Consensus or Controversy? Clinical Investigators Provide Perspectives on Biomarker Assessment and Related Treatment Decision-Making for Patients with Colorectal Cancer

Part 2 of a 2-Part CME Symposium Series Held in Conjunction with the 2024 ASCO Gastrointestinal Cancers Symposium

Friday, January 19, 2024

6:15 PM – 8:15 PM PT (9:15 PM – 11:15 PM ET)

Faculty

Tanios Bekaii-Saab, MD

Andrea Cercek, MD

Cathy Eng, MD

John Strickler, MD

Moderator

Christopher Lieu, MD

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Faculty

Tanios Bekaii-Saab, MD
Professor, Mayo Clinic College of Medicine and Science
Program Leader, Gastrointestinal Cancer
Mayo Clinic Cancer Center
Consultant, Mayo Clinic in Arizona
Chair, ACCRU Research Consortium
Phoenix, Arizona

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

Cathy Eng, MD
Professor of Medicine, Hematology and Oncology
David H Johnson Endowed Chair in Surgical and Medical Oncology
Director for Strategic Relations
Co-Chairman, NCI GI Steering Committee
Co-Director, GI Oncology
Co-Leader, GI Cancer Research Program
Director, Young Adult Cancers Program
Vanderbilt-Ingram Cancer Center
Nashville, Tennessee

John Strickler, MD
Associate Professor
Associate Director, Clinical Research – GI
Duke University
Durham, North Carolina

Moderator
Christopher Lieu, MD
Associate Professor of Medicine
Associate Director for Clinical Research
Co-Director, GI Medical Oncology
University of Colorado Cancer Center
Aurora, Colorado

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Dr Bekaii-Saab — Disclosures
Faculty

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Dr Cercek — Disclosures
Faculty

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Contracted Research	GSK, Seagen Inc

Dr Eng — Disclosures
Faculty

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Dr Strickler — Disclosures
Faculty

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Data and Safety Monitoring Board/Committee	BeiGene Ltd, Seagen Inc
Stock Options — Private Company	Triumvira Immunologics

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Dr Lieu — Disclosures
Moderator

No relevant conflicts of interest to disclose.

Dr Ciombor — Disclosures
Survey Participant

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Dr Dasari — Disclosures
Survey Participant

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Consensus or Controversy? Investigator Perspectives on the Current and Future Role of Immune Checkpoint Inhibitors in the Management of Hepatobiliary Cancers

A CME-Accredited Virtual Event Held in Conjunction with the 2024 ASCO Gastrointestinal Cancers Symposium

Saturday, January 20, 2024

5:30 AM – 6:30 AM PT (8:30 AM – 9:30 AM ET)

Faculty

Ahmed Omar Kaseb, MD, CMQ

Arndt Vogel, MD, PhD

Moderator

Neil Love, MD

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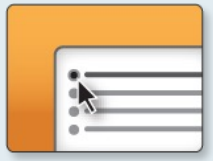
Clinicians in the Meeting Room

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 premeeting survey.

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.

Complete Your Evaluation: Tap the CME/NCPD Evaluation button to complete your evaluation electronically to receive credit for your participation.

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

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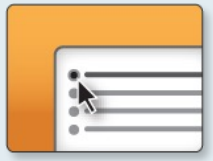
Clinicians Attending via Zoom

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



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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 video/PowerPoint 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**

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Consensus or Controversy? Clinical Investigators Provide Perspectives on Biomarker Assessment and Related Treatment Decision-Making for Patients with Colorectal Cancer

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Christopher Lieu, MD

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Agenda

Module 1 – Optimizing Biomarker Assessment and Treatment for Patients with Metastatic Colorectal Cancer (mCRC) – Dr Eng

Module 2 – Emerging Role of Biomarker-Based Decision-Making for Patients with Localized CRC – Dr Lieu

Module 3 – Identification and Clinical Care of Patients with mCRC and a BRAF V600E Mutation – Dr Bekaii-Saab

Module 4 – Integration of Immune Checkpoint Inhibitors into the Management of MSI-High/MMR-Deficient mCRC – Dr Cercek

Module 5 – HER2 and Other Emerging Biomarkers for Targeted Therapy in mCRC – Dr Strickler

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Consulting Faculty

Kristen K Ciombor, MD, MSCI
Associate Professor of Medicine
Division of Hematology/Oncology
Vanderbilt-Ingram Cancer Center
Nashville, Tennessee

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

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MODULE 1: Optimizing Biomarker Assessment and Treatment for Patients with Metastatic Colorectal Cancer (mCRC) – Dr Eng

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Biomarker assessment for patients with CRC

Arvind N Dasari, MD, MS

Kristen K Ciombor, MD, MSCI

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QUESTIONS FOR THE FACULTY

Arvind N Dasari, MD, MS

Kristen K Ciombor, MD, MSCI

What biomarker testing platform(s)/assay(s) do you generally employ for patients with newly diagnosed mCRC? Which specific alterations do you routinely assess?

How does liquid biopsy integrate into the assessment?

How long does it typically take to obtain biomarker results in your practice, and how important do you believe it is to wait for the results before initiating therapy?

Do you repeat biomarker assessment for patients with progressive disease (eg, prior to EGFR antibody rechallenge)?

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Initial therapy for RAS WT mCRC; anti-EGFR antibodies, sidedness

Kristen K Ciombor, MD, MSCI

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QUESTIONS FOR THE FACULTY

Kristen K Ciombor, MD, MSCI

What is your preferred first-line therapy for patients with RAS wild-type mCRC?

Do you recommend EGFR antibodies to all patients with left-sided tumors based on the results of the PARADIGM study, or are there patients for whom you still prefer bevacizumab?

Do you conduct extended biomarker testing to look for mutations such as PIK3CA or PTEN loss to inform the use of first-line EGFR antibody therapy?

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What was the age of the last patient in your practice with newly diagnosed metastatic colorectal cancer (mCRC) who started treatment? What was their biomarker profile, and what treatment did they receive?

	Age	Biomarker profile (Positive biomarkers)	Treatment
 Dr Bekaii-Saab	59 years	KRAS G12V	FOLFOXIRI/bev
 Dr Cercek	43 years	Wild type	FOLFOX
 Dr Eng	32 years	RAS, HER2	Clinical trial of BRAF-targeted tx
 Dr Lieu	32 years	RAS, left sided	mFOLFOX6/bev
 Dr Strickler	44 years	RAS	FOLFOX/bev
 Dr Ciombor	41 years	RAS, TP53, APC	FOLFOX/bev
 Dr Dasari	38 years	RAS, TP53, APC	FOLFOX/bev

FOLFOXIRI = FOLFIRI with oxaliplatin; bev = bevacizumab

What is your usual first-line treatment recommendation for a 60-year-old patient with microsatellite stable (MSS), pan-RAS wild-type, BRAF wild-type mCRC if their tumor is right sided? Left sided?

	Right side	Left side
 Dr Bekaii-Saab	FOLFOXIRI + bevacizumab	FOLFOXIRI + bevacizumab
 Dr Cercek	FOLFOX/CAPOX + bevacizumab	FOLFOX/CAPOX
 Dr Eng	FOLFOX/CAPOX + bev or FOLFIRI/CAPIRI + bev	FOLFOX/CAPOX + bev or EGFR Ab OR FOLFIRI/CAPIRI + bev or EGFR Ab
 Dr Lieu	FOLFOX/CAPOX + bevacizumab	FOLFOX/CAPOX + panitumumab
 Dr Strickler	FOLFOXIRI + bevacizumab	FOLFOX/CAPOX + panitumumab
 Dr Ciombor	FOLFIRI + bevacizumab	FOLFIRI + bevacizumab
 Dr Dasari	FOLFOX/CAPOX + bevacizumab	FOLFOX/CAPOX + EGFR antibody

Ab = antibody

For a patient with mCRC who has received EGFR antibody-containing therapy and experienced disease progression, under what circumstances, if any, would you rechallenge with the same or a different EGFR antibody later in the treatment course?

 Dr Bekaii-Saab	At least 1 line of therapy as bridge before rechallenge; liquid biopsy confirming absences of plasma RAS and BRAF V600E mutations
 Dr Cercek	If more than 6 months has passed and ctDNA is negative for RAS mutations
 Dr Eng	If NGS confirms RAS wildtype
 Dr Lieu	Potentially at 3rd line or later if ctDNA reveals no resistance mutations
 Dr Strickler	Exhausted standard chemotherapy and ctDNA shows absence of resistance variants (absence of KRAS, NRAS, BRAF variants)
 Dr Ciombor	If initial response noted to anti-EGFR therapy, repeat NGS shows RAS WT, at least 4 months since last anti-EGFR therapy
 Dr Dasari	No resistance alterations on liquid biopsy after EGFR treatment holiday

WT = wild-type

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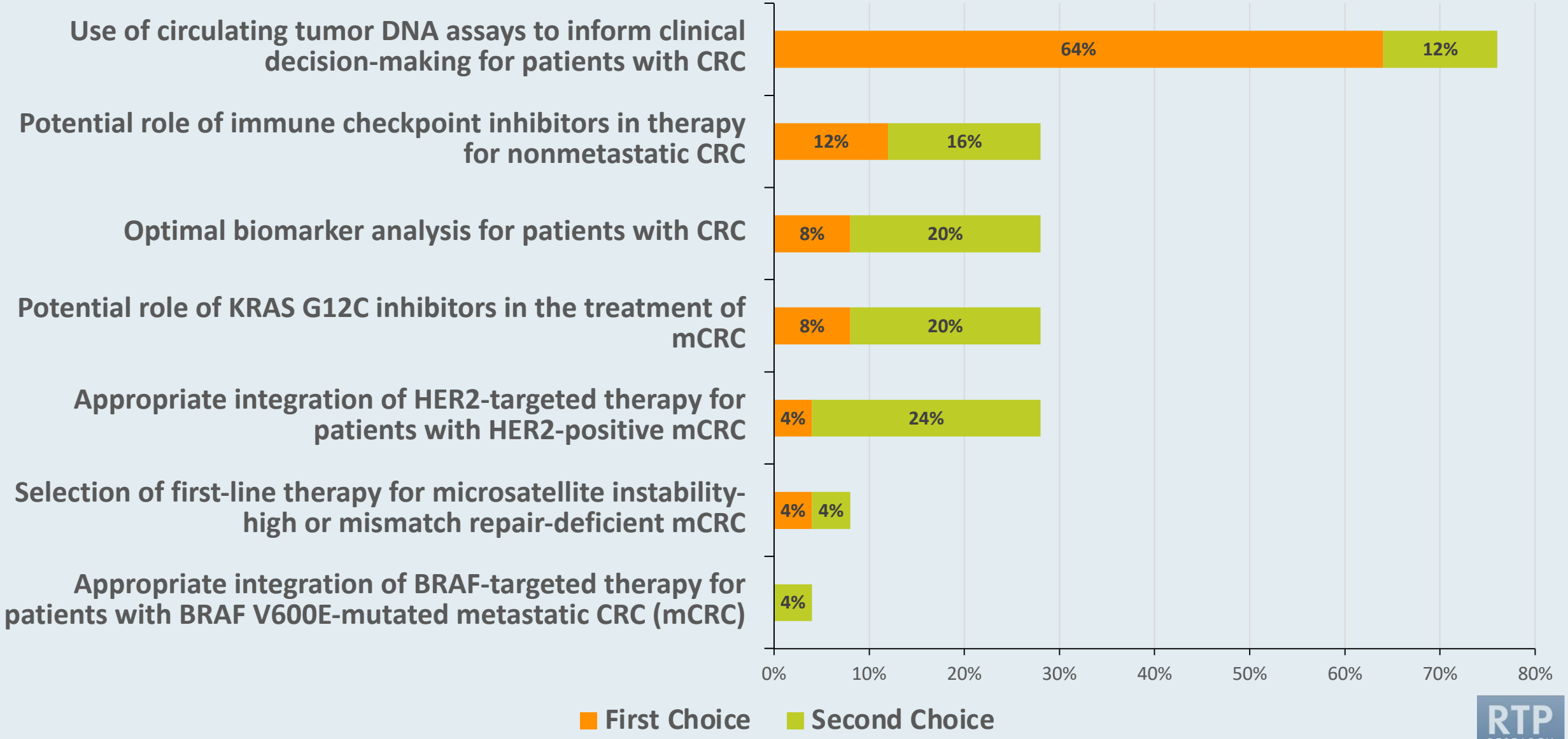
Topics of Interest for Future CME Programs



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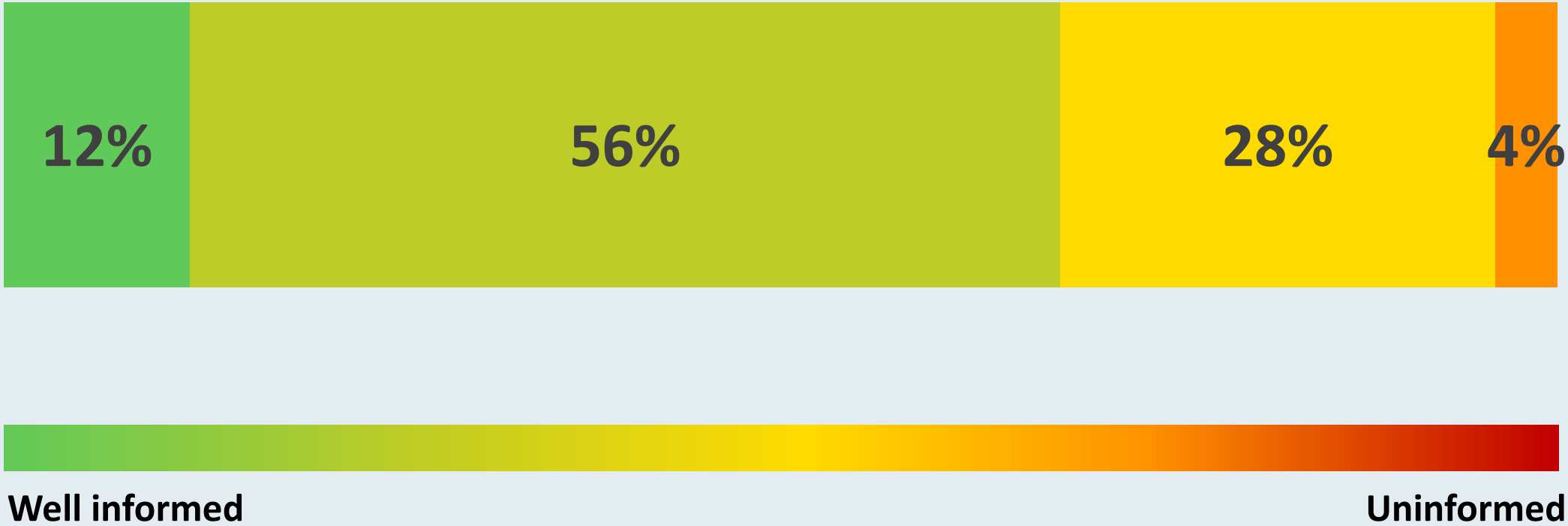
How comfortable/familiar are you with the published data sets, available guidelines, investigator perspectives and ongoing research studies pertaining to optimal biomarker analysis for patients with CRC?



Questions from General Medical Oncologists

- Is ERBB alteration on NGS equivalent to HER2 amplification on IHC/FISH when making treatment decisions?
- What other rare mutations do investigators see apart from KRAS, NRAS, BRAF, MSI high, and HER2 in colorectal cancer? Do they see any other targetable alteration or any success with targeted therapies?
- How often should NGS be done on CRC cases?
- If ERBB2 is negative in NGS, should we run IHC for HER2?
- I have a 57-year-old man with HNPCC and BRAF-mutated CRC. Would you opt for first-line IO or chemo prior to BRAF targeted therapy?
- In patients with CRC with ERBB2 (HER2) amplification, do you need to serially assess ERBB2 status? What do you do if ERBB2 (HER2) amplification is lost?
- Do biomarkers change during the disease progression and [what is] the impact on treatment selections?
- Can you use MRD testing to decide on giving adjuvant therapy?
- Would like to be able to select stage II patients who may need adjuvant chemo
- What is the sensitivity of ctDNA testing, depending upon site of metastasis?

Questions from General Medical Oncologists

- Is there a role for biomarker testing outside of MSI high testing in patients with earlier stage colon cancer?
- Is there a role for targeted therapy in nonmetastatic CRC? In patients with metastatic disease, do you recommend doing a second biopsy of the primary to run NGS, as metastatic sites are not uncommonly poorly differentiated with negative testing?
- What biomarker to test for
- How do we optimize adjuvant treatment in early colorectal cancer with KRAS positivity?
- MSI-H vs TMB — Significance of each?
- Do you need to serially check biomarkers to see if pts develop resistance or new mutations while they're on treatment the way you do for metastatic HR+ breast cancer?
- Discrepancy between different test methods, for example amplification in blood tests and IHC staining: which one should be used to make treatment decision?
- What is the optimal treatment sequence for KRAS mutated mCRC?
- Is there a biomarker analysis in a flow chart/algorithm pattern that allows selection of treatment for newly diagnosed and relapsed/refractory CRC?

Questions from General Medical Oncologists

- Do you think that an "extended NGS panel" is enough, or should we do Foundation One® or similar with each patient?
- How to manage a patient with positive ctDNA but negative scans
- Can ctDNA pick up resistance mutations in progressing CRC?
- Colorectal cancer therapy is still primarily based on 5-FU-based therapies. Is there adequate data to continue FU in second-line therapy?
- What is the role of rechecking NGS panels in pts with progression?
- Clinical experience and selection of patients for fruquintinib? What line?

Optimizing Biomarker Assessment for Patients with Colorectal Cancer (CRC)

Cathy Eng, MD, FACP, FASCO
David H. Johnson Endowed Chair in Surgical and Medical Oncology
Professor of Medicine, Hematology and Oncology
Director for Strategic Relations
Co-Director, GI Oncology
Co-Leader, Gastrointestinal Cancer Research Program
Director, Young Adults Cancer Program
January 19, 2024

Contact Info: cathy.eng@vumc.org
Twitter: @cathyengmd
FB: cathy eng-mdcancer
www.youngadultswithcancer.com

Discussion Points

- Prevalence of validated biomarkers
- Benefits and limitations of available testing platforms
- Appropriate timing of biomarker assessment
- Real-world implementation of biomarker analysis and current barriers to testing
- Published clinical research findings establishing the correlation between the location of the primary tumor (right versus left side) and outcomes in mCRC

Incidence and Mortality of Colorectal CA in the US: 2023 (2024: Pending)

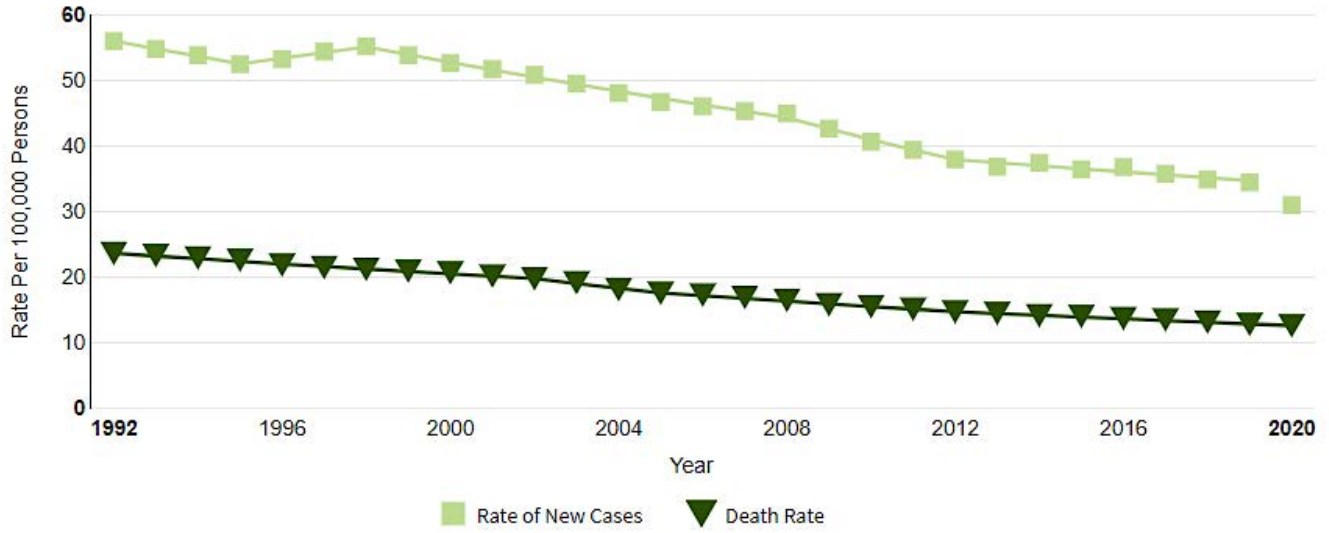
Estimated New Cases in 2023	153,020
% of All New Cancer Cases	7.8%

Estimated Deaths in 2023	52,550
% of All Cancer Deaths	8.6%

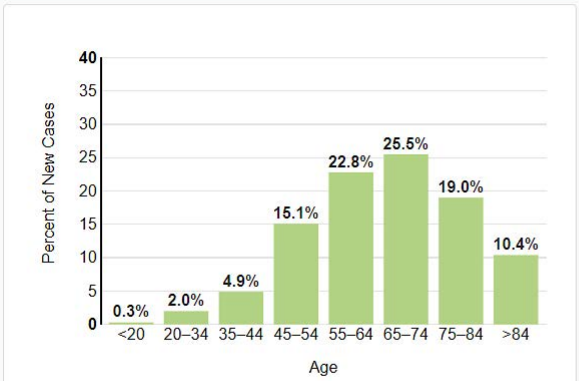
5-Year Relative Survival

65.0%

2013–2019



Percent of New Cases by Age Group: Colorectal Cancer



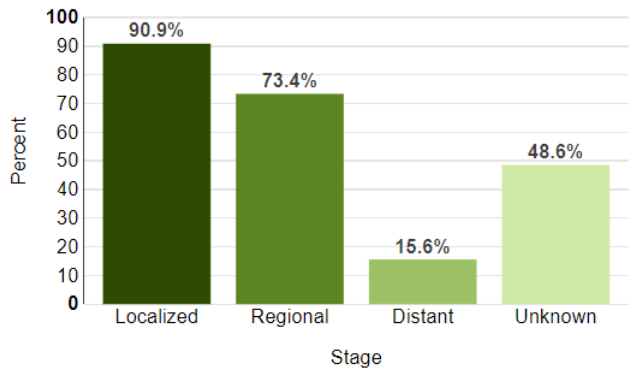
Colorectal cancer is most frequently diagnosed among people aged 65–74.

Median Age At Diagnosis

66

SEER 22 2016–2020, All Races, Both Sexes

5-Year Relative Survival

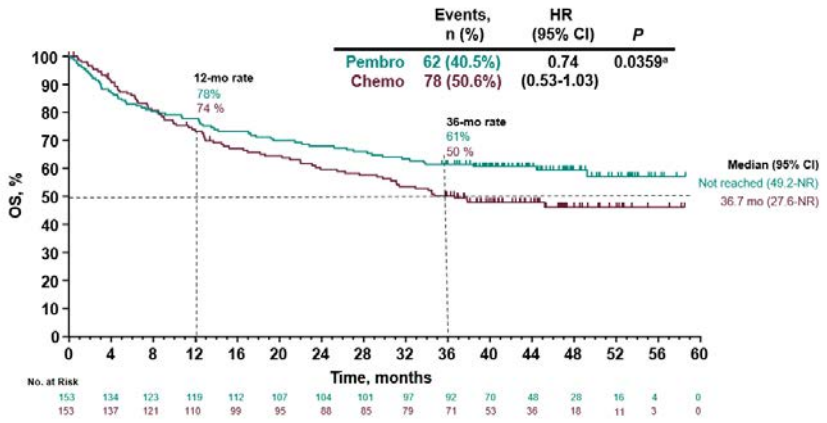


www.seer.gov

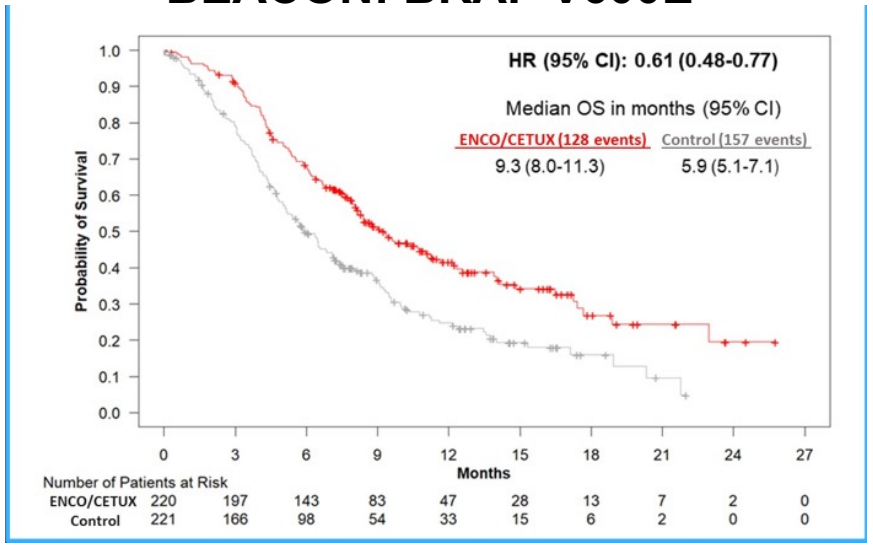
Background: The Promise of Precision Oncology

- Until recently, standard 5-FU based therapies served as the foundation for mCRC
- Pivotal trials over the past 3 years have resulted in FDA approved indications

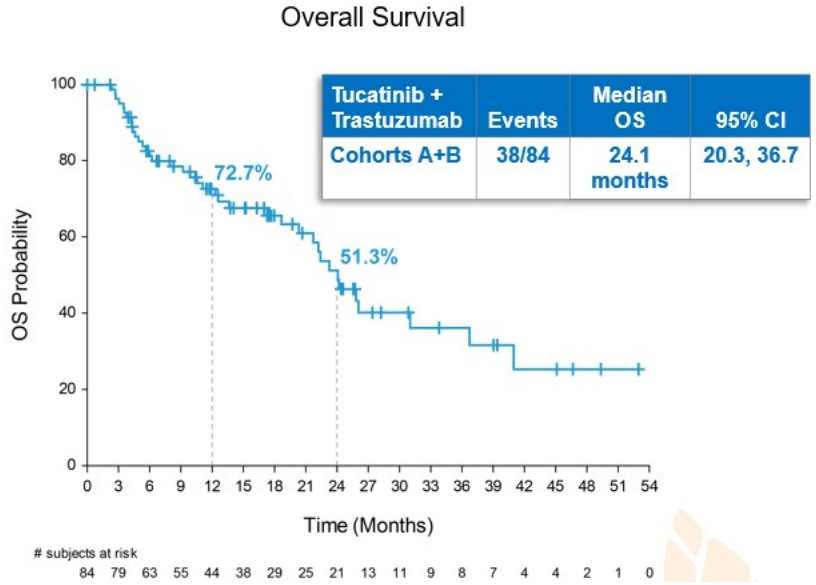
KN-177: Pembrolizumab (MSI-H)



BEACON: BRAF V600E

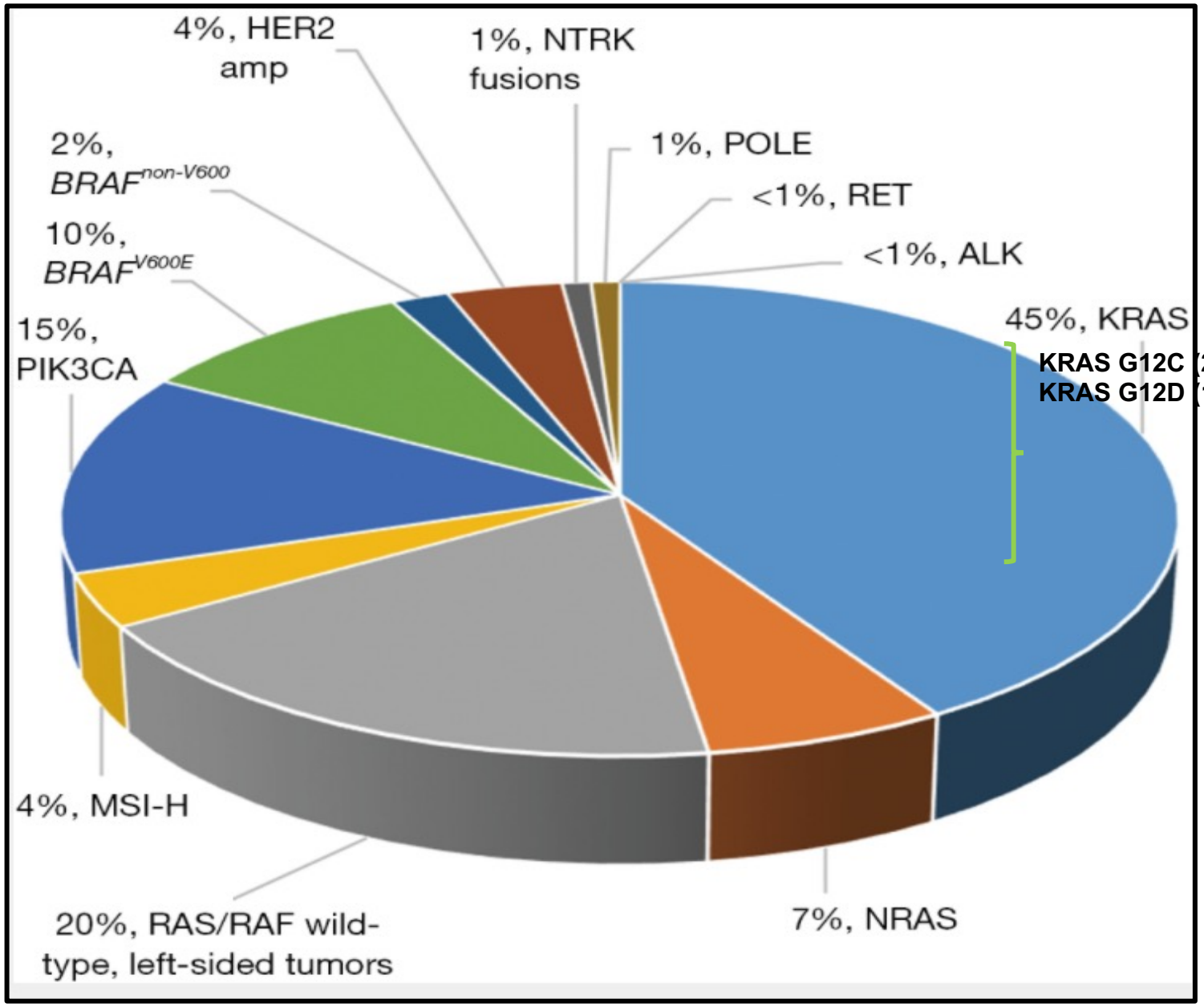


MOUNTAINEER: HER2 (+)



Andre et al: NEJM, 2020; Tabernero et al: JCO, 2021; Strickler et al: Lanc Onc, 2023

Additional Molecular Subsets: Precision Oncology



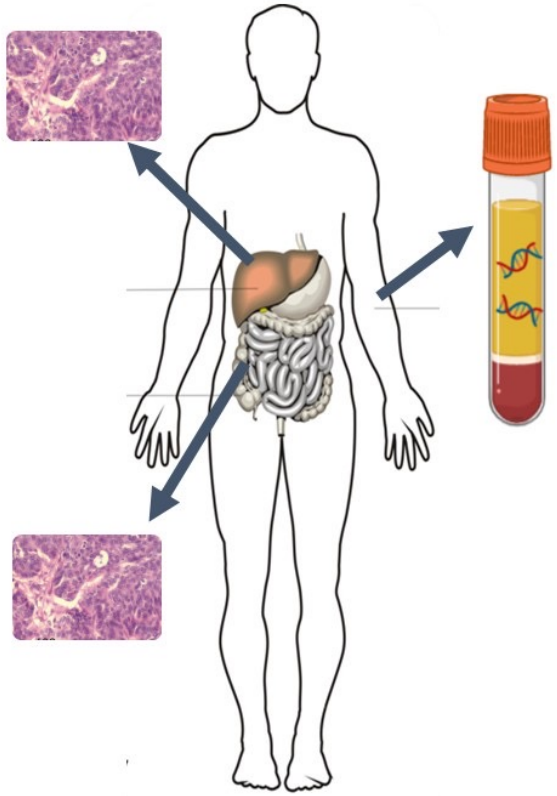
Henry et al, CCO, 2019

Benefits and Limitations

Tumor Tissue vs. Blood NGS Testing

Tumor Tissue Assay

- **Delayed** results
- Invasive, biopsy risk, serial biopsy more difficult
- Represent one small tumor region
- Uses existing tissue processing approaches
- No assessment of tumor load
- Larger panel
- Limitations: Accessibility, quality, and quantity



ctDNA Assay

- **Quick** results
- Less invasive, easy serial testing
- More representative of whole tumor or all metastatic sites
- Requires special processing or use cell stabilizing tubes
- Quantitative analysis correlates with tumor load
- Reduced logistics
- Smaller biomarker panel

*Excellent concordance previously demonstrated

Acknowledgement: Jeanne Tie, ASCO 2022; Bardelli et al: Cell Press, 2022

Tissue IHC/FISH vs Tissue NGS vs ctDNA

	ERBB2 gene amp	HER2 over-expression
IHC		•
FISH	•	
Tissue NGS	•	
ctDNA (NGS)	•	

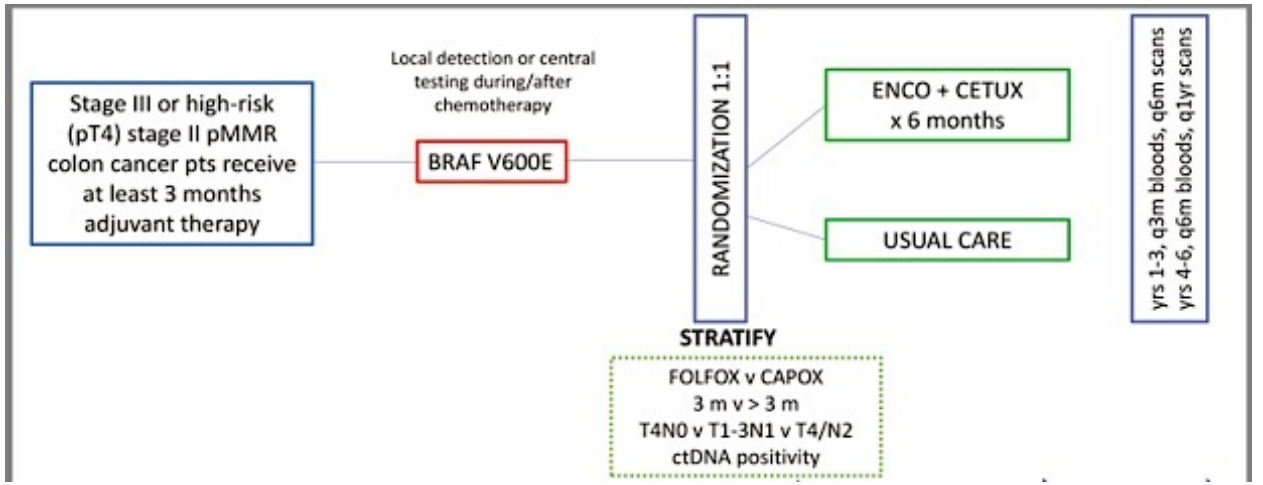
	Blood NGS vs tissue NGS	IHC/FISH vs tissue NGS	IHC/FISH vs blood NGS
n/N	47/58	63/68	66/83
%	**81.0**	**92.6**	**79.5**
90% CI	68.6-90.1	83.7-97.6	69.2-87.6

Strickler JH, et al, presented at ASCO 2023

Timing of Biomarker Assessment

Timing of Biomarker Assessment

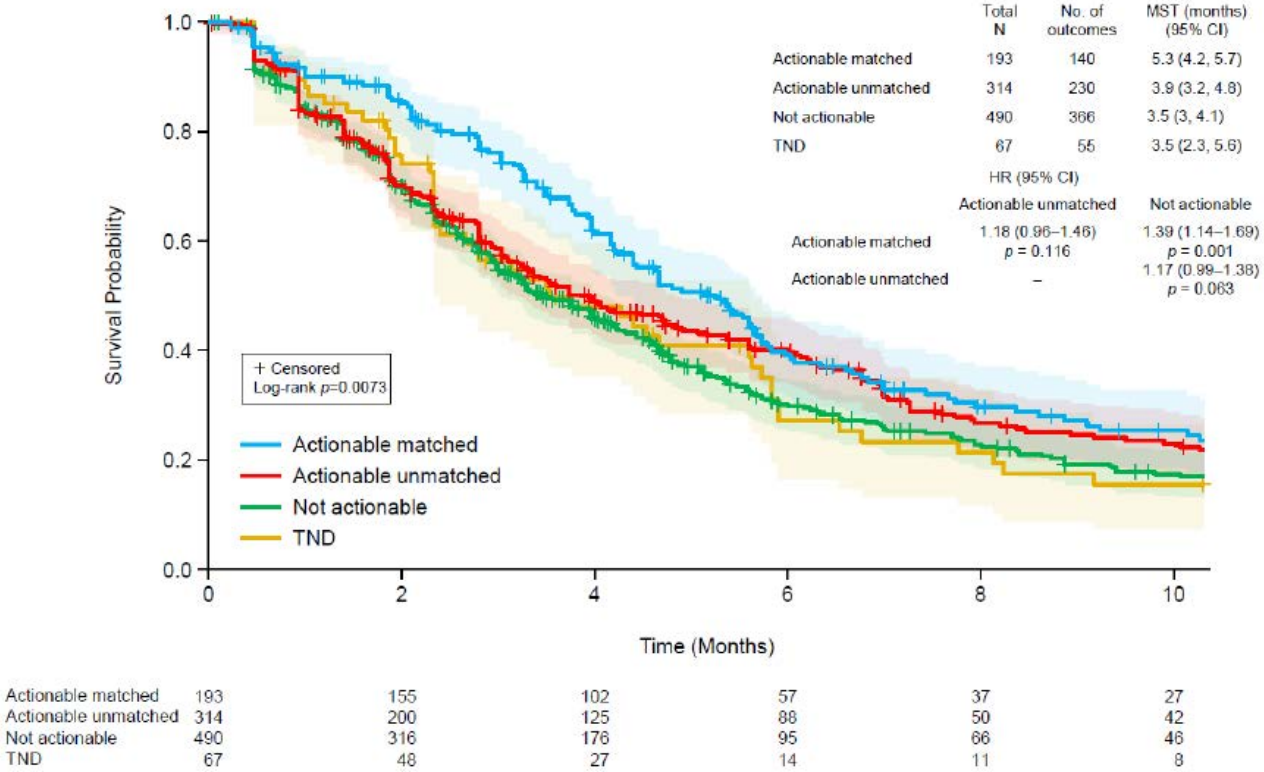
- MSI testing should be completed on **ALL** patients regardless of stage
- **Locally advanced disease**: No role for other biomarker testing at this time in locally advanced colorectal cancer unless indicated for a clinical trial [e.g., BRAF V600E MT (stage II/III) colon CA] **A022004** (see schema)



- **Metastatic disease**
  - Immediately upon diagnosis or initial patient visit
  - RAS status: Rechallenge

Real World Impact of NGS Testing

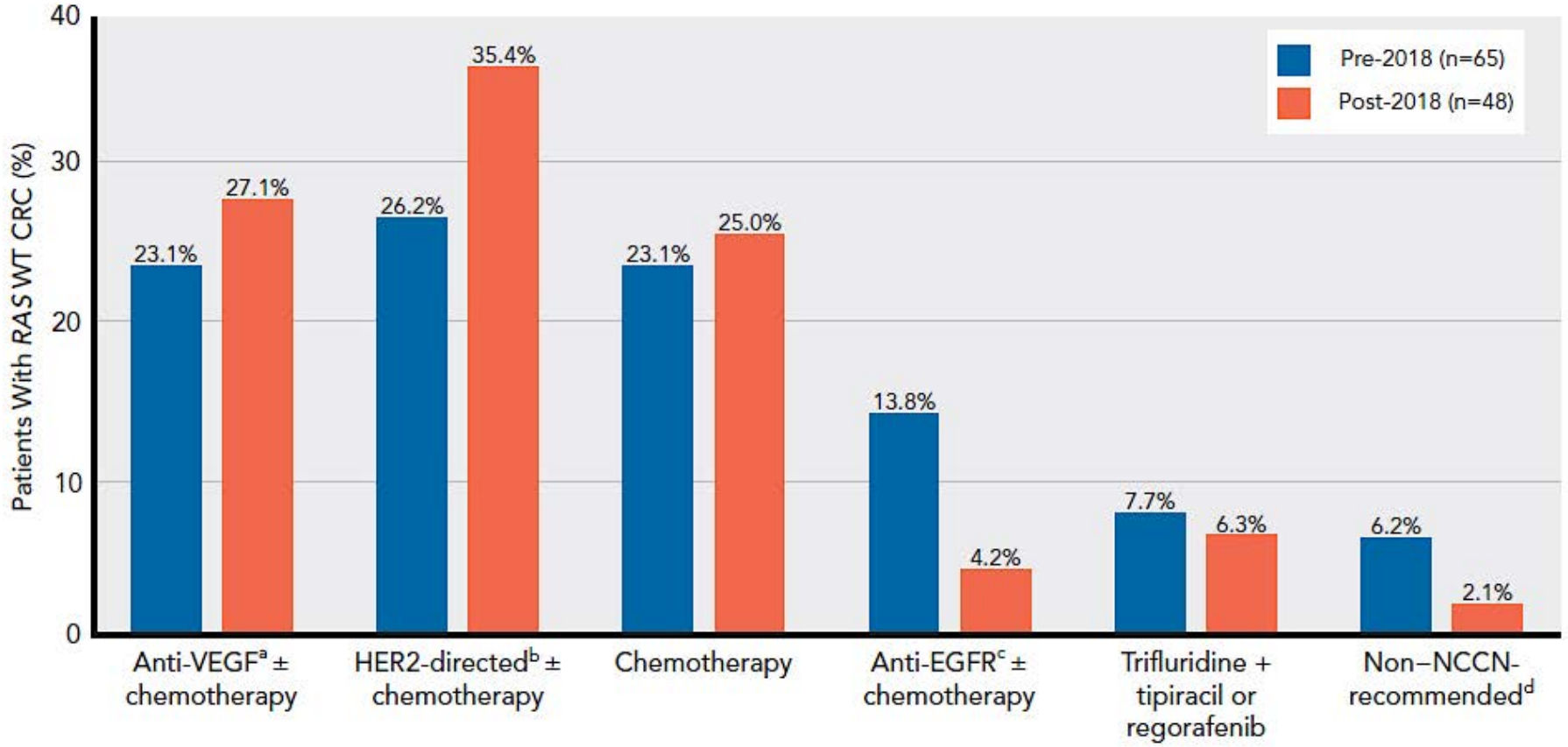
Class of Treatment	Second-Line Cohort (n = 642) n	Second-Line Cohort (n = 642) Informed, n (%)	Third-Line Cohort (n = 422) n	Third-Line Cohort (n = 422) Informed, n (%)
Chemotherapy only	184	96 (52.2%)	105	68 (64.8%)
VEGF inhibitor (with or without chemotherapy, no targeted treatment)	275	148 (53.8%)	162	96 (59.3%)
Any non-targeted *	459	244 (53.2%)	267	164 (61.4%)
EGFR-targeted	132	77 (58.3%)	101	79 (78.2%)
BRAF-targeted	9	8 (88.9%)	7	5 (71.4%)
ERBB2-targeted	11	11 (100%)	10	8 (80.0%)
Other targeted	1	1 (100%)	0	0
Immune checkpoint inhibitor	37	11 (32.4%)	41 †	5 (12.2%)
Any treatment	642	346 (53.9%)	422	257 (60.9%)



Akimura et al: Curr Onc, 2022

Real World Barriers: Provider and Patient Education for New Indications

Despite NCCN Guidelines in 2019: Continued underutilization of HER2 directed therapy



Strickler et al: JNCCN, 2023

Disparities in NGS Testing

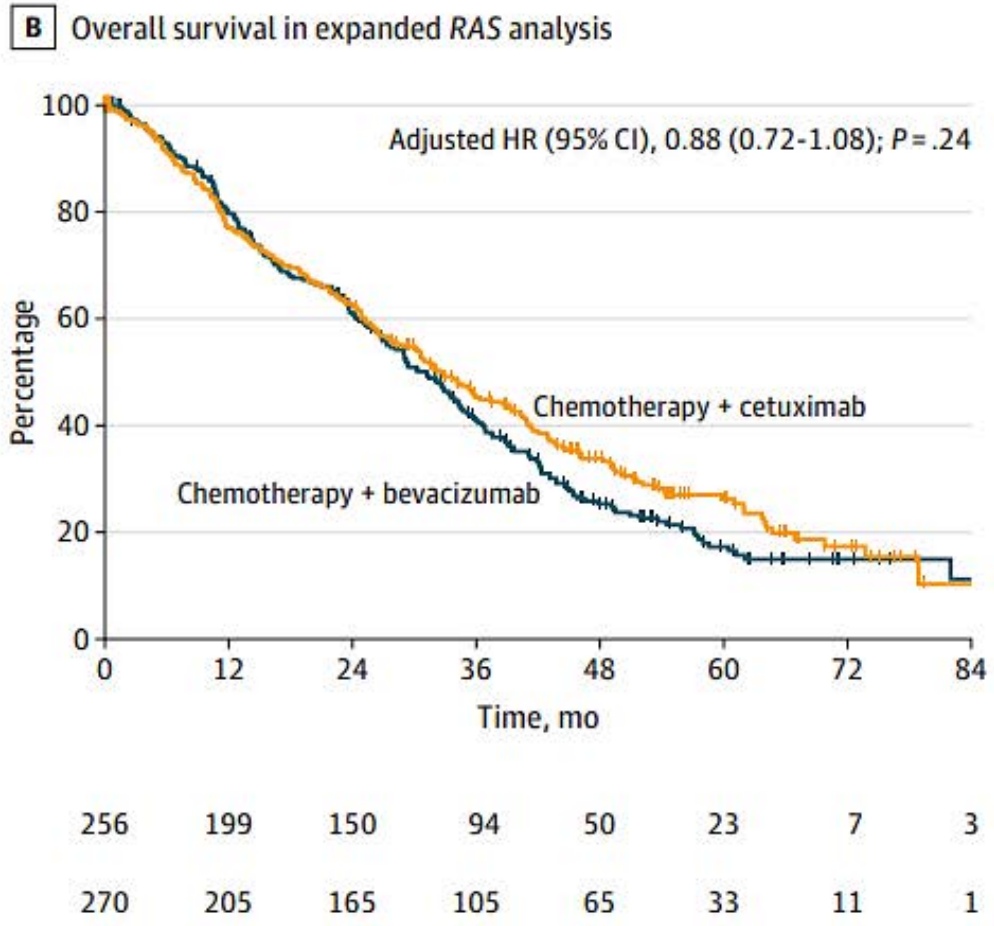
CRC Biomarker Testing	White (n = 4,803) No. (%)	Black/AA (n = 838) No. (%)	P[a]
Ever tested, any biomarker test	4,031 (83.9)	707 (84.4)	.7500
Any biomarker test before first-line therapy	3,253 (67.7)	601 (71.7)	.0200
Ever NGS tested	2,478 (51.6)	350 (41.8)	< .0001
NGS tested before first-line therapy	876 (18.2)	130 (15.5)	.0600

Clinical Trial Participation	White	Black/AA	P[a]
NSCLC	385/9,793 (3.9%)	24/1,288 (1.9%)	.0002
NS NSCLC	261/6,705 (3.9%)	19/922 (2.1%)	.0060
CRC	141/4,803 (2.9%)	24/838 (2.9%)	.9100
BC	193/3,314 (5.8%)	26/593 (4.4%)	.1600

Bruno et al: JCO Precis Onc, 2022

Sidedness and Impact on OS

CALGB-80405: Sidedness and OS Among Patients Randomized to Bevacizumab or Cetuximab



KRAS wt N = 1025	Left	Right	Hazard Ratio 95% CI	P (adjusted*)
		Overall Survival		
All pts	**33.3M**	**19.4M**	1.55 (1.32,1.82)	P < 0.0001
Cetuximab	**36.0M (N=355)**	**16.7M**	1.87 (1.48, 2.32)	P < 0.0001
Bev	**31.4M (N=334)**	**24.2M**	1.32 (1.05, 1.65)	P = 0.01

Venook et al: JAMA, 2017

PARADIGM Trial Design: All RAS in Left-sided Tumors

Phase 3, randomized, open-label, multicenter study (NCT02394795)

Patients with *RAS* WT mCRC

- Unresectable disease
- No previous chemotherapy[a]
- Age: 20–79 years
- ECOG performance status 0–1
- At least 1 evaluable lesion
- Adequate organ function
- Life expectancy ≥ 3 months

N=823

R
1:1

Panitumumab +mFOLFOX6[b]

Bevacizumab +mFOLFOX6[b]

Primary endpoint

- OS: left-sided[c] population; if significant, analyzed in overall population

Secondary endpoints

- PFS, RR, DOR, R0 resection: left-sided[c] and overall populations
- Safety: all treated patients

Exploratory endpoints

- ETS, depth of response, DCR: left-sided[c] and overall populations

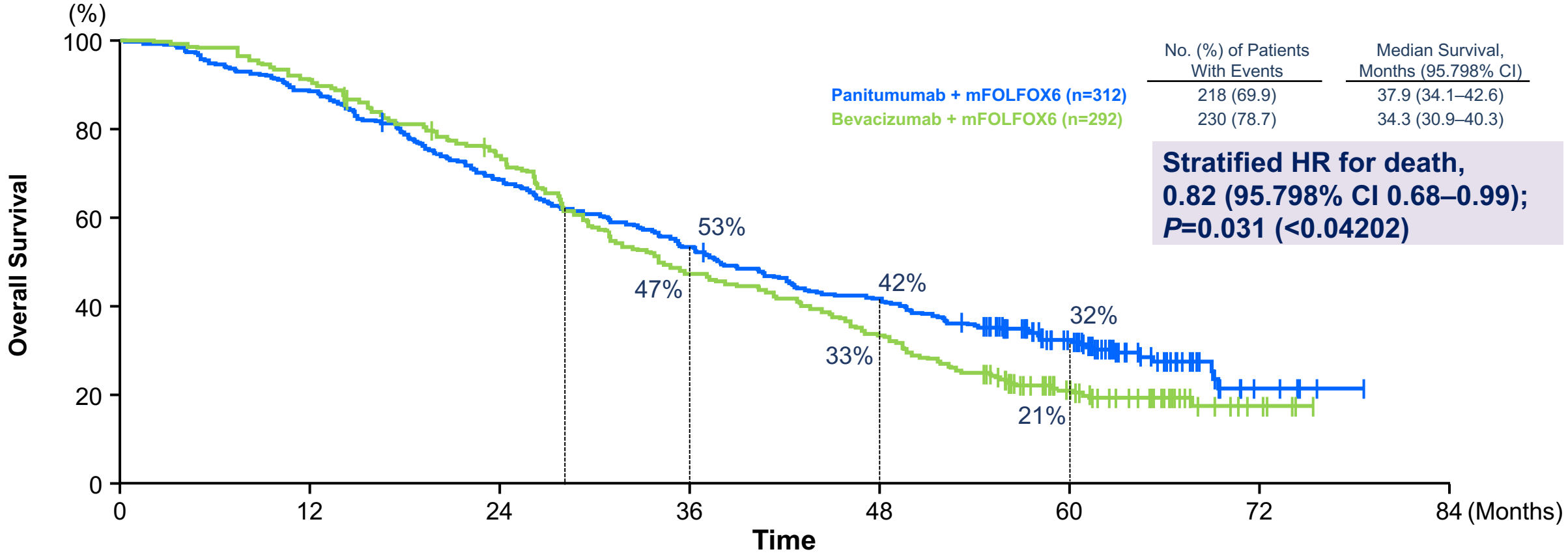
Stratification factors

- Institution
- Age: 20–64 vs 65–79 years
- Liver metastases: present vs absent

DCR, disease control rate; DOR; duration of response; ECOG, Eastern Cooperative Oncology Group; ETS, early tumor shrinkage; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression free survival; RR, response rate; R0, curative resection; WT, wild type.
[a]Adjuvant fluoropyrimidine monotherapy allowed if completed > 6 months before enrollment. [b]Until disease progression, unacceptable toxicity, withdrawal of consent or investigator's judgement or curative intent resection.
[c]Primary tumor in descending colon, sigmoid colon, rectosigmoid, and rectum.

Watanabe et al: Jama Network, 2023

Primary Endpoint 1; Overall Survival in Left-sided Population



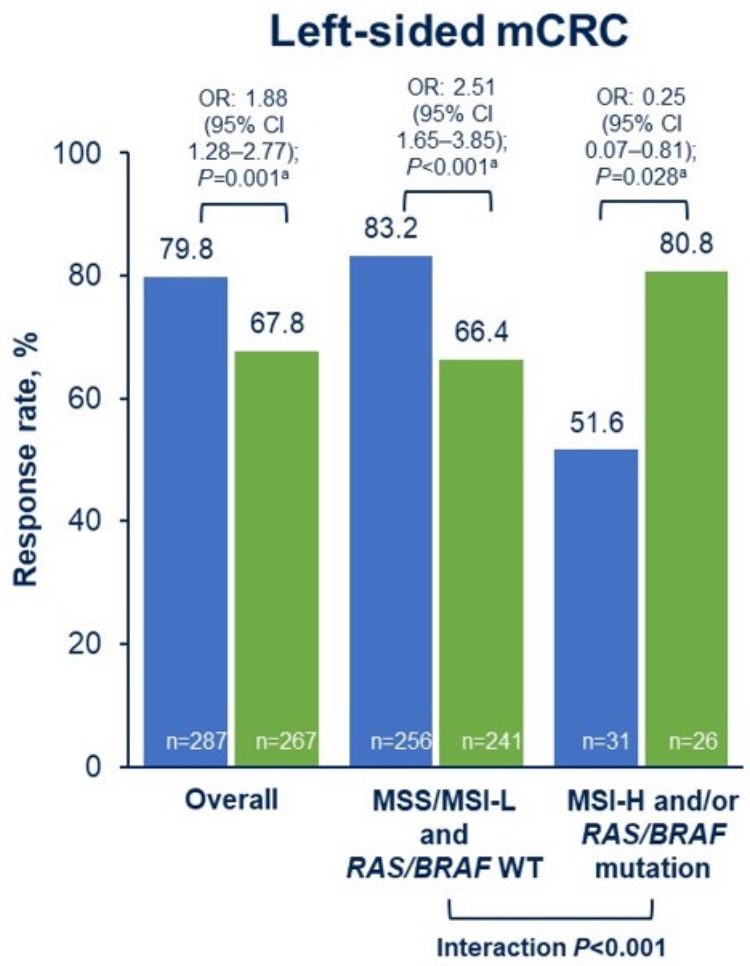
	No. (%) of Patients With Events	Median Survival, Months (95.798% CI)
Panitumumab + mFOLFOX6 (n=312)	218 (69.9)	37.9 (34.1–42.6)
Bevacizumab + mFOLFOX6 (n=292)	230 (78.7)	34.3 (30.9–40.3)

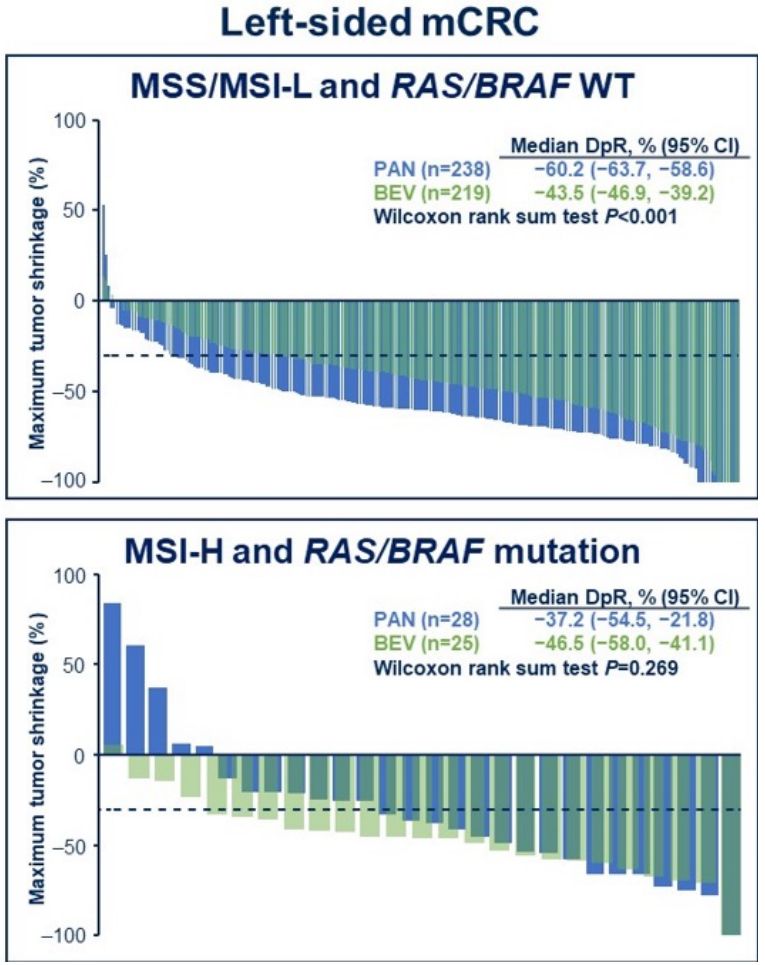
Stratified HR for death, 0.82 (95.798% CI 0.68–0.99); *P*=0.031 (<0.04202)

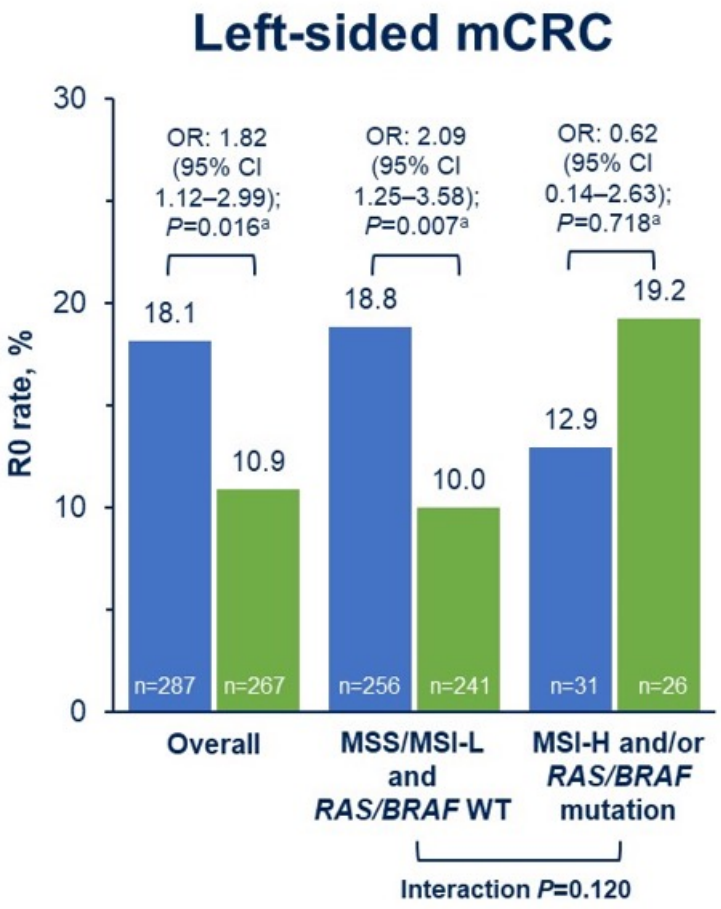
No. at risk								
Panitumumab	312	276	213	166	129	68	5	0
Bevacizumab	292	266	212	136	96	40	5	0

Watanabe et al: Jama Network, 2023

PARADIGM Updated Molecular Analysis: ORR, Depth of Response and R0 resection



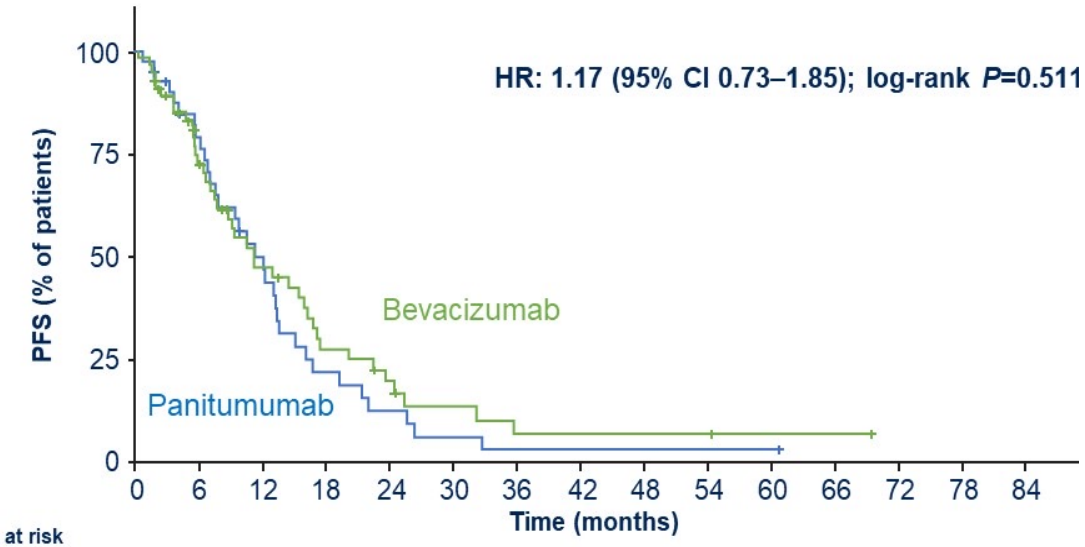




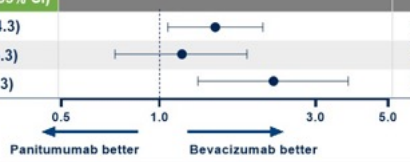
Yamazaki et al: ASCO 2023

PARADIGM Hyperselected Molecular Analysis: Right-sided: PFS, ORR, Depth of Response

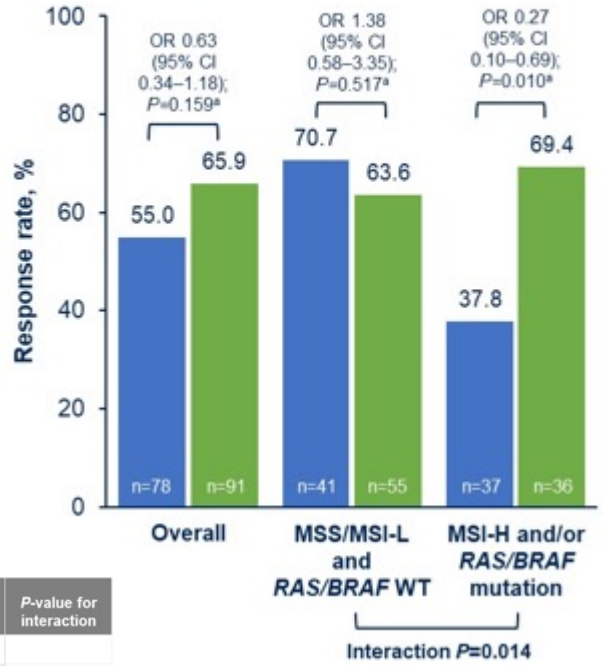
MSS/MSI-L and *RAS/BRAF* WT



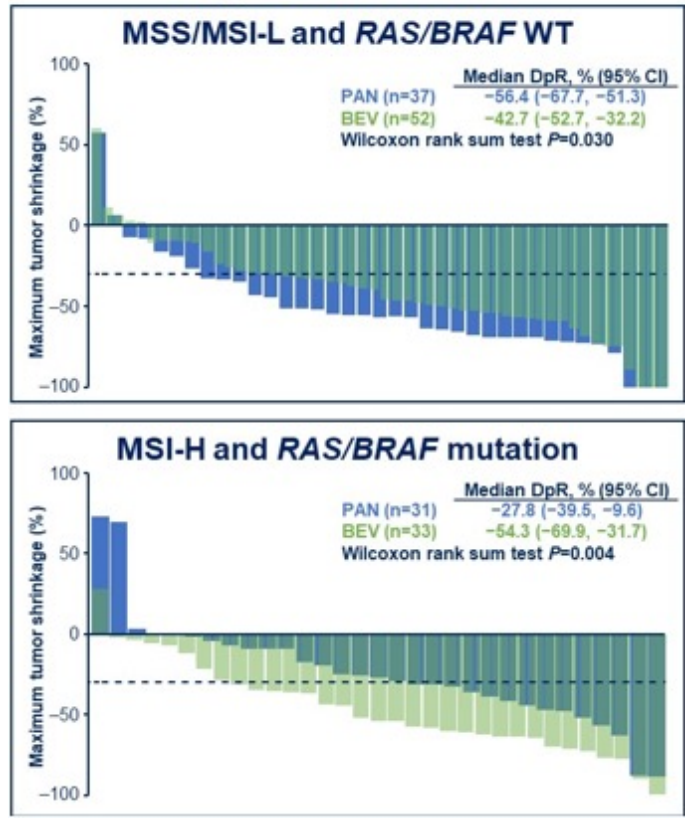
	Panitumumab		Bevacizumab		HR (95% CI)	*P*-value for interaction
	n	mPFS, months (95% CI)	n	mPFS, months (95% CI)		
All	78	7.7 (6.8–9.9)	91	10.6 (7.4–14.3)	1.48 (1.06–2.07)	
MSS/MSI-L and *RAS/BRAF* WT	41	11.3 (7.7–13.6)	55	11.3 (7.6–16.3)	1.17 (0.73–1.85)	0.055
MSI-H and/or *RAS/BRAF* mutation	37	6.8 (4.6–7.4)	36	7.6 (5.8–14.3)	2.23 (1.31–3.78)	



Right-sided mCRC

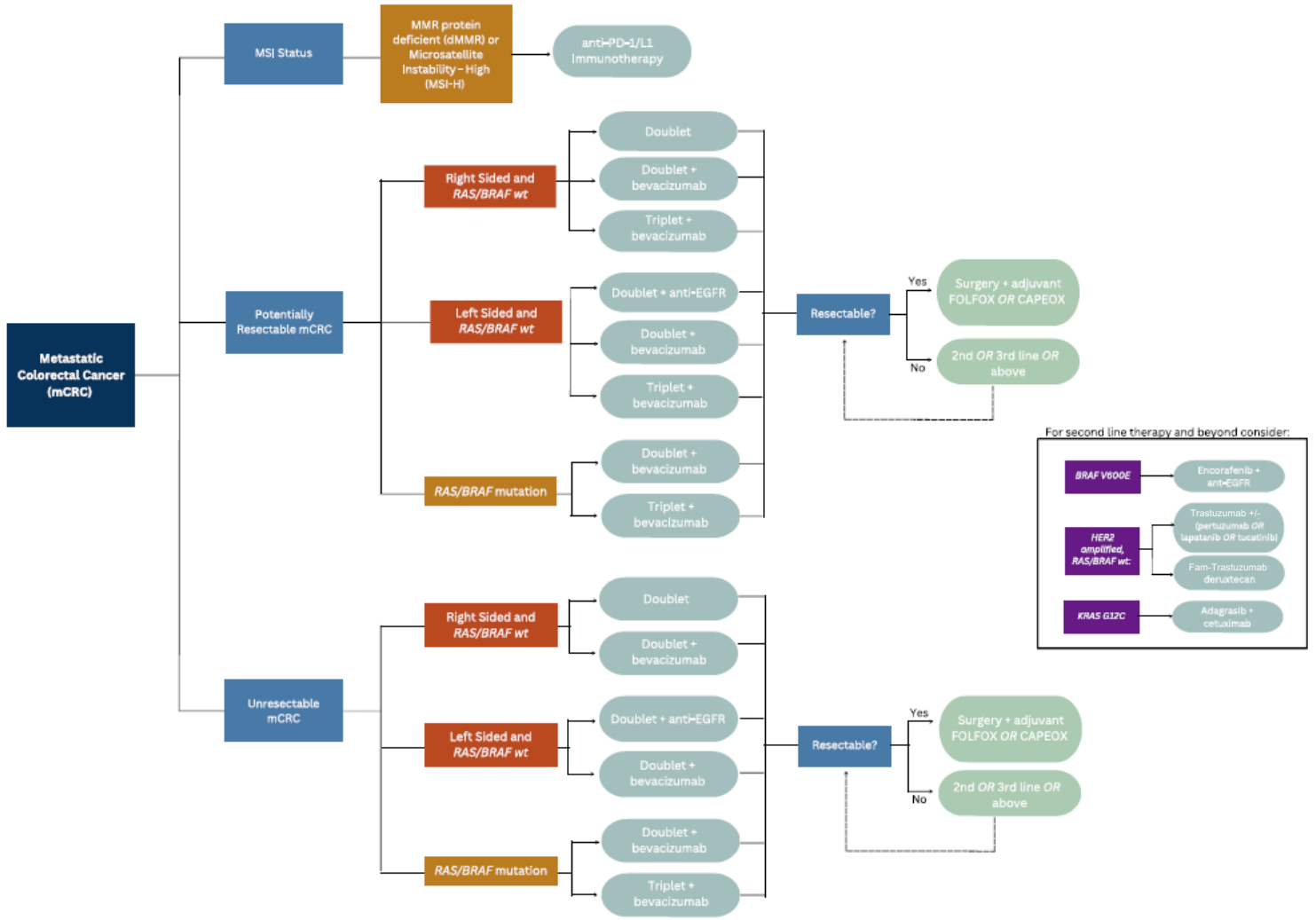


Right-sided mCRC



Yamazaki et al: ASCO 2023

Biomarker-Based Treatment Algorithm



Cann et al: Frontiers in Oncology, 2023

MODULE 2: Emerging Role of Biomarker-Based Decision-Making for Patients with Localized CRC – Dr Lieu

RTP
RESEARCH
TO PRACTICE

Integration of ctDNA assays for the management of CRC

Arvind N Dasari, MD, MS

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Arvind N Dasari, MD, MS

In what settings are you ordering ctDNA assays in your practice, and in which of these are you comfortable using the results to inform treatment decision-making?

Which ctDNA assay do you prefer?

RTP RESEARCH TO PRACTICE

ctDNA assays in treatment decision-making in the localized and metastatic disease settings

Arvind N Dasari, MD, MS

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Arvind N Dasari, MD, MS

What adjuvant systemic therapy would you recommend for a patient with Stage III (T3N1) CRC for whom a tumor-informed ctDNA assay returned negative for MRD?

How would you approach a patient who has undergone (neo)adjuvant chemotherapy and resection of oligometastatic disease to the liver with a negative postoperative tumor-informed ctDNA assay that turns positive after 9 months of surveillance?

RTP
RESEARCH
TO PRACTICE

What was the age and disease stage of the last patient in your practice with localized colorectal cancer (CRC) for whom you ordered a circulating tumor DNA (ctDNA) assay outside of a clinical trial? Which ctDNA assay did you order?

	Age	Disease stage	ctDNA assay
 Dr Bekaii-Saab	27 years	IIB	Signatera™
 Dr Cercek	53 years	IV (resection)	Signatera
 Dr Eng	52 years	IV (resection)	Signatera
 Dr Lieu	65 years	II (low risk)	Signatera
 Dr Strickler	78 years	IIIA (T2N1)	Signatera
 Dr Ciombor	50 years	II (T3N0)	Signatera
 Dr Dasari	48 years	IIIB	Signatera

For the patient with localized CRC in the previous scenario, what were the results of the ctDNA assay? How did these results affect your treatment approach?

	Results of ctDNA assay	Effect on Tx approach
 Dr Bekaii-Saab	Negative	Facilitated decision of observation only
 Dr Cercek	Initially negative, then positive	Follow-up was more challenging due to ctDNA positivity and NED on imaging
 Dr Eng	Positive	Earlier imaging and eventual PET
 Dr Lieu	Negative	Continued with original plan to not administer chemotherapy
 Dr Strickler	Negative	Reinforced patient's decision to pursue active surveillance
 Dr Ciombor	Negative	Felt a little better about decision not to administer adjuvant chemotherapy
 Dr Dasari	Negative	Continued with adjuvant chemotherapy

NED = no evidence of disease

In general, in which settings, if any, do you order a ctDNA assay for your patients with CRC outside of a clinical trial?

 Dr Bekaii-Saab	Stage II, III and resected oligometastatic disease
 Dr Cercek	None
 Dr Eng	Metastatic CRC
 Dr Lieu	Stage II and metastatic CRC
 Dr Strickler	Stage II and select cases of Stage III CRC, elevated CEA with negative imaging
 Dr Ciombor	Stage II and III, and resected metastatic CRC
 Dr Dasari	Stage II

CEA = carcinoembryonic antigen

Based on current available data and/or your personal clinical experience, what is your global view of tumor-informed versus tumor-uninformed ctDNA assays for patients with localized CRC (eg, ease of use, accuracy)?

 Dr Bekaii-Saab	Tumor-informed has better sensitivity and predictive value overall
 Dr Cercek	I prefer tumor-informed assay
 Dr Eng	Signatera is my preferred assay
 Dr Lieu	Tumor-informed provides greater sensitivity, but tumor-uninformed is much easier to perform (due to lack of tissue testing) and is much faster
 Dr Strickler	Head-to-head data aren't available, have most data with tumor-informed assays, however, sometimes these assays are too slow to return results or not available
 Dr Ciombor	Tumor-informed assays take longer to result, but I tend to trust them more for MRD purposes; tumor-uninformed assays good for NGS
 Dr Dasari	Tumor-informed appear to be more sensitive, but turnaround time is longer with the initial test

MRD = minimal residual disease

RTP RESEARCH TO PRACTICE

For a patient with CRC and a solitary hepatic metastasis who received neoadjuvant FOLFOX and underwent hepatic resection, would you assess ctDNA as part of the postoperative workup?

 Dr Bekaii-Saab	Yes
 Dr Cercek	No
 Dr Eng	Yes
 Dr Lieu	Yes
 Dr Strickler	Yes, if we have a plan to treat a positive result
 Dr Ciombor	Yes
 Dr Dasari	Yes

Cancer Center

NCI-DESIGNATED CONSORTIUM
COMPREHENSIVE CANCER CENTER

Emerging Role of Biomarker-Based Decision-Making for Patients with Localized CRC

Christopher Lieu, MD
Director, GI Medical Oncology
Associate Director for Clinical Research
University of Colorado

NCI Designated Comprehensive Cancer Center

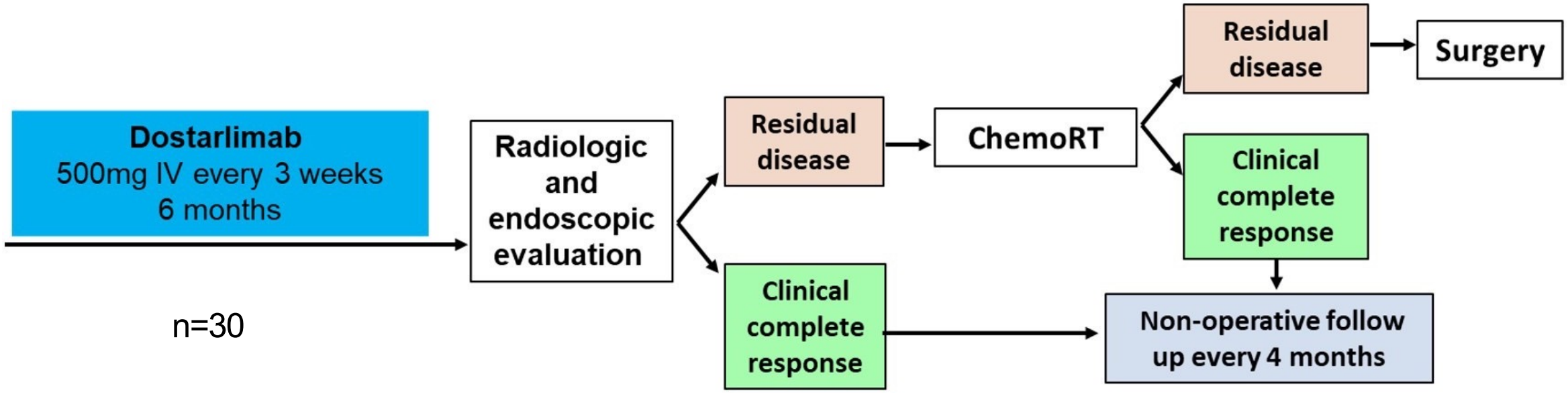
Topics for Discussion

- Early data with the use of immune checkpoint inhibitors for patients with non-metastatic CRC

- Rationale for the use of ctDNA-based MRD monitoring in early-stage CRC

Immune checkpoint inhibitors for patients with non-metastatic CRC

Dostarlimab for MSI-H Stage II-III RectalCancer



- Primary endpoints
  - Overall response rate at 6 months per MSKCC regression criteria
  - pCR or cCR rate at 12 months
- Secondary endpoint
  - Safety and tolerability

Cercek A, et al. *N Engl J Med* 2022.

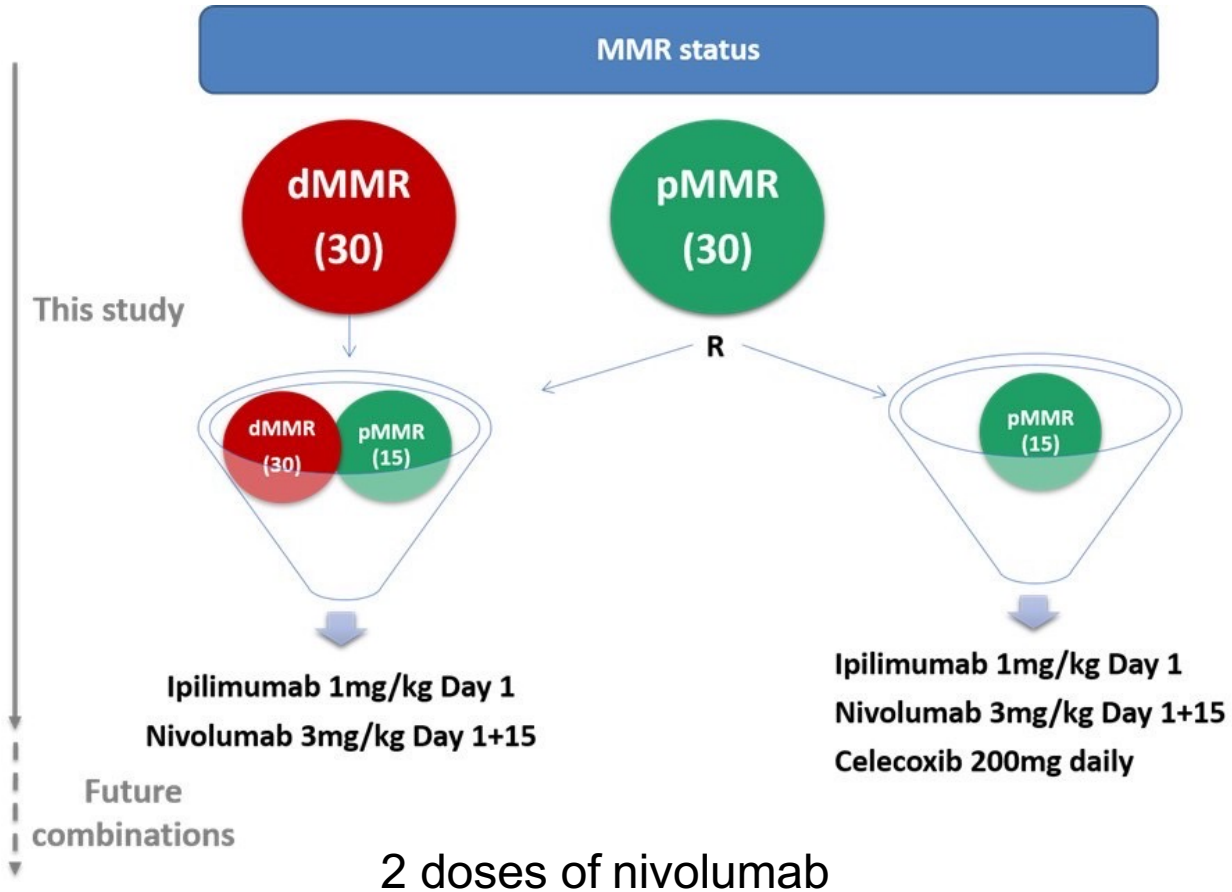
Dostarlimab Led to a 100% Clinical CR Rate

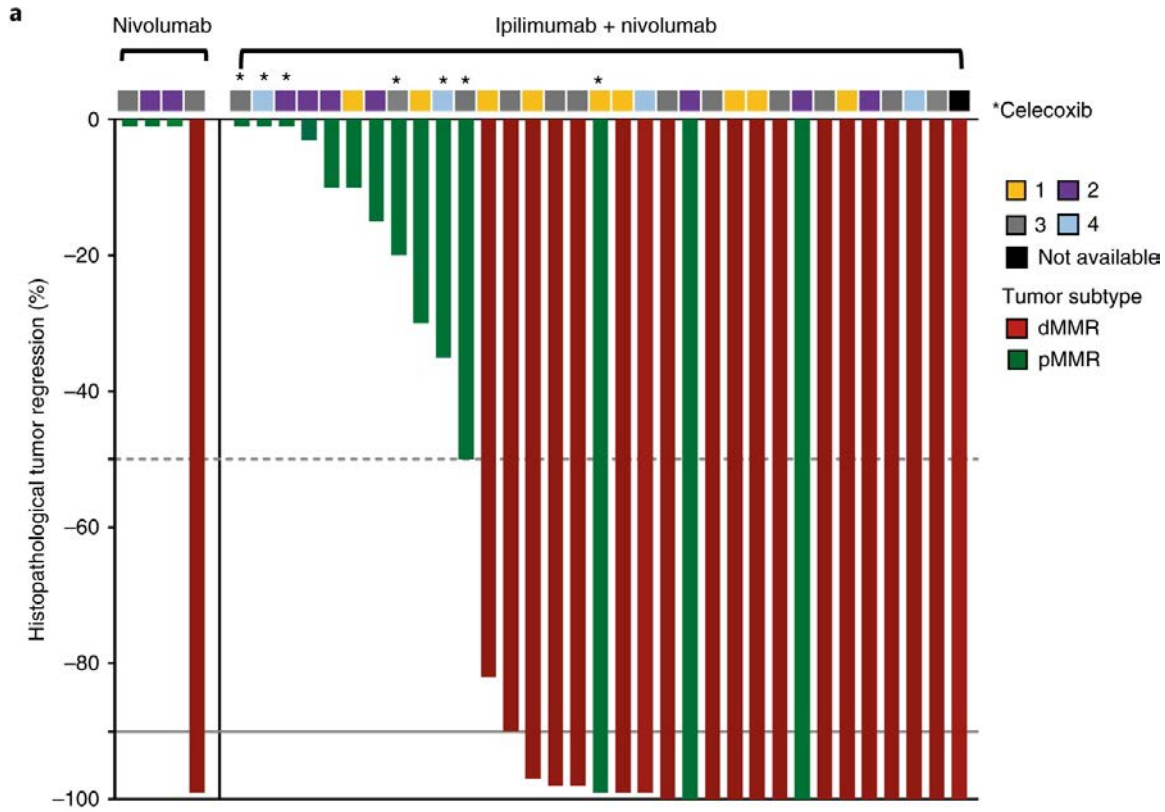
ID	Age	Stage T	Stage N	FU (months)	Digital rectal exam response	Endoscopic best response	Rectal MRI best response	Overall response
1	38	T4	N+	23.8	CR	CR	CR	**cCR**
2	30	T3	N+	20.5	CR	CR	CR	**cCR**
3	61	T1/2	N+	20.6	CR	CR	CR	**cCR**
4	28	T4	N+	20.5	CR	CR	CR	**cCR**
5	53	T1/2	N+	9.1	CR	CR	CR	**cCR**
6	77	T1/2	N+	11.0	CR	CR	CR	**cCR**
7	77	T1/2	N+	8.7	CR	CR	CR	**cCR**
8	55	T3	N+	5.0	CR	CR	CR	**cCR**
9	68	T3	N+	4.9	CR	CR	CR	**cCR**
10	78	T3	N-	1.7	CR	CR	CR	**cCR**
11	55	T3	N+	4.7	CR	CR	CR	**cCR**
12	27	T3	N+	4.4	CR	CR	CR	**cCR**
13	26	T3	N+	0.8	CR	CR	CR	**cCR**
14	43	T3	N+	0.7	CR	CR	CR	**cCR**

Cercek A, et al. *N Engl J Med* 2022.

NICHE Study:

Nivolumab and Ipilimumab Neoadjuvant Therapy





2 doses of nivolumab
1 dose of ipilimumab

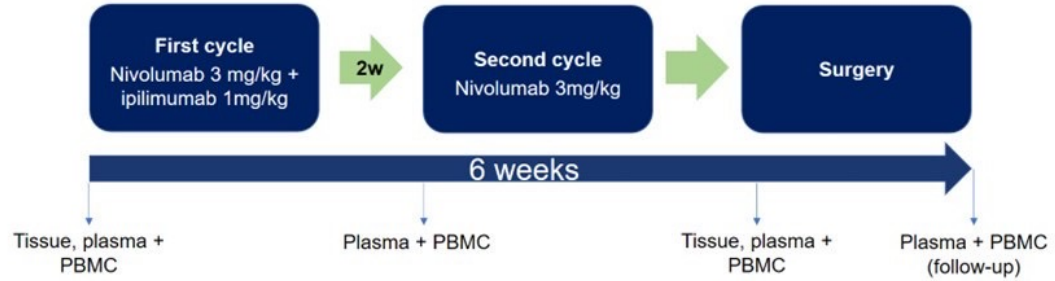
29% path response in pMMR tumors

Verschoor YL et al. ASCO 2022; Abstract3511.

Chalabi M et al. *Nat Med* 2020;26(4):566-576.

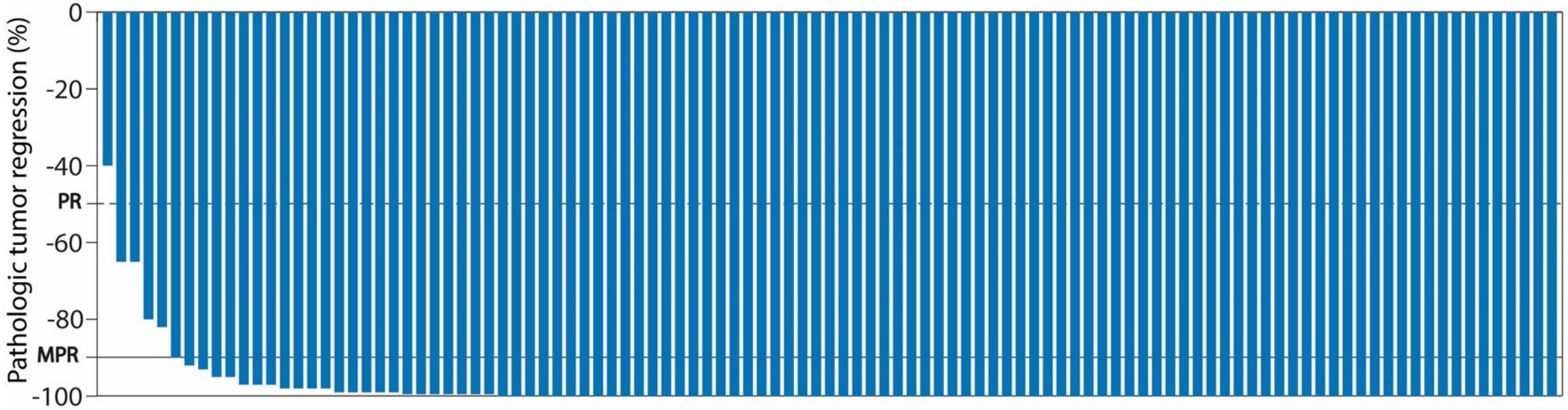
Prevent and conquer cancer. **Together**.

NICHE-2 Study: Nivo/Ipi dMMR colon cancer



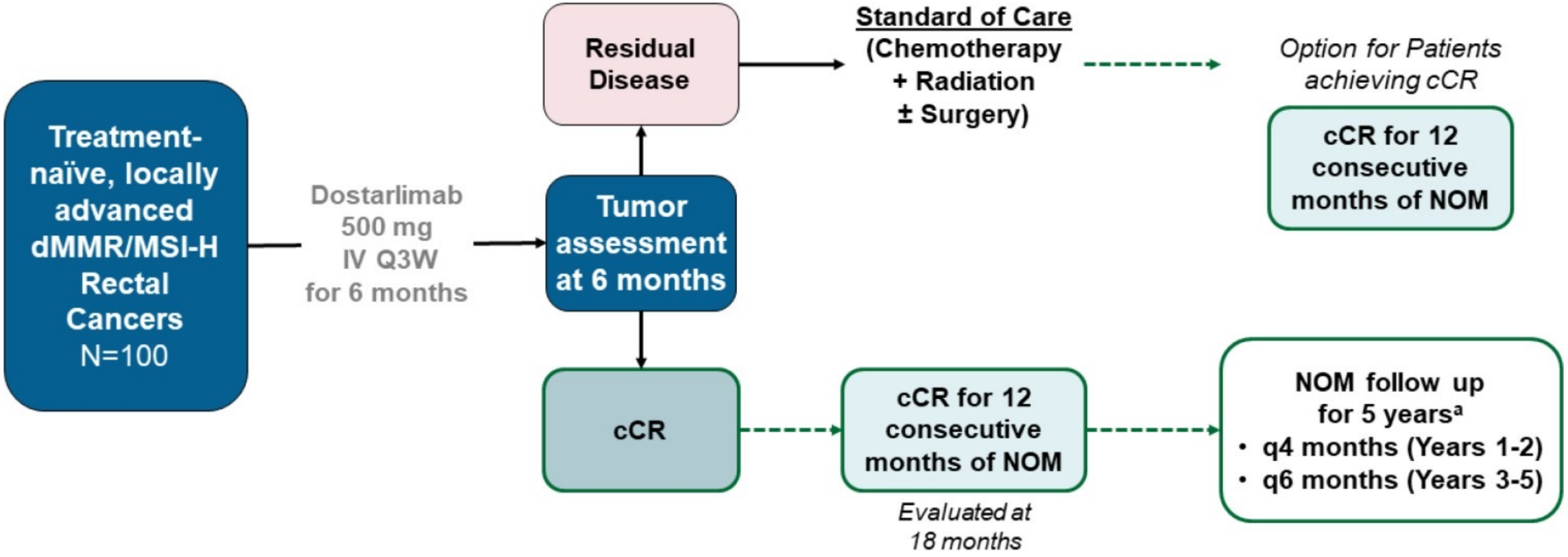
In locally advanced MMR-deficient colon cancers

- **95% MPR; 67% pCR**



Chalabi et al. LBA7 2022 ESMO Annual Meeting.

AZUR-1: Dostarlimab in dMMR/MSI-H Locally Advanced Rectal Cancer

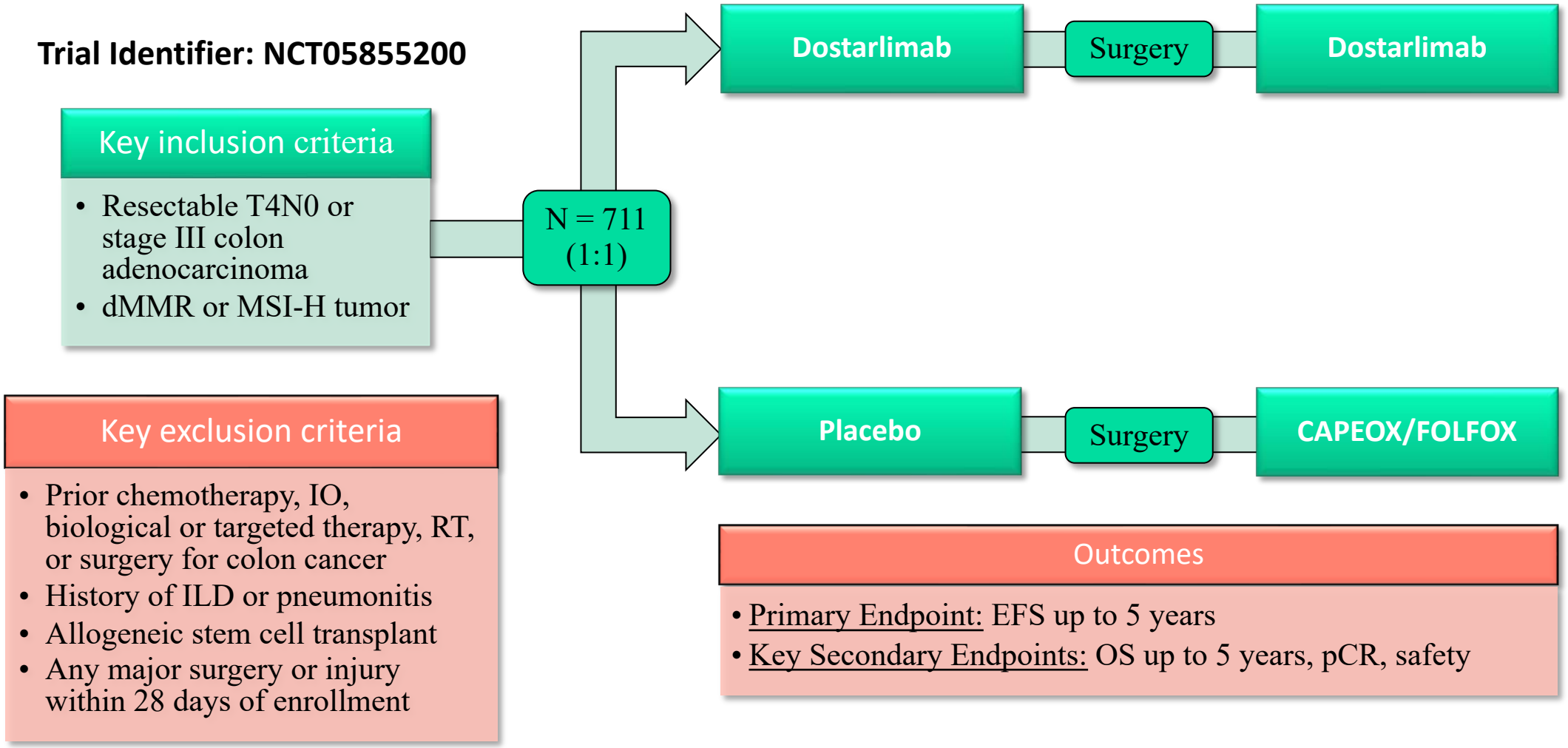


NCT05723562

Cercek A et al. *J Clin Oncol* 2023;41(16_suppl):TPS3639.

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

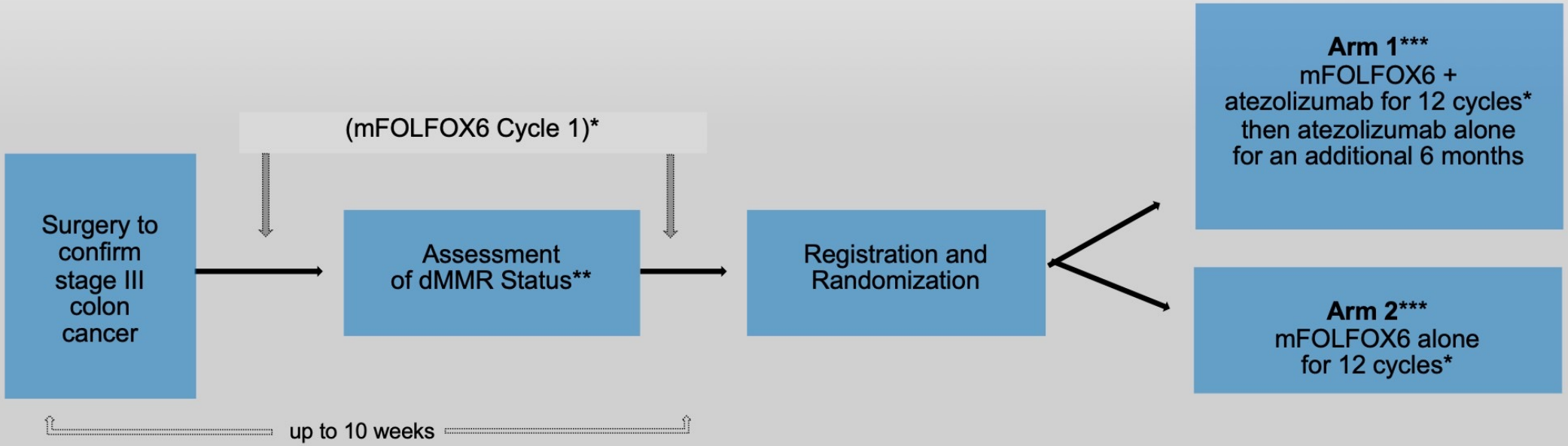
Trial Identifier: NCT05855200



dMMR = defective mismatch repair MSI-H = microsatellite instability high IO = immunotherapy RT = radiation therapy ILD = interstitial lung disease
CAPEOX = capecitabine/oxaliplatin FOLFOX = fluorouracil/leucovorin/oxaliplatin EFS = event-free survival OS = overall survival pCR = pathological complete response

www.clinicaltrials.gov; Accessed January 2024.

Alliance A021502 (ATOMIC): A Phase III Study of Adjuvant Atezolizumab



* 1 cycle = 14 days. One cycle of mFOLFOX6 is allowed prior to registration. If Cycle 1 is started prior to registration, then the first post-registration cycle will be mFOLFOX6 Cycle 2. For patients who started Cycle 1 prior to registration and who are randomized to Arm 1, atezolizumab will start with Cycle 2.

** Assessment of dMMR status may be performed locally or at a reference laboratory. Retrospective central confirmation of dMMR testing is required for all patients. See Section 6.2.2 for specimen submission requirements and instructions.

*** The standard of care for the time window between the end of mFOLFOX6 Cycle 1 and the start of mFOLFOX6 Cycle 2 is 14 days; however, up to 28 days are allowed between the end of Cycle 1 and the start of Cycle 2 if delays are made due to toxicity.

Patients will be followed for recurrence every 6 months for two years after registration, and then annually for an additional 3 years. Patients will be followed for survival every 6 months for 8 years after registration.

NCT02912559 Sinicrope FA et al. ASCO 2019;Abstract e15169.
https://www.allianceforclinicaltrialsinoncology.org/main/public/standard.xhtml?path=%2FPublic%2FA021502

Selected Ongoing Clinical Trials:

Immune Checkpoint Inhibitors for Early-Stage Colorectal Cancer

Study	Design	Study Population	Intervention	End Points of Study
NCT04357587	Phase I	Patients with MMR-D rectal cancer	Pembrolizumab in combination with capecitabine-based chemoradiation as neoadjuvant therapy	Safety, feasibility, and radiologic and pathologic tumor regression
NCT03926338	Phase II	Patients with resectable MMR-D locally advanced colon and rectal cancers	Toripalimab with or without celecoxib as neoadjuvant therapy	Pathologic complete response
NCT05116085	Phase II	Patients with stage II-III MMR-D colon cancer	Tislelizumab monotherapy as neoadjuvant therapy	Pathologic complete response
NCT05231850	Phase II	Patients with high-risk stage II-III colon cancer	Tislelizumab monotherapy as adjuvant therapy	Disease-free survival and overall survival
NCT05118724	Phase II	Patients who are oxaliplatin-ineligible with stage III colon and rectal cancer	Atezolizumab with/without IMM-101 (immune-stimulating molecule) as perioperative therapy	Disease-free survival and overall survival

Abbreviations: MMR-D, mismatch repair–deficient.

Sahin et al. *JCO Onc Prac* 2023;19:251-259.

TAKE HOME POINTS:

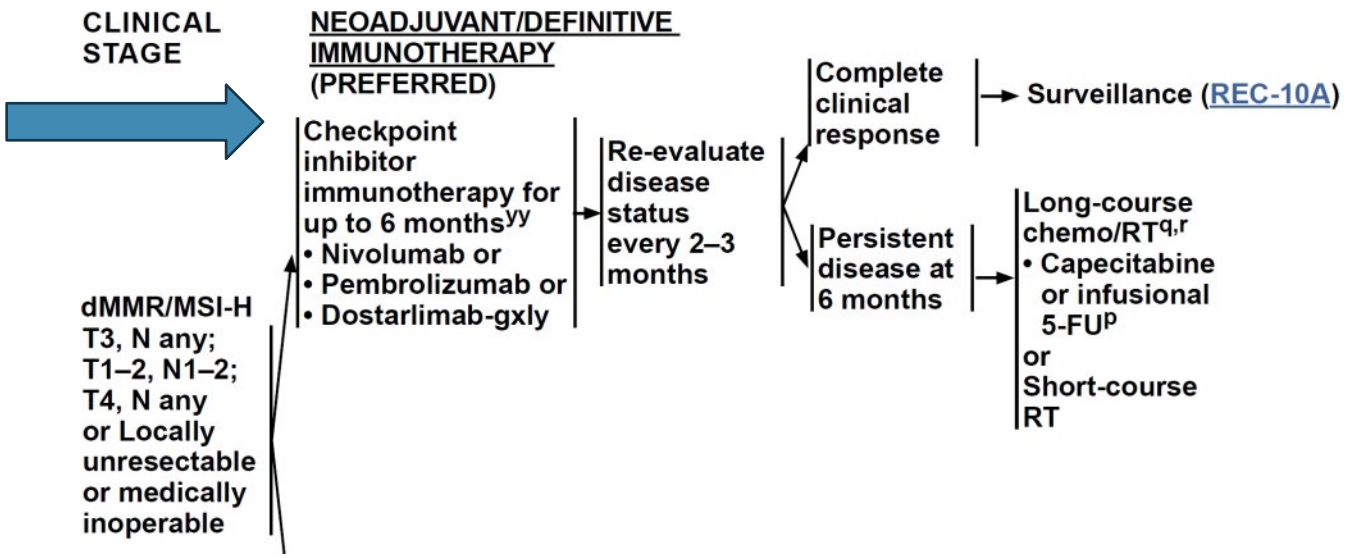
Neoadjuvant immune checkpoint inhibition appears ready for primetime for dMMR/MSI-H

QUESTIONS:

What do long-term outcomes look like?

Does pCR mean cure?

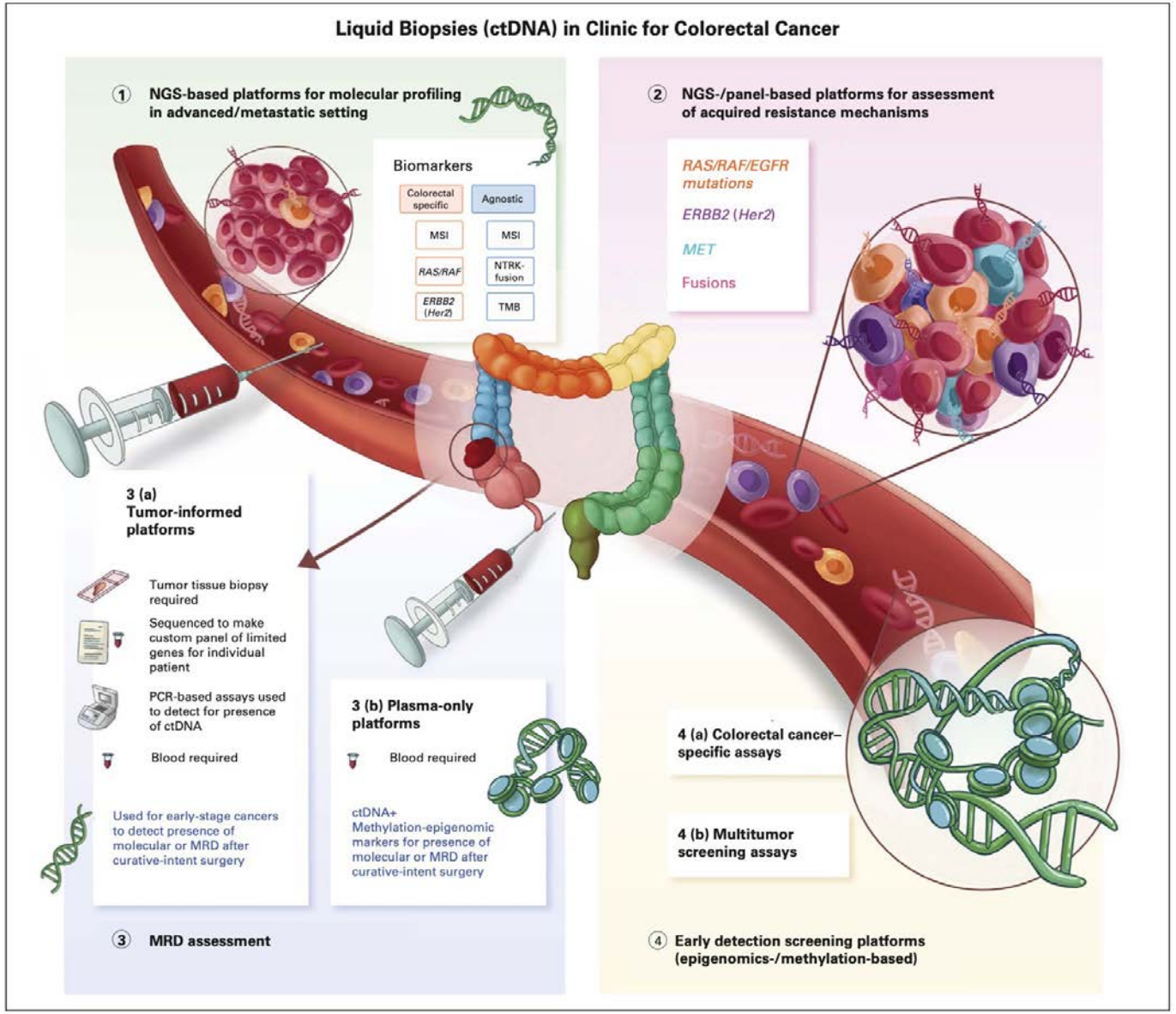
What is the impact on pMMR/MSS patients?



NCCN Guidelines Version 6.2023

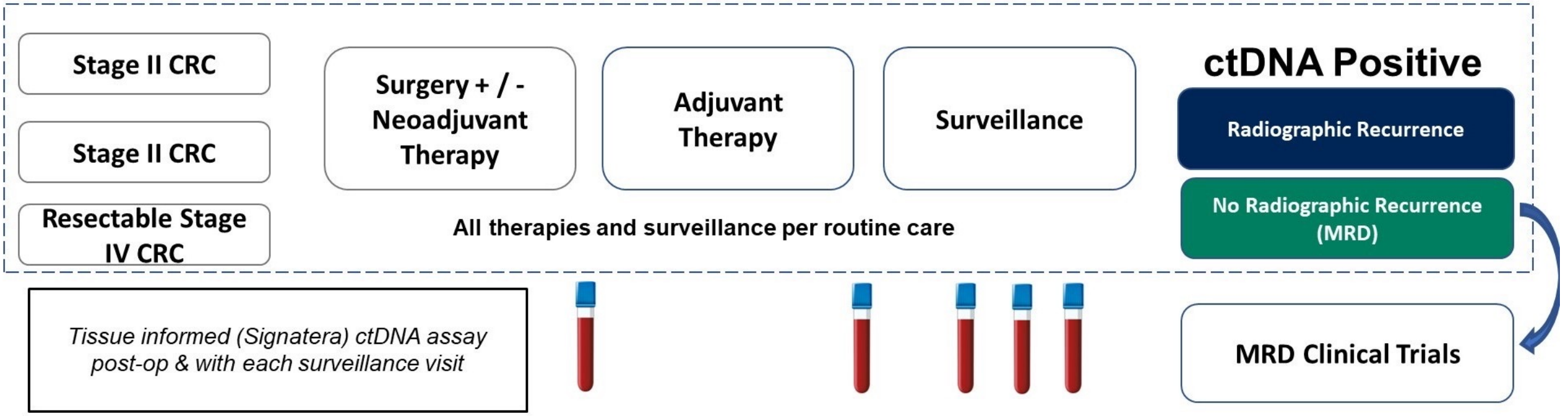
Is ctDNA ready for primetime?

Rationale for ctDNA-Based MRD Monitoring in Localized CRC



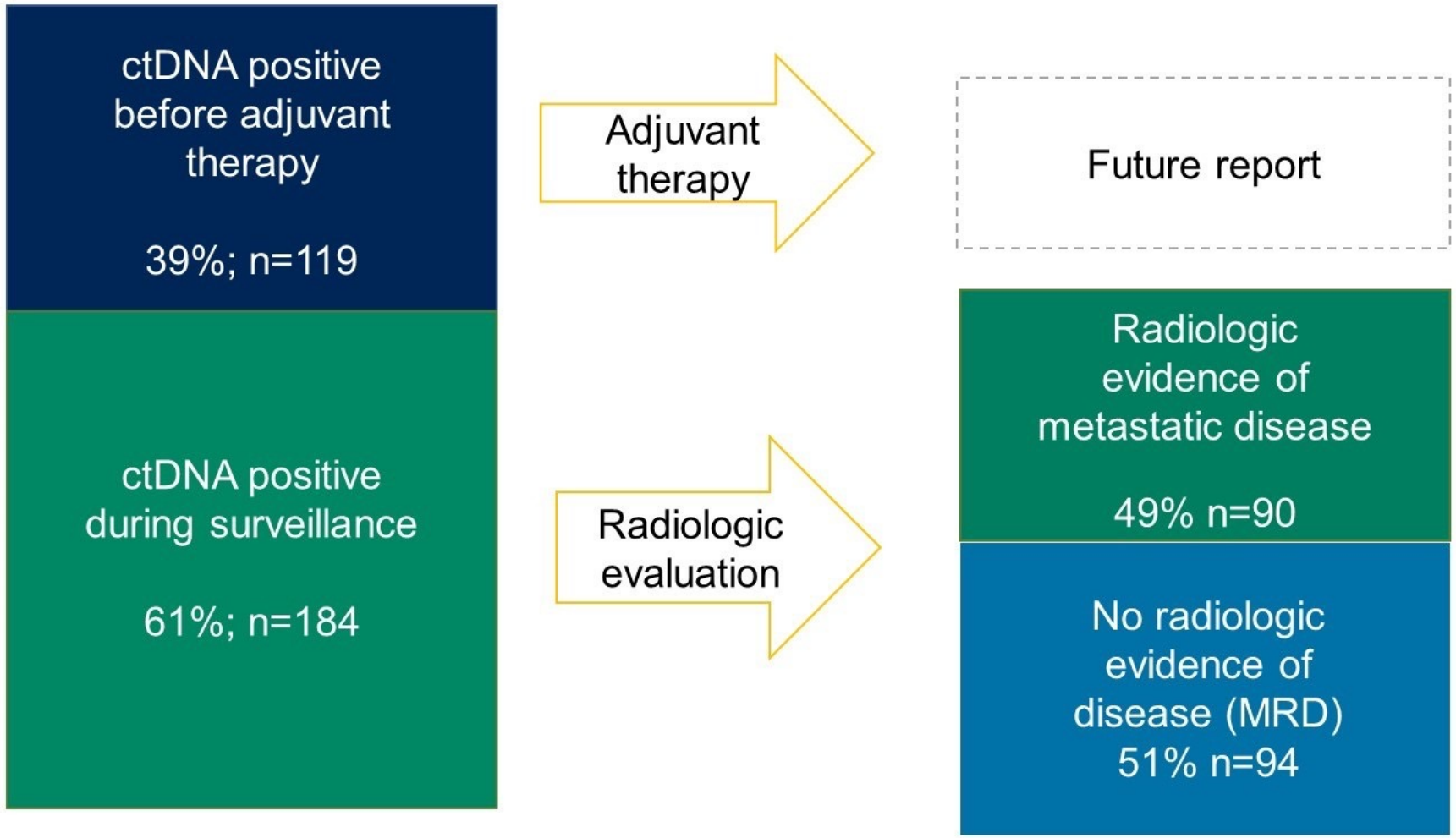
Malla M et al. *J Clin Oncol* 2022;40(24):2846-57.

INTERCEPT Study Design



Dasari A et al. 2023 ASCO Annual Meeting. Abstract 3522.

Clinical Utility: Radiographic Findings of Patients ctDNA+ During Surveillance, n = 184



Roughly half of patients with positive ctDNA will have radiologic evidence of metastatic disease

Dasari A et al. 2023 ASCO Annual Meeting. Abstract 3522.

DYNAMIC Study Design

ACTRN12615000381583

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

Plasma Collections

Week 4 + 7 post-op

R
2:1

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

Endpoints

Primary
- RFS rate at 2 years

Key Secondary
- Proportion receiving adjuvant chemo

Secondary
- RFS by ctDNA status for ctDNA-guided arm
- TTR
- OS

Stratification Factors
- T stage (T3 vs T4)
- Type of participating center (metropolitan vs regional)

Surveillance:
- CEA → 3-monthly for 24M, then 6-monthly for 36M
- CT C/A/P → 6-monthly for 24M, then at 36M

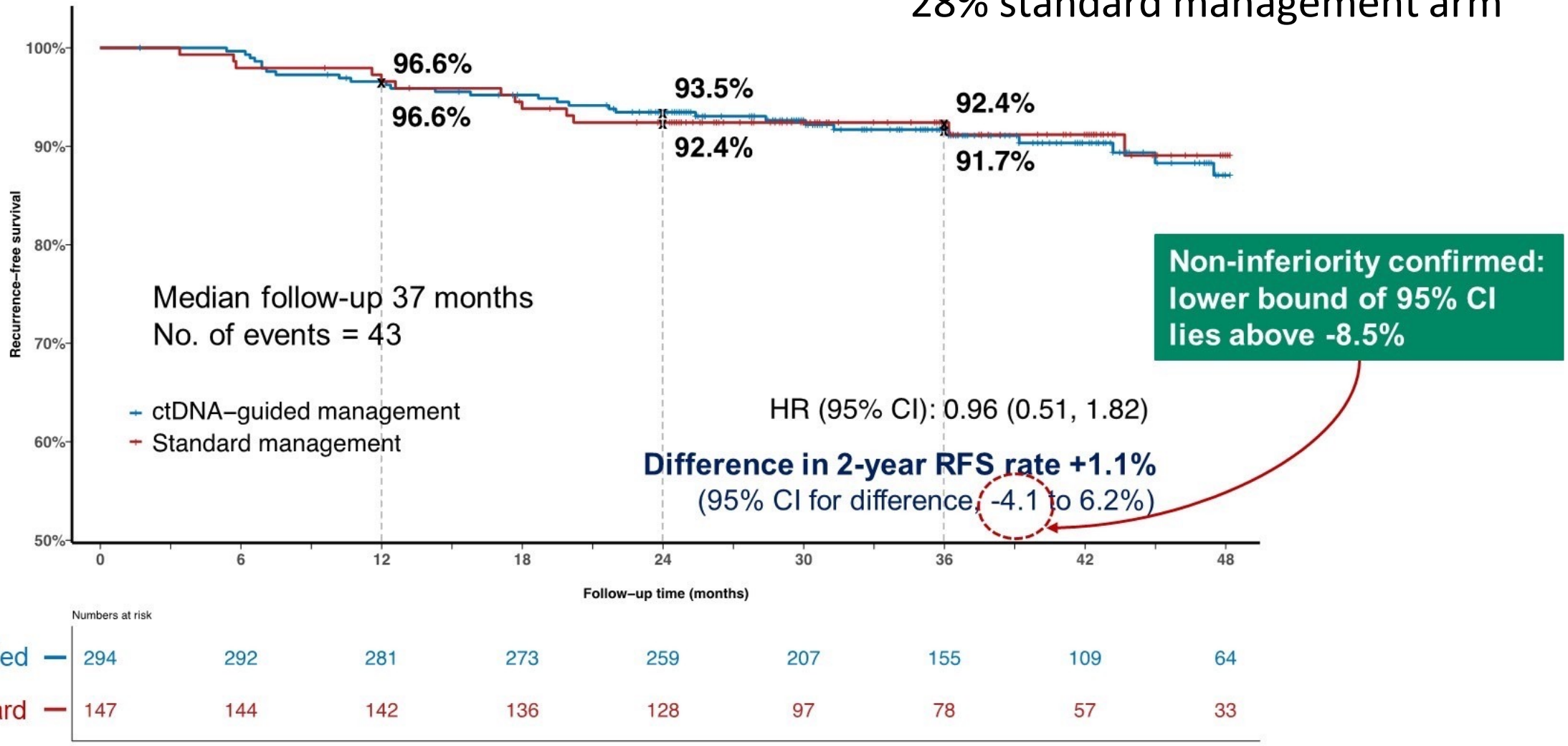
Tie J et al. 2022 ASCO Annual Meeting. LBA100. Tie J et al. *N Engl J Med*. 2022;386(24):2261-2272.

Recurrence-Free Survival

Adjuvant therapy received:

15% ctDNA-guided arm

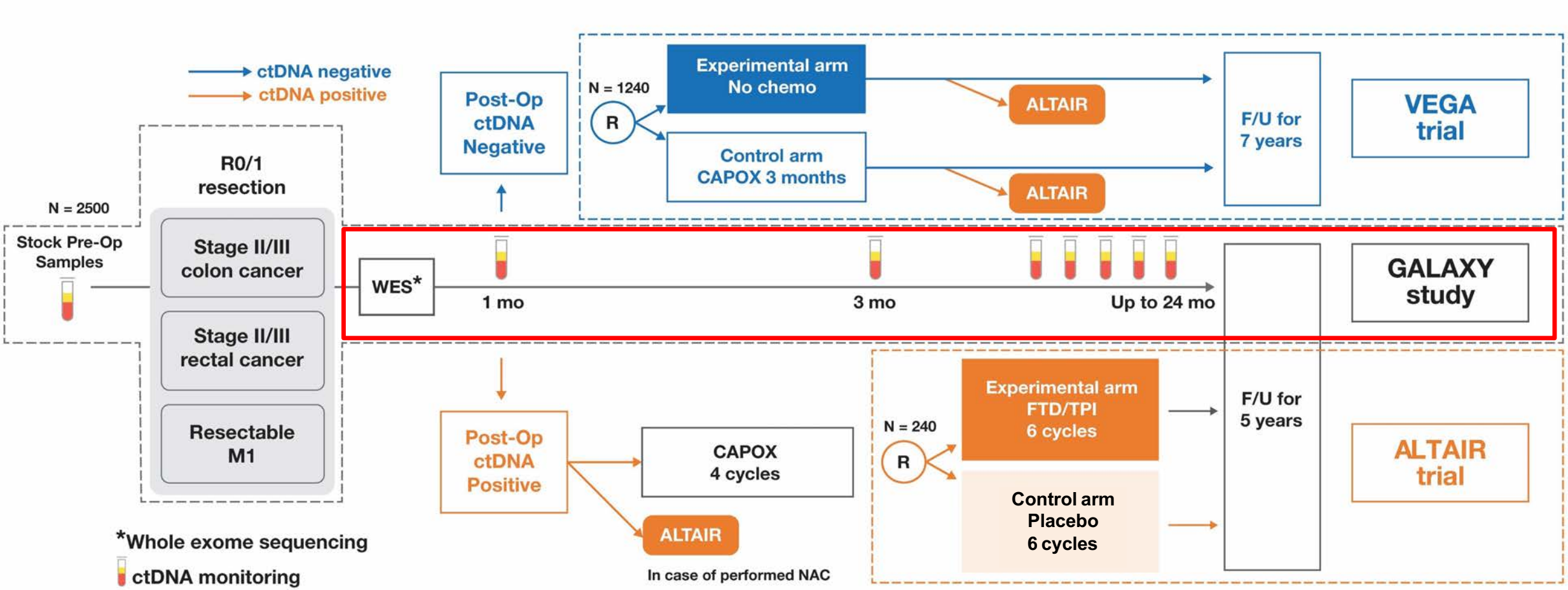
28% standard management arm



Tie J et al. 2022 ASCO Annual Meeting. LBA100.

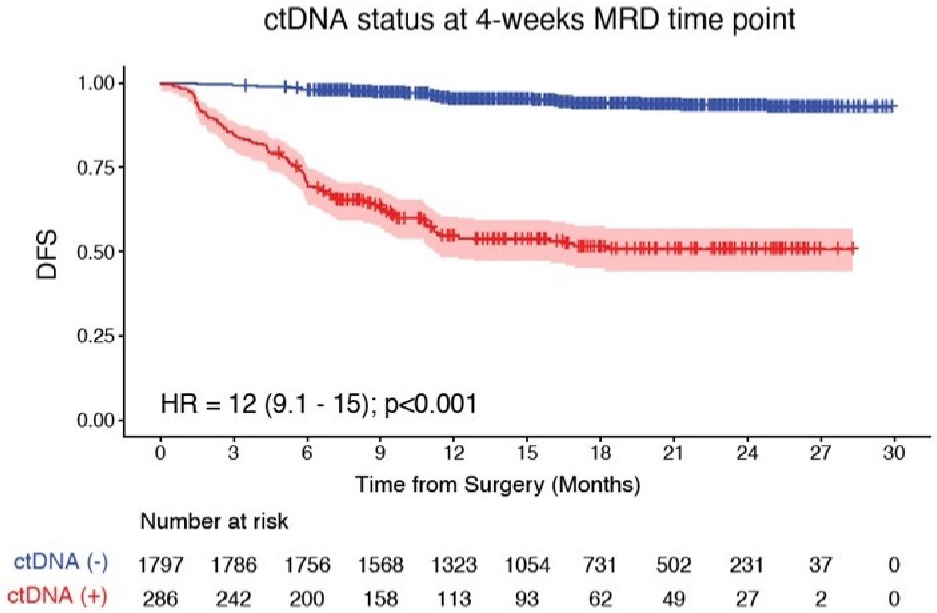
Tie J et al. *N Engl J Med*. 2022;386(24):2261-2272.

CIRCULATE-Japan Overview

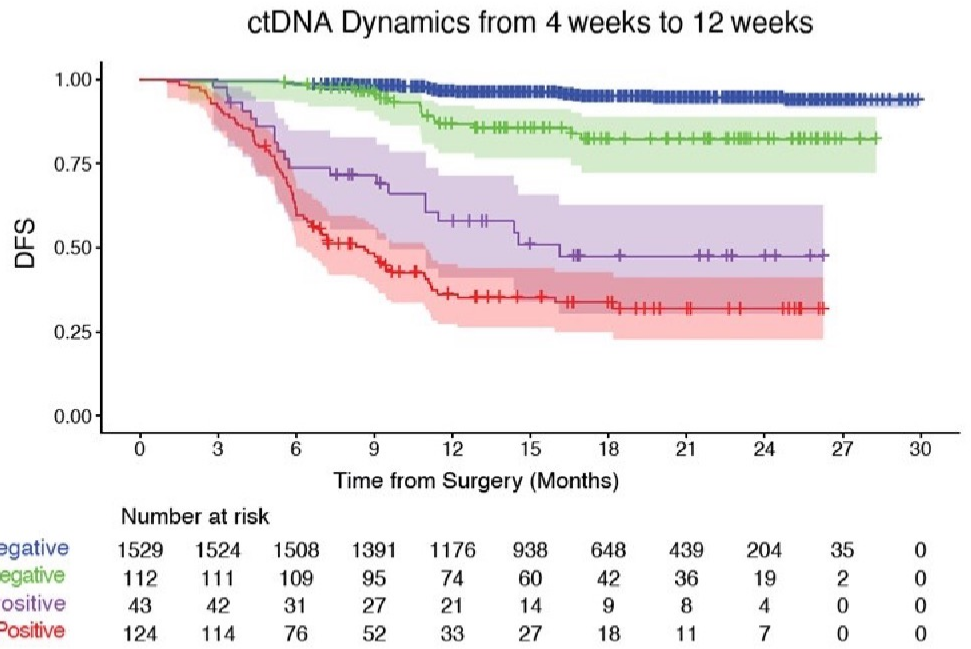


Oki E et al. 2023 ASCO Annual Meeting. Abstract 3521.

ctDNA dynamics between weeks 4 and 12 post surgery is prognostic of DFS



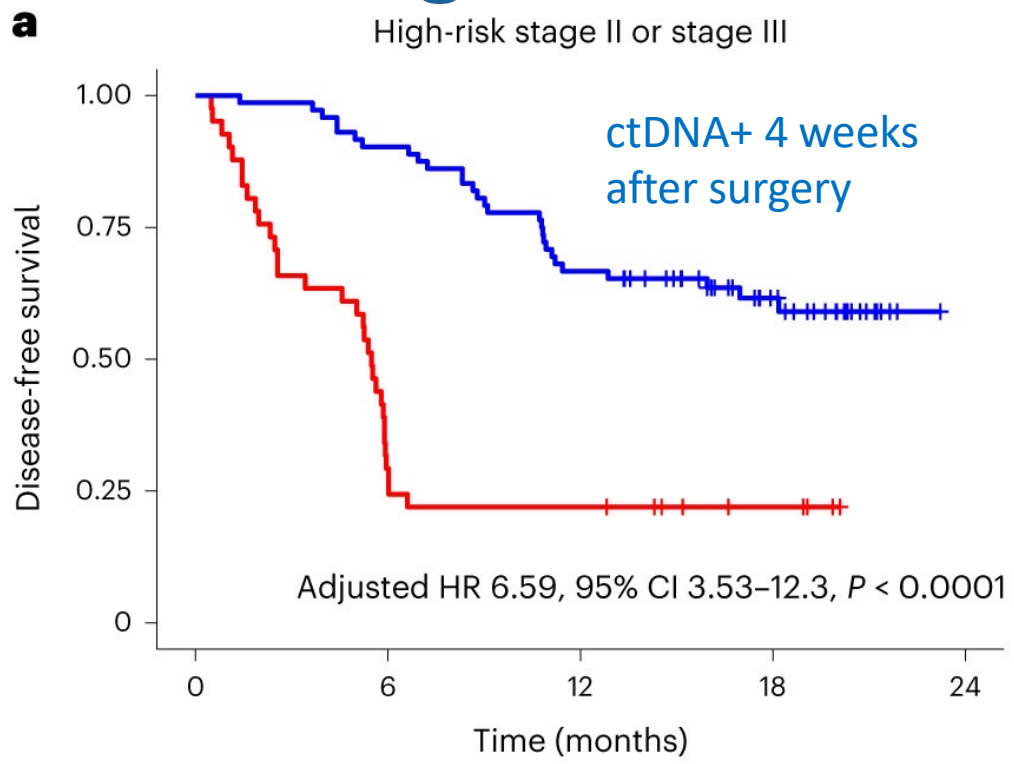
Dynamics	ctDNA Negative	ctDNA Positive
Events (n)	96/1797 (5.3%)	130/286 (45.5%)
18M - DFS	93.9 (92.5 - 95)	51.6 (45.2 - 57.6)
HR	Reference	12
95% CI	Not applicable	9.1 - 15
P	Not applicable	<0.001

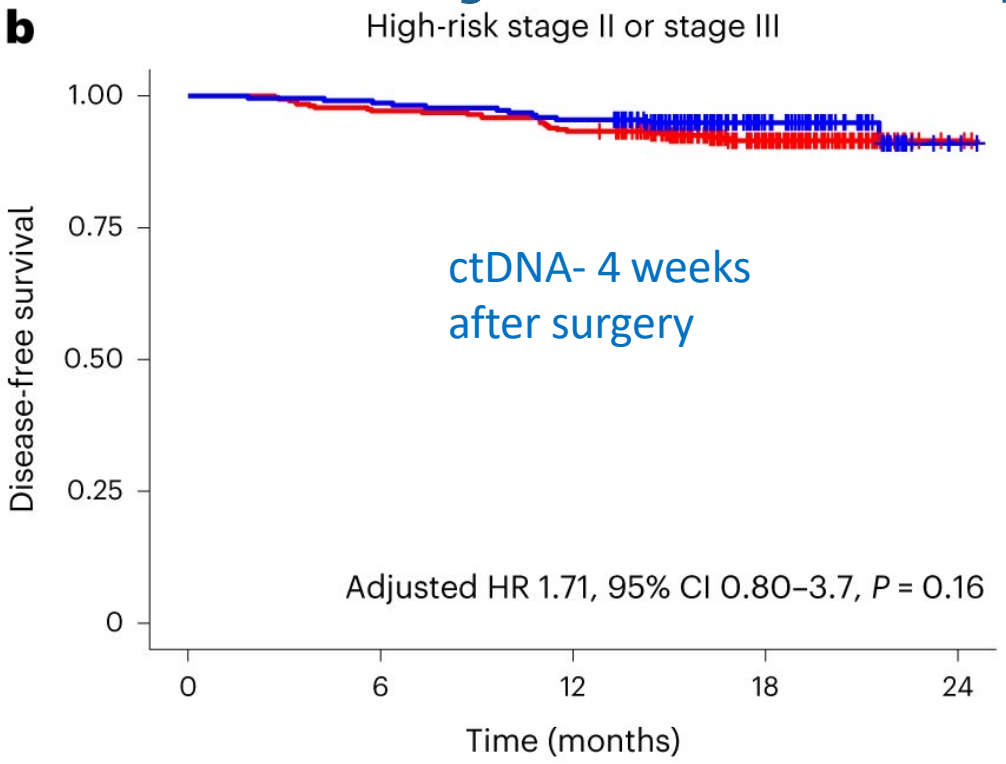


Dynamics	Persistently Negative	Converted Negative	Converted Positive	Persistently Positive
Events (n)	69/1529 (4.5%)	16/112 (14.3%)	20/43 (46.5%)	78/124 (62.9%)
18M - DFS	94.9 (93.5 - 96)	82.2 (72.3 - 88.9)	47.4 (30.4 - 62.7)	33.8 (25 - 42.8)
HR	Reference	3.5	14.5	25.4
95% CI	Not applicable	1.9 - 5.8	8.8 - 23.8	18.3 - 35.3
P	Not applicable	<0.001	<0.001	<0.001

Oki E et al. 2023 ASCO Annual Meeting. Abstract 3521.

ctDNA Testing Predicts Response to Adjuvant Therapy





Number at risk

Observation	41	12	9	4	0
ACT	72	65	48	26	0

Treatment	Number of events	6M-DFS (95% CI)	12M-DFS (95% CI)	18M-DFS (95% CI)
Observation	32 out of 41	29.3% (16.4–43.4)	22.0% (10.9–35.5)	22.0% (10.9–35.5)
ACT	28 out of 72	90.3% (80.7–95.2)	66.7% (54.5–76.3)	61.6% (49.0–71.9)

Number at risk

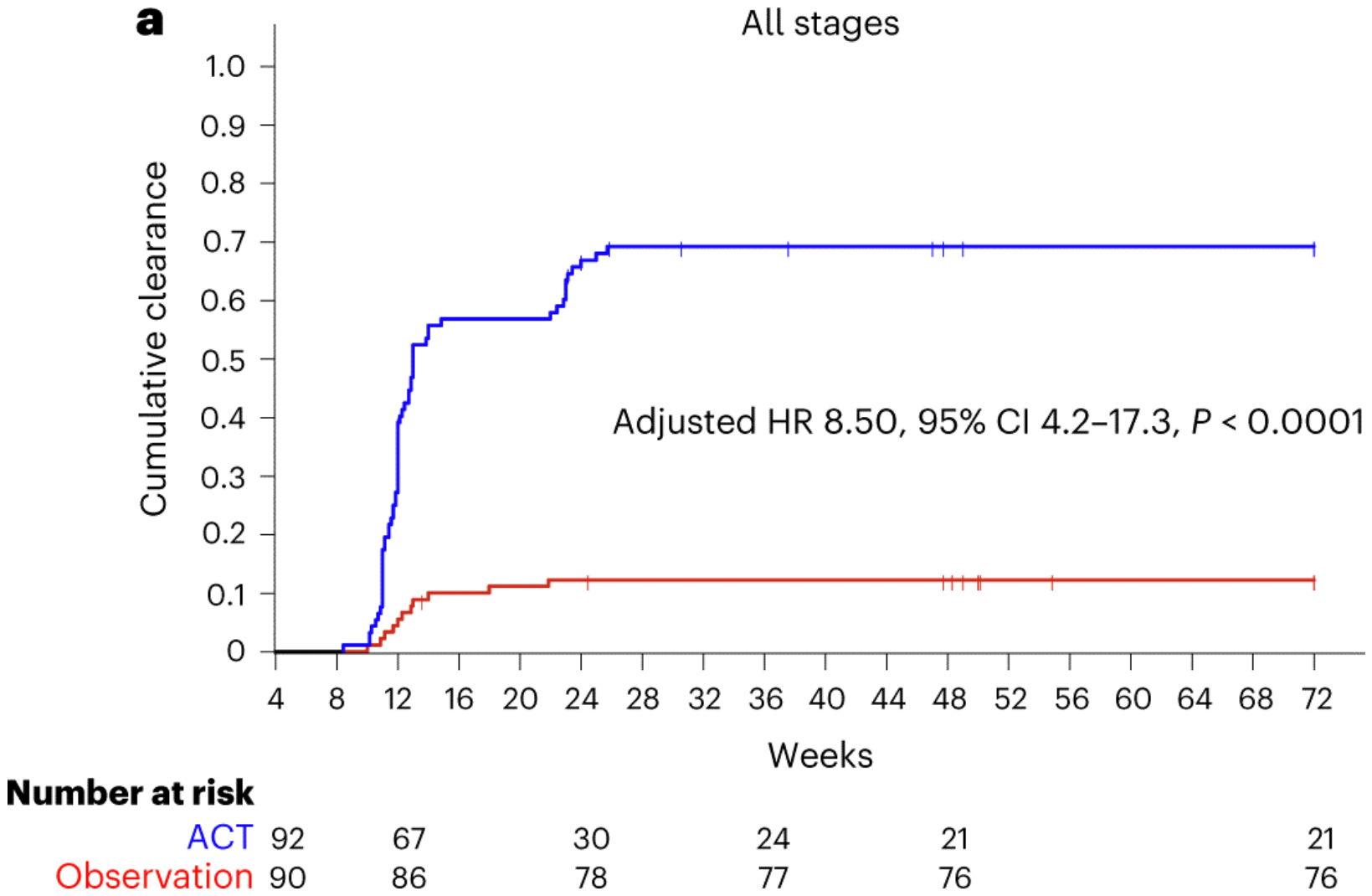
Observation	312	303	291	131	2
ACT	219	216	209	87	2

Treatment	Number of events	6M-DFS (95% CI)	12M-DFS (95% CI)	18M-DFS (95% CI)
Observation	25 out of 312	97.1% (94.5–98.5)	93.3% (89.9–95.6)	91.5% (87.6–94.2)
ACT	12 out of 219	98.6% (95.8–99.6)	95.4% (91.7–97.5)	94.9% (91.0–97.2)

Kotani D et al. *Nat Med.* 2023;29(1):127-134.

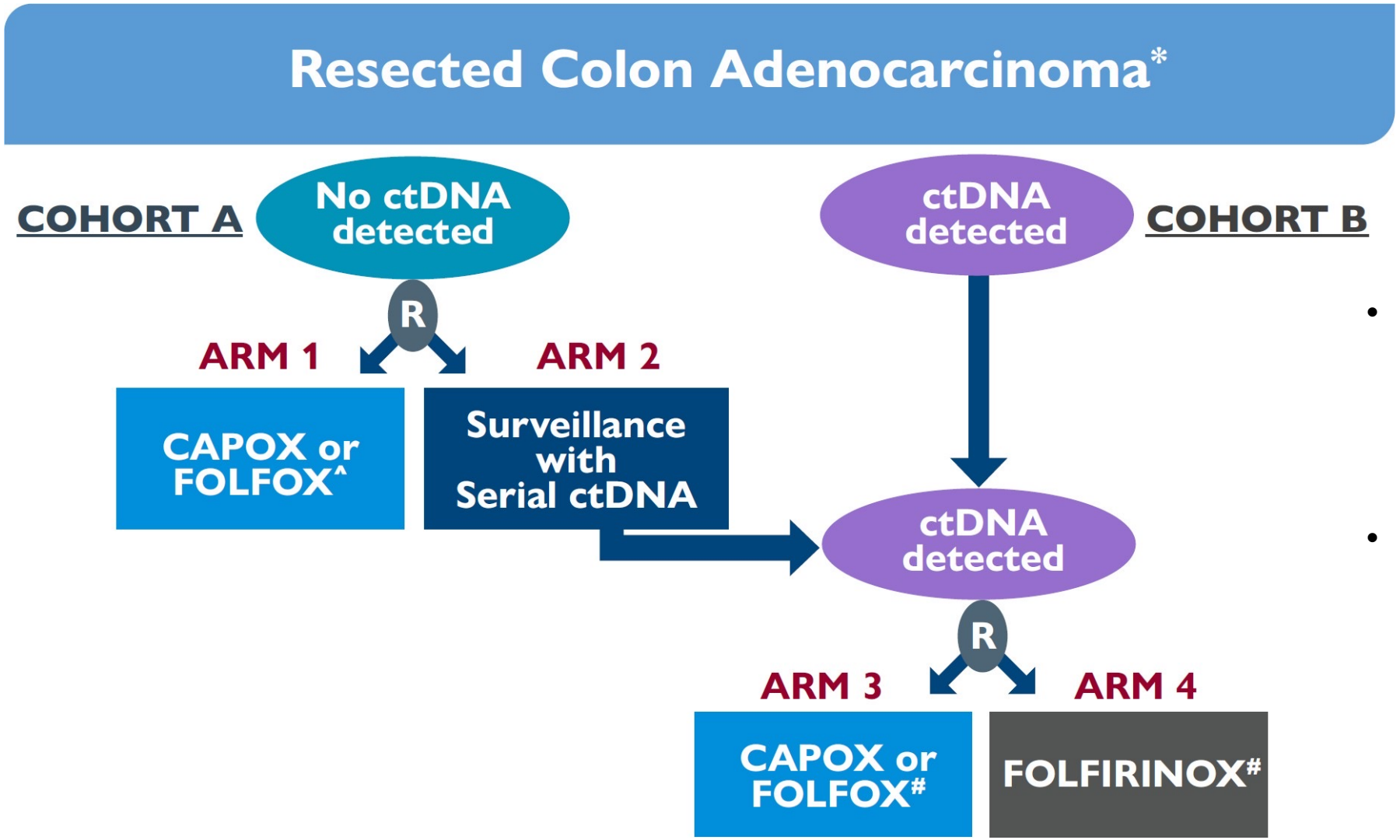
ctDNA clearance rate (stages I-IV)

68% with adjuvant chemotherapy versus 12% without



Kotani D et al. *Nat Med.* 2023;29(1):127-134.

CIRCULATE North America: Stage III Colon Cancer Study
Amended Schema

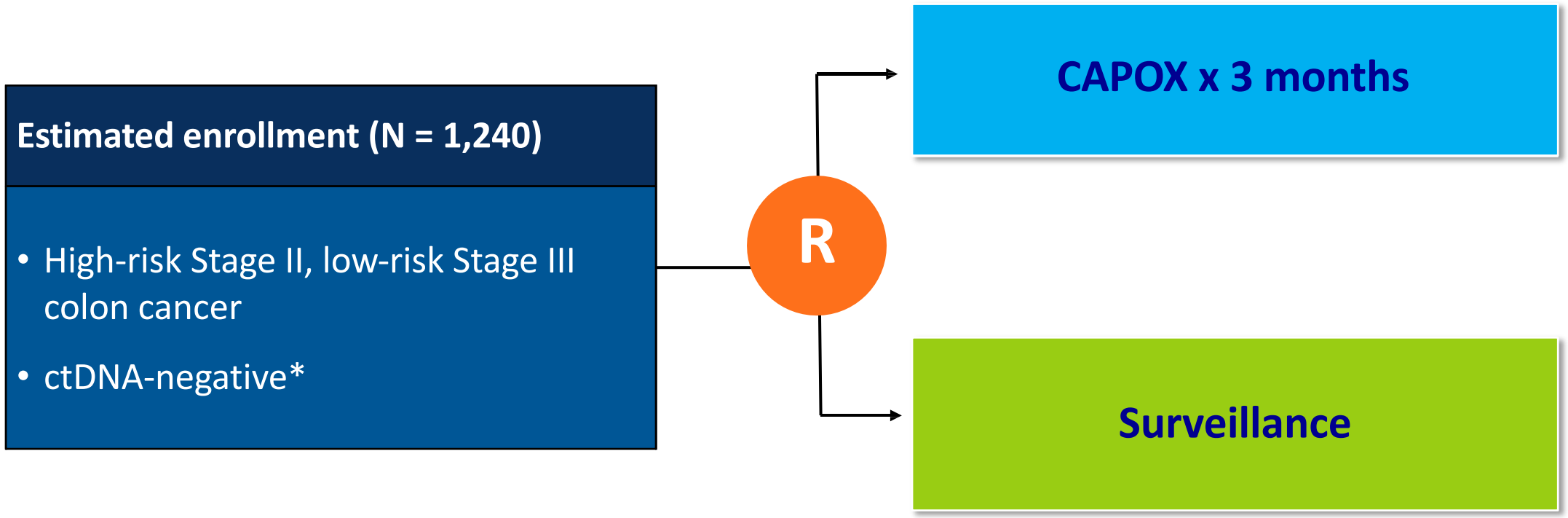


- Study population amended to include <u>all</u> patients with Stage IIB, IIC, and Stage III colon adenocarcinoma
- One dose of chemotherapy allowed while awaiting Step 2 randomization

PIs: Dasari and Lieu (NRG-GI008 – NCT0517416)

NRG ONCOLOGY™

VEGA Phase III Study Schema



*** Patients to be enrolled in the ALTAIR study if ctDNA becomes positive at 3 months**

Naidoo M et al. *Cancers* 2021;13(2):346.

ALTAIR Phase III Study Schema in the CIRCULATE Platform

- Colorectal adenocarcinoma
- After curative resection
- Prior adjuvant systemic therapy if applicable
- Age ≥ 20
- Informed consent

ctDNA Monitoring

signatera

ctDNA Positive

N=240

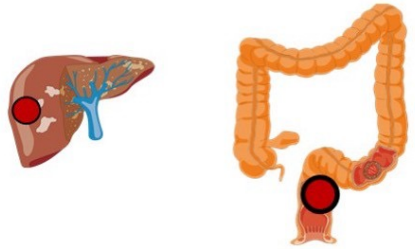
R

Monitoring by ctDNA and CT imaging for every 2 months

Control arm
Placebo
6 cycles

Experimental arm
FTD/TPI
6 cycles

F/U for 3 years



Stratification factors:

Age (>70 / ≥70), Institution, Stage (≤Stage II / Stage III / M1)

Primary site (Right colon / Left colon / Rectum)

ctDNA status at 1 month postoperatively (positive / negative or unmeasurable)

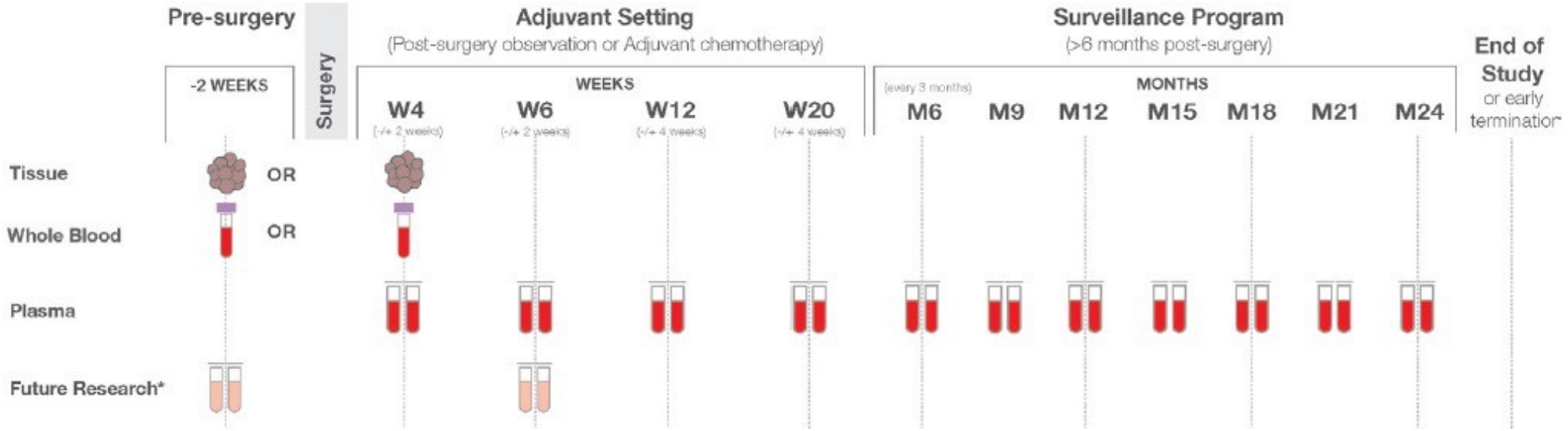
Primary Endpoint: DFS
Secondary Endpoints: ctDNA clearance rate, OS, Others

Shirasu H et al. Gastrointestinal Cancers Symposium 2022;Abstract TPS215.

BESPOKE CRC: A Prospective, Case-Controlled Observational Study

Estimated enrollment (N = 2,000)

- Stage I-IV CRC or Stage IV CRC with oligometastatic disease eligible for post-operative systemic therapy



NCT04264702 Kasi PM et al. *BMJ Open* 2021;11:e047831.

Take Home Points:

- Stage II Colon Cancer:
  - ctDNA may be ready for primetime for low-risk stage II colon cancer
    - *If ctDNA is positive, who would not offer adjuvant chemotherapy?*

- Stage III Colon Cancer:
  - Adjuvant chemotherapy can clear ctDNA and outcomes appear improved in patients with negative ctDNA
  - Ongoing studies are critically needed to determine if ctDNA can be used to guide the management of patients with stage III colon cancer

MODULE 3: Identification and Clinical Care of Patients with mCRC and a BRAF V600E Mutation – Dr Bekaii-Saab

RTP
RESEARCH
TO PRACTICE

Treatment of BRAF mutation-positive mCRC

Arvind N Dasari, MD, MS

Kristen K Ciombor, MD, MSCI

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Arvind N Dasari, MD, MS

Kristen K Ciombor, MD, MSCI

What is your preferred first-line therapy for patients with mCRC and BRAF V600E mutations, and do you ever offer up-front targeted therapy?

Are there any situations in which you prefer triplet (eg, encorafenib/binimetinib/EGFR antibody) over doublet (eg, encorafenib/EGFR antibody) targeted therapy for patients with mCRC and BRAF V600E mutations?

How often do you see patients with atypical BRAF mutations, and how do you approach their treatment?

RTP RESEARCH TO PRACTICE

Experience with BRAF-targeted therapy as first-line treatment for mCRC

Kristen K Ciombor, MD, MSCI

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Kristen K Ciombor, MD, MSCI

Would you offer up-front targeted therapy to an older patient with comorbidities and BRAF-mutant mCRC who was not a candidate for chemotherapy?

What are the key tolerability issues with encorafenib/EGFR antibody therapy?

Regulatory and reimbursement issues aside, for a patient with pan-RAS wild-type mCRC with a BRAF V600E mutation, in which line of therapy would you generally administer BRAF-targeted therapy?

 Dr Bekaii-Saab	Second
 Dr Cercek	Second
 Dr Eng	Second
 Dr Lieu	Second
 Dr Strickler	Second
 Dr Ciombor	Second
 Dr Dasari	Second

RTP RESEARCH TO PRACTICE

Have you administered or would you administer a BRAF inhibitor in combination with an EGFR antibody as first-line therapy for a patient with mCRC with a BRAF V600E mutation who could not tolerate or did not wish to receive chemotherapy?

 Dr Bekaii-Saab	I have
 Dr Cercek	I have not but would for the right patient
 Dr Eng	I have not but would for the right patient
 Dr Lieu	I have
 Dr Strickler	I have not but would for the right patient
 Dr Ciombor	I have not but would for the right patient
 Dr Dasari	I have

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, for a patient with mCRC with a BRAF V600E mutation to whom you would administer BRAF-targeted therapy, what would be your preferred treatment?

 Dr Bekaii-Saab	Encorafenib/cetuximab
 Dr Cercek	Encorafenib/panitumumab
 Dr Eng	Encorafenib + EGFR antibody
 Dr Lieu	Encorafenib/cetuximab
 Dr Strickler	Encorafenib/panitumumab
 Dr Ciombor	Encorafenib/panitumumab
 Dr Dasari	Encorafenib/cetuximab

Based on currently available data and/or your own clinical experience, which subsets of patients with mCRC with a BRAF V600E mutation, if any, might derive greater benefit from triplet (eg, encorafenib/binimetinib/EGFR antibody) than from doublet (eg, encorafenib/EGFR antibody) targeted therapy?

 Dr Bekaii-Saab	None
 Dr Cercek	None
 Dr Eng	None
 Dr Lieu	In patients needing a response, either for palliation or for possible resection
 Dr Strickler	To my knowledge there is no patient subpopulation that derives greater benefit from the triplet compared to the doublet
 Dr Ciombor	Unclear – I wonder if adding a MEK inhibitor would help overcome developing resistance to anti-EGFR/BRAF but no data here
 Dr Dasari	Have not used triplet or a MEK inhibitor for mCRC outside of clinical trial

What is the longest duration of response that you have observed in a patient with mCRC with a BRAF V600E mutation who received doublet therapy with encorafenib and an EGFR inhibitor?

 Dr Bekaii-Saab	14 months
 Dr Cercek	22 months
 Dr Eng	4 months
 Dr Lieu	12 months
 Dr Strickler	8 months
 Dr Ciombor	24 months
 Dr Dasari	14 months

What other BRAF mutations, beyond V600E, have you observed in your patients with mCRC?

 Dr Bekaii-Saab	Multiple non-V600E
 Dr Cercek	All the others
 Dr Eng	Cannot recall
 Dr Lieu	G469A, G469V, L597R
 Dr Strickler	Non-V600E BRAF mutations are seen with regularity
 Dr Ciombor	D594, G469
 Dr Dasari	D594G, D594N, G466V, G469A

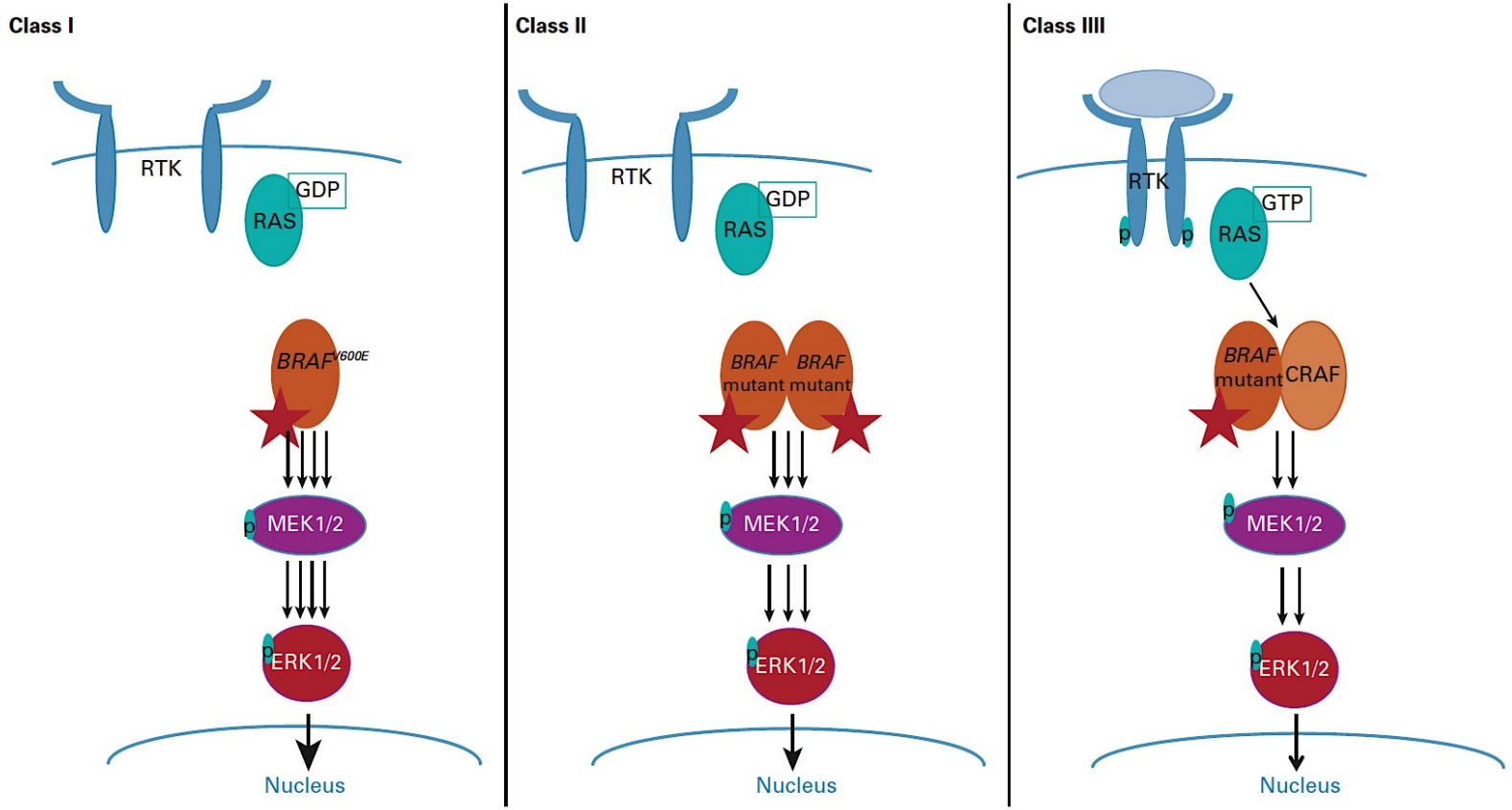
RTP RESEARCH TO PRACTICE

Identification and Management of Patients with mCRC and a BRAF V600E Mutation

Tanios Bekaii-Saab, MD
Professor , Mayo Clinic College of Medicine and Science
Chair , Hematology and Medical Oncology
Consultant, Mayo Clinic AZ

Characteristics of Classes of BRAF Mutations

BRAF-Mutant Class	Alterations
Class I	V600E/K/D/R/M
Class II	P367L/S G464V/E G469A/V/R L485F/W N486_A489delinsK N486_P490del L525R E586K L597Q/R/S/V T599I/K/TT/TS K601E/N/T K601_S602delinsNT BRAF kinase duplication Fusions of the BRAF kinase domain
Class III	F247L D287H T310I E451K V459L G466A/E/V S467L G469E R558Q N581I/S/T D594A/G/H/N F595L G596D/R



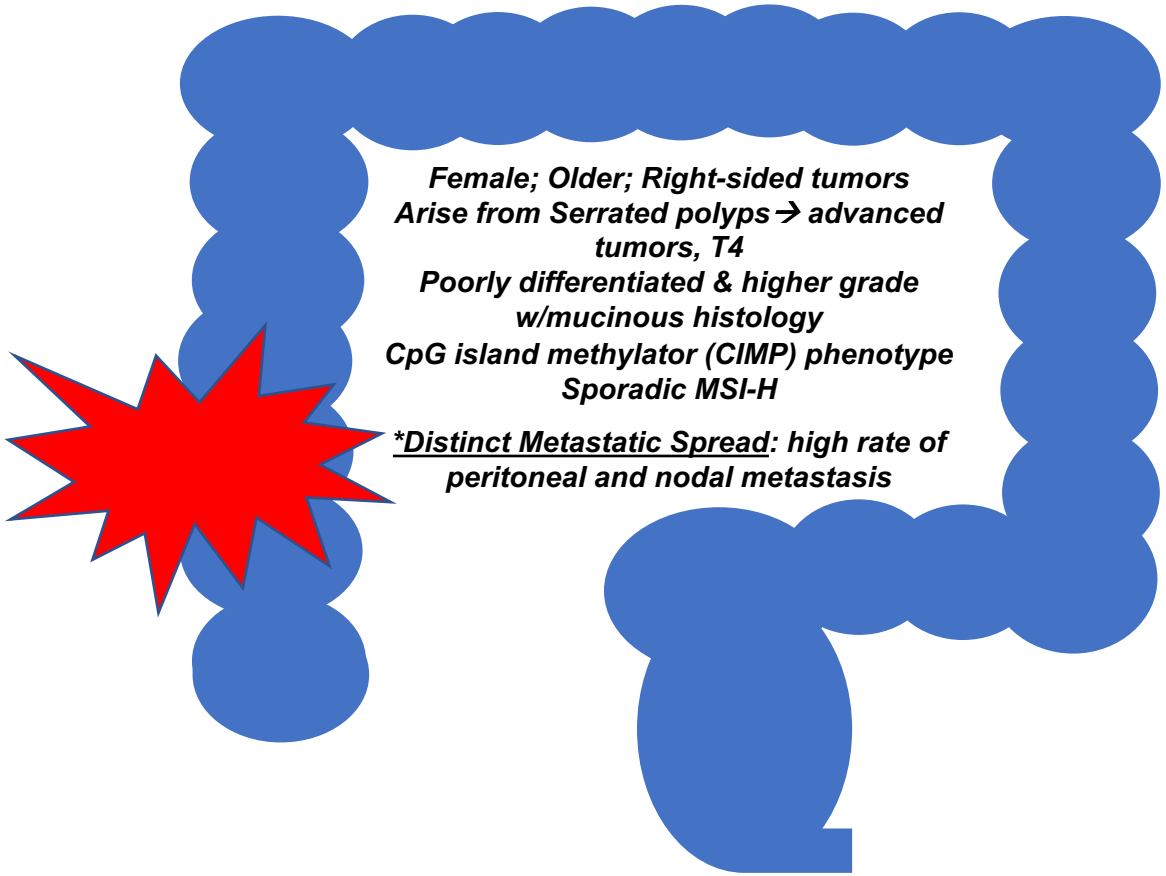
Signal as constitutively active monomers

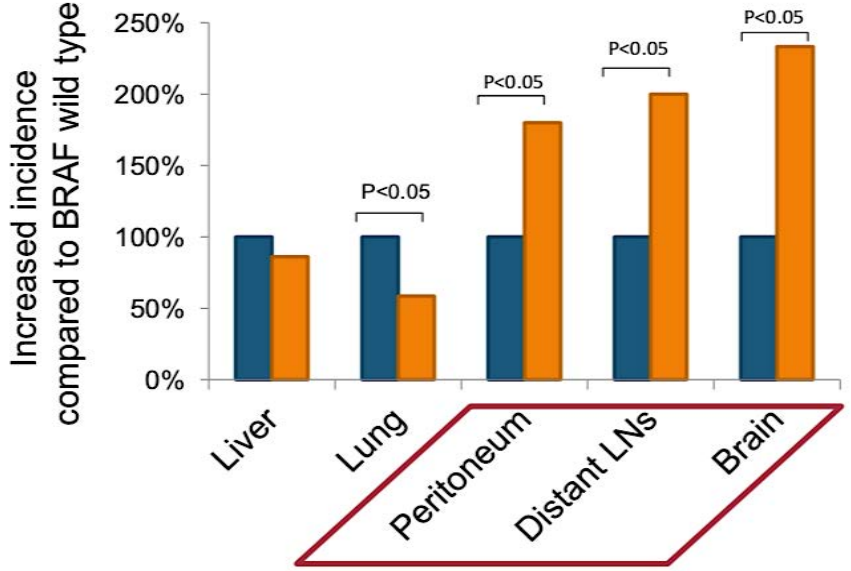
Signal as constitutively activated mutant dimers

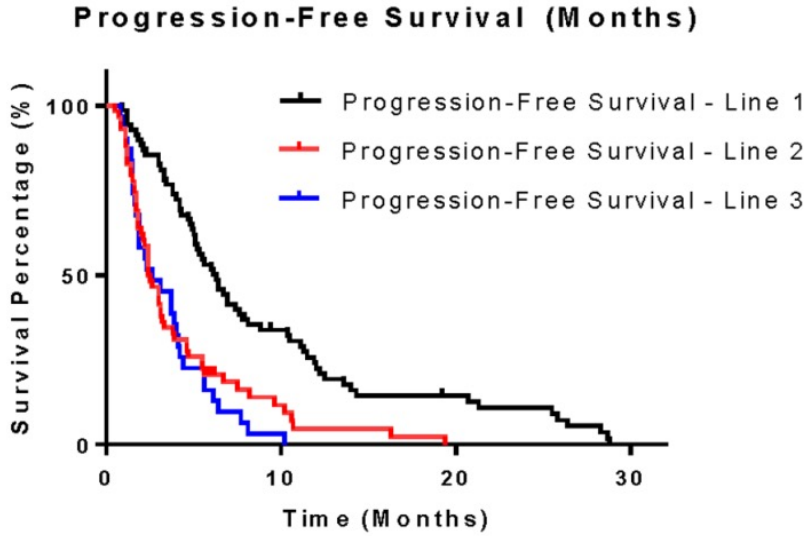
Amplify signal by binding tightly to RAS and CRAF

Ciombor KK et al. *J Clin Oncol* 2022;40:2706-15.

BRAF^{V600E} mCRC: Unique Clinical & Pathologic Features

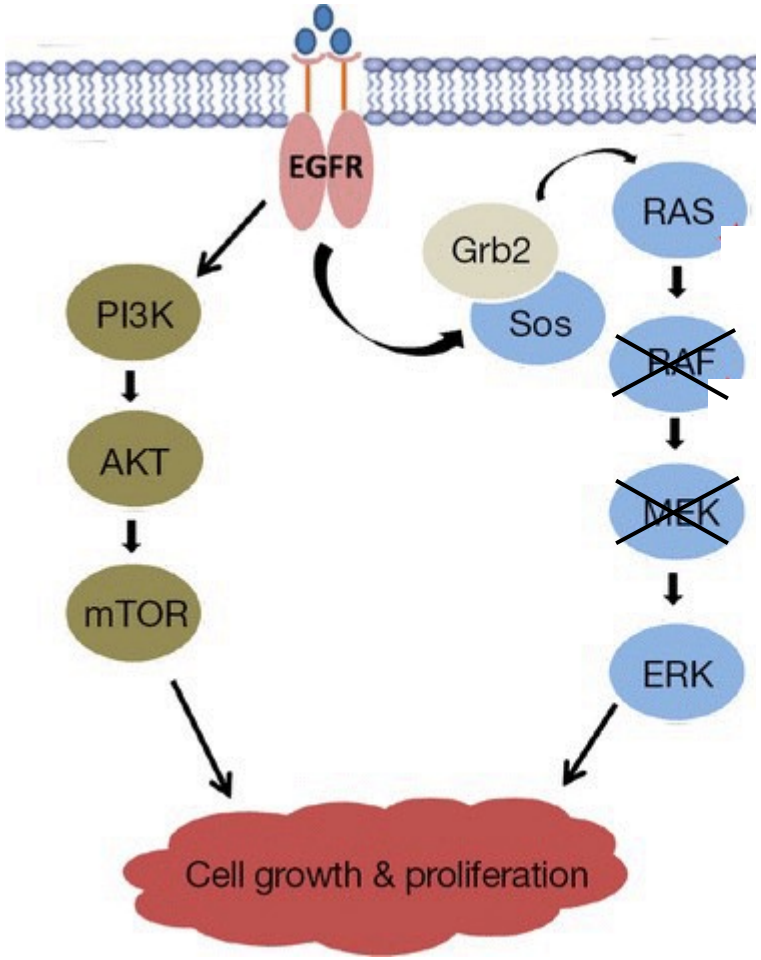






Tie J, et al. *Int J Canc*. 2010
Tran B, et al. *Cancer*. 2011;117:4623-32
Morris VK, et al. *Clin Colorectal Cancer.* 2014

BRAF^{V600E} as a Therapeutic Target in Cancer



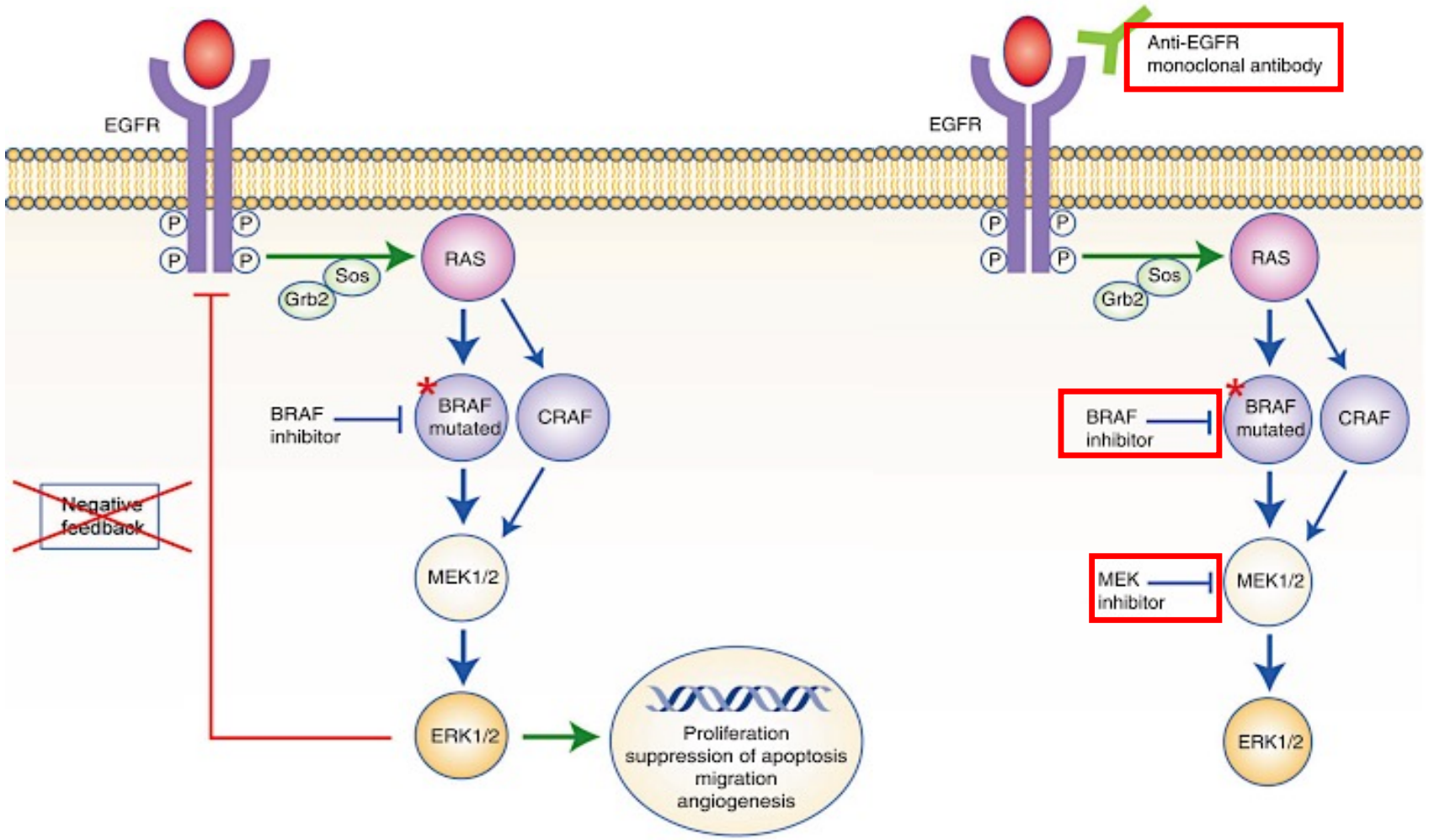
- **Activated *BRAF* perpetuates MAPK activity, leading to cell cycle progression and tumor cell proliferation**
- **Single Agent *BRAF* inhibitors have activity in:**
  - Melanoma (RR 34-53%)
  - NSCLC (RR 42%) *~5% CRC*
  - Papillary thyroid cancer (RR 29%)
  - Refr. hairy cell leukemia (RR 85-100%)
- ***BRAF* + MEK targeted therapies have activity in:**
  - metastatic melanoma (RR 64-69%)
  - metastatic NSCLC (RR 63%)
  - anaplastic thyroid cancer (RR 69%)
  - low grade gliomas (69%)
  - cholangiocarcinoma (50%)

  ~10% CRC

In 131 patients from 3 basket studies, 41% RR with dabrafenib and trametinib

MacArthur, et al. *Lancet Oncol*. 2014; Ribas, et al. *Lancet Oncol*. 2014; Falchook, et al. *Thyroid*. 2015; Tiacci, et al. *NEJM*. 2015; Hyman, et al. *NEJM*. 2015; Gandara, et al. AILCC 2017.

Co-targeting EGFR overcomes resistance to BRAF +/- MEK inhibitors



Adapted from Taieb J et al, Br J Cancer. 2019;121:434-442.

Completed Trials in BRAF V600E Mutant mCRC

TABLE 2. Key Completed Clinical Trials for *BRAF*^{V600E}-Mutant Metastatic Colorectal Cancer

Name/ClinicalTrials.gov Identifier	Study Design	Line of Therapy	Agents Investigated	Key Eligibility	Key Efficacy Outcomes
NCT00405587[41]	Phase II	2L+	Vemurafenib	*BRAF*^{V600E} mutation, *RAS* WT	ORR 4.8%, mPFS 2.1 months, mOS 7.7 months
NCT01072175[42]	Phase I/II	1L+	Dabrafenib plus trametinib	*BRAF*^{V600E} mutation	ORR 11.6%, mPFS 3.5 months
NCT04790448[44]	Phase Ib	2L+	VIC	*BRAF*^{V600E} mutation, *KRAS/NRAS* WT	ORR 35.3%, mPFS 7.7 months
SWOG 1406/ NCT02164916[45]	Phase II	2L, 3L	VIC *v* IC	*BRAF*^{V600E} mutation, *NRAS/KRAS* WT	VIC: ORR 17%, mPFS 4.2 months IC: ORR 4%, mPFS 2.0 months
FIRE 4.5 (AIO KRK-0116)/ NCT04034459[40]	Phase II	1L	FOLFOXIRI plus bevacizumab (arm A) *v* FOLFOXIRI plus cetuximab (arm B)	*BRAF*^{V600E} mutation, *RAS* WT	Arm A: ORR 66.7%, mPFS ATP 10.1 months, mOS 17.1 months Arm B: ORR 52.0%, mPFS ATP 6.3 months, mOS 15.2 months
BEACON CRC/ NCT02928224[46]	Phase III	2L, 3L	Binimetinib plus encorafenib plus cetuximab (triplet) *v* encorafenib plus cetuximab (doublet) *v* investigator's choice (cetuximab plus irinotecan or cetuximab plus FOLFIRI; control)	*BRAF*^{V600E} mutation	Triplet: ORR 26.8%, mPFS 4.5 months, mOS 9.3 months Doublet: ORR 19.5%, mPFS 4.3 months, mOS 9.3 months Control: ORR 1.8%, mPFS 1.5 months, mOS 5.9 months
ANCHOR/ NCT03693170[48]	Phase II	1L	Binimetinib plus encorafenib plus cetuximab	*BRAF*^{V600E} mutation	ORR 47.8%, mPFS 5.8 months, mOS 17.2 months

Abbreviations: ATP, according to protocol; FOLFIRI, fluorouracil, leucovorin, and irinotecan; FOLFOXIRI, fluorouracil, leucovorin, oxaliplatin, and irinotecan; IC, irinotecan plus cetuximab; mCRC, metastatic colorectal cancer; mOS, median overall survival; mPFS, median progression-free survival; ORR, objective response rate; VIC, vemurafenib plus cetuximab plus irinotecan; WT, wild-type.

Ciombor K, Bekaii-Saab *et al.,* JCO 2022

BEACON CRC: Phase 3 in 2nd/ 3rd Line *BRAF* V600E mut mCRC

Patients with *BRAF*^{V600E} mCRC with disease progression after 1 or 2 prior regimens; ECOG PS of 0 or 1; and no prior treatment with any RAF inhibitor, MEK inhibitor, or EGFR inhibitor

ENCORAFENIB + BINIMETINIB + CETUXIMAB
N = 30

Encorafenib 300 mg PO daily
Binimetinib 45 mg PO bid
Cetuximab standard weekly dosing

R 1:1:1

Triplet therapy
ENCORAFENIB + BINIMETINIB + CETUXIMAB
n = 205

Doublet therapy
ENCORAFENIB + CETUXIMAB
n = 205

Control arm
FOLFIRI + CETUXIMAB, or irinotecan + CETUXIMAB
n = 205

Primary Endpoints:

Triplet vs Control

OS
(All randomized Pts)

ORR – Blinded Central Review
(1st 331 randomized Pts)

Randomization was stratified by ECOG PS (0 vs. 1), prior use of irinotecan (yes vs. no), and cetuximab source (US-licensed vs. EU-approved)

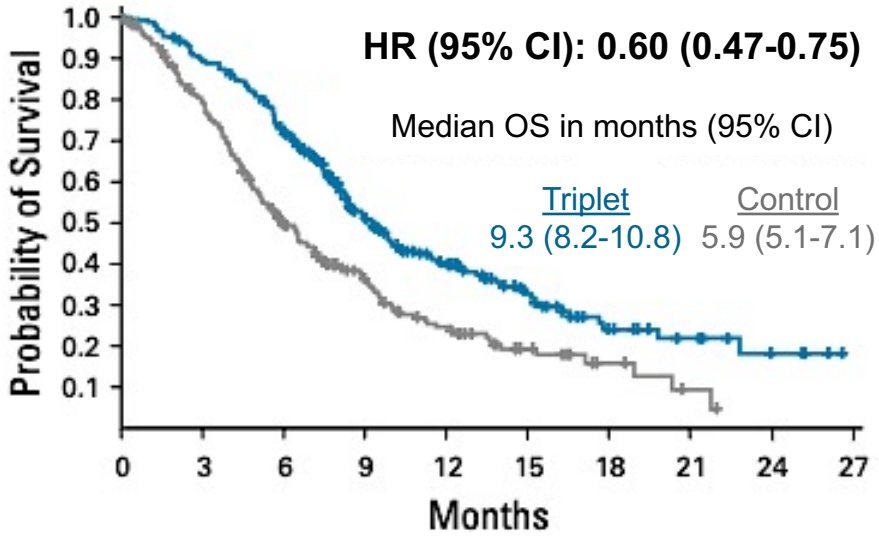
Secondary Endpoints: Doublet vs Control and Triplet vs Doublet - OS & ORR, PFS, Safety

QOL Assessments: EORTC QOL Questionnaire (QLQ C30), Functional Assessment of Cancer Therapy Colon Cancer, EuroQol 5D5L, and Patient Global Impression of Change).

Kopetz et al., NEJM 2019

BEACON CRC: Overall Survival and Objective Response Rate

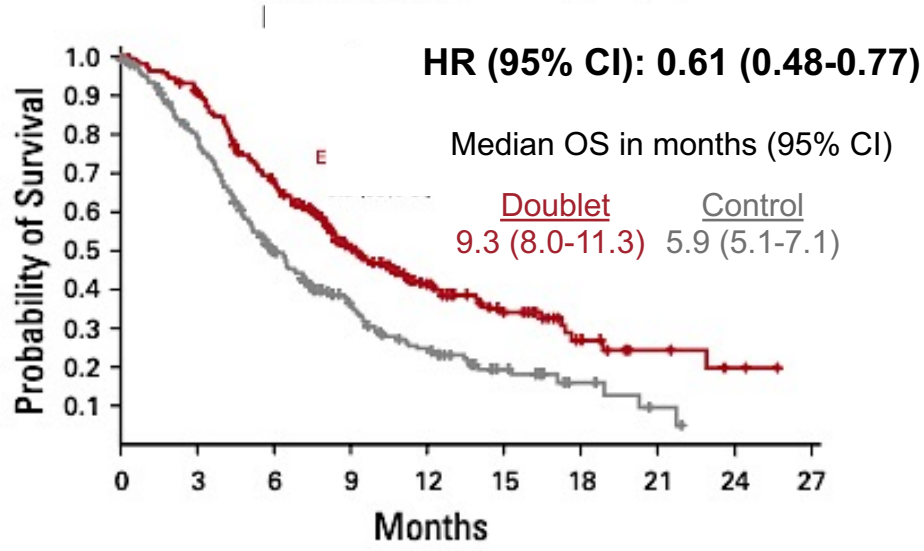
Triplet vs Control



Number of patients at risk

ENCO/BINI/CETUX	224	198	157	89	56	33	15	9	4	0
Control	221	166	98	54	33	15	6	2	0	0

Doublet vs Control



Number of patients at risk

ENCO/CETUX	220	197	143	83	47	28	13	7	2	0
Control	221	166	98	54	33	15	6	2	0	0

Objective Response Rate (first 331 randomized patients)

Confirmed Response by BICR	Triplet N = 111	Doublet N = 113	Control N = 107
Objective response rate	**26%**	**20%**	**2%**
(95% CI)	(18–35)	(13–29)	(<1–7)
P value vs control	<.0001	<.0001	

Tabernero J, Grothey A, et al. JCO 2021; Kopetz S, Grothey A, et al. *N Engl J Med*. 2019;381:1632-1643.

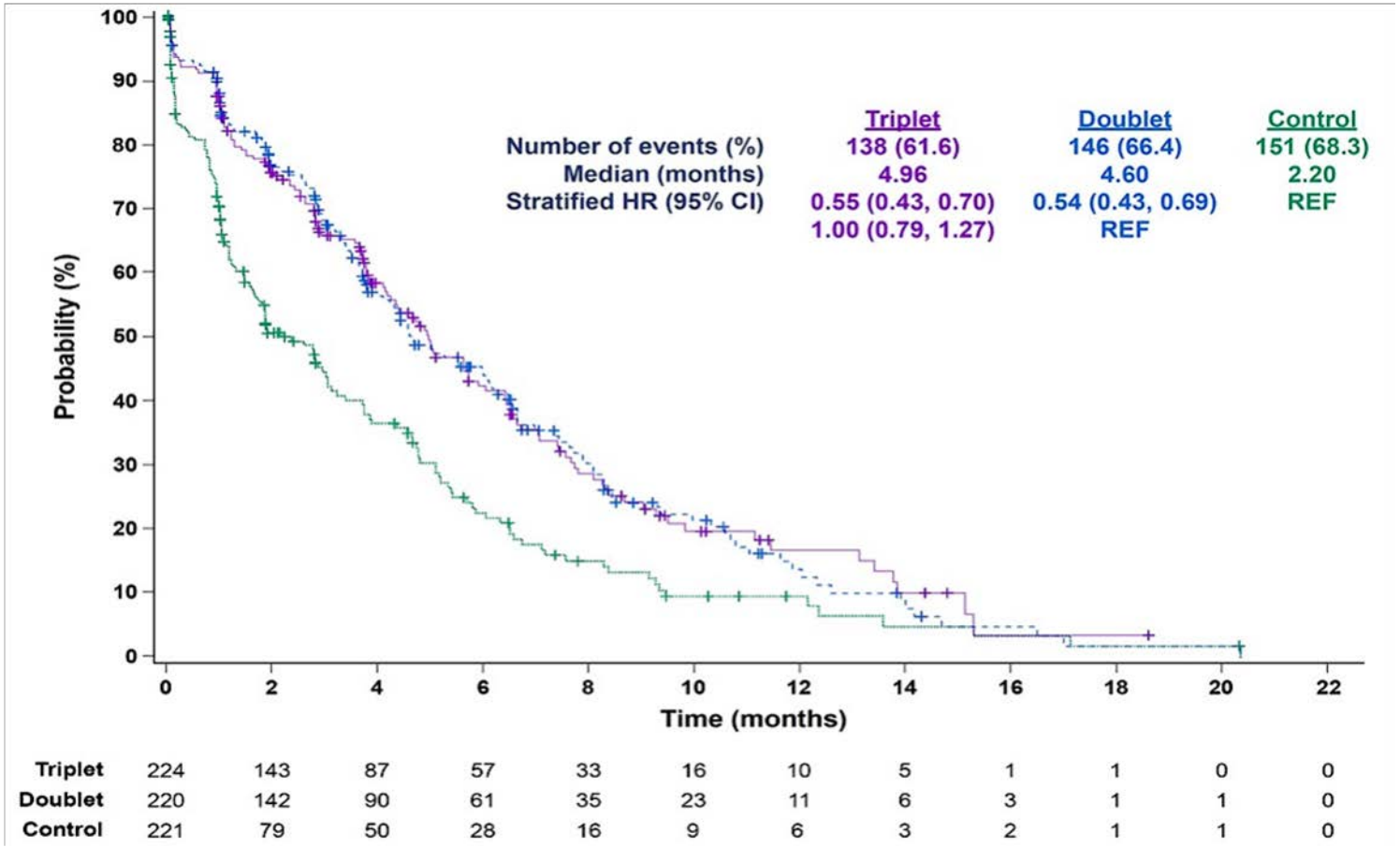
BEACON CRC: Adverse Events

Variable	Triplet Regimen (N=222)		Doublet Regimen (N=216)		Control (N=193)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)					
Adverse events						
Any adverse event	217 (98)	128 (58)	212 (98)	108 (50)	188 (97)	117 (61)
Diarrhea	137 (62)	22 (10)	72 (33)	4 (2)	93 (48)	19 (10)
Acneiform dermatitis	108 (49)	5 (2)	63 (29)	1 (<1)	76 (39)	5 (3)
Nausea	100 (45)	10 (5)	74 (34)	1 (<1)	80 (41)	2 (1)
Vomiting	85 (38)	9 (4)	46 (21)	3 (1)	56 (29)	5 (3)
Fatigue	73 (33)	5 (2)	65 (30)	9 (4)	53 (27)	8 (4)
Abdominal pain	65 (29)	13 (6)	49 (23)	5 (2)	48 (25)	9 (5)
Decreased appetite	63 (28)	4 (2)	58 (27)	3 (1)	52 (27)	6 (3)
Asthenia	55 (25)	7 (3)	46 (21)	7 (3)	49 (25)	9 (5)
Constipation	55 (25)	0	33 (15)	0	35 (18)	2 (1)
Dry skin	46 (21)	2 (1)	24 (11)	0	13 (7)	1 (1)
Pyrexia	45 (20)	4 (2)	35 (16)	2 (1)	27 (14)	1 (1)
Rash	42 (19)	1 (<1)	25 (12)	0	27 (14)	3 (2)
Stomatitis	31 (14)	1 (<1)	12 (6)	0	44 (23)	4 (2)
Palmar–plantar erythrodysesthesia syndrome	28 (13)	0	9 (4)	1 (<1)	14 (7)	0
Pruritus	28 (13)	0	20 (9)	0	9 (5)	0
Back pain	25 (11)	2 (1)	22 (10)	2 (1)	23 (12)	2 (1)
Blurred vision	25 (11)	0	8 (4)	0	1 (1)	0
Peripheral edema	24 (11)	1 (<1)	18 (8)	0	13 (7)	1 (1)
Weight decreased	24 (11)	1 (<1)	21 (10)	1 (<1)	11 (6)	0
Arthralgia	23 (10)	0	41 (19)	2 (1)	1 (1)	0
Cough	23 (10)	0	16 (7)	1 (<1)	10 (5)	0
Myalgia	18 (8)	0	29 (13)	1 (<1)	4 (2)	0
Dyspnea	17 (8)	2 (1)	23 (11)	2 (1)	17 (9)	5 (3)
Headache	16 (7)	0	42 (19)	0	5 (3)	0
Pain in extremity	15 (7)	0	22 (10)	0	1 (1)	0
Insomnia	11 (5)	0	24 (11)	0	11 (6)	0
Musculoskeletal pain	6 (3)	0	27 (12)	0	3 (2)	0
Melanocytic nevus	1 (<1)	0	31 (14)	0	0	0
Abnormal laboratory values						
Alanine aminotransferase	51 (23)	4 (2)	36 (17)	0	50 (26)	5 (3)
Aspartate aminotransferase	50 (23)	4 (2)	31 (14)	3 (1)	38 (20)	3 (2)
Bilirubin	12 (5)	5 (2)	16 (7)	5 (2)	16 (8)	6 (3)
Creatine kinase	52 (23)	6 (3)	6 (3)	0	13 (7)	0
Creatinine	166 (75)	10 (5)	109 (50)	5 (2)	65 (34)	2 (1)
Hemoglobin	125 (56)	24 (11)	70 (32)	9 (4)	85 (44)	8 (4)

Kopetz S, et al. *N Engl J Med.* 2019;381:1632-1643.

Maintenance of Quality of Life: EORTC QLQ-C30

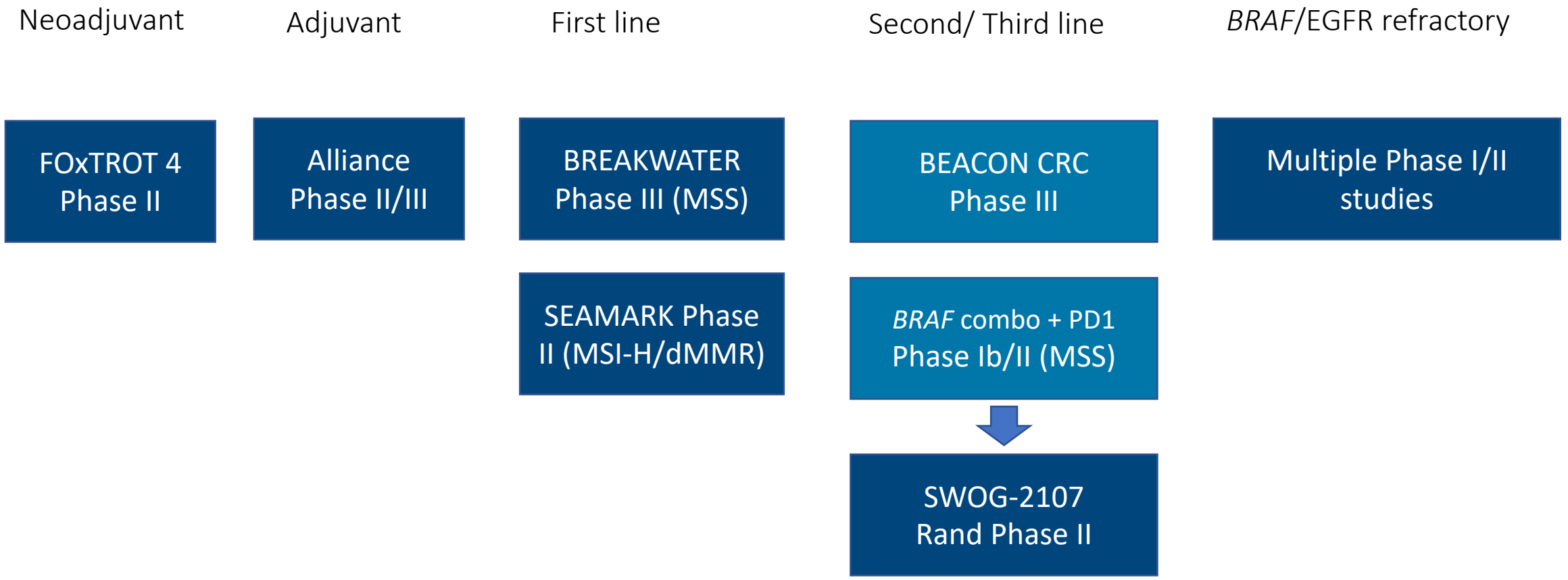
Time to Definitive Deterioration in EORTC QLQ-C30 Global Health Status



*The time to definitive deterioration is defined as the time from the date of randomization to the date of event, which is defined as at least 10% worsening relative to baseline of the corresponding scale score with no later improvement above this threshold observed during the course of the study or death due to any cause.
Presented by Scott Kopetz, MD

Kopetz S, et al. *ASCO GI 2020*; Abstract 8.

Where is the field going from here?

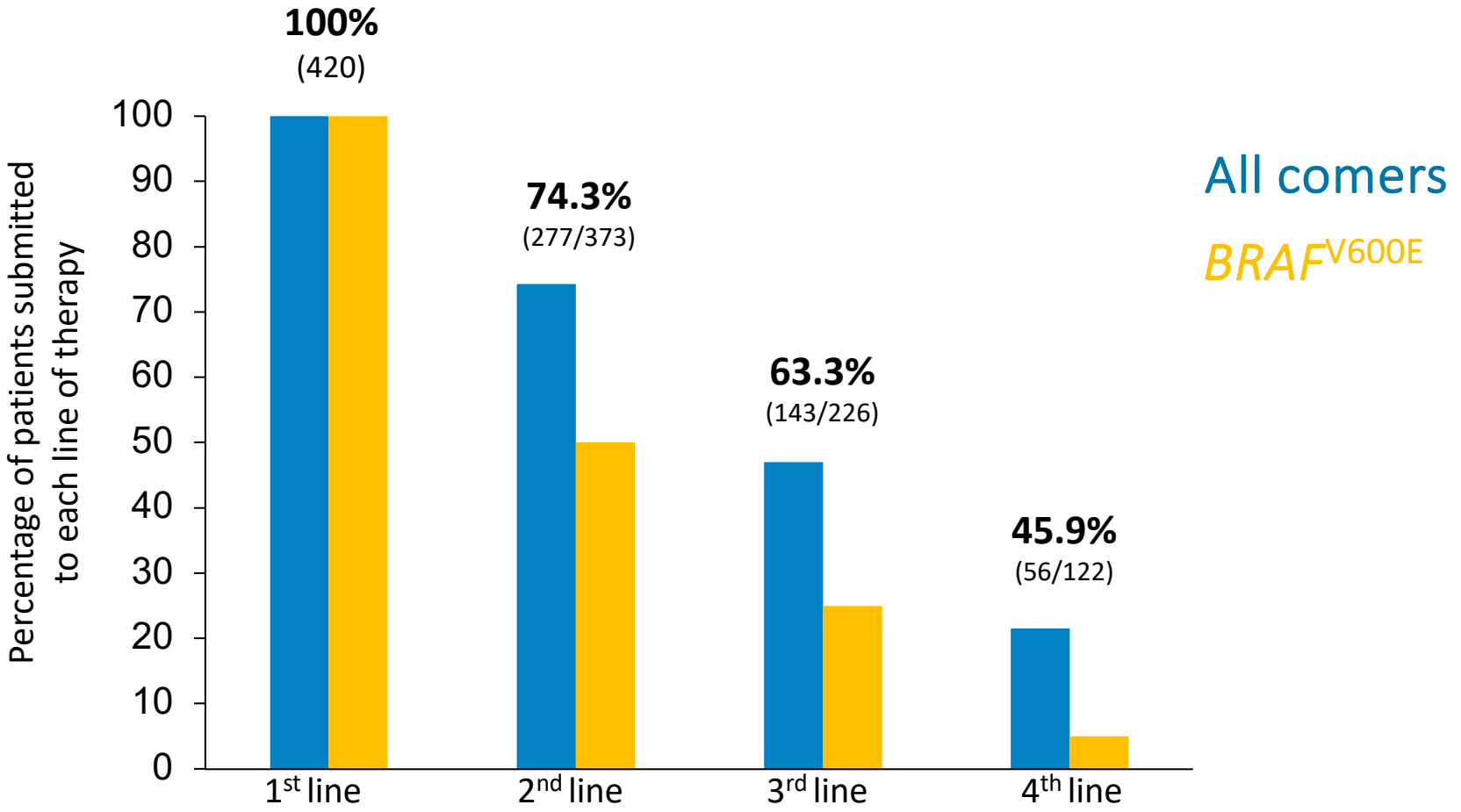


Not a comprehensive list….

Completed Enrolling

Need your best option early for *BRAF*^{V600E}

Probability of receiving therapy beyond 1st line drop, especially for patients with *BRAF*



Tampellini M, et al. *Clin Colorectal Cancer*. 2017;16:372-76, integrated with Morris, et al. *Clin Colorectal Cancer.* 2014;13(3):164-71

Early *BRAF* Combination Treatment *May* Result in Better Outcomes

Response Rates	First line (ANCHOR)	Second line (BEACON CRC)	Third line (BEACON CRC)
Triplet of *BRAF* + EGFR + MEK	48%	34%	22%
Doublet of *BRAF* + EGFR	N/A	14%	16%

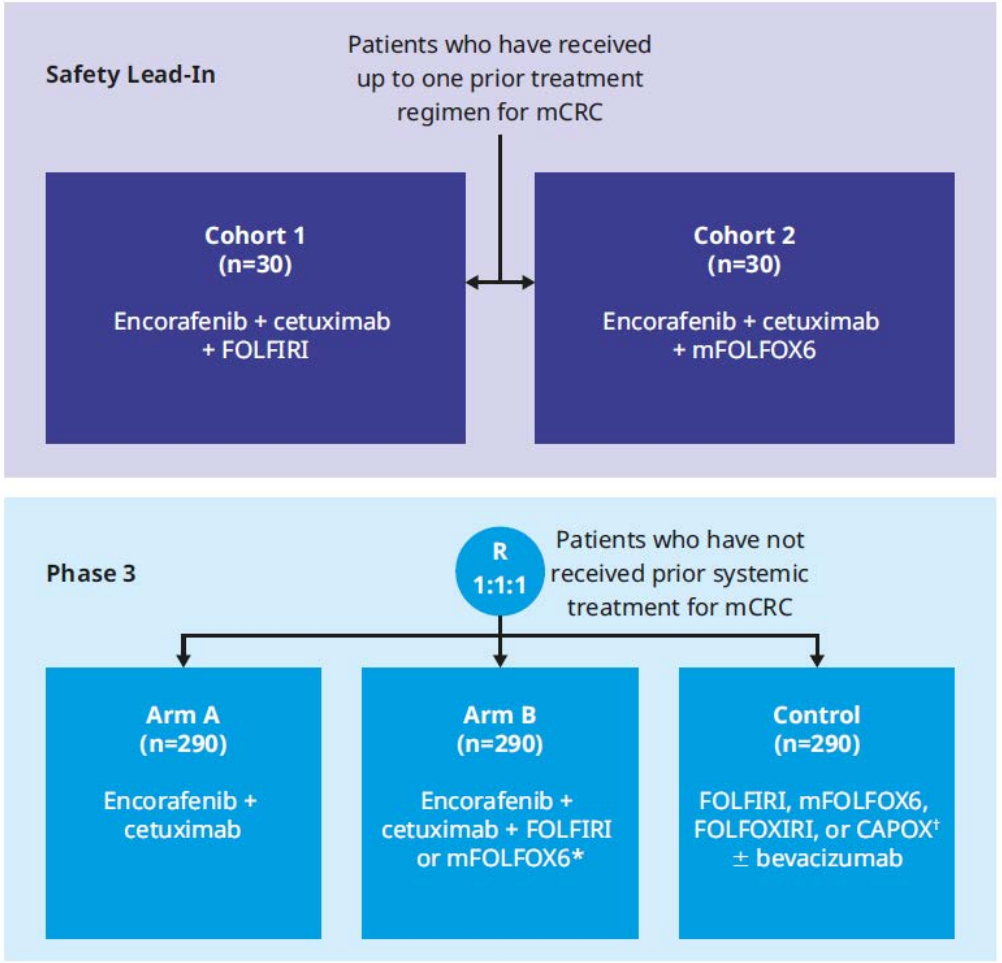
If this is confirmed, treatment earlier in the disease course may be beneficial.
Why do we see this effect?

- Patient factors?
- Tumor biology?
- Cross-resistance with chemotherapy?

BREAKWATER: First-line Encorafenib + Cetuximab ± Chemotherapy Versus SOC in Patients With *BRAF* V600E–Mutant mCRC

Key Eligibility Criteria (N=930)

- Patients aged ≥16 (phase 3)
- Measurable, histologically or cytologically confirmed CRC adenocarcinoma (phase 3)
- Presence of metastatic disease
- *BRAF* V600E mutation present in tumor tissue or blood
- No dMMR/MSI-H disease
- Participants who received ≤1 (safety lead-in) or no (phase 3) prior systemic regimens for metastatic disease; No previous treatment with BRAFi or EGFRi
- ECOG PS of 0 or 1



Primary Endpoints

- Safety lead-in: Incidence of dose-limiting toxicities
- Phase 3: PFS by BICR of Arm A vs Arm C and Arm B vs Arm C

NCT04607421

A multicenter, open-label, randomized, interventional study to determine the safety, tolerability, and efficacy of encorafenib + cetuximab with or without chemotherapy versus standard of care chemotherapy in patients with previously untreated *BRAF* V600E-mutant mCRC. Prior to the phase 3 portion, a safety lead-in will be conducted to evaluate the safety/tolerability and PK of encorafenib + cetuximab in combination with either mFOLFOX6 or FOLFIRI

1. ClinicalTrials.gov https://www.clinicaltrials.gov/ct2/show/NCT04607421. Accessed October 29, 2020.

BREAKWATER Safety Lead-In: Safety Summary

Primary endpoint: Frequency of DLTs

- One patient in the EC + FOLFIRI cohort had a DLT of grade 4 neutropenia lasting >7 days; no other DLTs were reported

Secondary endpoint: Safety

	EC + mFOLFOX6		EC + FOLFIRI	
	n=27		n=30	
All causality, n (%)				
TEAEs	27 (100.0)		30 (100.0)	
SAEs	13 (48.1)		10 (33.3)	
Grade ≥3 TEAEs	21 (77.8)		13 (43.3)	
TEAEs leading to dose reduction (any drug)	18 (66.7)		10 (33.3)	
TEAEs leading to permanent discontinuation (any drug)	5 (18.5)		5 (16.7)	
Treatment-related, n (%)				
TEAEs related to any drug	27 (100.0)		27 (90.0)	
SAEs related to any drug	7 (25.9)		4 (13.3)	
Deaths related to TEAEs	0		0	
	Any grade	**Grade ≥3**	**Any grade**	**Grade ≥3**
Most frequent (≥30%) all causality TEAEs[a]	**27 (100.0)**	**21 (77.8)**	**30 (100.0)**	**13 (43.3)**
Nausea	20 (74.1)	0	13 (43.3)	0
Pyrexia	13 (48.1)	1 (3.7)	7 (23.3)	0
Vomiting	11 (40.7)	1 (3.7)	4 (13.3)	0
Diarrhea	10 (37.0)	2 (7.4)	13 (43.3)	1 (3.3)
Peripheral sensory neuropathy	9 (33.3)	1 (3.7)	2 (6.7)	0
Fatigue	8 (29.6)	0	13 (43.3)	1 (3.3)
Constipation	7 (25.9)	0	13 (43.3)	1 (3.3)
Dermatitis acneiform	7 (25.9)	0	12 (40.0)	1 (3.3)

Data cutoff: 16 May 2022

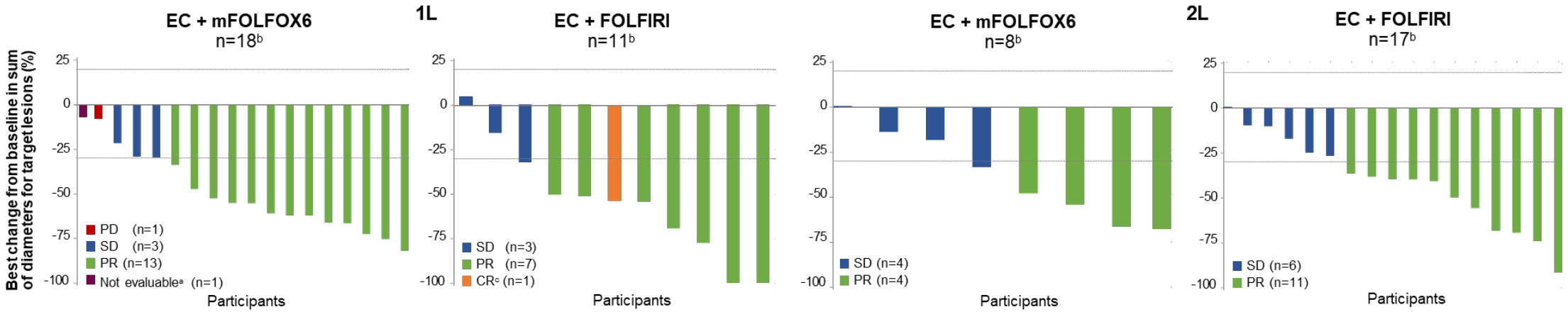
[a]All grade in ≥30% of participants in either the EC + mFOLFOX6 arm or the EC + FOLFIRI arm.

AE, adverse event; DLT, dose-limiting toxicity; EC, encorafenib + cetuximab; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Tabernero et al., presented at ESMO 2022

BREAKWATER Safety Lead-In: Overview of response

	1L		2L	
	EC + mFOLFOX6	EC + FOLFIRI	EC + mFOLFOX6	EC + FOLFIRI
Confirmed best overall response by investigator, n (%)	**n=19**	**n=12**	**n=8**	**n=18**
ORR, % (95% CI)	68.4 (46.0–84.6)	66.7 (39.1–86.2)	50.0 (21.5–78.5)	61.1 (38.6–79.7)
CR	0	1 (8.3)	0	0
PR	13 (68.4)	7 (58.3)	4 (50.0)	11 (61.1)
SD	3 (15.8)	3 (25.0)	4 (50.0)	6 (33.3)
PD	1 (5.3)	0	0	0
Non-CR/non-PD	1 (5.3)	1 (8.3)	0	0
Not evaluable[a]	1 (5.3)	0	0	1 (5.6)
Responders	**n=13**	**n=8**	**n=4**	**n=11**
mTTR, weeks (range)	6.9 (5.9–25.9)	6.6 (6.1–7.0)	9.4 (6.4–18.9)	12.9 (6.1–37.0)
mDOR, months (95% CI)	7.6 (4.1–not estimable)	Not estimable (10.6–not estimable)	Not estimable (2.7–not estimable)	Not estimable (3.4–not estimable)
≥6 months, n (%)	6 (46.2)	7 (87.5)	2 (50.0)	6 (54.5)



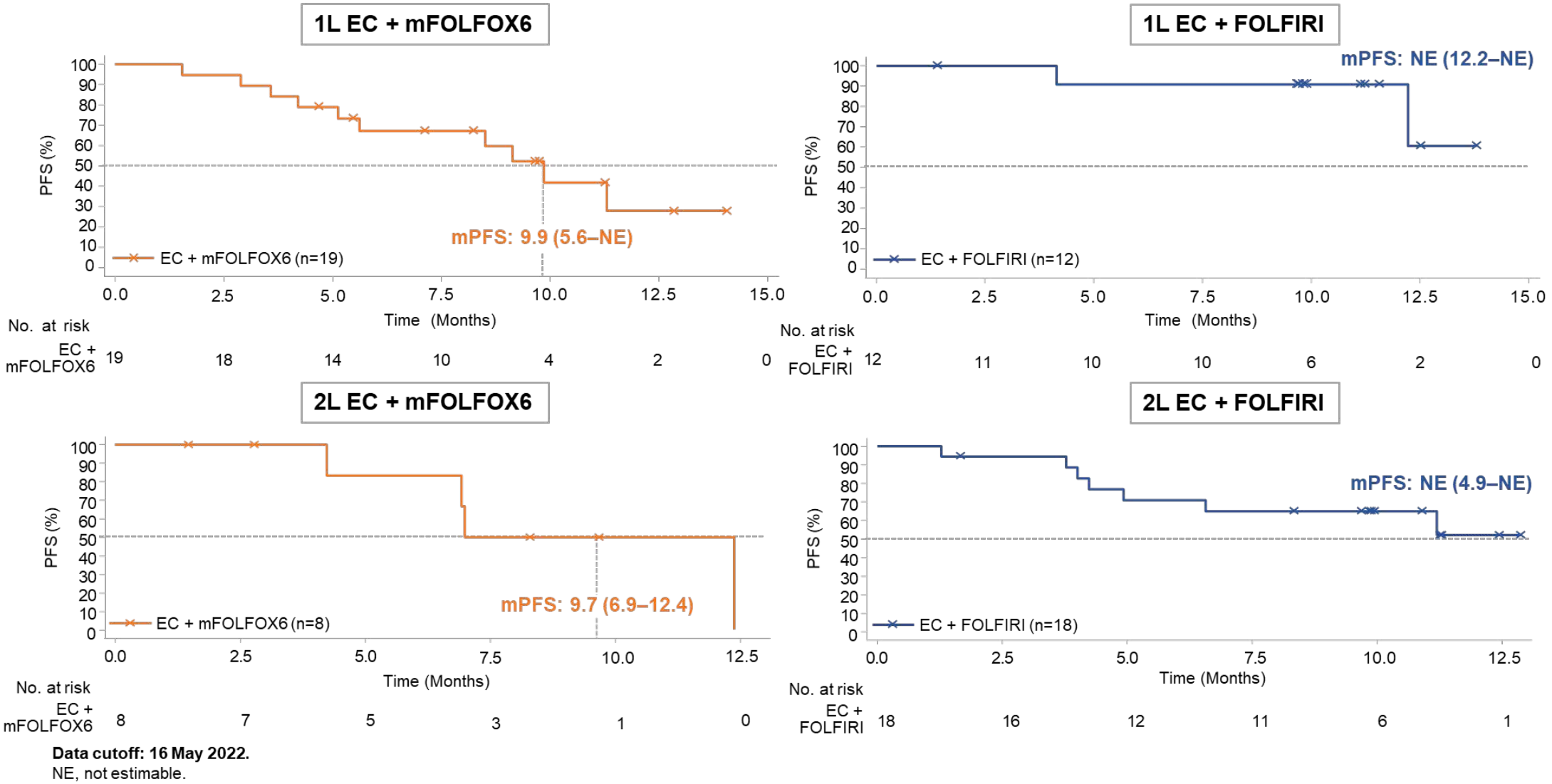
Data cutoff: 16 May 2022

[a]Reasons included SD <6 weeks after treatment start date (1 patient in the EC + mFOLFOX6 arm in the 1L setting) and early death (1 patient in the EC + FOLFIRI arm in the 2L setting). [b]Only includes participants with target lesions at baseline and ≥1 non-missing post-baseline % change from baseline assessment up to time of PD or new anti-cancer therapy. [c]This participant had a nodal target lesion that did not completely disappear but became non-pathological by size (<10 mm).

CR, complete response; EC, encorafenib + cetuximab; PD, progressive disease; PR, partial response; SD, stable disease.

Tabernero et al., presented at ESMO 2022

BREAKWATER Safety Lead-In: PFS
(investigator assessed)

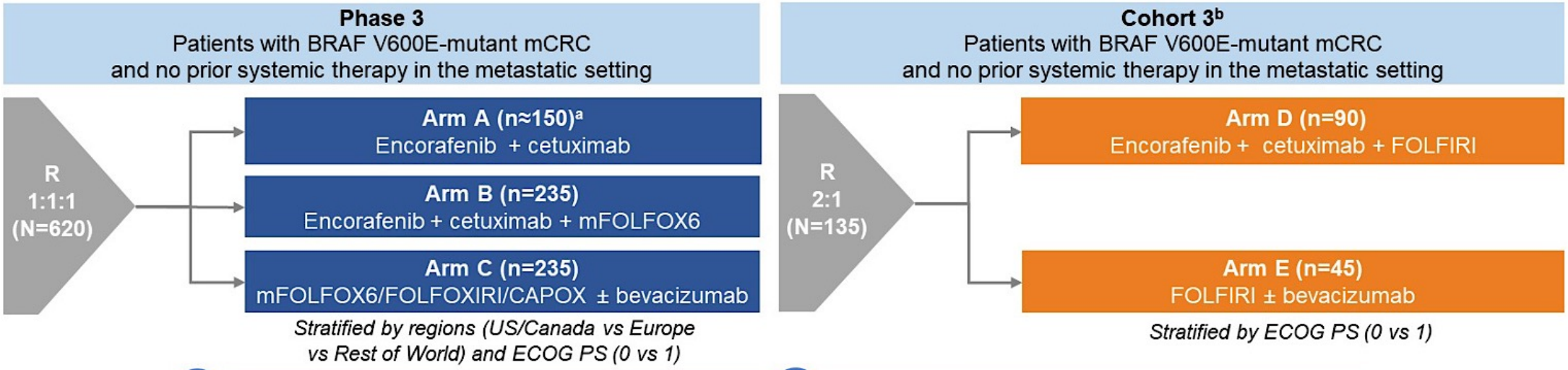


Data cutoff: 16 May 2022.
NE, not estimable.

Tabernero et al., presented at ESMO 2022

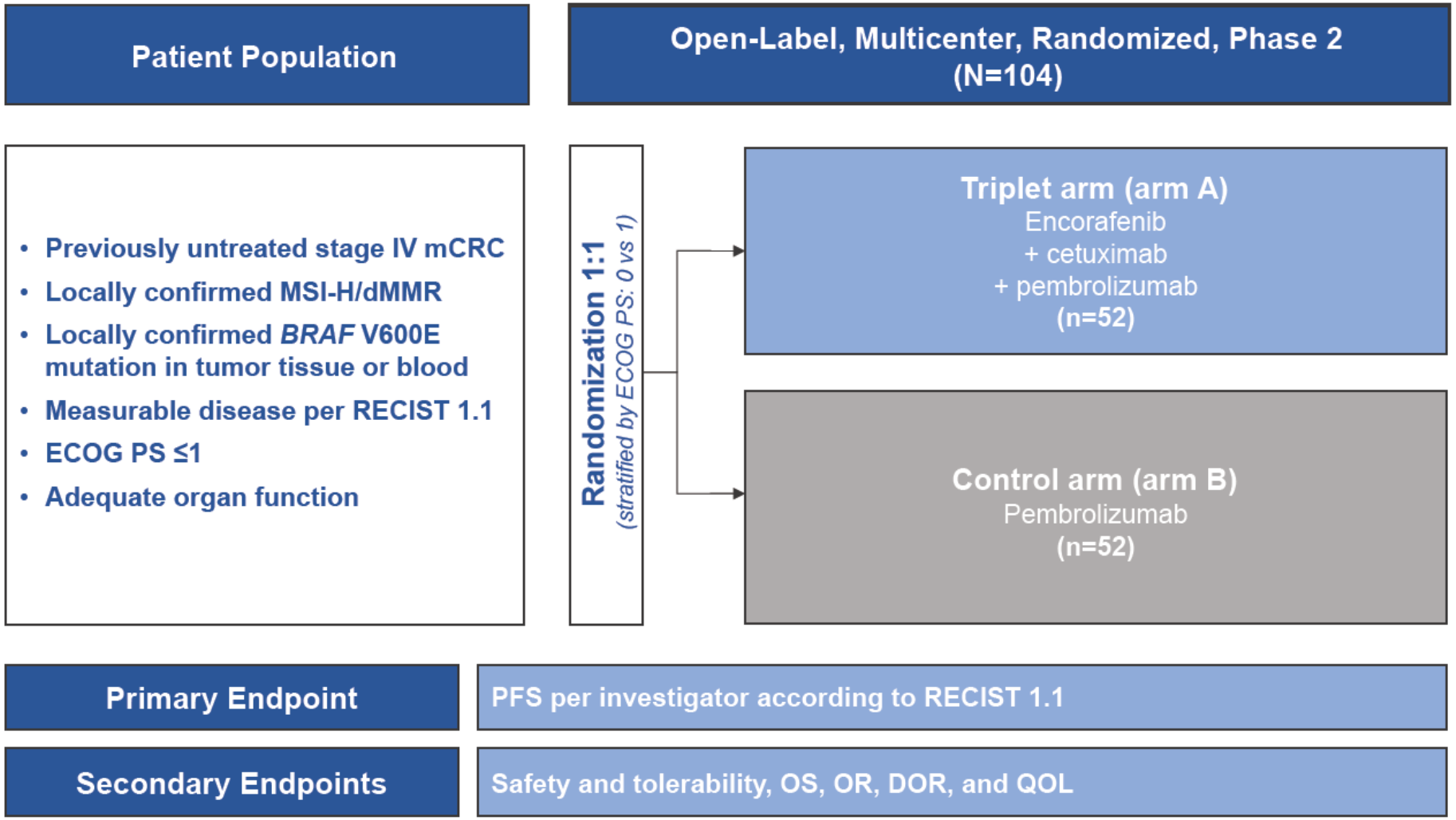
BREAKWATER: Updated Phase III Trial Design

- BREAKWATER (NCT04607421) is an ongoing, open-label, multicenter, randomized, phase 3 study evaluating 1L EC ± CT vs SOC CT alone in patients with BRAF V600E-mutant mCRC
  - In the BREAKWATER SLI, which evaluated 57 patients with mCRC who had received ≤1 prior treatment, EC + CT showed encouraging antitumor activity
  - Based on these SLI results, EC + mFOLFOX6 was selected as the recommended phase 3 regimen

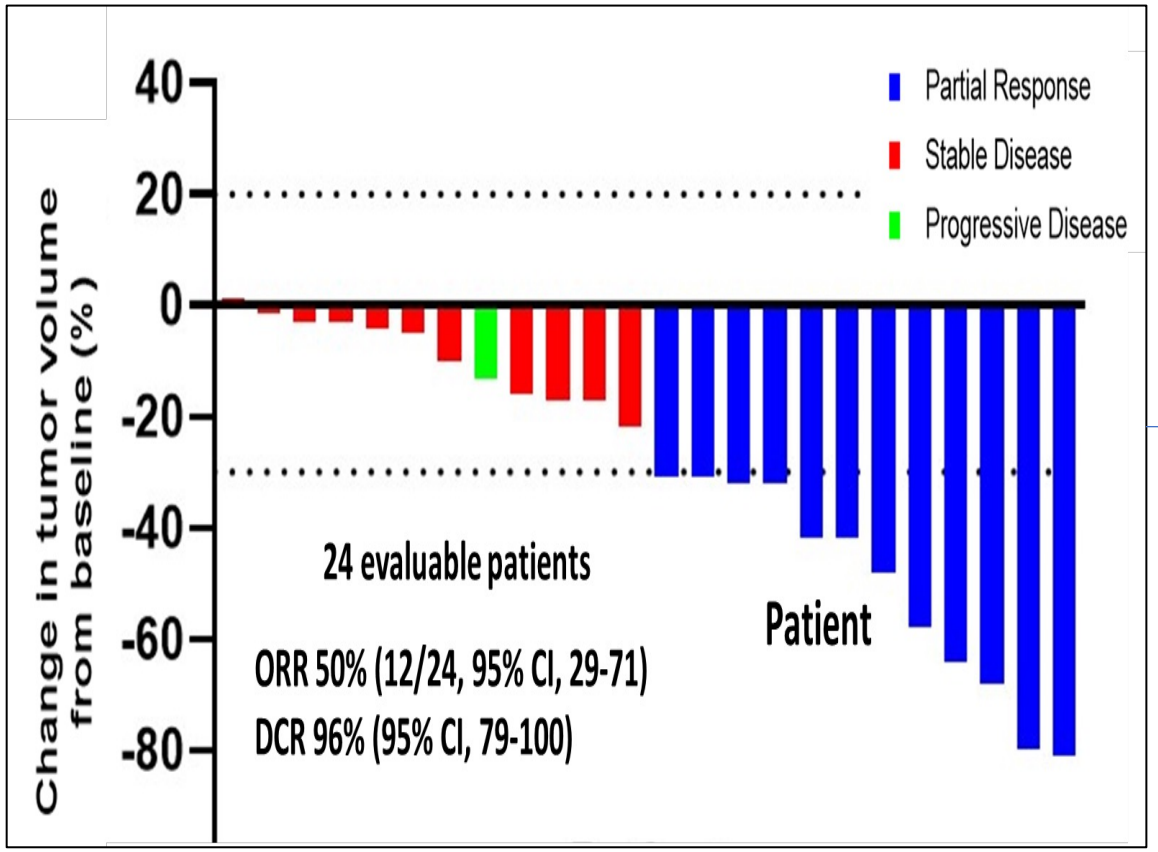


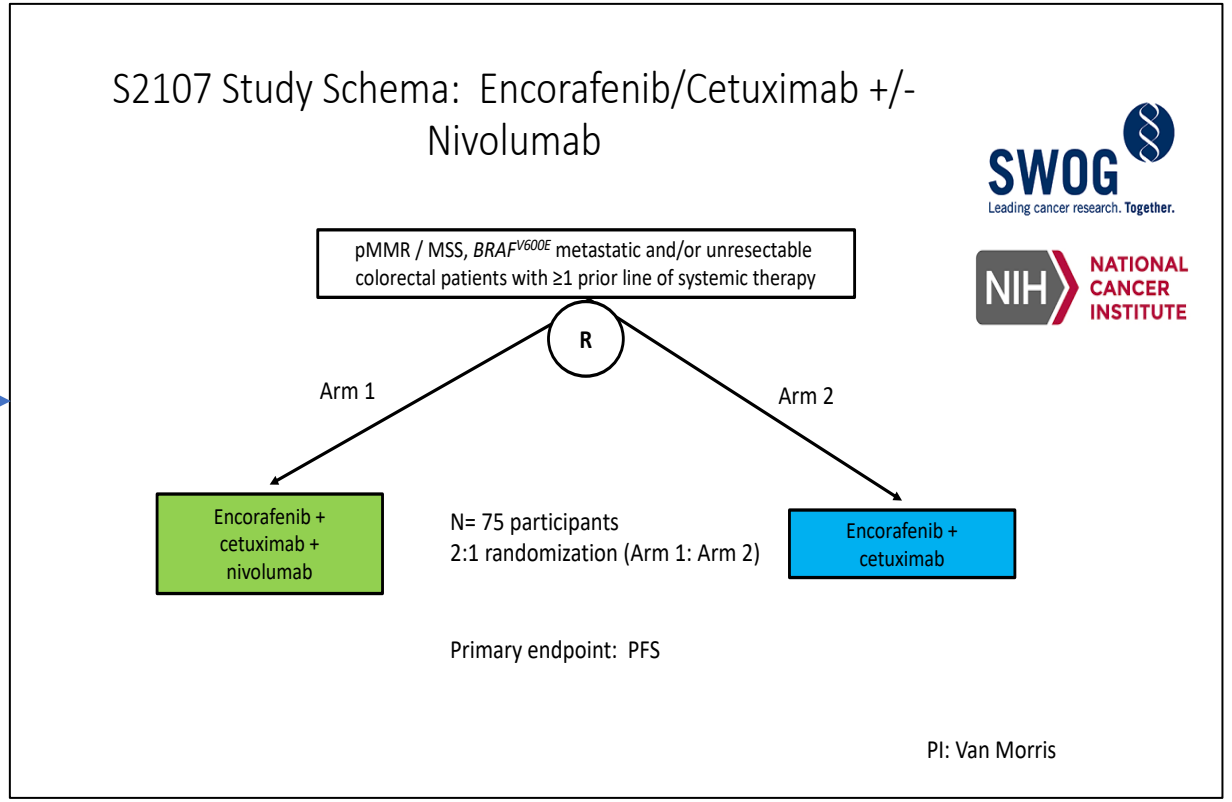
Kopetz S et al. ASCO 2023;Abstract TPS3627.

SEAMARK Phase 2 Study: Immunotherapy +/- Encorafenib/Cetuximab in *BRAF*^{V600E}, MSI-H



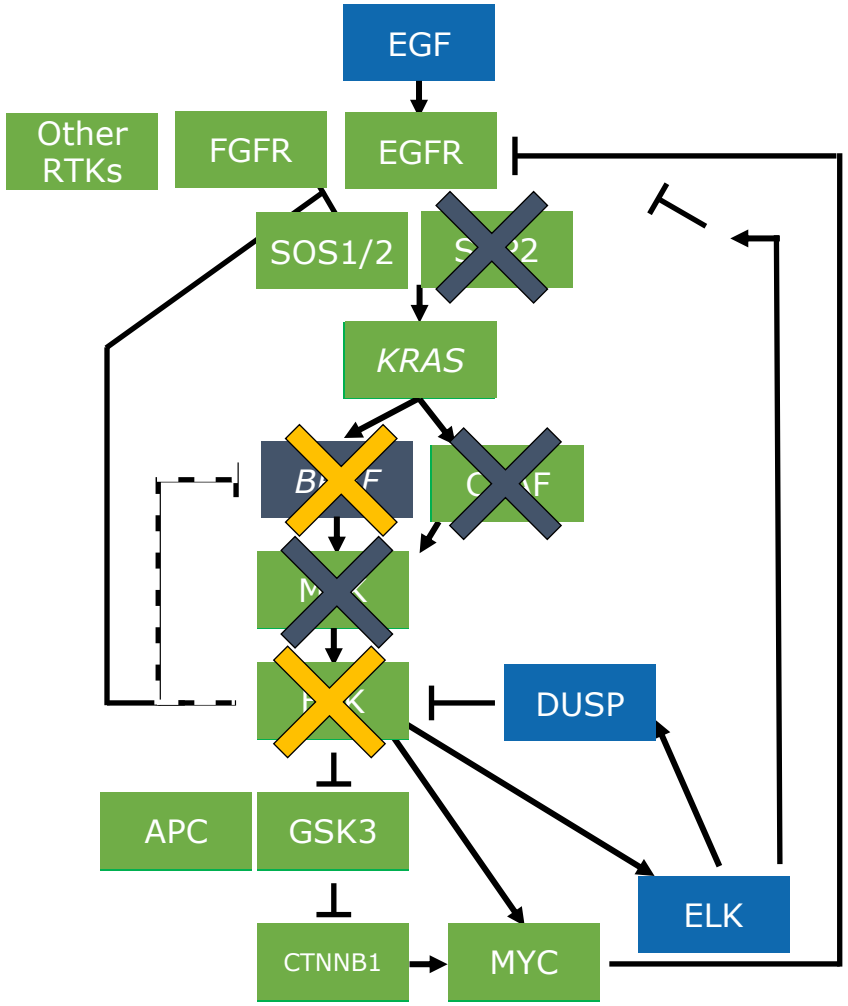
Encorafenib + Cetuximab + Nivolumab for MSS, *BRAF*^{V600E} mCRC





Morris VK, et al. ASCO 2022

Combinations Being Explored in Patients Progressing on E+C



- ERAS-007 – ERK1/2 inhibitor
- LTT462 – ERK1/2 inhibitor
- Trametinib (TMT212) – MEK inhibitor
- LXH254 – B/C RAF inhibitor
- TNO155 – SHP2 inhibitor
- LY3214996 – ERK1/2 inhibitor

Conclusions

- *BRAF*^{V600E} mutations have poor prognosis and novel therapeutic options
- *BRAF* should be part of the routine testing panel
- Combination strategies to target *BRAF*^{V600E} have been successful
  - Encorafenib, cetuximab is current standard of care for 2nd, 3rd line (BEACON CRC)
  - Management of skin toxicity, arthralgia/myalgia, and rare renal toxicity
- Next steps for the field:
  - Evaluation in first line metastatic disease and (neo)**adjuvant setting (ctDNA+ defined and traditional Phase 3)**
  - Randomized studies with anti-PD1 with *BRAF*/EGFRi are initiating in MSS and MSI_H
  - Novel combinations are coming: panRAF, ERK, SHP2, BRD2/4

MODULE 4: Integration of Immune Checkpoint Inhibitors into the Management of MSI-High/MMR-Deficient mCRC – Dr Cercek

Postulated mechanisms of resistance to immunotherapy

Arvind N Dasari, MD, MS

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Arvind N Dasari, MD, MS

What are the underlying mechanisms of intrinsic resistance to immunotherapy in patients with MSI-high mCRC, and what strategies are available to overcome them?

Are there situations in which you would consider dual immune checkpoint inhibitor therapy or a combination of chemotherapy and immunotherapy for a patient with MSI-high mCRC in the first-line setting?

Treatment selection for MSI-H, BRAF-mutant mCRC

Arvind N Dasari, MD, MS

QUESTIONS FOR THE FACULTY

Arvind N Dasari, MD, MS

How do you typically sequence immunotherapy and BRAF-targeted therapy for patients with MSI-high, BRAF-mutant mCRC?

Would you ever combine immunotherapy and BRAF-targeted therapy for these patients?

What was the age of the last patient in your practice with MSI-high/MMR-deficient (dMMR) mCRC who received immunotherapy? Which immunotherapy did they receive?

	Age	Immunotherapy
 Dr Bekaii-Saab	45 years	Pembrolizumab
 Dr Cercek	31 years	Pembrolizumab
 Dr Eng	62 years	Pembrolizumab
 Dr Lieu	80 years	Pembrolizumab
 Dr Strickler	51 years	Pembrolizumab
 Dr Ciombor	53 years	Pembrolizumab
 Dr Dasari	68 years	Pembrolizumab

For an asymptomatic patient with MSI-high mCRC who experienced slow disease progression on anti-PD-1 therapy alone, have you switched or would you consider switching to the combination of nivolumab and ipilimumab?

 Dr Bekaii-Saab	I have
 Dr Cercek	I have
 Dr Eng	I have not and would not
 Dr Lieu	I have
 Dr Strickler	I have not but would for the right patient
 Dr Ciombor	I have
 Dr Dasari	I have

RTP RESEARCH TO PRACTICE

Based on currently available data and/or your own clinical experience, which autoimmune conditions do you believe to constitute an absolute contraindication to treatment with an immune checkpoint inhibitor for a patient with MSI-high/dMMR mCRC?

 Dr Bekaii-Saab	Any severe autoimmune disorder that is not well controlled; solid organ transplant
 Dr Cercek	Active autoimmune disease
 Dr Eng	High dose steroids
 Dr Lieu	Pneumonitis, any autoimmune cardiomyopathies
 Dr Strickler	Uncontrolled severe/life-threatening autoimmune disorder requiring systemic therapy; history of lung transplant
 Dr Ciombor	History of organ transplant, myasthenia gravis, uncontrolled autoimmune disease or those requiring systemic therapy
 Dr Dasari	Active autoimmune conditions requiring ongoing steroids and/or immunosuppressive medications

RTP RESEARCH TO PRACTICE

In general, for a patient with MSI-high/dMMR mCRC who is receiving immunotherapy, for how long do you continue the treatment if the patient is tolerating it well?

 Dr Bekaii-Saab	Maximum of 24 months
 Dr Cercek	2 years
 Dr Eng	1 year
 Dr Lieu	2 years
 Dr Strickler	Maximum 2 years in most cases
 Dr Ciombor	2 years
 Dr Dasari	Up to 2 years

RTP
RESEARCH TO PRACTICE

How would you generally sequence BRAF-targeted therapy and immunotherapy for a patient with MSI-high mCRC with a BRAF mutation?

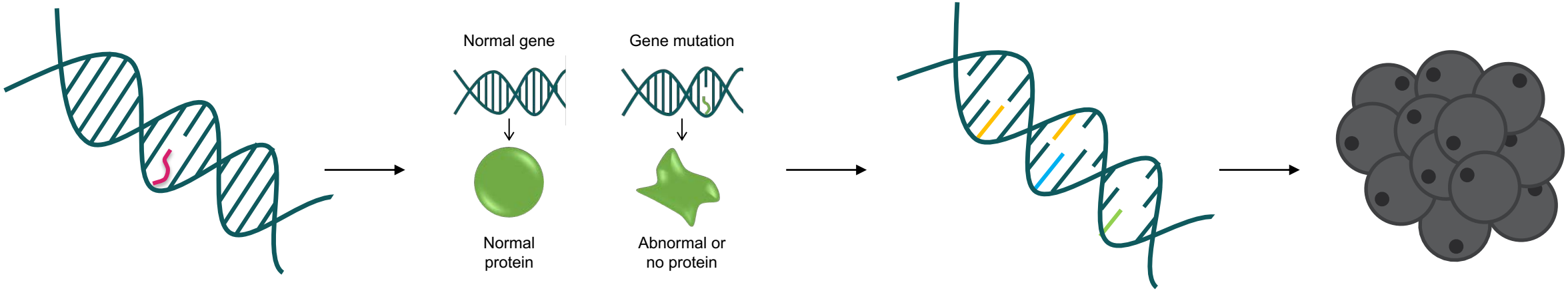
 Dr Bekaii-Saab	Immunotherapy → BRAF-targeted therapy
 Dr Cercek	Immunotherapy → BRAF-targeted therapy
 Dr Eng	Immunotherapy → BRAF-targeted therapy
 Dr Lieu	Immunotherapy → BRAF-targeted therapy
 Dr Strickler	Immunotherapy → BRAF-targeted therapy
 Dr Ciombor	Immunotherapy → BRAF-targeted therapy
 Dr Dasari	Immunotherapy → BRAF-targeted therapy

RTP RESEARCH TO PRACTICE

Incorporating Immunotherapy into Treatment of dMMR/MSI Metastatic Colorectal Cancer

Andrea Cercek, MD
Section Head, Colorectal Cancer
Associate Attending Physician
Memorial Sloan Kettering Cancer Center
January 19, 2024

Mismatch repair protein deficiency / MSI-H



Sporadic or Lynch syndrome-related mutations can occur in MMR genes *MLH1*, *MSH2*, *MSH6* or *PMS2*[1,2]

Mutations in MMR genes lead to the loss of MMR protein activity, resulting in DNA mismatches[1,2]

The persistence of DNA mismatches results in MSI, and mutations are incorporated into the genetic code[1]

The accumulation of genetic mutations promotes tumourigenesis[1]

Figure adapted from Boland CR et al. 2010 and Kawakami H et al. 2015.

MMR, mismatch repair; MSI, microsatellite instability.

1. Boland CR et al. *Gastroenterology* 2010;138:2073–2087; 2. Kawakami H et al. *Curr Treat Options Oncol* 2015;16:30.

Pembrolizumab for previously treated, microsatellite instability–high/mismatch repair–deficient advanced colorectal cancer: final analysis of KEYNOTE-164

Dung T. Le [a,*], Luis A. Diaz Jr. [b,c], Tae Won Kim [c,d], Eric Van Cutsem [e], Ravit Geva [f], Dirk Jäger [g], Hiroki Hara [h], Matthew Burge [i], Bert H. O'Neil [j], Petr Kavan [k], Takayuki Yoshino [l], Rosine Guimbaud [m], Hiroya Taniguchi [n], Elena Élez [o,p], Salah-Eddin Al-Batran [q,r], Patrick M. Boland [s], Yi Cui [t], Pierre Leconte [u], Patricia Marinello [v], Thierry André [w,x]

Eur J Cancer 2023;186:185-95.

KEYNOTE-164: Response Data

Table 1
Best response assessed per RECIST v1.1 by BICR in patients with MSI-H/dMMR unresectable locally advanced unresectable or metastatic colorectal cancer in cohorts A and B.

	Cohort A n = 61	Cohort A: ≥2 prior lines of therapy	Cohort B n = 63	Cohort B: ≥1 prior lines of therapy
	n	% (95% CI)[a]	n	% (95% CI)[a]
ORR	20	32.8 (21.3–46.0)	22	34.9 (23.3–48.0)
Best overall response				
CR	3	4.9 (1.0–13.7)	9	14.3 (6.7–25.4)
PR	17	27.9 (17.1–40.8)	13	20.6 (11.5–32.7)
SD	11	18.0 (9.4–30.0)	13	20.6 (11.5–32.7)
PD	28	45.9 (33.1–59.2)	25	39.7 (27.6–52.8)
Non-evaluable	2	3.3 (0.4–11.3)	3	4.8 (1.0–13.3)
DCR[b]	31	50.8 (37.7–63.9)	35	55.6 (42.5–68.1)
DOR median (range),[c] months	NR (6.2–58.5+)		NR (4.4–52.4+)	
Estimated DOR[c] ≥ 36 months, %	89.7		95.5	

BICR, blinded independent central review; CI, confidence interval; CR, complete response; dMMR, mismatch repair deficient; DCR, disease control rate; DOR, duration of response; MSI-H, microsatellite instability–high; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; SD, stable disease.

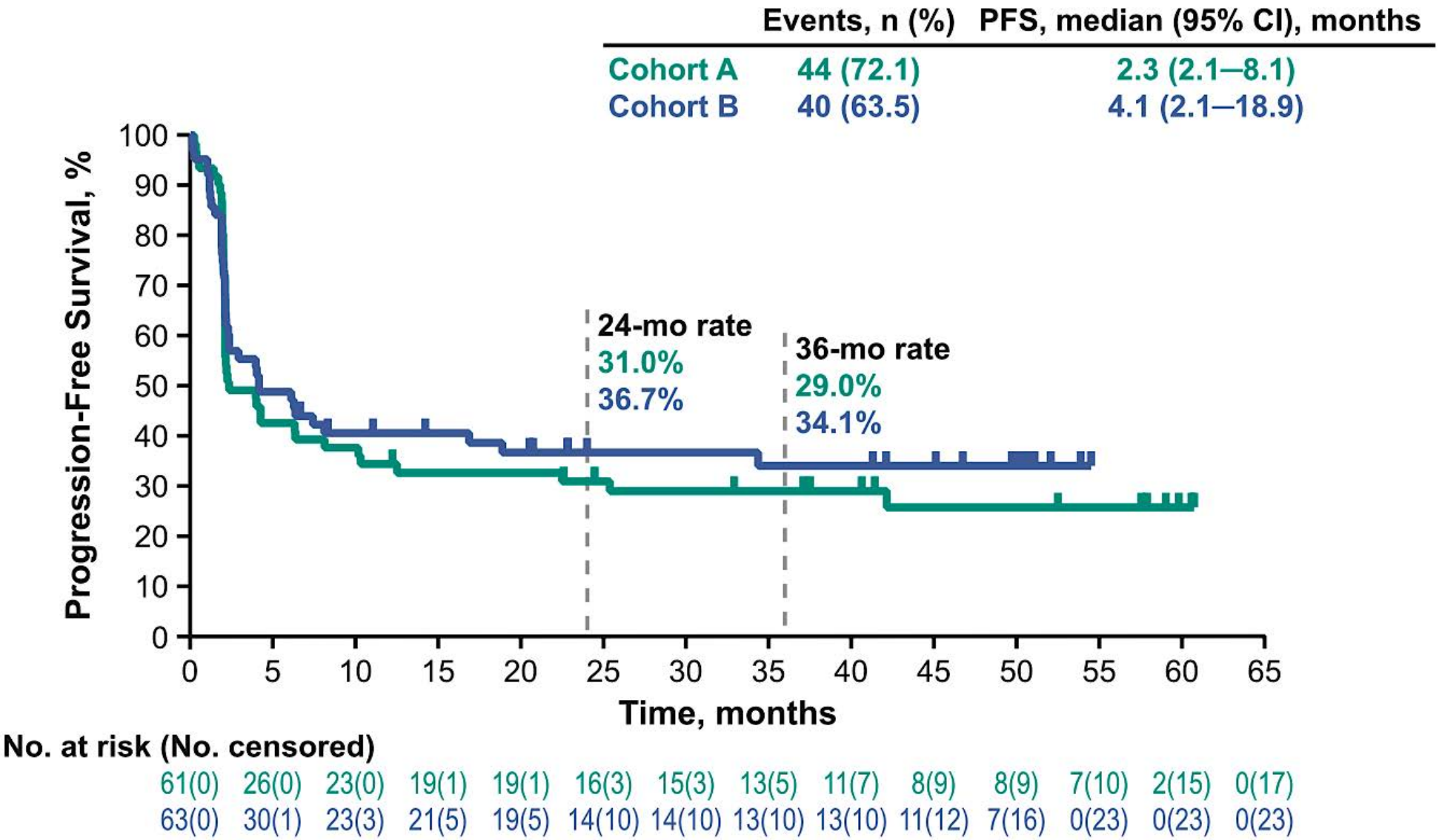
[a] Based on binomial exact confidence interval method.

[b] CR + PR + SD ≥24 weeks.

[c] From product-limit (Kaplan-Meier) method for censored data.

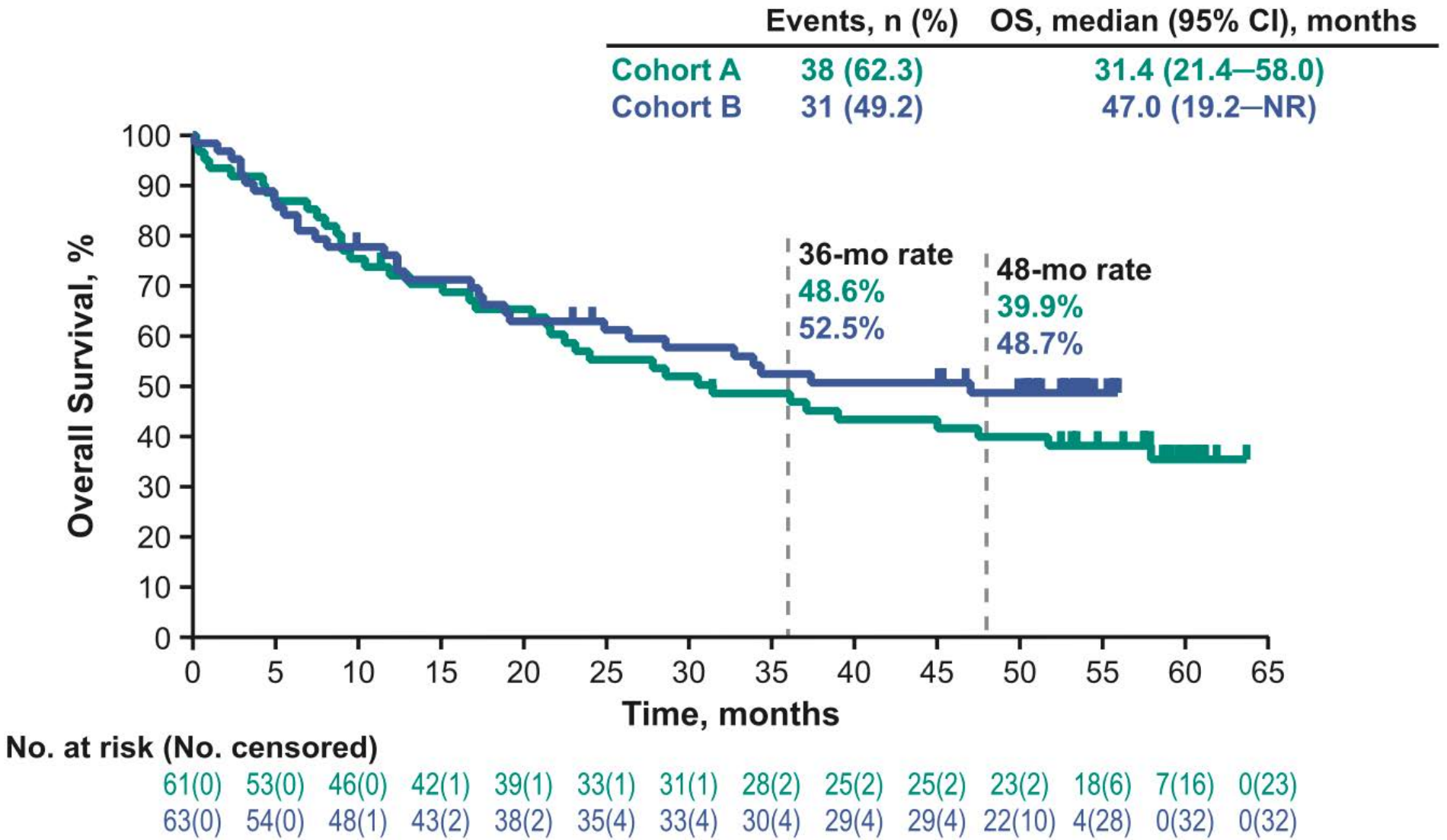
Le DT et al. *Eur J Cancer* 2023;186:185-95.

KEYNOTE-164: Progression-Free Survival (PFS) Analysis



Le DT et al. *Eur J Cancer* 2023;186:185-95.

KEYNOTE-164: Overall Survival (OS) Analysis



Le DT et al. *Eur J Cancer* 2023;186:185-95.

KEYNOTE-164: Safety

Table 3
Immune-mediated AEs[a] in patients with MSI-H/dMMR locally advanced unresectable or metastatic colorectal cancer in cohorts A and B.

n (%)	Cohort A, n = 61		Cohort B, n = 63	
Any grade immune-mediated AEs	13 (21.3)		24 (38.1)	
Grade 3/4 immune-mediated AEs[b]	4 (6.6)		3 (4.8)	
Immune-mediated AE leading to discontinuation	1 (1.6)		2 (3.2)	
All immune-mediated AEs	*Any grade*	*Grade 3/4*	*Any grade*	*Grade 3/4*
Hypothyroidism	6 (9.8)	0	13 (20.6)	0
Hyperthyroidism	3 (4.9)	0	7 (11.1)	0
Pancreatitis	3 (4.9)	2 (3.3)	0	0
Pneumonitis	3 (4.9)	1 (1.6)	3 (4.8)	1 (1.6)
Colitis	1 (1.6)	0	1 (1.6)	1 (1.6)
Hepatitis	1 (1.6)	1 (1.6)	0	0
Infusion reaction	1 (1.6)	0	1 (1.6)	0
Myositis	1 (1.6)	0	1 (1.6)	0
Severe skin reaction	1 (1.6)	1 (1.6)	0	0
Sarcoidosis	0	0	1 (1.6)	0
Vasculitis	0	0	1 (1.6)	1 (1.6)

AE, adverse event; dMMR, mismatch repair deficient; MSI-H, microsatellite instability–high.
[a] Based on a list specified by the sponsor and considered regardless of attribution to treatment or immune relatedness by investigator.
[b] No grade 5 immune-related AEs or infusion reactions occurred in either cohort.

Le DT et al. *Eur J Cancer* 2023;186:185-95.

ASCO 2022;Abstract 3510

Nivolumab ± ipilimumab in patients with microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: ~ 5-year follow-up from CheckMate 142

Michael J. Overman,[1] Heinz-Josef Lenz,[2] Thierry Andre,[3] Massimo Aglietta,[4] Mark Wong,[5] Gabriele Luppi,[6] Eric Van Cutsem,[7] Ray McDermott,[8] Alain Hendlisz,[9] Dana Cardin,[10] Michael Morse,[11] Bart Neyns,[12] Andrew Hill,[13] Maria Luisa Limon,[14] Pilar Garcia-Alfonso,[15] Anuradha Krishnamurthy,[16] Franklin Chen,[17] Sandzhar Abdullaev,[18] Samira Soleymani,[18] Sara Lonardi[19]

[1]University of Texas MD Anderson Cancer Center, Houston, TX; [2]University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; [3]Hôpital Saint Antoine, Assistance Publique Hôpitaux de Paris and Sorbonne Université, Paris, France; [4]Candiolo Cancer Institute and University of Torino Medical School, Candiolo, Italy; [5]Westmead Hospital, Sydney, Australia; [6]University Hospital of Modena, Modena, Italy; [7]University Hospitals Gasthuisberg/Leuven and KU Leuven, Leuven, Belgium; [8]St Vincent's University Hospital and Cancer Trials Ireland, Dublin, Ireland; [9]Institut Jules Bordet, Brussels, Belgium; [10]Vanderbilt-Ingram Cancer Center, Nashville, TN; [11]Duke University Medical Center, Durham, NC; [12]Universitair Ziekenhuis Brussel, Brussels, Belgium; [13]Tasman Oncology Research Ltd, Southport, Australia; [14]Hospital Universitario Virgen del Rocio, Sevilla, Spain; [15]Hospital Gral Universitario Gregorio Marañon, Madrid, Spain; [16]University of Pittsburgh Cancer Institute, Pittsburgh, PA; [17]Novant Health Cancer Institute, Winston-Salem, NC; [18]Bristol Myers Squibb, Princeton, NJ; [19]Veneto Institute of Oncology IOV-IRCCS, Padua, Italy

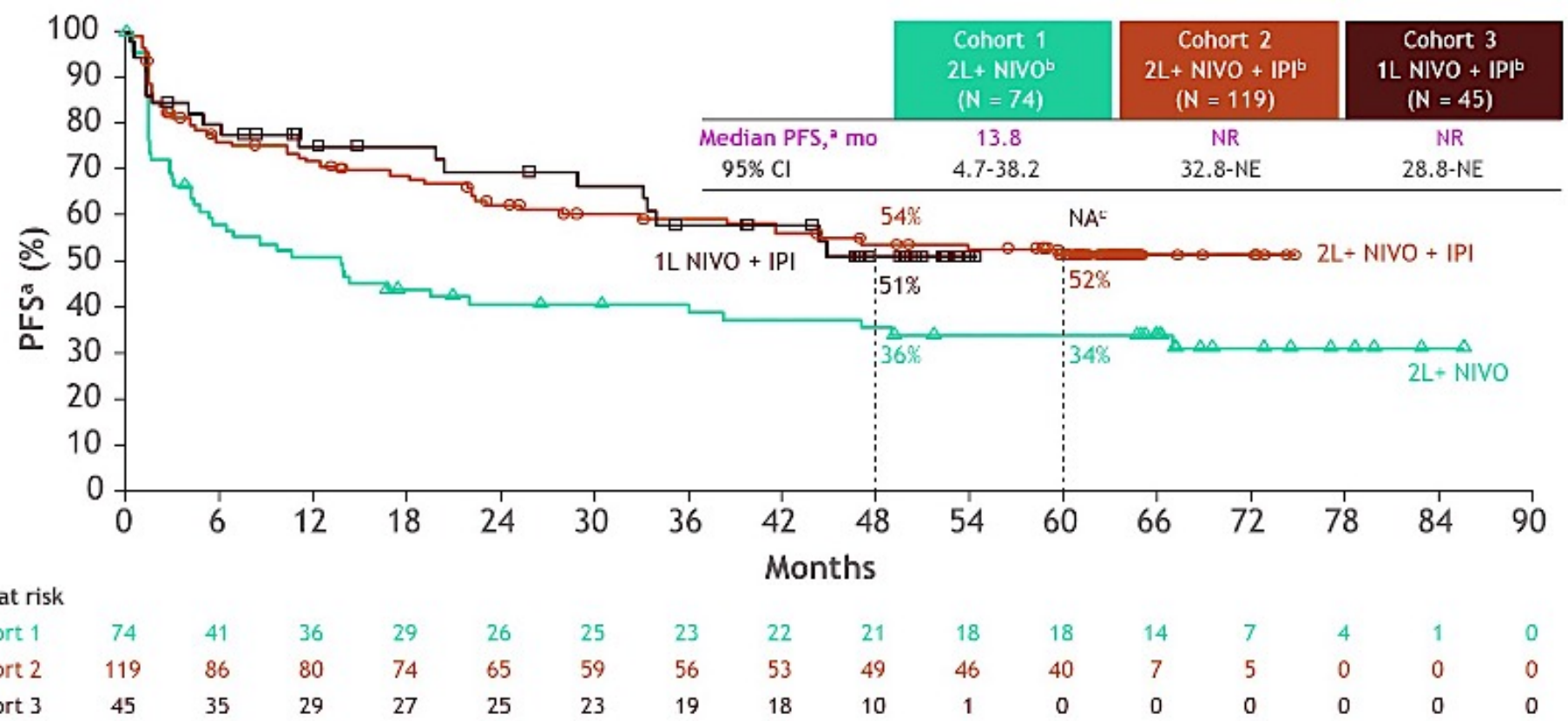
CheckMate 142: Response, Disease Control and Durability

Outcome[a]	Cohort 1 2L+ NIVO[b] (N = 74)	Cohort 2 2L+ NIVO + IPI[b] (N = 119)	Cohort 3 1L NIVO + IPI[b] (N = 45)
ORR,[c] n (%)	29 (39)	77 (65)	32 (71)
95% CI	28-51	55-73	56-84
Best overall response, n (%)			
CR	12 (16)	20 (17)	9 (20)
PR	17 (23)	57 (48)	23 (51)
SD	22 (30)	25 (21)	6 (13)
PD	19 (26)	14 (12)	7 (16)
Unable to determine	4 (5)	3 (3)	0
DCR,[d] n (%)	51 (69)	96 (81)	38 (84)
95% CI	57-79	72-87	71-94
Median TTR (range),[e] months	2.8 (1.2-46.3)	2.8 (1.1-37.1)	2.7 (1.2-27.7)
Median DOR (95% CI),[e] months	NR (NE)	NR (NE)	NR (41.5-NE)
36-month rate (95% CI), %	81 (60-92)	79 (67-87)	75 (52-88)
42-month rate (95% CI), %	77 (55-89)	75 (63-84)	69 (44-84)
60-month rate (95% CI), %	77 (55-89)	73 (60-82)	NA

[a]Per investigator; [b]Study cohorts were neither randomized nor designed for a formal comparison; [c]Patients with BOR of CR + PR divided by the number of treated patients; [d]Patients with CR, PR, or SD for ≥ 12 weeks divided by the number of treated patients; [e]Evaluated in patients who had an objective response. CI, confidence interval; NA, not available; NE, not evaluable; NR, not reached; TTR, time to response.

Overman MJ et al. ASCO 2022;Abstract 3510.

CheckMate 142: Progression-Free Survival

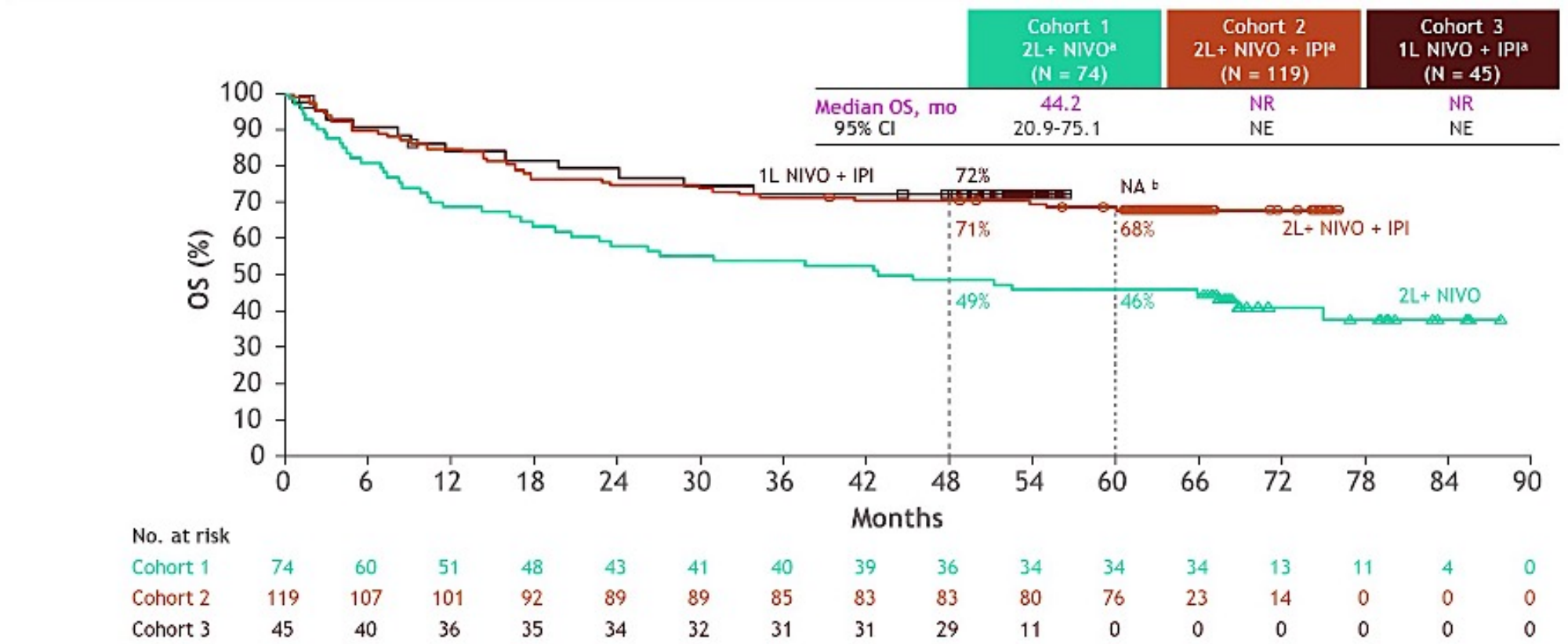


- Median PFS was 13.8 months in cohort 1 and not reached in cohorts 2 and 3
  - 48-month PFS rates were 36% (cohort 1), 54% (cohort 2), and 51% (cohort 3)
  - 60-month PFS rates were 34% (cohort 1), 52% (cohort 2), and not available for cohort 3

[a]Per investigator; [b]Study cohorts were neither randomized nor designed for a formal comparison; [c]Minimum follow-up for cohort 3 was 47.6 months. mo, months.

Overman MJ et al. ASCO 2022;Abstract 3510.

CheckMate 142: Overall Survival



- Median OS was 44.2 months in cohort 1 and not reached in cohorts 2 and 3
  - 48-month OS rates were 49% (cohort 1), 71% (cohort 2), and 72% (cohort 3)
  - 60-month OS rates were 46% (cohort 1), 68% (cohort 2), and not available for cohort 3

[a]Study cohorts were neither randomized nor designed for a formal comparison; [b]Minimum follow-up for cohort 3 was 47.6 months.

Overman MJ et al. ASCO 2022;Abstract 3510.

CheckMate 142: Summary of Treatment-Related Adverse Events

Patients,[a] n (%)	Cohort 1 2L+ NIVO[b] (N = 74)		Cohort 2 2L+ NIVO + IPI[b] (N = 119)		Cohort 3 1L NIVO + IPI[b] (N = 45)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Any TRAEs[c]	58 (78)[d]	20 (27)	101 (85)	38 (32)	36 (80)	9 (20)
Serious TRAEs[c]	11 (15)[d]	9 (12)	27 (23)	24 (20)	7 (16)	5 (11)
TRAEs leading to discontinuation[c]	7 (9)	5 (7)	16 (13)	12 (10)	7 (16)	2 (4)
Treatment-related deaths[e]	1 (1)[f]		0		1 (2)[g]	
Any-grade TRAEs occurring in ≥ 20% of patients in any cohort						
Diarrhea	17 (23)	1 (1)	32 (27)	3 (3)	7 (16)	0
Fatigue	17 (23)	1 (1)	23 (19)	2 (2)	7 (16)	0
Pruritus	14 (19)	1 (1)	25 (21)	2 (2)	17 (38)	0
Arthralgia	5 (7)	0	12 (10)	1 (< 1)	9 (20)	0

- With extended follow-up of ~ 5 years, no new safety signals were identified with 2L+ NIVO ± IPI and 1L NIVO + IPI

[a]Patients who received ≥ 1 dose of study drug; [b]Study cohorts were neither randomized nor designed for a formal comparison; [c]Includes events reported between first dose and 30 days after last dose of study drug; [d]1 grade 5 event (sudden death); [e]Treatment-related deaths were reported regardless of timeframe; [f]1 event of sudden death; [g]1 event of respiratory failure. TRAE, treatment-related adverse event.

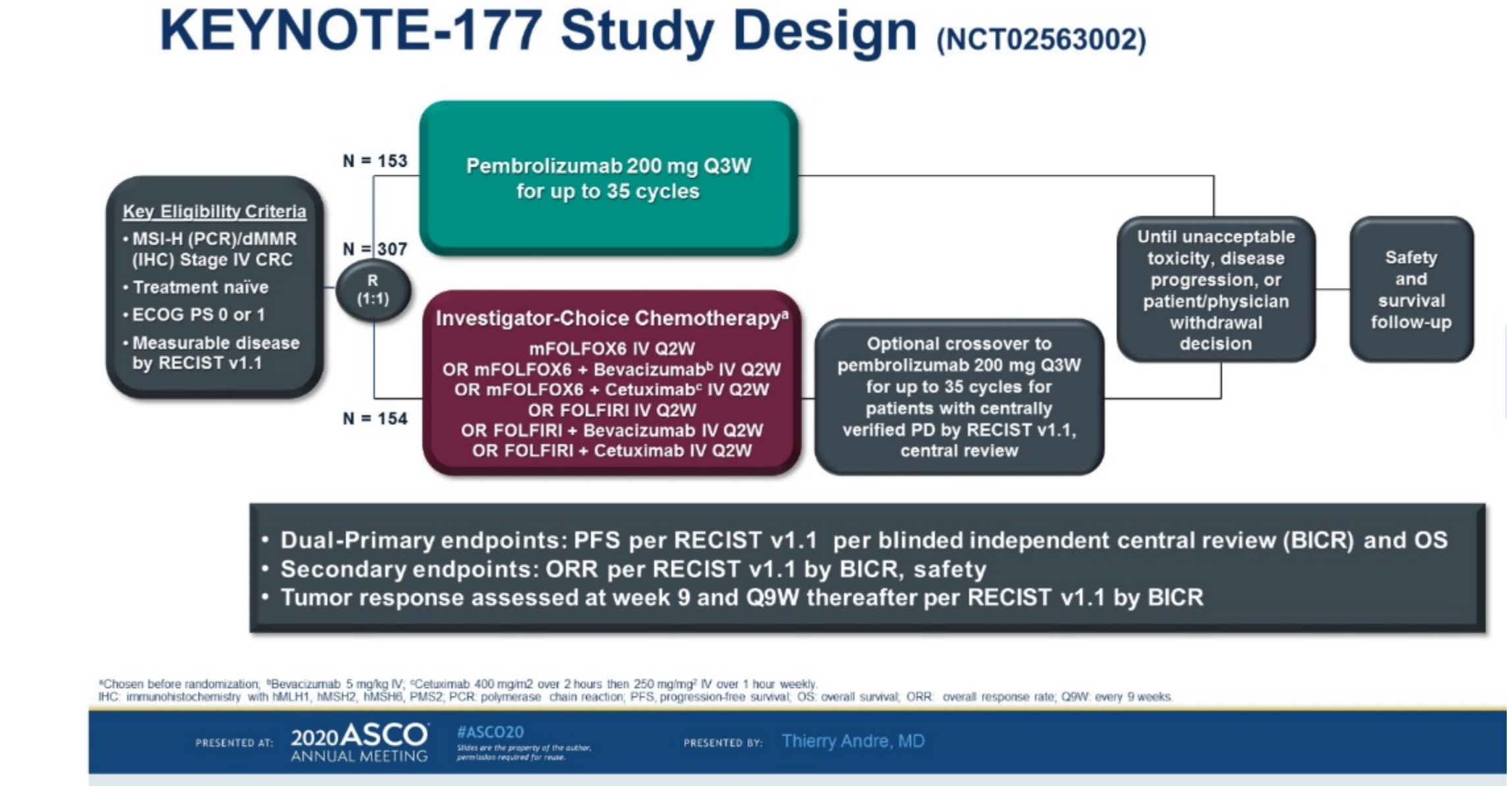
Overman MJ et al. ASCO 2022;Abstract 3510.

First-Line (1L) Nivolumab (NIVO) + Ipilimumab (IPI) in Patients (pts) with Microsatellite Instability-High/Mismatch Repair Deficient (MSI-H/dMMR) Metastatic Colorectal Cancer (mCRC): 64-Month (mo) Follow-Up from CheckMate 142

Lenz H-J et al.

Gastrointestinal Cancers Symposium 2024;Abstract 97.
Saturday, January 20, 2024 | Poster session begins at 6:30 AM PT

First Line MSI mCRC



Andre T et al. *J Clin Oncol.* 2020;38(suppl): Abstract LBA4.

Andre T et al. ASCO 2021: Abstract 3500.

KEYNOTE-177: PFS (5-year updated analysis)

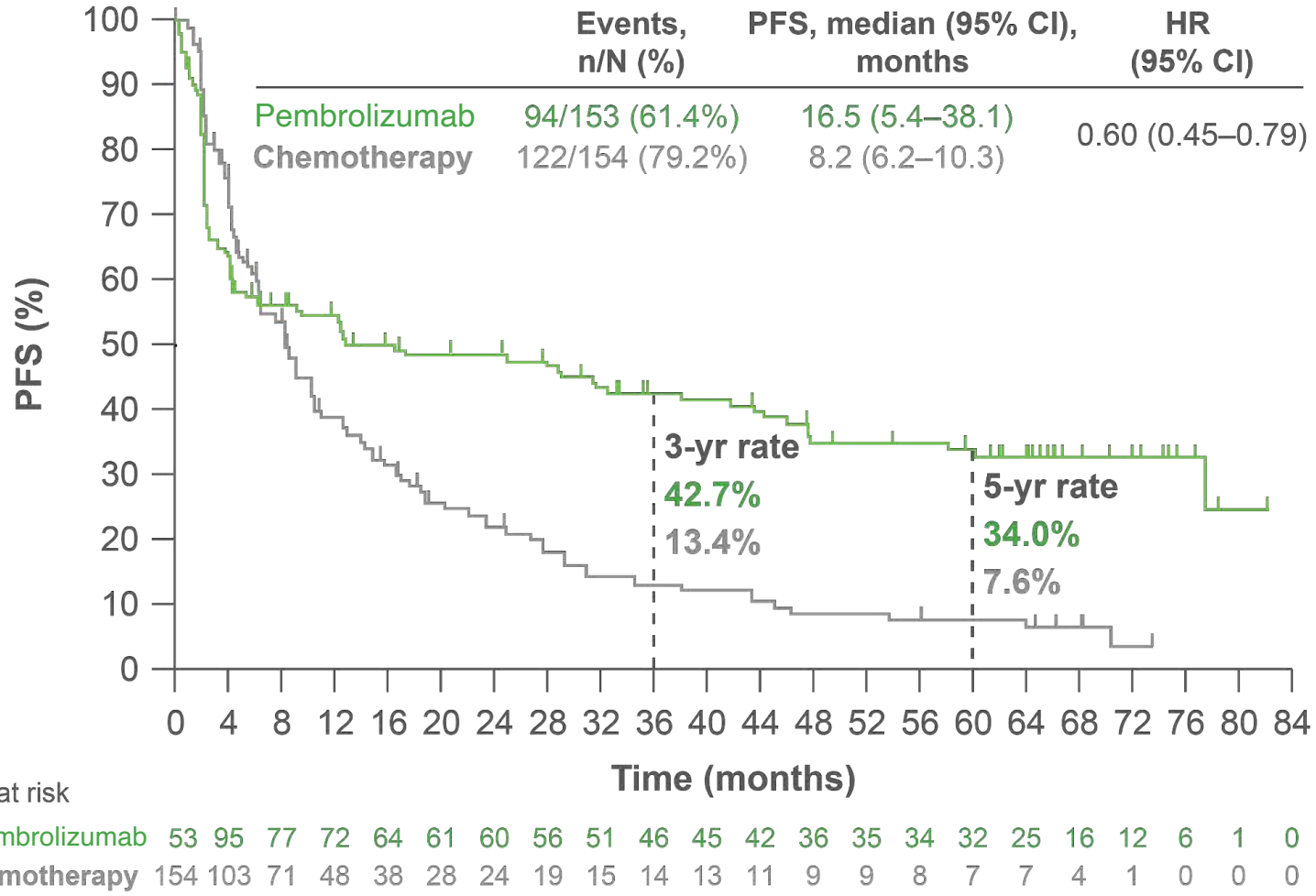


Figure adapted from Shiu KK et al. 2023.

This was an exploratory analysis; significance was not tested, so results should be interpreted with caution

Data cut-off: 17 July 2023.

[a]PFS was assessed per RECIST v1.1 by BICR.

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors Version 1.1; yr, year.

Shiu KK et al. Presented at the European Society for Medical Oncology (ESMO) Congress 2023, 20–24 October 2023, Madrid, Spain.

KEYNOTE-177: OS (5-year updated analysis)

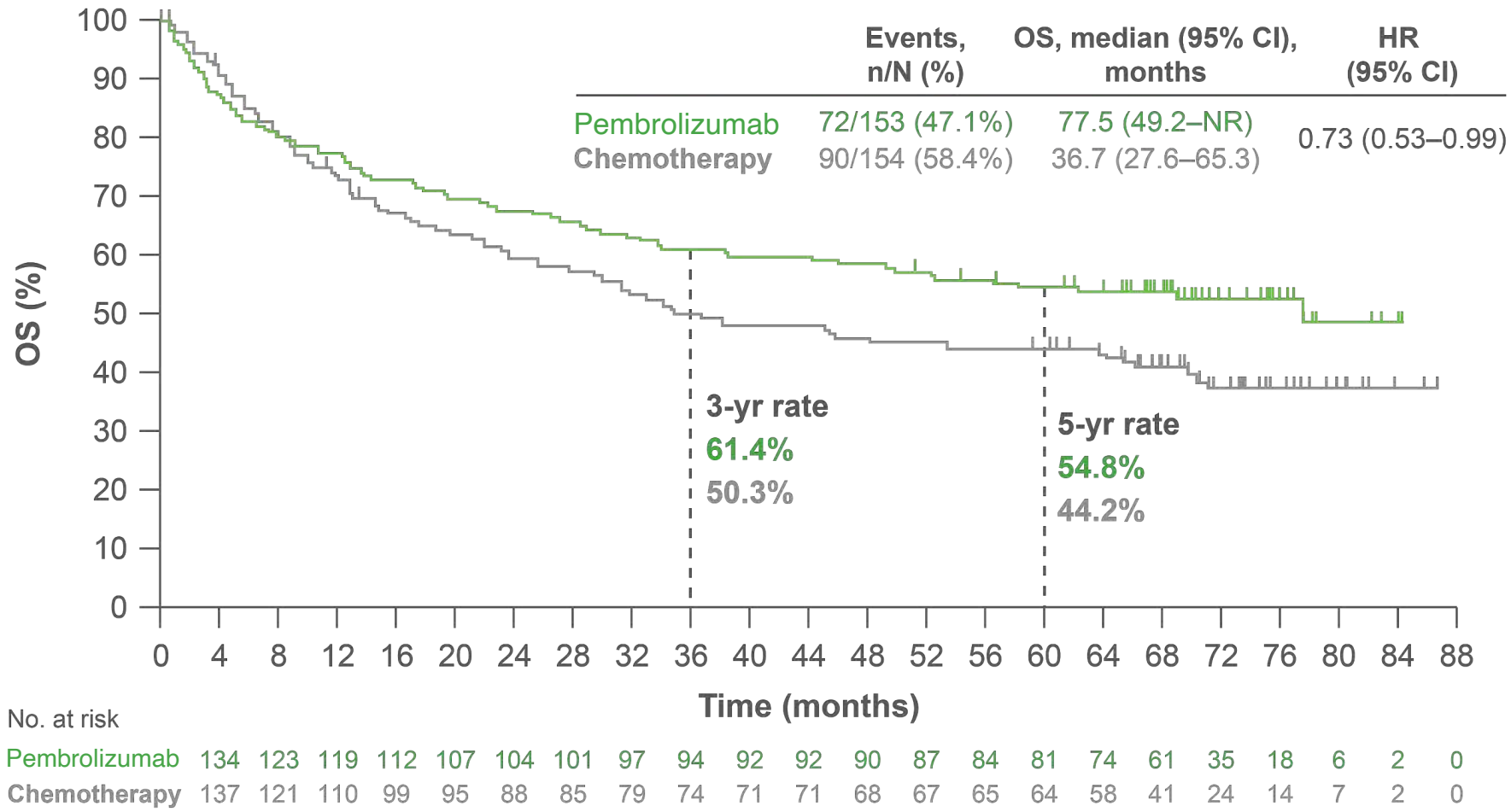


Figure adapted from Shiu KK et al. 2023.

When last formally tested at the final analysis in 2021, the OS improvement did not reach statistical significance and was not formally re-tested

Shiu KK et al. Presented at the European Society for Medical Oncology (ESMO) Congress 2023, 20–24 October 2023, Madrid, Spain.

KEYNOTE-177: Duration of response (5-year updated analysis)

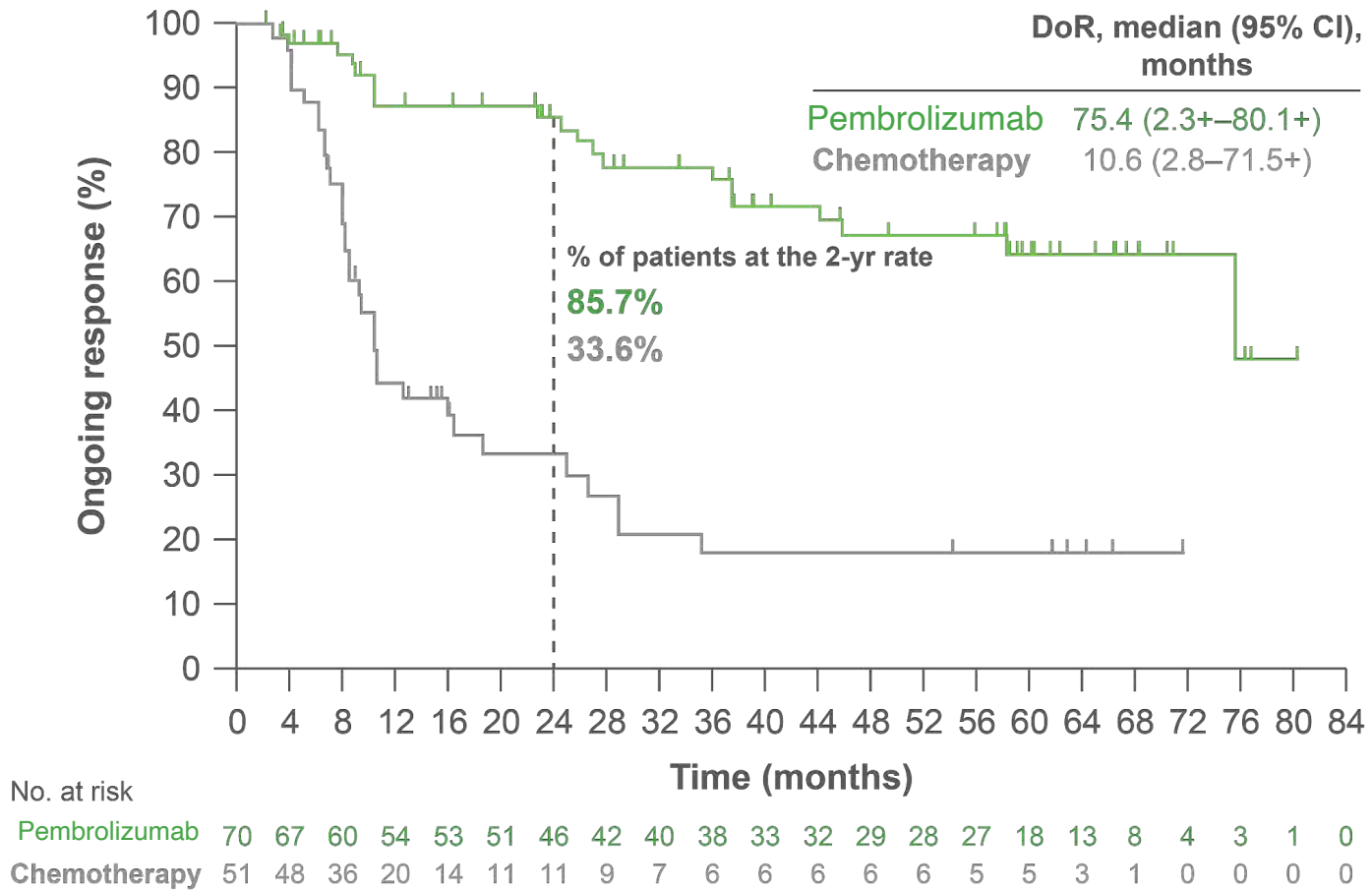
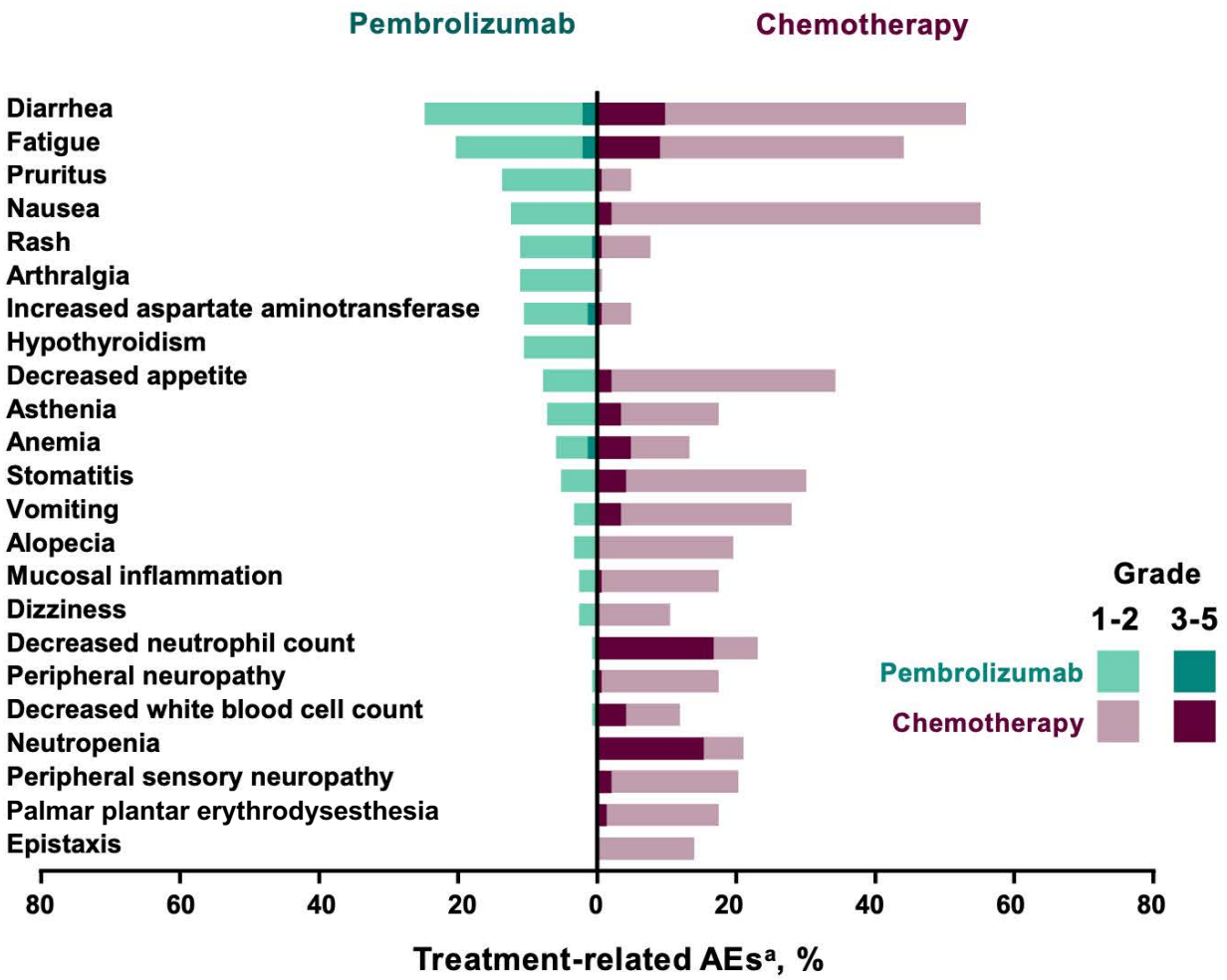


Figure adapted from Shiu KK et al. 2023.

Endpoint was not powered for statistical comparison in subgroups

Shiu KK et al. Presented at the European Society for Medical Oncology (ESMO) Congress 2023, 20–24 October 2023, Madrid, Spain.

KEYNOTE-177: AEs



n (%)	Pembrolizumab N = 153	Chemotherapy N = 143
Any AE	**149 (97.4)**	**142 (99.3)**
Treatment-related AE	**122 (79.7)**	**141 (98.6)**
Grade 3-5	33 (21.6)	96 (67.1)
Led to treatment discontinuation	15 (9.8)	10 (7.0)
Led to death	0	1 (0.7)
Immune-mediated AEs and Infusion Reactions		
All	51 (33.3)	23 (16.1)
Grade 3-5	16 (10.5)	3 (2.1)
Led to death	0	0

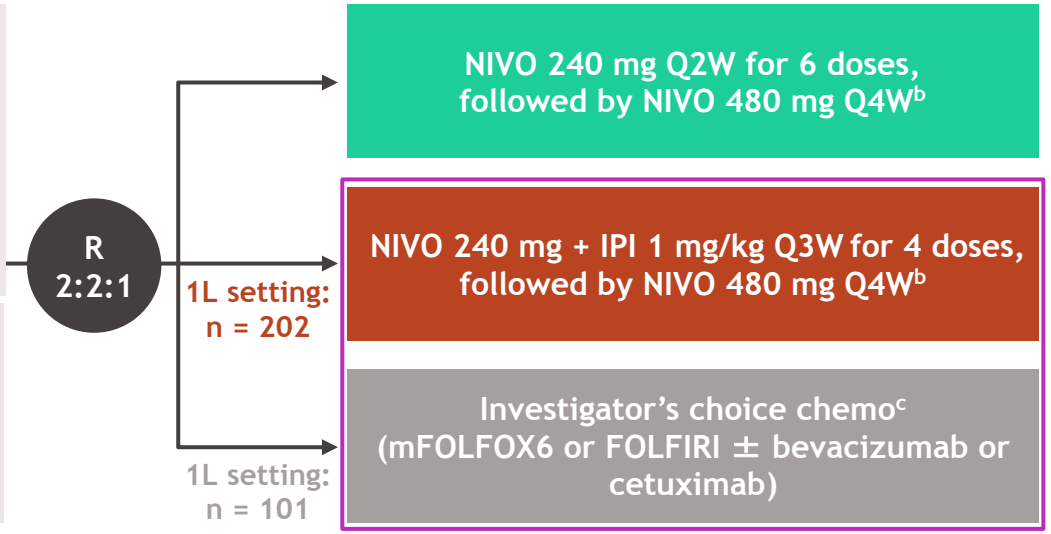
Shiu KK et al. Presented at the European Society for Medical Oncology (ESMO) Congress 2023, 20–24 October 2023, Madrid, Spain.

CheckMate 8HW 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
- 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[d]:
- PFS by BICR[e] (NIVO + IPI vs chemo in the 1L setting)
- PFS by BICR[e] (NIVO + IPI vs NIVO across all lines)

Other select endpoints:
- Safety
- OS; ORR by BICR[e]; PROs

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

[a]ClinicalTrials.gov. NCT04008030. [b]Patients with ≥ 2 prior lines are randomized only to the NIVO or NIVO + IPI arms. [c]Patients receiving investigator's choice of chemotherapy are eligible to receive NIVO + IPI upon progression (crossover treatment). [d]Confirmed using either immunohistochemistry and/or polymerase chain reaction-based tests. [e]Evaluated using RECIST v1.1. [f]Time between randomization and last known date alive or death.

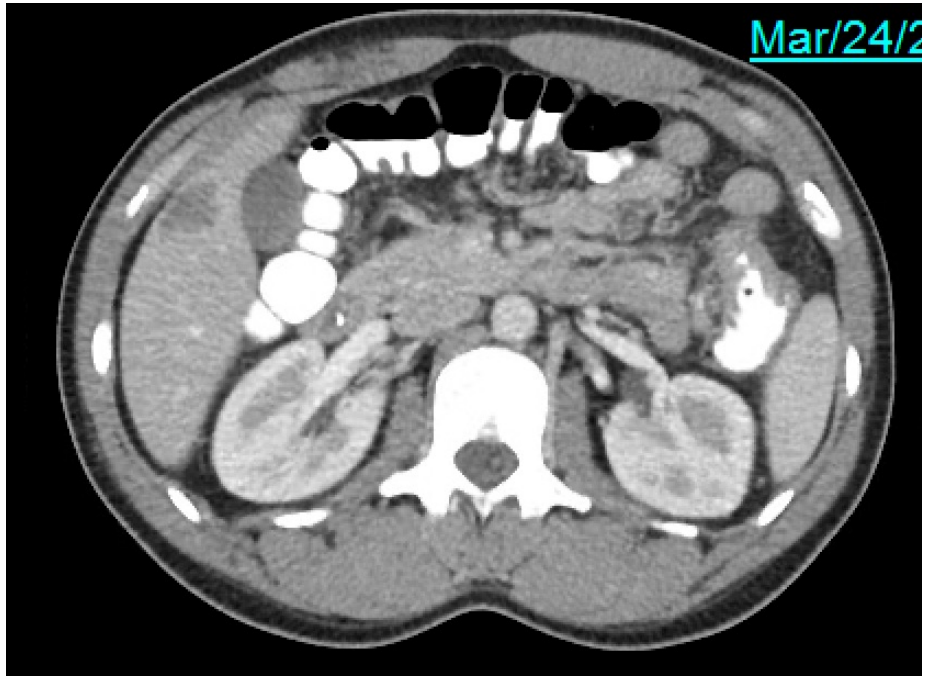
Nivolumab (NIVO) plus Ipilimumab (IPI) vs Chemotherapy (Chemo) as First-Line (1L) Treatment for Microsatellite Instability-High/Mismatch Repair-Deficient (MSI-H/dMMR) Metastatic Colorectal Cancer (mCRC): First Results of the CheckMate 8HW Study

Andre T et al.

Gastrointestinal Cancers Symposium 2024;Abstract LBA768.
Saturday, January 20, 2024 | 9:15 AM PT

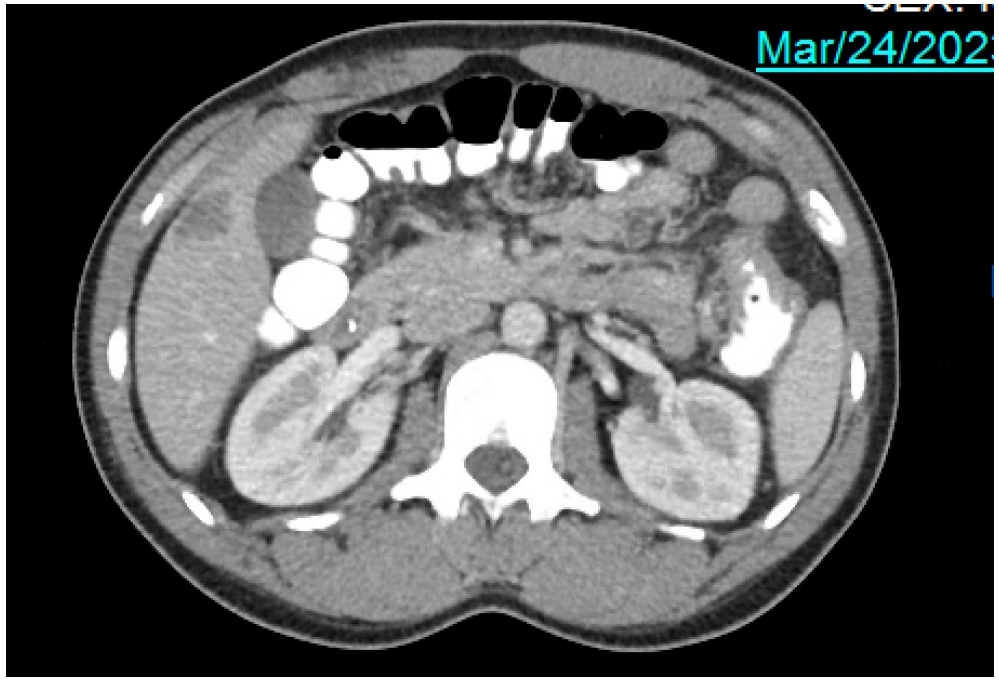
Case study

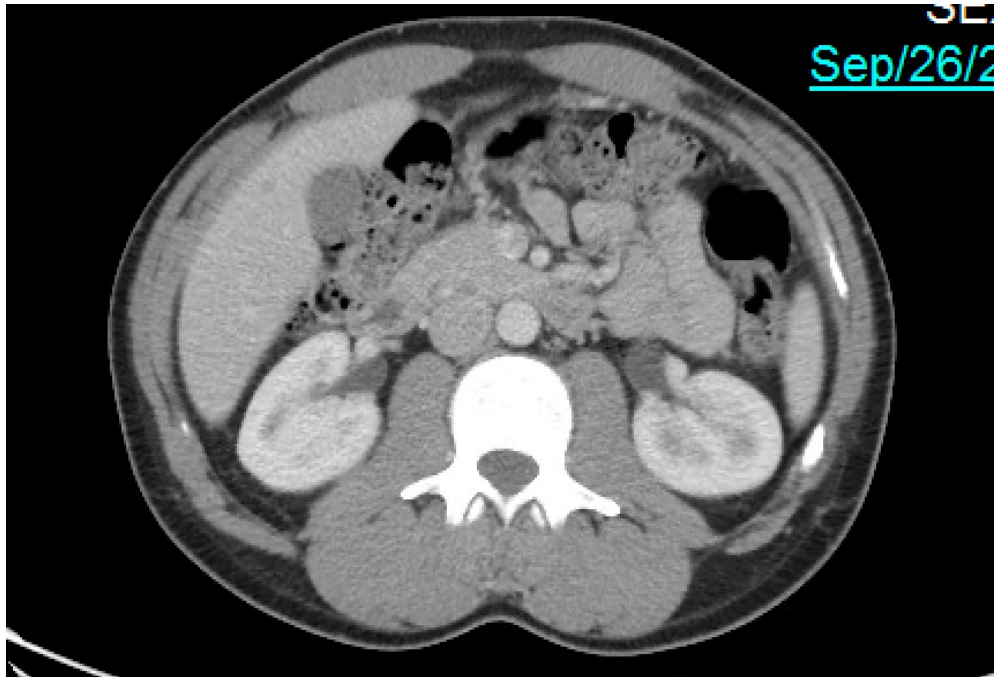
- Patient is a 32-year-old man with no significant medical history
- Presented with 2 months of abdominal pain
- Saw a primary care physician and was referred for a colonoscopy
- Colonoscopy was complete to the cecum; a notable ulcerated 4 cm mass in the transverse colon was observed
- Bx + adenocarcinoma; IHC loss of PMS2
- CT CAP notable for a 2.1 cm right hepatic mass confirmed by an MRI
- CEA 3.0
- NGS testing confirmed MSI; TMB 35.4



Please note that this is one individual, and cases may vary. Images provided by the speaker.
Bx, biopsy; CAP, chest, abdomen, and pelvis; CEA, carcinoembryonic antigen; CT, computed tomography; IHC, immunohistochemistry; MRI, magnetic resonance imaging; MSI, microsatellite instability; NGS, next generation sequencing; PMS2, PMS1 homolog 2; TMB, tumour mutational burden.

- Patient initiated pembrolizumab per KEYNOTE-177 trial
- Abdominal pain resolved and a 6-month CT CAP showed notable significant tumour regression
- The patient currently remains on treatment





Please note that this is one individual, and cases may vary. Images provided by the speaker.
CAP, chest, abdomen, and pelvis; CT, computed tomography.

Important clinical considerations

- Germline testing
- Duration of therapy – 2 years
- Plan for resection with primary and one lesion vs. continued treatment?
- Single agent PD1 vs combination therapy

Please note that this is one individual, and cases may vary.

MODULE 5: HER2 and Other Emerging Biomarkers for Targeted Therapy in mCRC – Dr Strickler

RTP
RESEARCH
TO PRACTICE

Trastuzumab deruxtecan: Indications, prevention and management of interstitial lung disease

Arvind N Dasari, MD, MS

QUESTIONS FOR THE FACULTY

Arvind N Dasari, MD, MS

How do you think through the sequencing of anti-HER2 therapies in mCRC?

What is your approach to the detection and management of trastuzumab deruxtecan-associated ILD?

RTP RESEARCH TO PRACTICE

Treatment of HER2-positive mCRC; KRAS G12C inhibitors and other novel strategies under development

Kristen K Ciombor, MD, MSCI

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Kristen K Ciombor, MD, MSCI

What is your experience with the combination of trastuzumab/pertuzumab in HER2-positive mCRC?

What other targeted strategies are you most excited about for patients with mCRC?

RTP RESEARCH TO PRACTICE

What was the age of the last patient in your practice with HER2-positive mCRC who received targeted treatment? Which targeted treatment did they receive, and what was their response to therapy?

	Age	Targeted Tx	Response
 Dr Bekaii-Saab	53 years	Tucatinib/trastuzumab	PR
 Dr Cercek	47 years	Tucatinib/trastuzumab	PR
 Dr Eng	52 years	Tucatinib	PR
 Dr Lieu	45 years	Tucatinib/trastuzumab	PR
 Dr Strickler	42 years	Tucatinib/trastuzumab	Near CR
 Dr Ciombor	60 years	Trastuzumab/pertuzumab (prior to MOUNTAINEER approval)	PR
 Dr Dasari	43 years	Tucatinib/trastuzumab	PR

PR = partial response

Regulatory and reimbursement issues aside, what would be your most likely first- and second-line anti-HER2 treatments for a patient with HER2-positive mCRC?

	First line	Second line
 Dr Bekaii-Saab	Tucatinib/trastuzumab	Trastuzumab deruxtecan
 Dr Cercek	Tucatinib/trastuzumab	Trastuzumab deruxtecan
 Dr Eng	Tucatinib/trastuzumab	Trastuzumab deruxtecan
 Dr Lieu	Tucatinib/trastuzumab	Trastuzumab deruxtecan
 Dr Strickler	Tucatinib/trastuzumab	Trastuzumab deruxtecan
 Dr Ciombor	Tucatinib/trastuzumab	Trastuzumab deruxtecan
 Dr Dasari	Tucatinib/trastuzumab	Trastuzumab deruxtecan

Regulatory and reimbursement issues aside, what would be your most likely anti-HER2 treatment for a patient with HER2-positive mCRC and brain metastases?

 Dr Bekaii-Saab	Tucatinib/trastuzumab
 Dr Cercek	Tucatinib/trastuzumab
 Dr Eng	Tucatinib/trastuzumab
 Dr Lieu	Tucatinib/trastuzumab
 Dr Strickler	Tucatinib/trastuzumab
 Dr Ciombor	Trastuzumab deruxtecan
 Dr Dasari	Tucatinib/trastuzumab

RTP RESEARCH TO PRACTICE

Please provide at least 1 impediment or barrier you have encountered in your attempts to deliver high-quality care to your patients with CRC.

- Keeping up with tumor-specific advances/nuances as a general medical oncologist
- Sometimes getting patients enrolled in clinical trials quickly in the community once the patients run out of regular options
- Lack of knowledge about all different targeted options
- Insurance coverage
- Insurance coverage of NGS and ctDNA testing
- Access to good quality trials in previously treated patients
- The possibility of the utilization of neoadjuvant therapy prior to surgical interventions
- No new drugs
- Rapidly evolving data set and keeping up
- Once the patient is progressing past combination chemotherapy/bev, there seem to be no good options for HER2 WT or MSS colon ca
- None
- Inability to fully decode the role of ctDNA in CRC. A clear set of directives would help general oncologists use it widely. Also, there is issue with reimbursement for ctDNA

Please provide at least 1 impediment or barrier you have encountered in your attempts to deliver high-quality care to your patients with CRC. (Continued)

- Need more therapy options for second line and beyond
- Community hospital does not send tumor markers in time or insurance would not pay for broad molecular test
- Which therapies to use in different lines of therapy and the role of serial ctDNA monitoring
- Metastatic CRC and treatment-free interval post adjuvant therapy; MRD-directed therapy and possible discontinuation
- Difficulty keeping up with abundance of data and publications, especially in a general oncology clinic
- Insurance approval can take a long time
- Insurance approval
- Insurance
- Insurance issues leading to breaks in care
- Hard to keep up with all the new data
- Financial toxicity
- Authorization from insurance

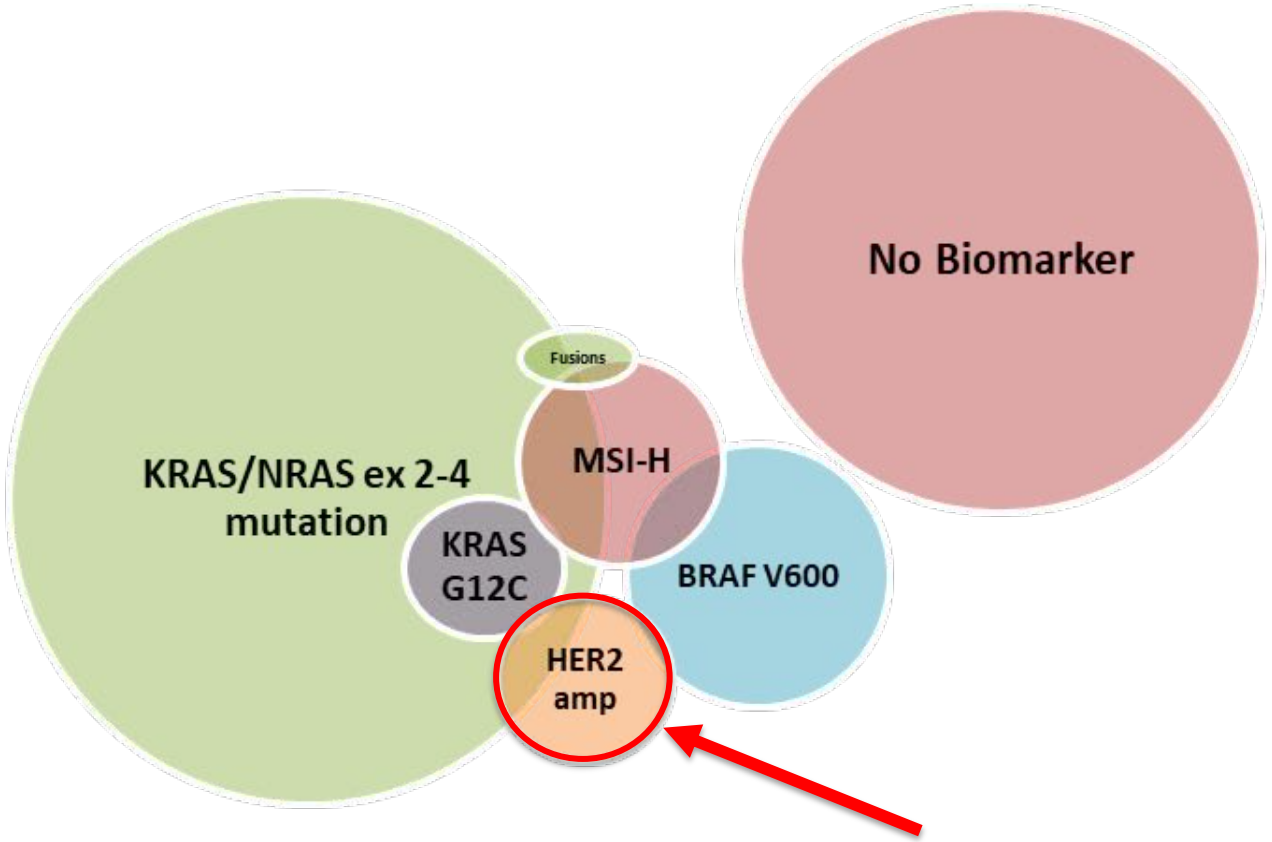
HER2 and Other Emerging Biomarkers for Targeted Therapy in metastatic CRC

John H. Strickler, MD
Associate Professor of Medicine
Duke University Medical Center

January 19, 2024

HER2 as an emerging precision cancer medicine target in metastatic CRC

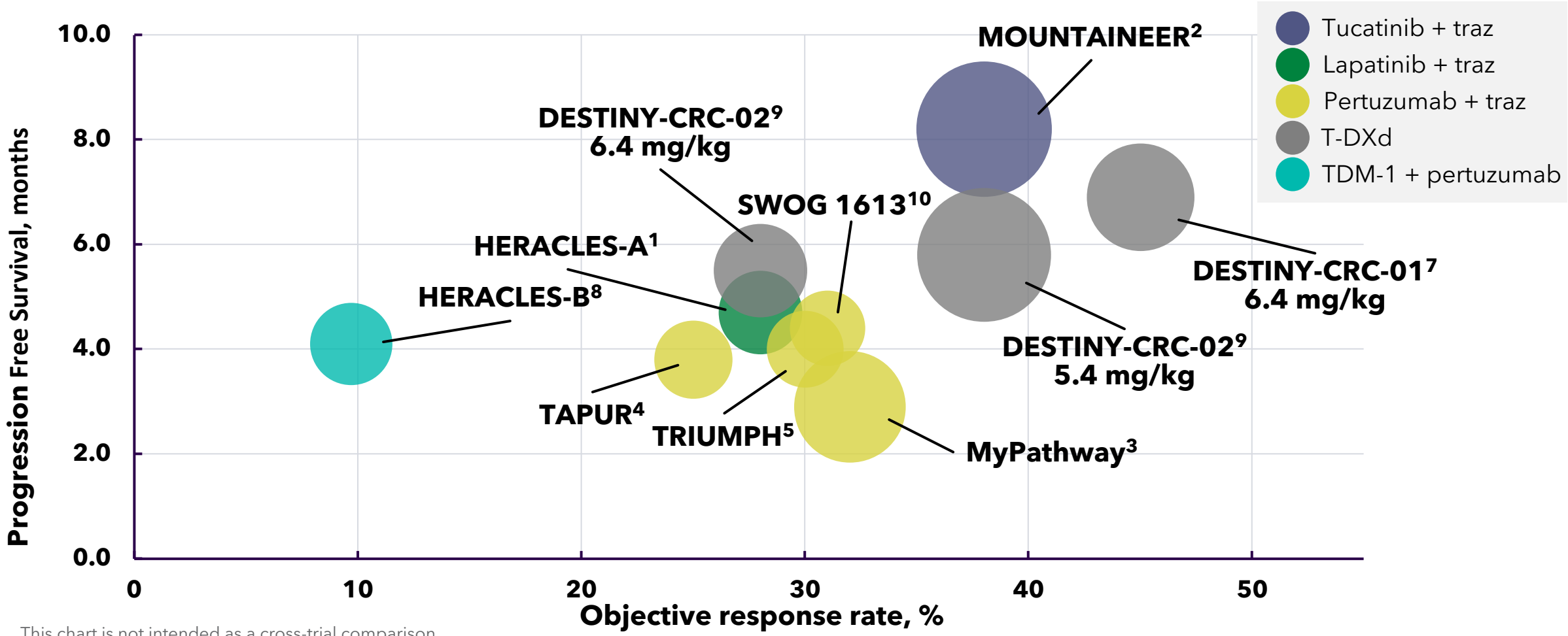
Actionable targets in metastatic CRC



- Usually <u>left sided</u>
- <u>Not</u> mutually exclusive with *RAS* or *BRAF* mutations
- Associated with lung and brain metastases
- May predict resistance to EGFR antibodies

Therapeutic landscape for HER2+ metastatic CRC

Size of data point adjusted for sample size

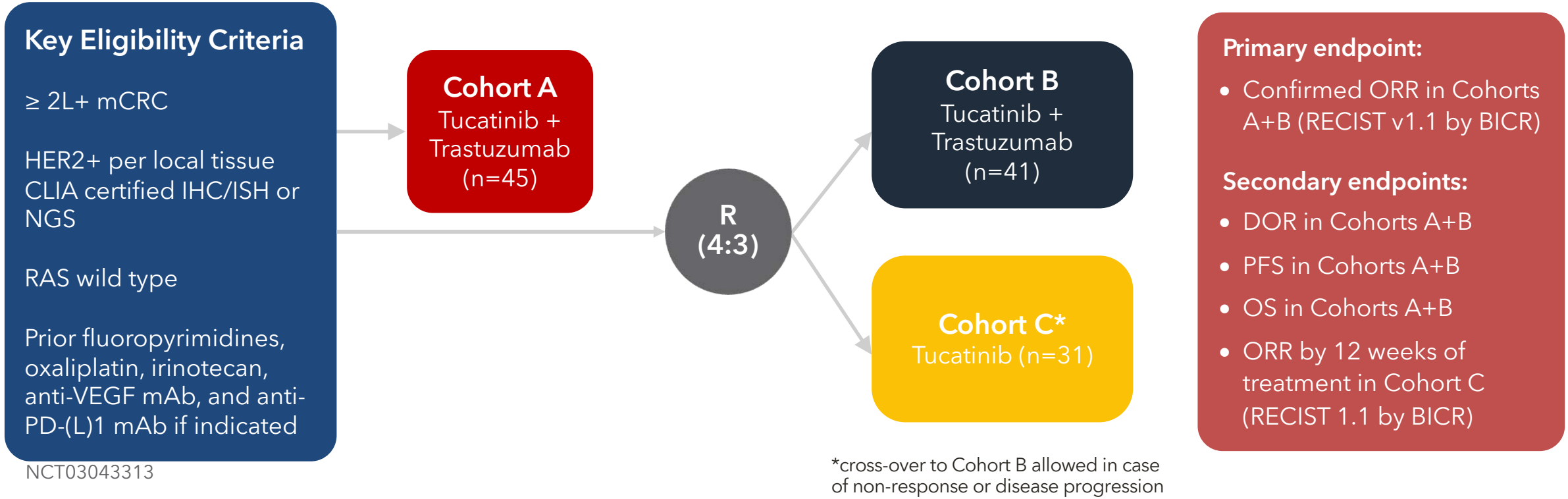


This chart is not intended as a cross-trial comparison.

CRC, colorectal cancer; HER2, human epidermal growth factor receptor 2; HER2+, HER2 gene amplification; T-DXd, trastuzumab-deruxtecan; TDM-1, trastuzumab emtansine; traz, trastuzumab.

1. Tosi F et al., Clin Colorectal Cancer 2020; 2. Strickler JH et al., Lancet Oncol. 2023; 3. Meric-Bernstam F et al., Lancet Oncol 2019; 4. Gupta et al., J Clinical Oncol. 2020; 5. Nakamura Y et al., Nature Medicine 2021; 6. Meric-Bernstam F et al., Ann Oncol. 2019; 7. Yoshino T et al., Nat. Commun. 2023. 8. Sartore-Bianchi A et al., ESMO Open 2020; 9. Raghav K et al., presented at ASCO Annual Meeting 2023, Chicago (USA), June 2-6, Oral Abstract 3501; 10. Raghav K et al., J Clin Oncol. 2023.

MOUNTAINEER: Tucatinib + Trastuzumab for HER2+ mCRC - Phase 2 Study Design



- Tucatinib is an oral, small molecule TKI that targets HER2
- Highly selective for the HER2 receptor
- Selectivity may improve tolerability (skin rash, diarrhea, etc.) compared to non-selective TKIs

Strickler JH et al. *Lancet Oncol.* 2023;24(5):496-508. Corti C et al. *ESMO Open.* 2021;6(2):100063. Moulder SL et al. *Clin Cancer Res.* 2017;23(14):3529-3536.

MOUNTAINEER: Tucatinib + Trastuzumab: Summary – Efficacy and Safety

Overview efficacy Tucatinib + Trastuzumab Cohorts A+B (n=84)[1]

Confirmed ORR, % (95% CI)	**38.1%** (27.7-49.3)
mDOR, months (95% CI)	**12.4 months** (8.5-25.5)
DCR, n (%)	**60** (71%)
PFS, months (95% CI)	**8.2 months** (4.2-10.3)
OS, months (95% CI)	**24.1 months** (20.3-36.7)

Overview safety Tucatinib + Trastuzumab Cohorts A+B (n=86)[2]

TEAEs, n (%)	Tucatinib + Trastuzumab
Any grade AEs	82 (95.3)
Tucatinib-related	63 (73.3)
Trastuzumab-related	58 (67.4)
Grade ≥3 AEs	33 (38.4)
Tucatinib-related	8 (9.3)
Trastuzumab-related	6 (7.0)
SAEs	19 (22.1)
Tucatinib-related	3 (3.5)
Trastuzumab-related	2 (2.3)
AEs leading to study treatment discontinuation[a,b]	5 (5.8)
AEs leading to tucatinib dose modification	22 (25.6)
Deaths due to AEs	0

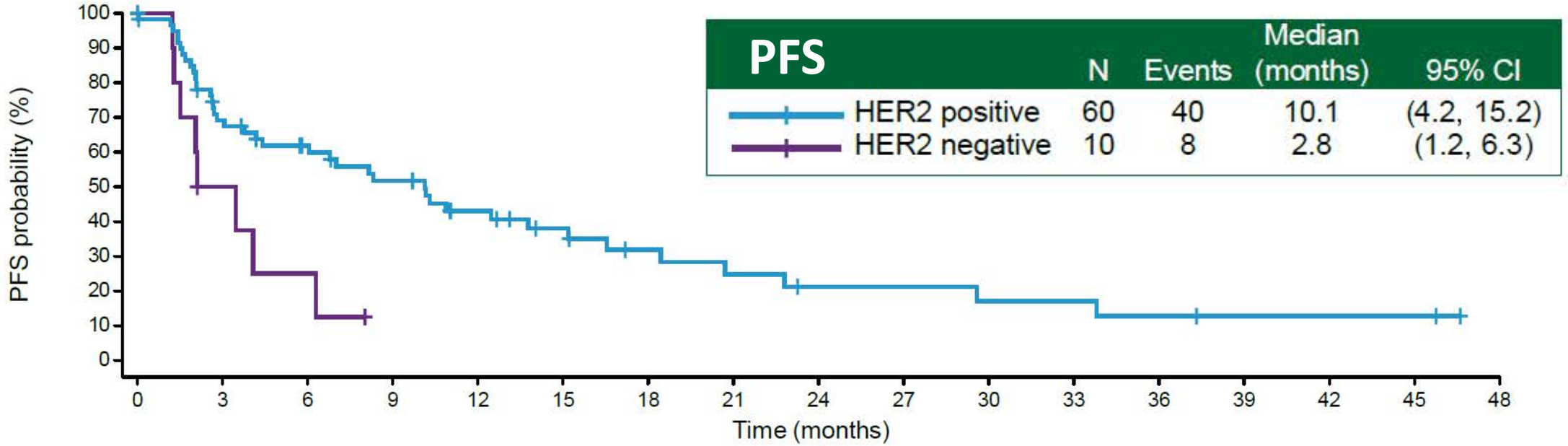
[a] TEAEs leading to discontinuation of tucatinib included alanine aminotransferase increase (2.3%), COVID-19 pneumonia (1.2%), cholangitis (1.2%), and fatigue (1.2%);
[b] TEAEs leading to discontinuation of trastuzumab included alanine aminotransferase increase (2.3%) and COVID-19 pneumonia (1.2%).

AE, adverse event; CI, confidence interval; DCR, disease control rate; mDOR, median duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

1. Strickler JH et al. *Lancet Oncol.* 2023;24(5):496-508. 2. Strickler JH et al. 2022 ESMO GI Congress. Abstract LBA-2.

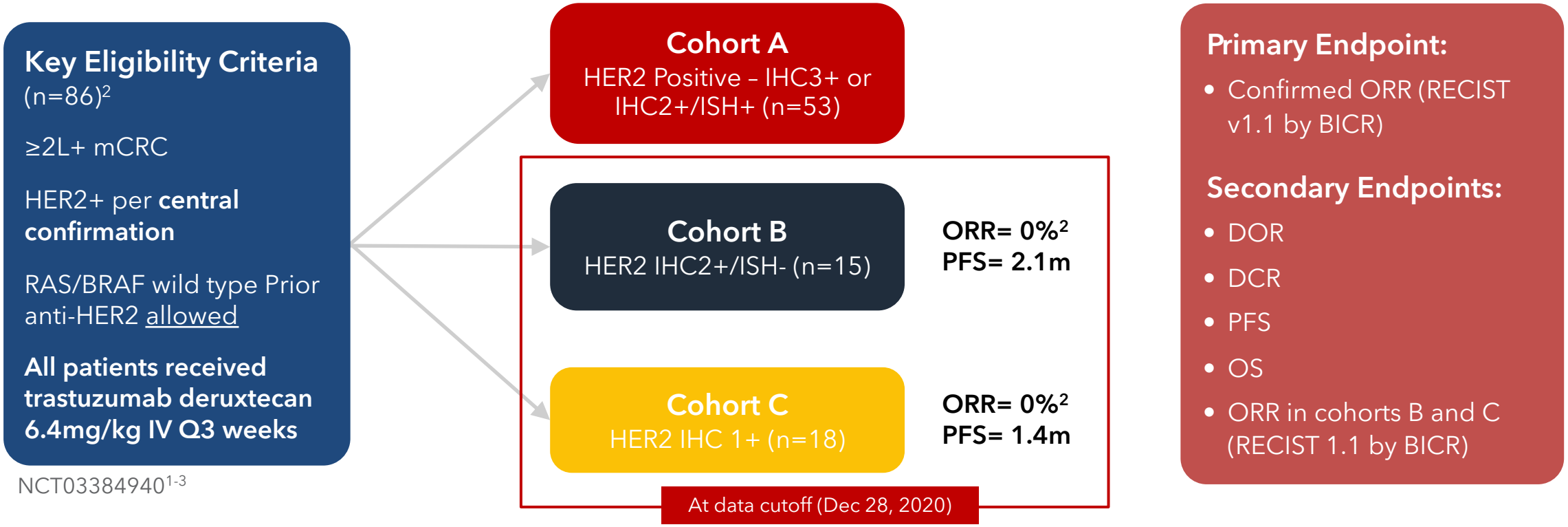
MOUNTAINEER Cohorts A+B
Response Assessment by Central IHC/FISH

Response	Central IHC + FISH		
	Positive (IHC3+) (n=45)	Positive (IHC2+/ISH+) (n=15)	Negative (n=10)
cORR, n (%) (95% CI)	21 (46.7%) (31.7-62.1)	3 (20.0%) (4.3-48.1)	1 (10.0%) (0.3-44.5)
mDOR, mo (95% CI)	16.4 (10.6, 25.5)		-



Strickler JH et al. 2023 ASCO Annual Meeting. Abstract 3528.

DESTINY-CRC01: Trastuzumab deruxtecan (T-DXd; DS-8201a) for HER2+ mCRC - Phase 2 Study Design



1. Siena S et al. *Lancet Oncol.* 2021;22(6):779-789.
2. Yoshino T et al. 2021 ASCO Annual Meeting. Abstract 3505.
3. Yoshino T et al. *Nat Commun.* 2023;14(1):3332.

DESTINY-CRC01: Trastuzumab deruxtecan for HER2+ mCRC - Efficacy Outcomes

Cohort A, N=53 (response assessed by BICR)[1-3]

Confirmed ORR, % (95% CI)	45.3% (31.6-59.6)
mDOR, months (95% CI)[2]	7.0 months (5.8-9.5)
Disease control rate, % (95% CI)	83.0% (70.2-91.9)
PFS, months (95% CI)[2]	6.9 months (4.1-8.7)
OS, months (95% CI)[2]	15.5 months (8.8-20.8)

Data cutoff (Dec 28, 2020)

BICR, blinded independent central review; CI, confidence interval; HER2+, HER2 gene amplification; mCRC, metastatic colorectal cancer; NE, not evaluable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

1. Siena S et al. *Lancet Oncol.* 2021;22(6):779-789. 2. Yoshino T et al. 2021 ASCO Annual Meeting. Abstract 3505. 3. Yoshino T et al. *Nat Commun.* 2023;14(1):3332.

DESTINY-CRC01: Trastuzumab deruxtecan for HER2+ mCRC - Most Common TEAEs (≥ 10%)

(All cohorts, N=86)

Preferred term	Any grade	Grade ≥3
Patients with any TEAE	86 (100)	56 (65.1)
Nausea	53 (61.6)	5 (5.8)
Anemia	31 (36.0)	12 (14.0)
Fatigue	31 (36.0)	1 (1.2)
Decreased appetite	30 (34.9)	0
Platelet count decreased	28 (32.6)	8 (9.3)
Vomiting	27 (31.4)	1 (1.2)
Neutrophil count decreased	26 (30.2)	19 (22.1)
Diarrhea	23 (26.7)	1 (1.2)

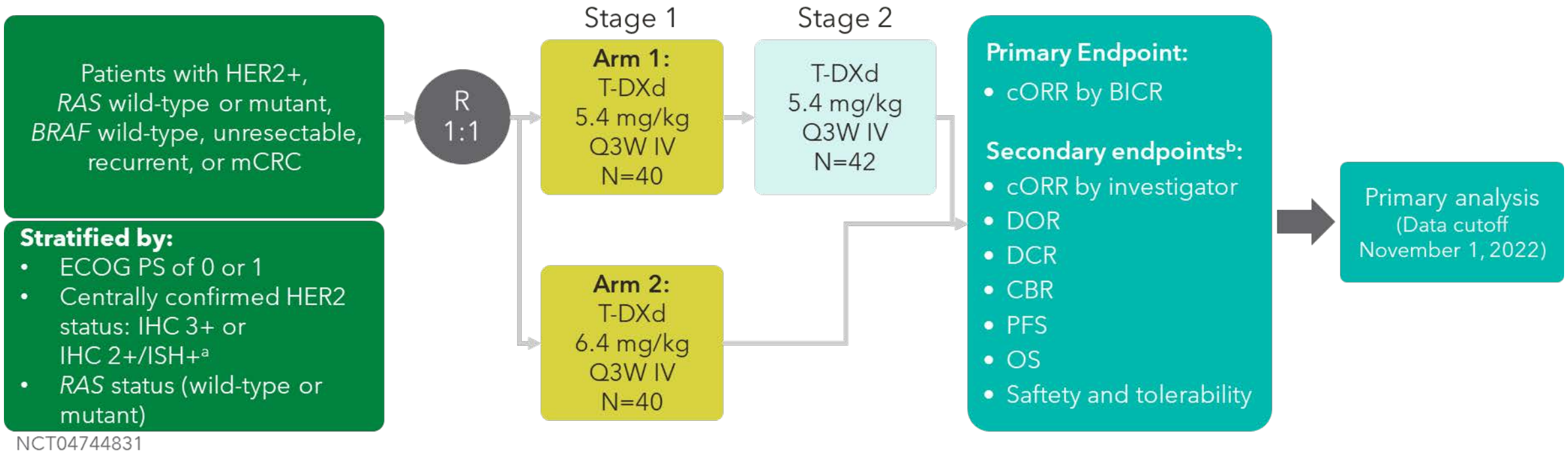
- Eight (9.3%) of 86 patients had interstitial lung disease or pneumonitis
  - Grade 2 = 4 patients
  - Grade 3 = 1 patient
  - Grade 5 = 3 patients
- Median time to onset date of interstitial lung disease or pneumonitis was 66.5 days
- 4 recovered, 1 did not recover and died of disease progression, and 3 died due to the AE

AE, adverse event; HER2, human epidermal growth factor receptor 2; HER2+, HER2 gene amplification; mCRC, metastatic colorectal cancer; TEAE, treatment-emergent adverse event.

Yoshino T et al. *Nat Commun.* 2023;14(1):3332.

DESTINY-CRC02 - Study Design

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



NCT04744831

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

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

Raghav K et al. 2023 ASCO Annual Meeting. Abstract 3501.

DESTINY-CRC02: Trastuzumab deruxtecan for HER2+ mCRC - Efficacy Outcomes

	5.4 mg/kg Q3W (n = 82)	6.4 mg/kg Q3W (n = 40)
Confirmed ORR, % (95% CI)	37.8% (27.3-49.2)	27.5% (14.6-43.9)
mDOR, months (95% CI)	5.5 mo 4.2-8.1)	5.5 months (3.7-NE)
Disease control rate, % (95% CI)		85.0% (70.2-94.3)
PFS, months (95% CI)	5.8 7.0)	5.5 (4.2-7.0)
OS, months (95% CI)	13.4 months (12.5-16.8)	NE (9.9-NE)

5.4mg/kg wins!

Raghav K et al. 2023 ASCO Annual Meeting. Abstract 3501.

DESTINY-CRC02: Adjudicated Drug-Related ILD/Pneumonitis by Independent Adjudication Committee

Adjudicated as drug-related ILD/pneumonitis, n (%)	T-DXd 5.4 mg/kg Q3W			T-DXd 6.4 mg/kg Q3W
	Stage 1 n = 41[a]	Stage 2 n = 42	Total N = 83	Stage 1 N = 39
Any grade	4 (9.8)	3 (7.1)	7 (8.4)	5 (12.8)
Grade 1	1 (2.4)		1 (1.2)	2 (5.1)
Grade 2	3 (7.3)		(7.2)	2 (5.1)
Grade 3	0		0	0
Grade 4	0		0	0
Grade 5	0	0	0	1 (2.6)[b]

5.4mg/kg wins!

Raghav K et al. 2023 ASCO Annual Meeting. Abstract 3501.

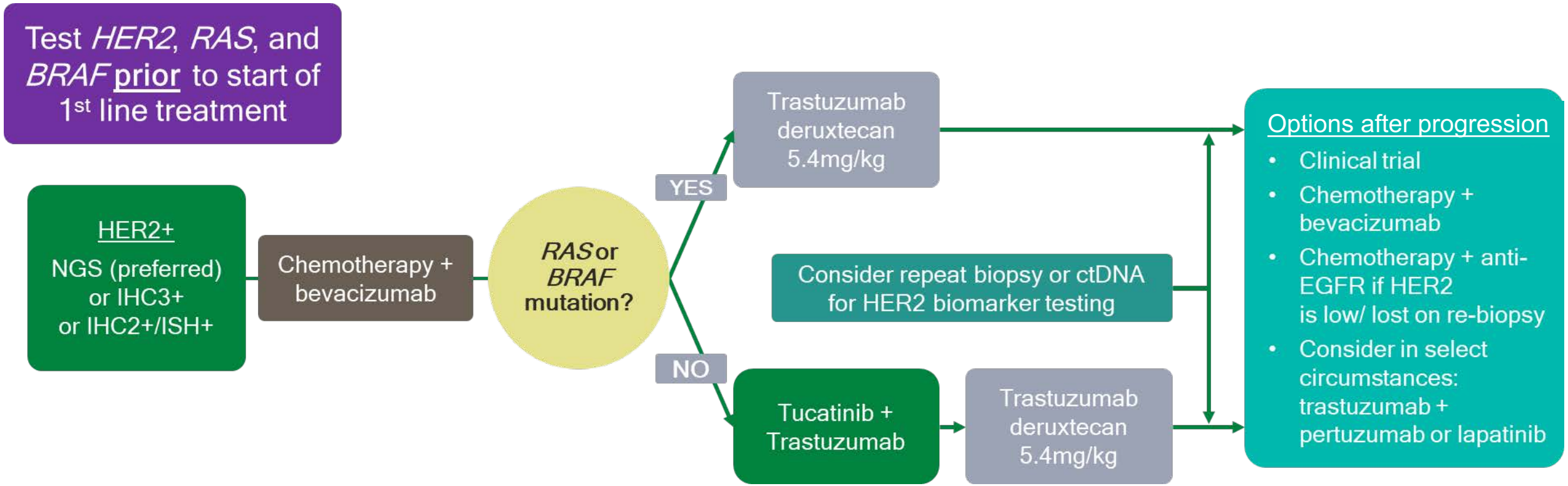
DESTINY-CRC02: Trastuzumab deruxtecan for HER2+ mCRC - Best ORR (BICR) by T-DXd 5.4 mg/kg subgroup

		ORR, % (n/N)	95% CI[a]
All patients (5.4 mg/kg)	**N = 82**	**37.8 (31/82)**	27.3-49.2
HER2 status	IHC 3+	**46.9 (30/64)**	34.3-59.8
	IHC 2+/ISH+	**5.6 (1/18)**	0.1-27.3
***RAS* status**	Wild-type	**39.7 (27/68)**	28.0-52.3
	Mutant[b]	**28.6 (4/14)**	8.4-58.1
ECOG PS	0	**39.1 (18/46)**	25.1-54.6
	1	**36.1 (13/36)**	20.8-53.8
Primary tumor site	Left colon[c]	**39.3 (24/61)**	27.1-52.7
	Right colon[d]	**33.3 (7/21)**	14.6-57.0
Prior anti-HER2 treatment	No	**36.9 (24/65)**	25.3-49.8
	Yes	**41.2 (7/17)**	18.4-67.1

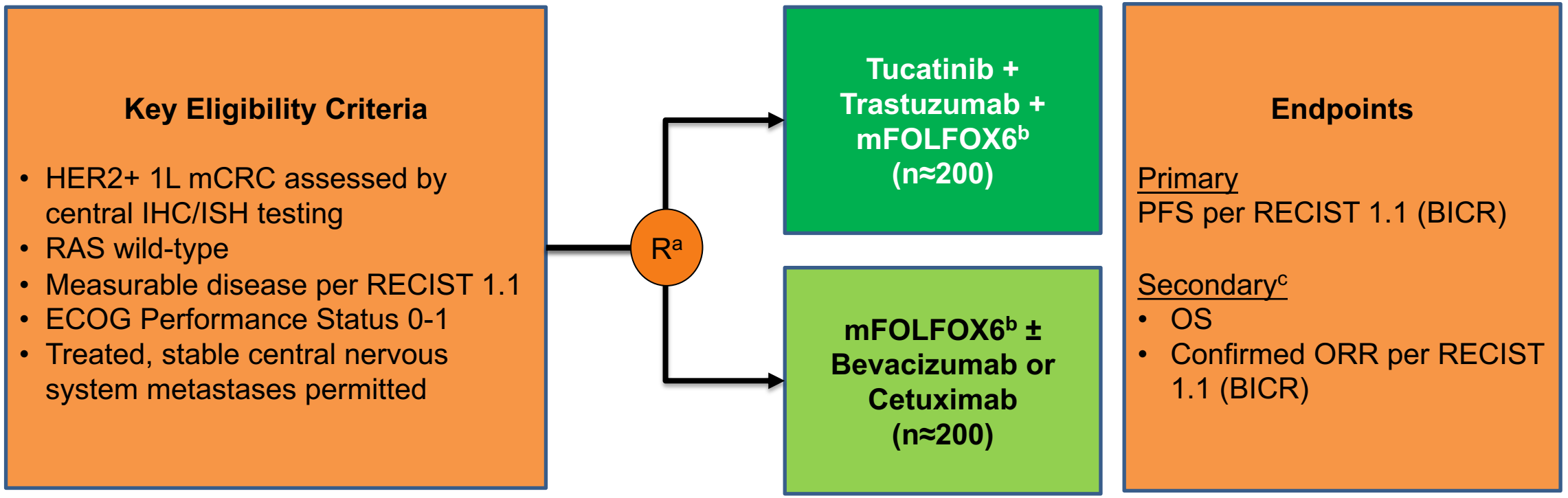
[a]Based on the exact Clopper-Pearson method for binomial distribution. [b]All RASm responders were IHC 3+. [c]Includes rectum, sigmoid, and descending. [d]Includes cecum, ascending, and transverse.
Trastuzumab deruxtecan is not approved by EMA in mCRC.

Raghav K et al., presented at ASCO Annual Meeting 2023, Chicago (USA), June 2-6, Oral Abstract 3501.

Evidence-Based Algorithm for HER2+ Metastatic CRC



MOUNTAINEER-03: Global, Randomised, Open-Label, Phase 3 Trial



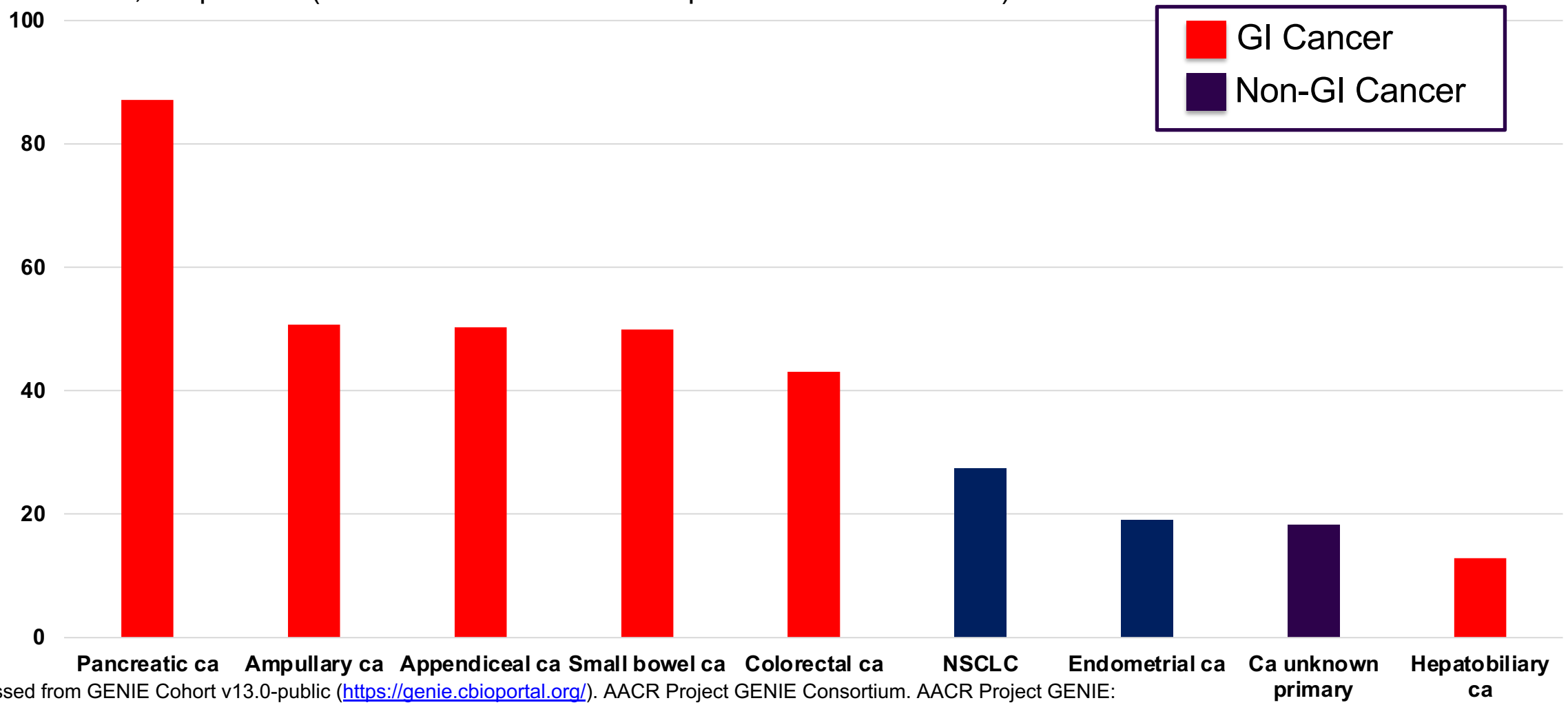
a Stratification: Primary tumor sidedness, liver metastases; b Levoleucovorin may be given in place of leucovorin; c Alpha-controlled

1L, first line; BICR, blinded independent central review; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; mCRC, metastatic colorectal cancer; mFOLFOX6, 5-fluorouracil, leucovorin, and oxaliplatin; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomisation; RAS, rat sarcoma virus; RECIST, Response Evaluation Criteria in Solid Tumors.

https://clinicaltrials.gov/ct2/show/NCT05253651 Bekaii-Saab TS et al. ASCO 2023; Abstract TPS3631.

KRAS: An Important Target for GI Cancers

N= 148,268 patients (tumors with *KRAS* mutation prevalence > 10% listed)



Accessed from GENIE Cohort v13.0-public (https://genie.cbioportal.org/). AACR Project GENIE Consortium. AACR Project GENIE: powering precision medicine through an international consortium. Cancer Discov 2017; 7: 818-31.

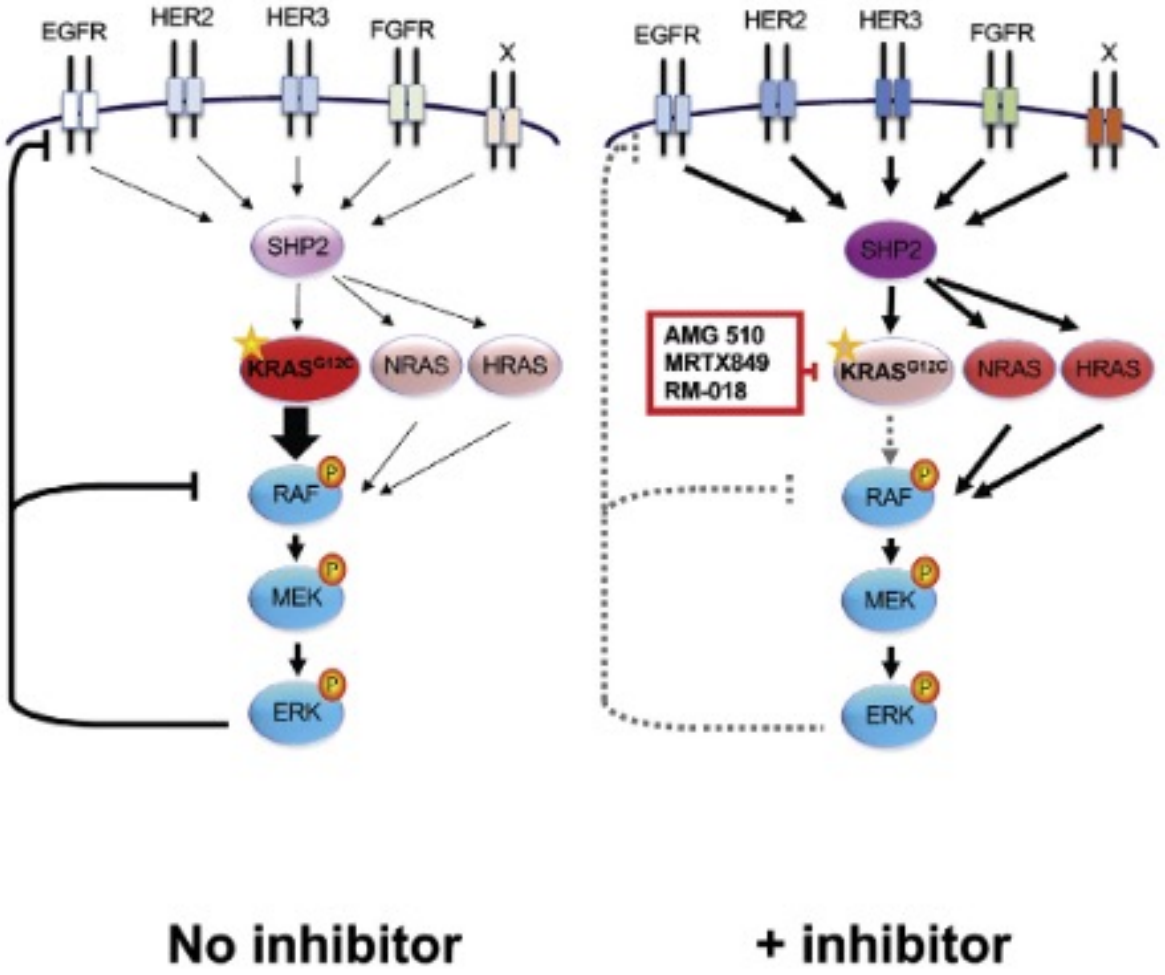
Sotorasib and Adagrasib Have Single-Agent Activity in *KRAS*^{G12C}-mutant Metastatic CRC

	Adagrasib (N=43)*	Sotorasib (N=62)
Objective response % (95% CI) per BICR	23% (12-39)	10% (4-20)
Median duration of response months (95%CI)	4.3 mo (2.3-8.3)	4.2 mo (2.9-8.5)
Median progression-free survival months (95%CI)	5.6 mo (4.1-8.3)	4.0 mo (2.8-4.2)
Median overall survival months (95%CI)	19.8 mo (12.5-23.0)	10.6 mo (7.7-15.6)
AE leading to dose reduction, n (%)	17 (39%)	11 (18%)**
AE leading to discontinuation, n (%)	0 (0%)	1 (2%)

Yaeger et al., N Engl J Med 2023; 388:44-54.
Fakih et al., Lancet Oncol 2022; 23: 115–24,

$KRAS^{G12C}$-independent Feedback Activation of Wild-type RAS Limits Single-agent Activity of $KRAS^{G12C}$ Inhibitors

- $KRAS^{G12C}$ inhibitors drive adaptive feedback reactivation of RAS-MAPK signaling via RTKs (EGFR, etc.)
- Activation of wild-type RAS (NRAS and HRAS) drives MAPK signaling in presence of $KRAS^{G12C}$ inhibition
- Vertical inhibition strategies (dual or triple inhibition with SHP2, MEK, and/or EGFR) enhance activity of $KRAS^{G12C}$ inhibitors



Ryan et al., Cell Reports 2022; 39(12) 1-14.
Amodio et al., Cancer Discov 2020;10:1129–39.

Dual Inhibition of $KRAS^{G12C}$ and EGFR Has Significant Activity for Refractory Metastatic CRC

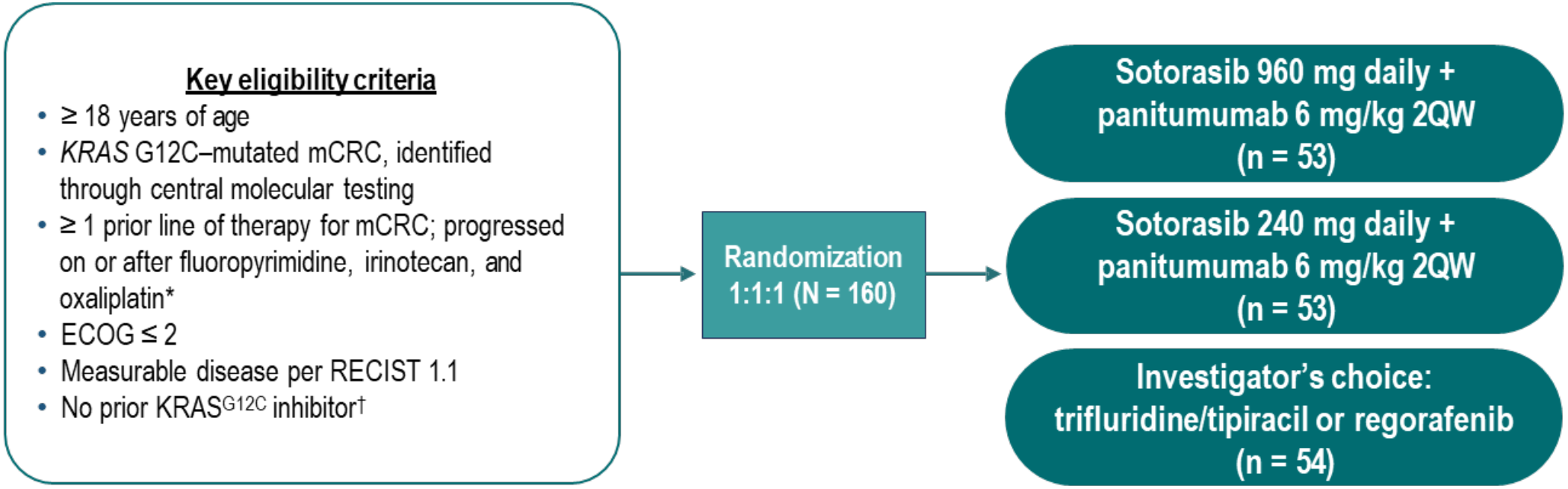
	Adagrasib+cetuximab (N=28)*	Sotorasib+panitumumab (N=40)
Objective response rate % (95% CI)	46% (28-66)	30% (17-47)
Median duration of response months (95%CI)	7.6 mo (5.7-NE)	5.3 mo (2.8-7.4)
Median progression-free survival months (95%CI)	6.9 mo (5.4-8.1)	5.7 mo (4.2-7.7)
Median overall survival months (95%CI)	13.4 mo (9.5-20.1)	15.2 mo (12.5-NE)

* 4 patients excluded from the efficacy analysis

Yaeger et al, N Engl J Med 2023; 388:44-54.
Kuboki et al, Nature Medicine (2024 Jan 4) Online ahead of print.

CodeBreaK 300 Phase 3 Study Design

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



Primary endpoint: PFS by BICR (measured by CT / MRI and assessed by RECIST v1.1)
Key secondary endpoints: OS, ORR

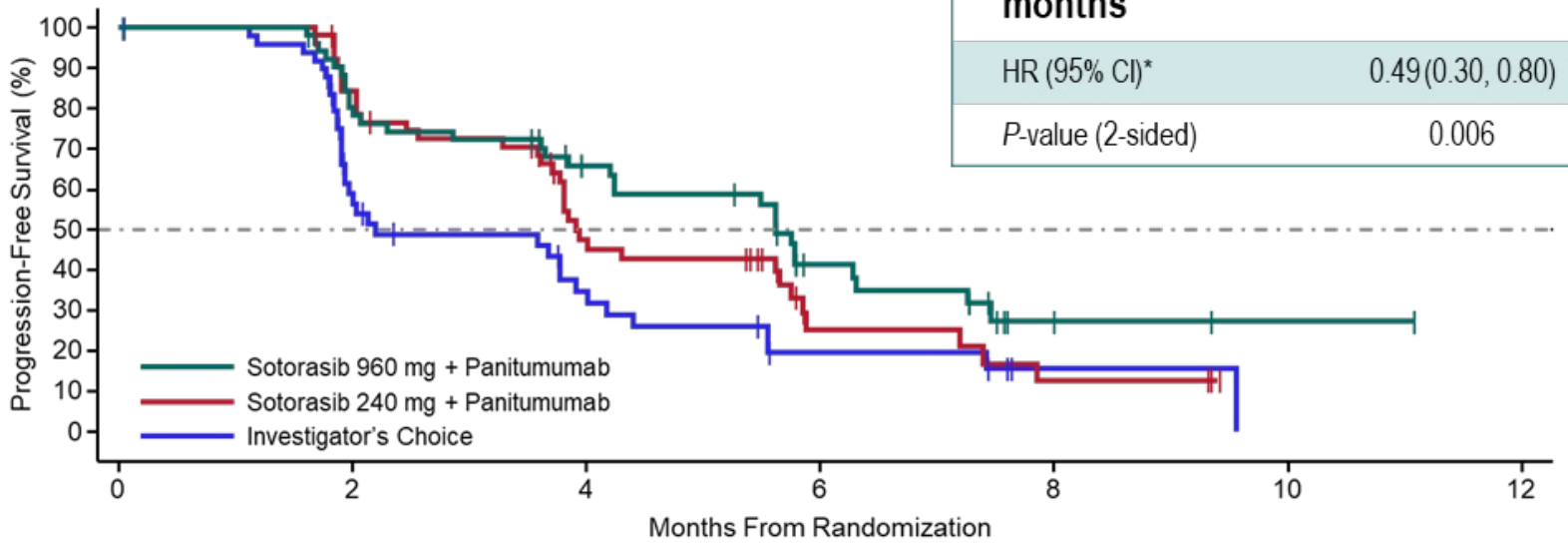
*Patients deemed by the investigator not to be candidates for fluoropyrimidine, irinotecan, or oxaliplatin may still be eligible if ≥ 1 prior line of therapy was received for metastatic disease and trifluridine and tipiracil and/or regorafenib were deemed appropriate next line of therapy. †Patients with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

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

Pietrantonio F et al., Presented at ESMO 2023.
Fakih et al., N Engl J Med 2023; 389:2125-2139

CodeBreaK 300: PFS for sotorasib+panitumumab vs investigator's choice (ITT)

	Sotorasib 960 mg + Panitumumab (n = 53)	Sotorasib 240 mg + Panitumumab (n = 53)	Investigator's Choice (n = 54)
Median PFS, months	**5.6**	**3.9**	**2.2**
HR (95% CI)*	0.49 (0.30, 0.80)	0.58 (0.36, 0.93)	–
P-value (2-sided)	0.006	0.030	–



Number of Patients at Risk:

Sotorasib 960 mg + Panitumumab	53	40	28	13	2	1	0
Sotorasib 240 mg + Panitumumab	53	43	20	6	3	0	
Investigator's Choice	54	24	12	5	1	0	

- After a median follow-up of 7.8 months, sotorasib (960 mg and 240 mg) + panitumumab significantly improved PFS vs IC
- Overall survival data were not mature at data cutoff
- Both sotorasib doses + panitumumab were tolerable, with no new safety signals and no fatal TRAEs

Pietrantonio F et al., Presented at ESMO 2023.
Fakih et al., N Engl J Med 2023; 389:2125-2139

CodeBreaK 300: ORR and DCR favor sotorasib + panitumumab

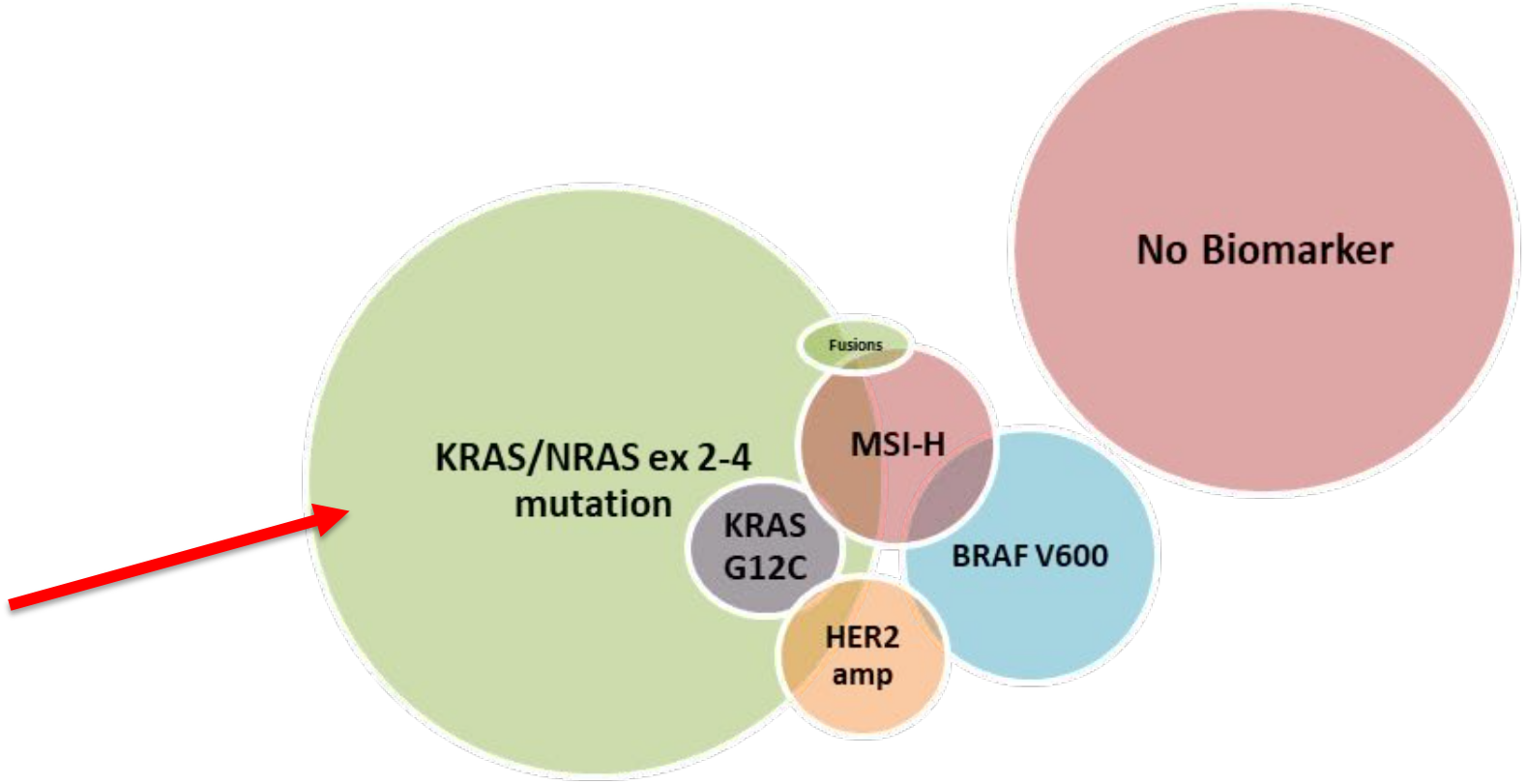
Response by BICR	Sotorasib 960 mg + Panitumumab (n = 53)	Sotorasib 240 mg + Panitumumab (n = 53)	Investigator's Choice (n = 54)
ORR, % (95% CI)*†	26 (15.3–40.3)	6 (1.2–15.7)	0 (0–6.6)
Complete response, n (%)	1 (2)	0	0
Partial response, n (%)	13 (25)	3 (6)	0
Stable disease, n (%)	24 (45)	33 (62)	25 (46)
Progressive disease, n (%)	12 (23)	13 (25)	17 (31)
Not evaluable / not done, n (%)	3 (6)	2 (4)	11 (20)
DCR, % (95% CI)*	72 (57.7–83.2)	68 (53.7–80.1)	46 (32.6–60.4)

The intention-to-treat analysis set included all patients who underwent randomization.
*95% CIs were estimated using the Clopper-Pearson method. BICR, blinded independent central review; DCR, disease control rate; ORR, objective response rate
†Two patients (4%) in the 240 mg arm and 1 patient (2%) in the investigator's choice arm had non-complete response/non-progressive disease; these patients had BICR assessed non-target disease only

Pietrantonio F et al., Presented at ESMO 2023.
Fakih et al., N Engl J Med 2023; 389:2125-2139

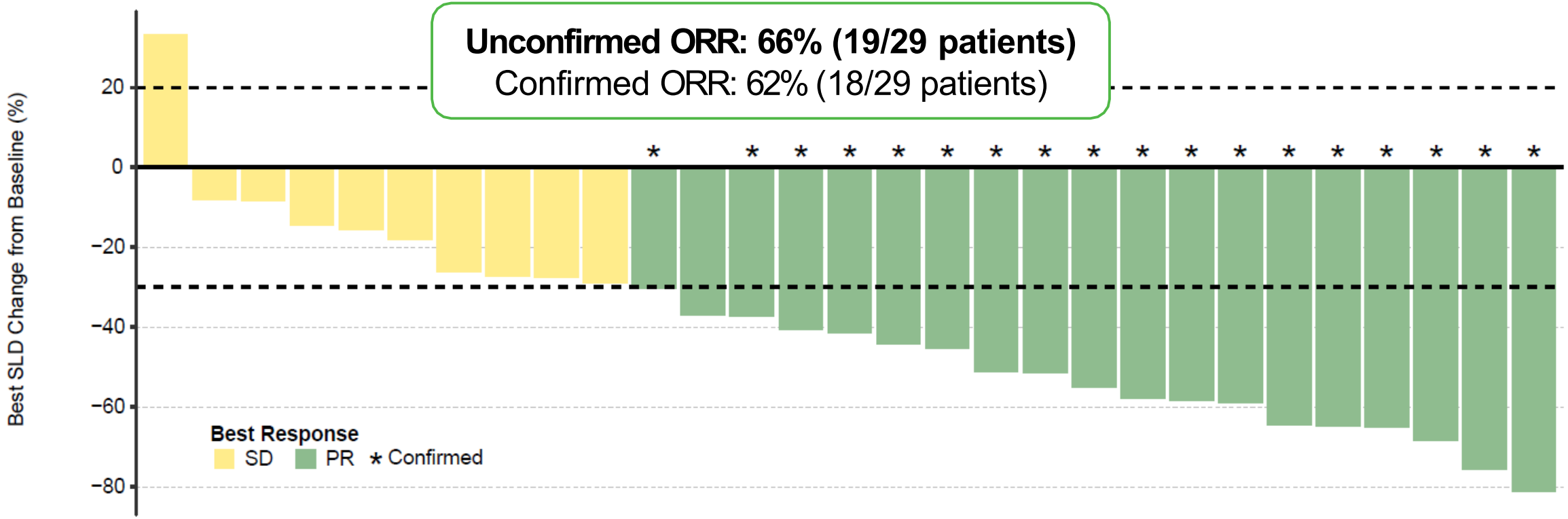
Other emerging precision cancer medicine targets in metastatic CRC

Actionable targets in metastatic CRC



GDC-6036 (Divarasib) + Cetuximab for Metastatic CRC

Unconfirmed ORR: 66% (19/29 patients)
Confirmed ORR: 62% (18/29 patients)



GDC-6036 Dose Level (mg)	400	400	400	400	200	400	400	400	400	200	200	400	400	400	400	400	400	400	400	400	400	400	400	400	400	400	400	400	400
Baseline SLD (mm)	15	74	87	144	90	121	84	84	109	38	43	65	59	59	87	86	33	43	35	189	90	24	83	59	57	83	35	62	53
Days on Treatment	181	167	181	49	84	80	169	210	167	232	138	140	197	173	167	92	168	138	183	124	174	294	161	213	342	160	188	71	265
Active on Treatment	Y	N	Y	Y	N	N	N	N	Y	N	N	Y	Y	Y	N	Y	N	Y	Y	Y	Y	N	Y	N	Y	Y	Y	Y	Y
Prior KRAS G12Ci	N	N	N	N	Y	N	N	N	Y	N	Y	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N

Indicates ≥4 months on treatment

Presented by Jayesh Desai at AACR Annual Meeting on April 17, 2023. Cancer Res (2023) 83 (8_Supplement): CT029.

Novel Therapeutic Strategies to Target Other KRAS Variants

High potency targeting

- 10^5-10^6 x improvement in target binding affinity
- Inhibition without covalent bonds
- Affinity for “on and off state” KRAS

Molecular glues

- RAS sticks to another protein to shut down the GTPase without degrading it
- Non-covalent pan-RAS inhibitor
- Inhibits wild-type proteins

Targeted degraders

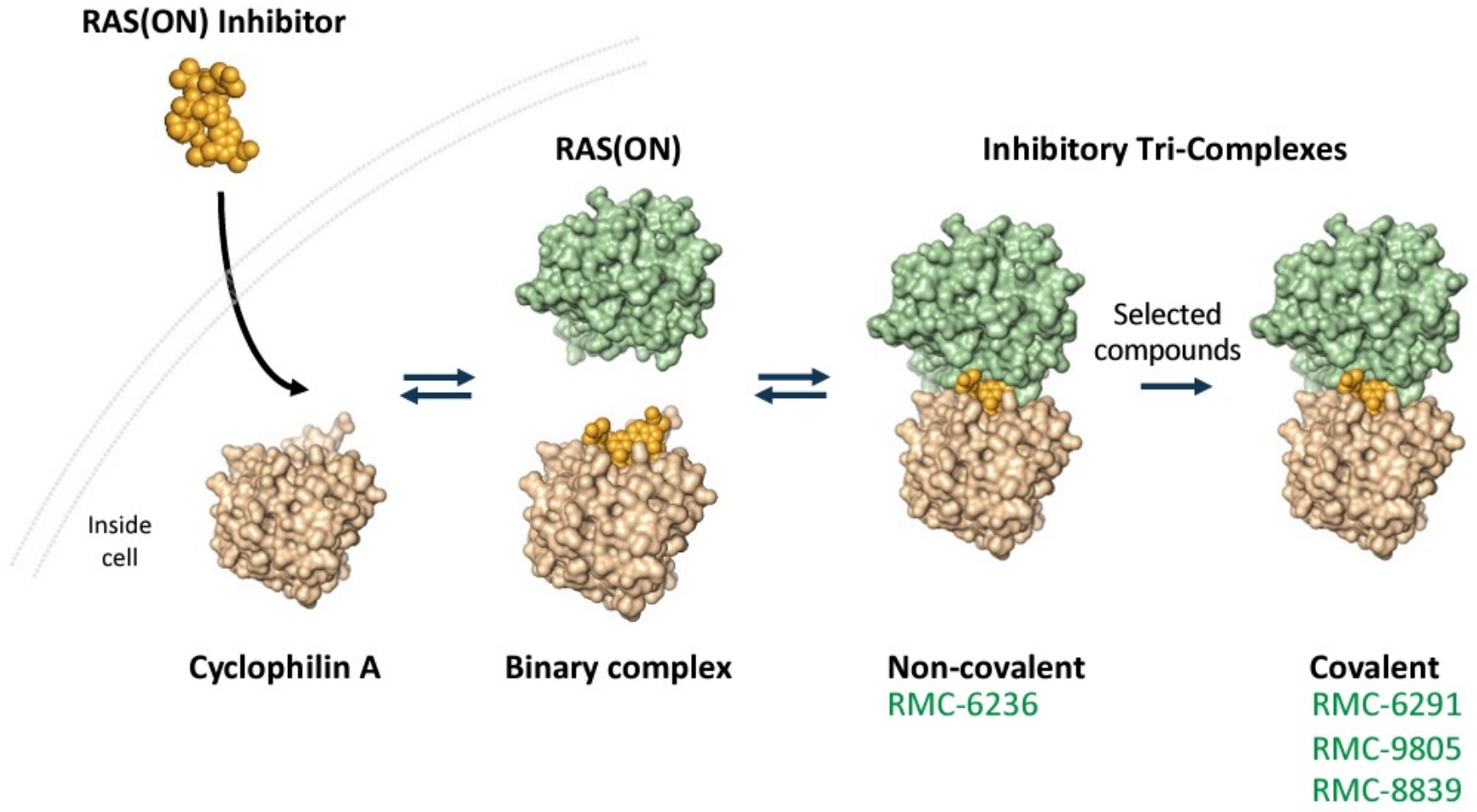
- Drug forms complexes between KRAS and ubiquitins to increase degradation
- Affinity for “on and off state” KRAS
- Rapid KRAS depletion

Covalent bonds with complexes

- 2-step process: 1) non-covalent complex with KRAS variant and another protein; 2) covalent bond then formed by drug to complex

Mullard Nature Reviews Drug Discovery (2023) 22, 167-171.

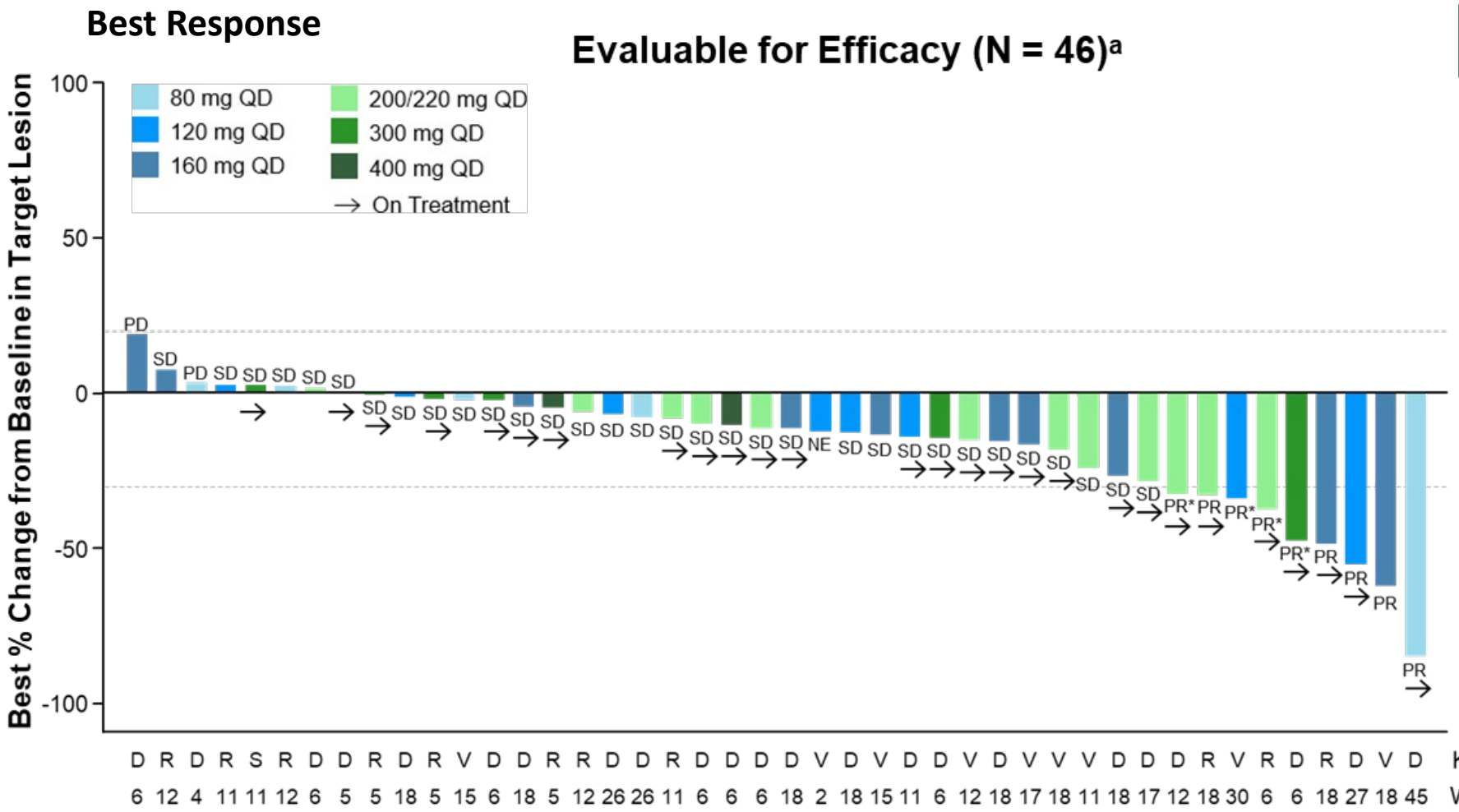
New Therapeutic Strategies in Development: Targeting RAS(ON) Proteins with a Tri-complex Platform



RAS(ON) INHIBITORS	
RMC-6236	RAS^{MULTI}
RMC-6291	$KRAS^{G12C}$
RMC-9805	$KRAS^{G12D}$
RMC-8839	$KRAS^{G13C}$
Additional	G12R, G12V, G13D, Q61X, other

Koltun ES et al. AACR 2022; Abstract 3597. Arbour et al. ESMO 2023; Abstract 6520.

RMC-6236 RAS^{MULTI}(ON) Inhibitor in Patients with *KRAS*^{G12X} mutant PDAC



Tumor Response (per RECIST 1.1)	
Best overall response, n (%)	
PR	9 (20)
SD	31 (67)
PD	3 (7)
NE[b]	3 (7)
ORR, n (%)	9 (20)
Confirmed, n	5
DCR (CR+PR+SD), n (%)	40 (87)

*Unconfirmed PR per RECIST 1.1.

[a]Patients who received first dose of RMC-6236 at least 8 weeks prior to data extract date.

[b]Two patients died prior to first post-baseline scan; 1 patient had scan after 11 days of treatment and subsequently died due to PD.

Koltun ES et al. AACR 2022; Abstract 3597. Arbour et al. ESMO 2023; Abstract 6520.

An incomplete list of KRAS therapies entering the clinic

	Drug	Target	Properties	Status
Variant specific inhibitors	ASP3082	KRAS-G12D	Targeted degrader	Ph 1
	HRS-4642	KRAS-G12D	Targeted inhibitor	Ph 1 (China)
	MRTX1133	KRAS-G12D	Non-covalent inhibitor	Ph 1/2
	RMC-9805	KRAS-G12D	Molecular glue inhibitor	IND-enabling
	RMC-8839	KRAS-G13C	Molecular glue inhibitor	IND-enabling
	QTX3046	KRAS-G12D	Non-covalent inhibitor	Preclinical
	BI-KRASG12D	KRAS-G12D	Non-covalent inhibitor	Preclinical
	JAB-22000	KRAS-G12D	Targeted inhibitor	Preclinical
	ERAS-4	KRAS-G12D	Targeted inhibitor	Preclinical
Pan-KRAS inhibitors	RMC-6236	Pan-KRAS	Molecular glue inhibitor	Ph 1
	NA	Pan-KRAS	Pan-KRAS degrader	Ph 1
	NA	Pan-KRAS	Pan-KRAS degrader	Preclinical
	QTX3034	Pan-KRAS	Allosteric KRAS inhibitor	Ph 1
On-state inhibitors	FMC-376	KRAS-G12C	Targeted inhibitor	IND-enabling
	BBO-8520	KRAS-G12C	Targeted inhibitor	IND-enabling

Source: Modified from Nature Reviews Drug Discovery 22, 167-171 (2023)

Consensus or Controversy? Investigator Perspectives on the Current and Future Role of Immune Checkpoint Inhibitors in the Management of Hepatobiliary Cancers

Saturday, January 20, 2024
5:30 AM – 6:30 AM PT (8:30 AM – 9:30 AM ET)

Faculty

Ahmed Omar Kaseb, MD, CMQ
Arndt Vogel, MD, PhD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

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