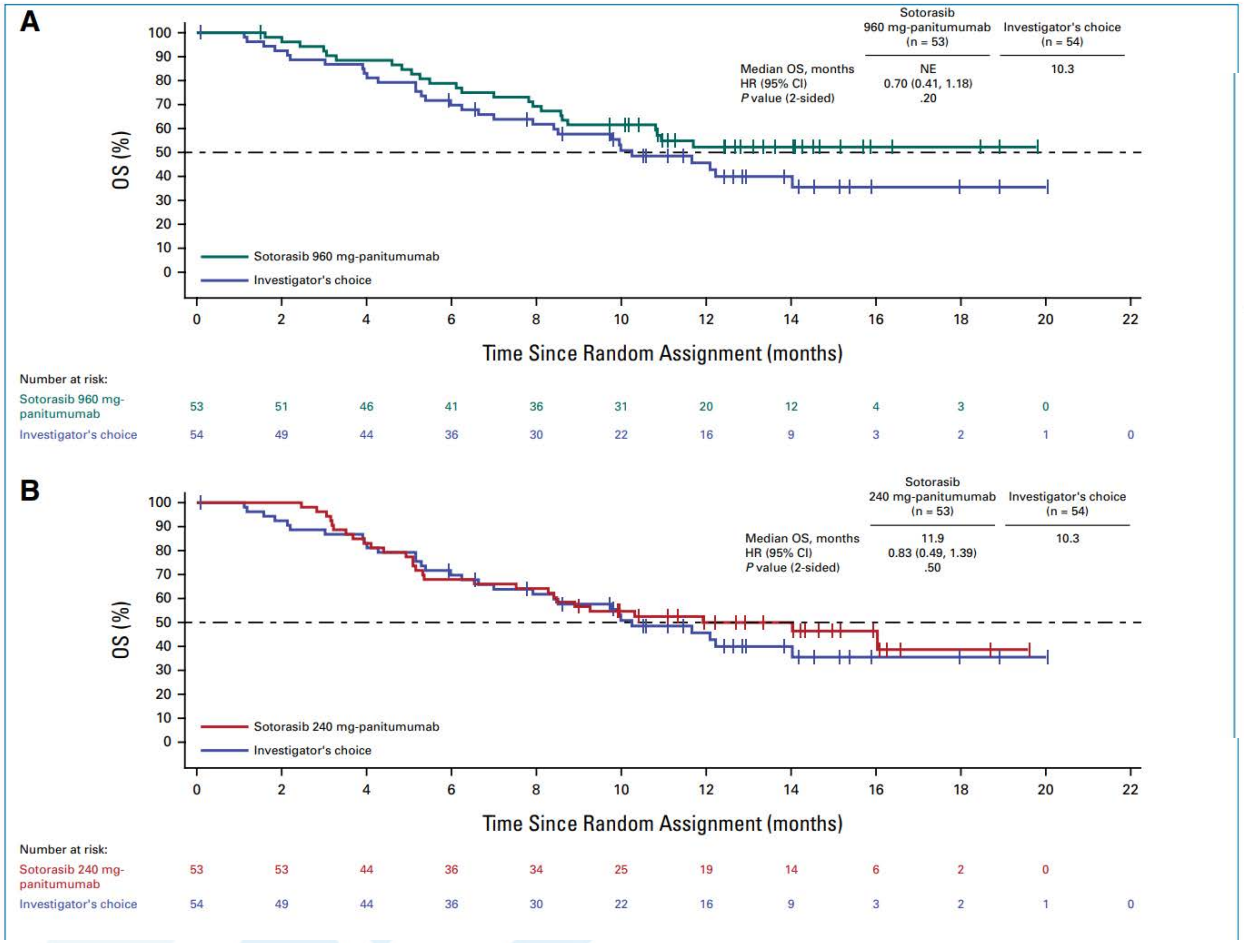
A Progression-free Survival (Intention-to-Treat Population)

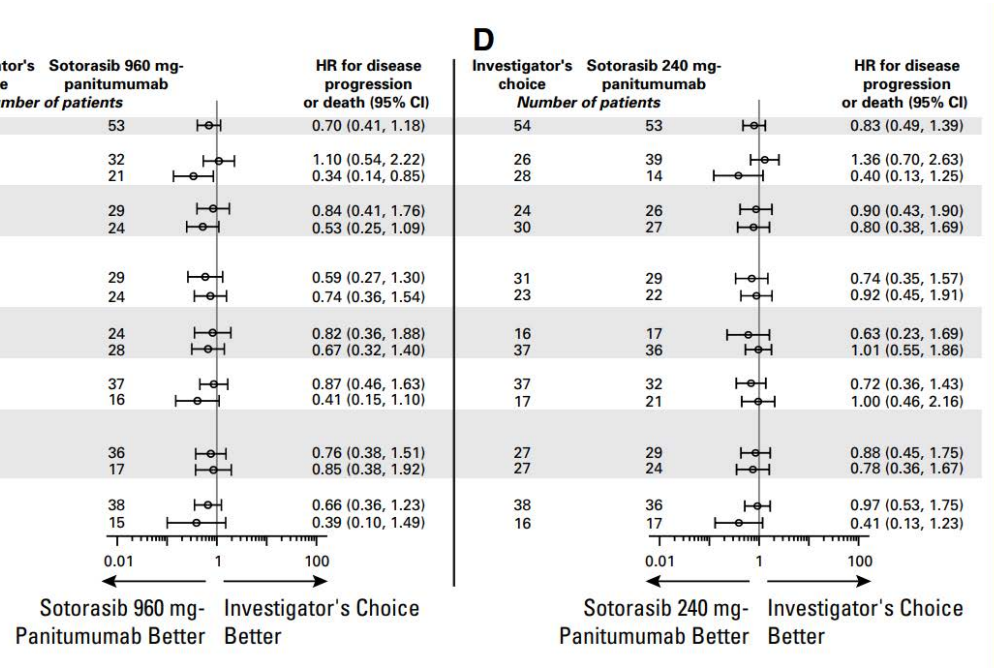


No. at Risk							
Sotorasib, 960 mg plus panitumumab	53	40	28	13	2	1	0
Sotorasib, 240 mg plus panitumumab	53	43	20	6	3	0	
Standard care	54	24	12	5	1	0	

	Median Progression-free Survival	Hazard Ratio for Disease Progression or Death (95% CI)	Two-Sided P Value
	mo		
Sotorasib, 960 mg plus Panitumumab	5.62	0.48 (0.30–0.78)	0.005
Sotorasib, 240 mg plus Panitumumab	3.91	0.59 (0.37–0.95)	0.036
Standard Care	2.04		

Targeting KRAS^{G12C}: Codebreak 300
Sotorasib + panitumumab





Updated objective response rates (ORRs; 95% CI)

- ✓ **Pani + Sot 960 mg: 30.2% (95% CI, 18.3 to 44.3)**
- ✓ **Pani + Sot 240 mg: 7.5% (95% CI, 2.1 to 18.2)**
- ✓ **Control: 1.9% (95% CI, 0.0 to 9.9)**

Pietrantonio F et al, J Clin Oncol 2025

Targeting KRAS^{G12C}: Adagrasib + cetuximab

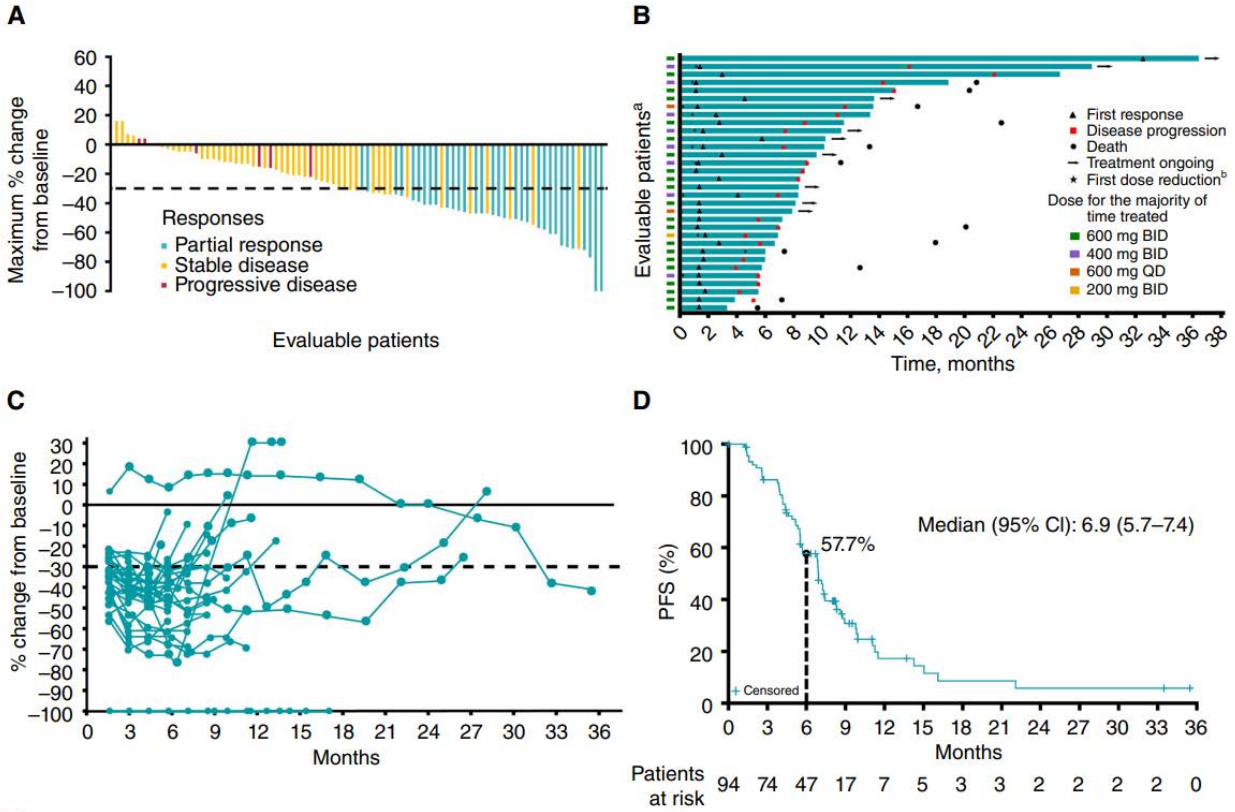


Figure 1. Efficacy outcomes with adagrasib plus cetuximab in previously treated patients with *KRAS*^{G12C}-mutated unresectable or metastatic CRC. **A,** Best change in tumor volume from baseline ($n = 86$; excludes eight patients without any postbaseline scans). **B,** Treatment duration ($n = 32$; only subjects with tumor response are displayed). **C,** Changes from baseline in sum of target lesion diameters over time for patients with tumor response. **D,** PFS. **E,** OS. Data as of June 30, 2023 (median follow-up: 11.9 months). Responses and PFS assessed by BICR per RECIST version 1.1. [a]Only patients with objective tumor responses are displayed ($n = 32$). [b]Time to first maintained dose reduction due to any cause. BICR, blinded-independent central review; BID, twice daily; CI, confidence interval; CRC, colorectal cancer; DOR, duration of response; OS, overall survival; PFS, progression-free survival; QD, once daily.

With a median follow-up of 11.9 mo

- ✓ **ORR: 34.0%**
- ✓ **disease control rate: 85.1%**
- ✓ **median duration of response: 5.8 mo (95% [CI], 4.2–7.6)**

- ✓ **Median PFS: 6.9 mo (95% CI, 5.7–7.4)**
- ✓ **Median OS: 15.9 mo (95% CI, 11.8–18.8)**

Yaeger R et al, Cancer Discovery 2024

KRYSTAL-10: Adagrasib + Cetuximab vs chemo in *KRAS* G12C Mutant mCRC

KRYSTAL-10 (849-010): Phase 3 Randomized, Open-Label Trial of 2L Adagrasib + Cetuximab vs Chemotherapy in mCRC With $KRAS^{G12C}$ Mutation

Key Eligibility Criteria

- Histologically confirmed diagnosis of metastatic CRC
- Confirmed $KRAS^{G12C}$ mutation in tumor
- Progression on 1L fluoropyrimidine-based oxaliplatin or irinotecan regimen

R 1:1

- Adagrasib, 600 mg BID + cetuximab (n=210)
- FOLFIRI or mFOLFOX6* (n=210)

*A VEGF/VEGFR inhibitor may be given per Investigator discretion

Outcome Measures

Primary: PFS, OS
Secondary: Safety, ORR (RECIST 1.1), DOR, PROs

Dosing: cetuximab, 500 mg/m2 q2w, FOLFIRI q2w [irinotecan, 180 mg/m2, 5-FU/LV with fluorouracil given as 400 mg/m2 IV bolus followed by a further 2400 mg/m2 dose given as continuous infusion over 46-48 hours], mFOLFOX6 q2w [oxaliplatin, 85 mg/m2, 5-FU/LV, with fluorouracil given as 400 mg/m2 IV bolus followed by a further 2400 mg/m2 dose given as continuous infusion over 46-48 hours].

1L, first line; 2L, second line; 5-FU/LV, 5-fluorouracil + leucovorin; BID, twice daily; mCRC, metastatic colorectal cancer; mFOLFOX6, modified FOLFOX6; OS, overall survival; PFS, progression free survival; q2w, every two weeks.

https://clinicaltrials.gov/ct2/show/NCT04793958

Targeting KRAS^{G12C}: Divarasib + cetuximab: a phase 1b trial

New generation inhibitors:

- Divarasib (GDC-6036) is an orally bioavailable, covalent KRAS G12C inhibitor that turns off its oncogenic signaling by irreversibly locking the protein in an inactive state.

- In vitro studies have also shown that divarasib is 5 to 20 times as potent and up to 50 times as selective as compared to the KRAS G12C inhibitors sotorasib and adagrasib.

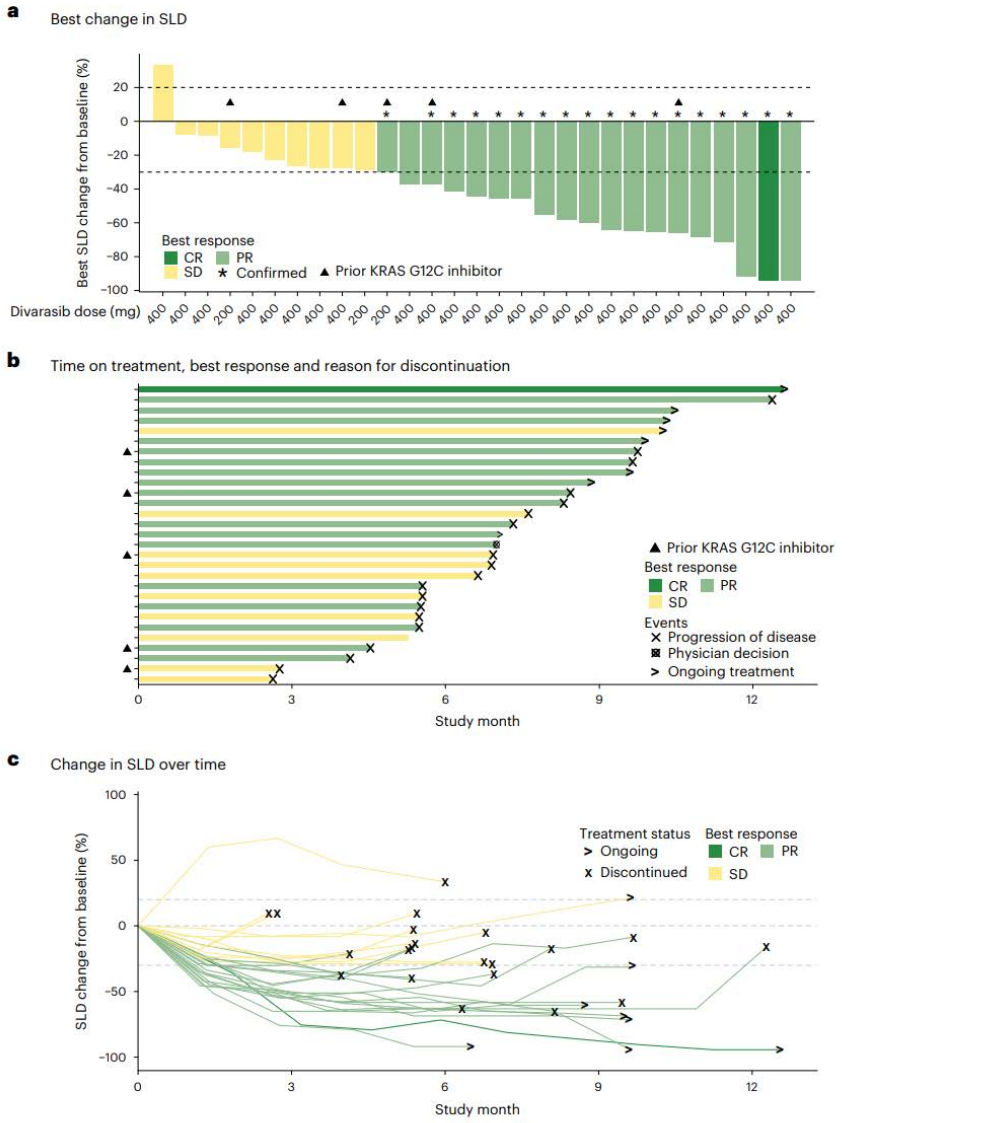


Fig. 2 | Antitumor activity for all patients. a, Waterfall plot showing the best percentage decrease from baseline in the tumor burden (defined as the sum of the longest diameters of all target lesions) in all 29 patients. **b**, Swimmer plot showing the time on study treatment, best response, and reason for treatment discontinuation for all 29 patients. **c**, Spider plot of the percentage changes from baseline in sum of tumor diameters over time in all 29 patients.

Desai J et al, Nat Med 2024

Targeting KRAS^{G12C}: Oral presentations in CRC session at ASCO 2025

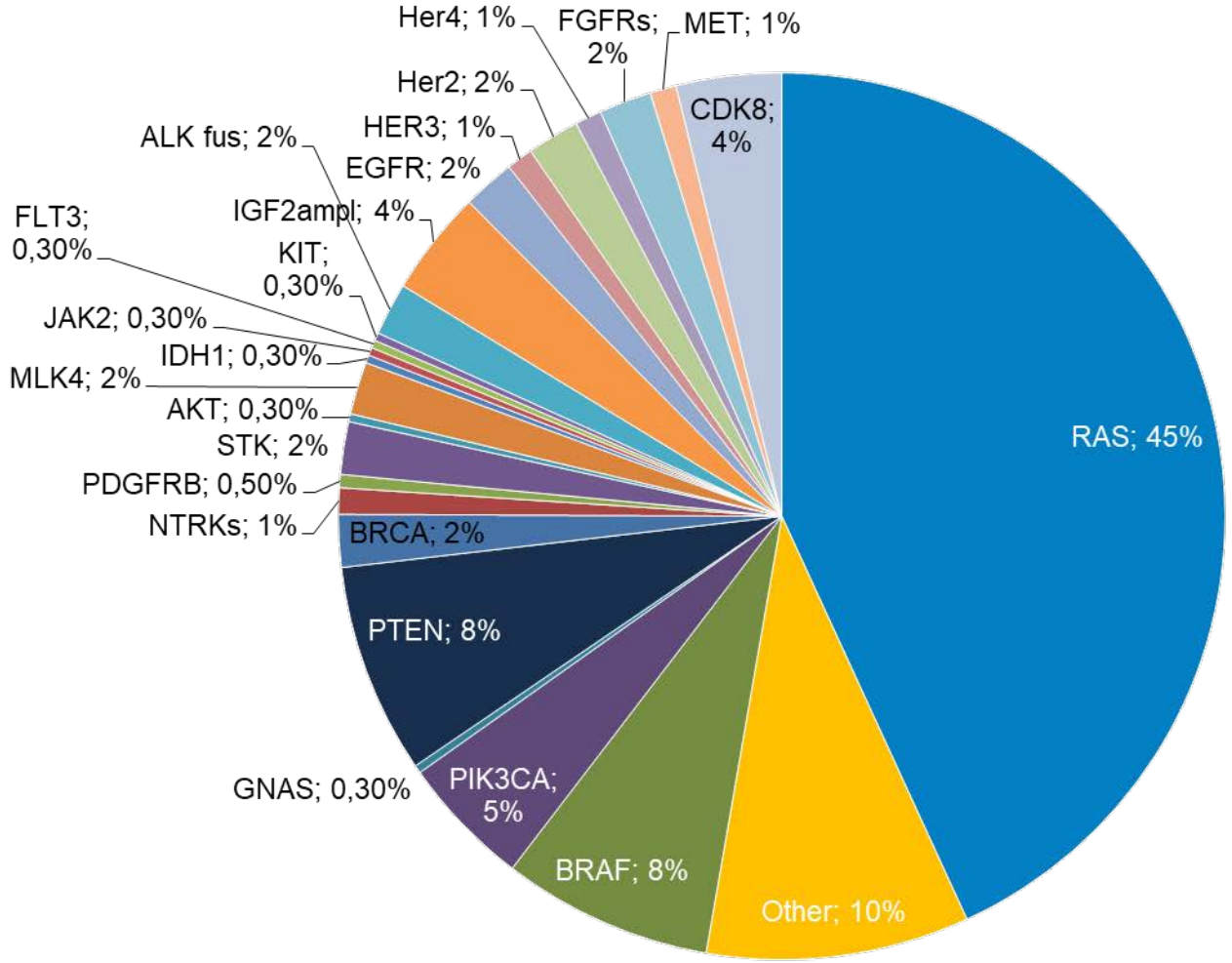
- **Long-term safety and efficacy of sotorasib plus panitumumab and FOLFIRI for previously treated KRAS G12C-mutated metastatic colorectal cancer (mCRC): CodeBreaK 101 (phase 1b).**
  - ✓ **Promising long-term safety and efficacy in pretreated KRAS G12C-mutated mCRC. Ongoing phase 3 study, CodeBreaK 301 (NCT06252649): evaluates this combination against standard of care in 1° line KRAS G12C-mutated mCRC.**
  - ✓ **Strickler J et al, ASCO 2025; Abstract 3506**

- **Efficacy and safety of olomorasib, a second-generation KRAS G12C inhibitor, plus cetuximab in KRAS G12C-mutant advanced colorectal cancer**
  - **Olomorasib + cetuximab demonstrated similar antitumor activity and favorable safety at both dose levels in pts with KRAS G12C-mutant CRC, with the optimal dose of olomorasib + cetuximab determined as 100 mg BID.**
  - **Hollebecque A et al, ASCO 2025; Abstract 3507**

- **The KRAS G12C inhibitor MK-1084 for KRAS G12C mutated advanced colorectal cancer (CRC): Results from KANDLELIT-001.**
  - ✓ **Preliminary data suggest that MK-1084 monotherapy, MK-1084 + cetuximab, and MK-1084 + cetuximab + mFOLFOX6 have manageable safety profiles and show evidence of antitumor activity in pts with advanced, KRAS G12C mutated CRC.**
  - ✓ **Lugowska I et al, ASCO 2025; Abstract 3508**

Treatment stratification by molecular subgroups

- **Molecular Subtypes in mCRC:**
  - **RAS**
    - ***RAS G12C: trials in pretreated***
  - **MSI-H:** first line; pretreated also?
  - **BRAF V600 E:** second line, but in first line determines also the strategy (anti-EGFR AB)
  - **HER-2:** pretreated
  - ***NTRK:*** pretreated
  - ***Other:*** anecdotal reports or trials in pretreated



Dr Priya Rudolph
(Athens, Georgia)

Case Presentation: 89-year-old woman with BRAF V600E-mutant sigmoid colon cancer and malignant ascites with disease progression on mFOLFOX6/bevacizumab

Dr Victoria Giffi
(Hagerstown, Maryland)

Case Presentation: 79-year-old woman with BRAF V600E-mutant colon carcinoma with disease progression on mFOLFOX6/bevacizumab

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

What would you recommend next for Dr Rudolph's 89-year-old patient? Would you restart FOLFOX/bevacizumab at a reduced dose? Switch to capecitabine/bevacizumab? Switch to encorafenib and an EGFR antibody, given her BRAF status?

Do you have any tricks of the trade for managing the rash associated with encorafenib/cetuximab? Can dosing frequency be decreased without compromising efficacy?

Outside of a clinical trial, have you or would you recommend a different BRAF inhibitor for a patient whose disease had progressed on encorafenib-containing therapy?

RTP
RESEARCH
TO PRACTICE

Case Presentation: 84-year-old woman with HER2-amplified (IHC 2+) MSS metastatic rectosigmoid cancer

Dr Stephen “Fred” Divers (Hot Springs, Arkansas)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

What would you recommend next for this woman with HER2-amplified (IHC 2+) disease?

In which line of treatment do you typically recommend HER2-targeted therapy for your patients with HER2-positive mCRC? Would you administer HER2-targeted therapy to a patient with previously untreated HER2-positive mCRC in any situations?

How do you choose between T-DXd and tucatinib/trastuzumab for your patients with HER2-positive mCRC? Are there any patients for whom you prefer one regimen over the other based on HER2 expression levels, RAS mutation status or site(s) of metastases?

Contributing General Medical Oncologists

Warren S Brenner, MD
Lynn Cancer Institute
Boca Raton, Florida

Gigi Chen, MD
John Muir Health Cancer
Medical Group
Walnut Creek, California

Stephen "Fred" Divers, MD
American Oncology Network
Hot Springs, Arkansas

Victoria Giffi, MD
Meritus Medical Center
Hagerstown, Maryland

Henna Malik, MD
Texas Oncology
Houston, Texas

Shachar Peles, MD
Florida Cancer Specialists
& Research Institute
Lake Worth, Florida

Priya Rudolph, MD, PhD
Georgia Cancer Specialists
Athens, Georgia

Erik Rupard, MD
Penn State Cancer Institute
Hershey, Pennsylvania

Syed F Zafar, MD
Florida Cancer Specialists
& Research Institute
Fort Myers, Florida

Neil Love, MD
Research To Practice
Miami, Florida

Thank you

Consensus or Controversy? Clinical Investigators Provide Perspectives on the Current and Future Clinical Care of Patients with Urothelial Bladder Cancer

Saturday, May 31, 2025
6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty

Andrea Necchi, MD
Thomas Powles, MBBS, MRCP, MD

Moderator

Matthew D Galsky, MD

RTP
RESEARCH
TO PRACTICE

Thank you for joining us!
Your feedback is very important to us.

Please complete the survey currently up on the iPads for attendees in the room and on Zoom for those attending virtually. The survey will remain open up to 5 minutes after the meeting ends.

How to Obtain CME Credit

In-person attendees: Please refer to the program syllabus for the CME credit link or QR code.
Online/Zoom attendees: The CME credit link is posted in the chat room.

RTP
RESEARCH
TO PRACTICE